THE UNIVERSITY *of* EDINBURGH

A CRITICAL ACCOUNT OF CLINICAL AND PHYSIOLOGICAL STUDIES IN RETT SYNDROME

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Abstract

A critical account of clinical and physiological studies in Rett Syndrome

Rett syndrome is the manifestation of an X linked, mainly female, genetic, neuro-developmental disorder that usually produces profound intellectual and physical disabilities including abnormal muscle tone, with a tendency to develop limb contractures, scoliosis, epilepsy and irregular respiration. There is characteristic hand stereotypy with poor voluntary hand use, locomotion is compromised and speech is rare. Although the disorder is not progressive many sequele shorten life especially in the most severely affected. Subtle abnormalities, present from birth, are frequently overlooked because there is some developmental progress until a period of regression at around one year of age when speech and hand use diminish. This thesis gives an account of clinical, physiological and genetic studies carried out between 1982 and 2005 with the aim of recording the natural history of the disorder and understanding its clinical manifestations.

The subjects of these studies have been people of all ages, mainly from the British Isles, reported to have Rett syndrome by their physicians and families or carers (British Isles Survey, n=1228). Most have been examined and recorded on video by myself, many repeatedly. Fully informed parental consent and appropriate ethical approval has been given for all procedures.

The early manifestations of the disorder were investigated from developmental histories and donated videos (78) taken by families before they were aware of the problem. The abnormal respiratory rhythms were investigated and characterised, using non-invasive measures of respiratory rhythm, carbon dioxide, oxygen, heart rate and blood pressure. The poor control of voluntary movement was investigated using electromagnetic stimulation of the cortex to record conduction in the motor pathways. Stereotyped hand movements were analysed from three-dimensional live recording and informal two-dimensional video. The prevalence of a toe anomaly was estimated, visual evoked potentials were recorded and a reported increase in urinary neopterin was investigated. The health of people in the British Survey was monitored longitudinally from family and physician reports and direct clinical examinations, data being stored on computer. Simple scores were generated to indicate separately the severity of the condition and health of the individual.

The survey data has been used to estimate the prevalence of the disorder (1 in 10,000 females), natural history from birth to death, the predictive value of the earliest signs, survival at different levels of severity, the impact of scoliosis surgery on health and has provided a foundation for studies relating clinical manifestations to specific mutations on the affected gene *MECP2* (Xq28). The studies have indicated the nature of the Rett disorder to be developmental and non-progressive, with primary impact on the processing functions of the brain, probably beginning in the brain stem before birth.

Aims and Hypothesis

My aim in these studies has been to achieve a better understanding of the disorder that underlies the Rett syndrome through longitudinal clinical and neurophysiological investigations. My particular focus of interest has been the earliest signs of the disorder and the relationships between bursts of abnormal respiration, mood, movement and electroencephalographic disturbance. The hypothesis has been that close observation of the behaviour of the individual and the changes, which occur over time, would provide important clues to the underlying process and contribute to tracing its origins and directing its management.

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Abbreviations

BDNGF brain derived neuronal growth factor

BIS (or BIRS) British Isles Survey (for Rett)

CSGE conformation sensitive gel electrophoresis

e.e.g. electro encephalogram / graph

EMS (or TMS) (transcranial) electromagnetic stimulation

HSQ Health survey questionnaire (used in BIS)

MAP2 microtubule associated protein 2

MBD methyl cytosine binding domain

NMDA non glutamate receptor

MECP2 gene for methyl CpG binding protein

MeCP2 methyl CpG binding protein

OFC occipito-frontal circumference

RSBQ Rett syndrome behavioural questionnaire

RS Rett syndrome

SSCP single stranded conformation polymorphism

TRD transcription repression domain

UBE3 gene associated with mutation in Angelman syndrome

VEP visual evoked potential

XCI X-inactivation

Section 1

Literature and background

1.1 Definition

The Rett disorder is a developmental, X-linked dominant condition resulting from mutation in the gene *MECP2* Xq28 (Amir et al 1999), usually manifesting as the Rett Syndrome (RTT). Prevalence at age 14 years in the UK is estimated at not less than 1 in 10,000 females, with both higher and lower estimates elsewhere (Asthana et al 1990, Kerr 1991, Kerr 1992, Hagberg & Hagberg 1997). There are far fewer males than females. The disorder presents with subtle signs of developmental deviation from birth (Burford et al 2003, Einspieler et al 2005) and developmental regression in infancy or early childhood when fine hand skills and communication skills decrease and stereotyped movements become evident. Severe or profound intellectual impairment is usual and there is little or no speech, respiratory rhythm is disturbed, feeding presents difficulties, epilepsy is common and there is a tendency to develop scoliosis and contracture of limb joints. In spite of their serious problems these are typically attractive people, enjoying company, not frankly dysmorphic and may live long and in good health although survival varies according the severity of the condition (Kerr 2002).

1.2 History of the research

The first full description of the Rett syndrome was published by Andreas Rett (Rett 1966, 1977) who noticed similar stereotyped hand movements in two children seated on the laps of parents waiting at his epilepsy clinic and with the help of his secretary gathered a number of cases he had seen previously. Rett recorded the clinical characteristics of the condition **(figure 1.2)** Having investigated his patients using an early and unrefined protocol for the estimation

of ammonia in the blood he became convinced that the disorder was due to an inborn error of ammonia metabolism, a possibility he later dismissed.

Without awareness of Rett's first German language description, Ishikawa and Japanese colleagues presented three cases (Ishikawa et al 1978), remarking upon their stereotyped hand movements, irregular breathing and apparent lack of progression over time. Also without prior knowledge of Rett's description, Hagberg began to notice such cases in Sweden. From their apparent early normality, which was followed by rapid deterioration, he thought that this might be due to a progressive metabolic disorder and with European colleagues, investigated a cohort of cases (Hagberg et al 1983). Research into the disorder was helped by collaboration between clinicians and laboratory scientists from Japan, Austria, Sweden, the UK, the USA and other countries who met in a series of international conferences beginning in 1984 at the invitation of Andreas Rett. These initiatives were encouraged by parents, notably Mrs Kathy Hunter in the USA, Yvonne Milne in England and Isobel Allan in Scotland who founded Rett Syndrome Associations. The conferences provided valuable contact between clinical and laboratory scientists, families and people with Rett, leading to research which was well focussed and sufficiently funded to provide knowledge of the clinical, pathological, physiological and genetic basis of the disorder and so to develop rational management.

1.3 Development of Diagnostic Criteria

While the aetiology and pathophysiology of the condition were still largely unknown it became important to define the terms used to describe the condition in order to distinguish it from other conditions leading to severe disabilities and to permit the scientific study of a homogeneous cohort. It was agreed to reserve the term 'classic Rett Syndrome' to describe the situation when all the cardinal signs were present without any other confounding factors and to use the term 'atypical' or 'non classic' Rett syndrome for cases with similarities but some differences.

It has required the growing experience from large national surveys and successive publications of criteria for the nature of these cardinal signs to be fully appreciated. Early proposals for criteria included a normal neonatal and early infancy period, autism, microcephaly and cerebral atrophy (Hagberg et al 1983). However in his 1986 review Opitz stated 'I remain unconvinced that any Rett syndrome child has truly or completely normal development at any time in life' and 'no evidence for a true degenerative disorder has ever been demonstrated in the Rett syndrome' (Opitz 1986). Other researchers have found evidence of subtle deviation from birth and the lack of evidence of progressive degeneration. (Kerr 1987, 1995, Naidu 1997, Leonard & Bower 1998, Burford & Kerr 2003, Einspieler et al 2005). That the disorder is not degenerative has now been clearly demonstrated pathologically as well as clinically (Armstrong 2000, 2002). Mutation testing and development of an animal model have made it possible to confirm the wide range of severity within the Rett disorder and to confirm that its impact is already felt before birth affecting somatic and brain growth (Huppke et al 2003, Armstrong et al 2003). The successive sets of criteria are shown in the appendix A **(Figures 1.3.1-7)**. The criteria adopted in this thesis are those approved by the Diagnostic Criteria Working Group **(Figure 1.3.5)** (Trevarthen et al 1988) with the modifications published in the International guidelines (Kerr et al 2001) **(Figure 1.3.7)**.

The evolution of the clinical picture throughout life was described by Hagberg and Witt Engerstrom as occurring in stages (Hagberg & Witt Engerstrom 1986), stage I being asymptomatic, stage II during regression, stage III a 'pseudo stationary' period and stage IV a later degenerative stage **(Figure 1.3.8)**. Adopting a different approach, Kerr and Stephenson described the stages as pre-regression, regression and post-regression, accepting no clearly normal early period and no inevitable later deterioration **(Figure 1.3.9)**. The predominant muscle tone was used to classify presentation according to 'subtype', hypotonic, dystonic, severely hypertonic or mildly hypertonic (Kerr & Stephenson 1985, 1986). There was tendency for early hypotonia to lead to later hypertonia.

A complex issue was raised by situations when Rett seemes a likely diagnosis in the absence of some of the cardinal signs or the presence of unexpected features, particularly when no other diagnosis could be confirmed. Hagberg described such cases as 'variants' of Rett syndrome (Hagberg & Witt-Engerstrom 1990b, Hagberg & Skjeldal 1994, Hagberg & Gillberg 1998), including male (Philippart 1990), congenital (Nomura et al 1985), early seizure (Hanefeld 1985), formes frustes Hagberg & Rasmussen 1986 (see **Figure 1.3.10)** and preserved speech variants (Zappella 1992). Other researchers have adopted the terms 'atypical' or 'non-classic' Rett' recording details of any differences from the classic description. The presumption has been that some non-classic cases do have the Rett disorder and that others have distinct and different disorders which are still to be recognised and which affect closely related neural networks.

1.4 Differential Diagnosis

At the earliest period when the child with Rett begins to show failure to progress in development the condition must be distinguished from other non-dysmorphic developmental disorders. At this stage deviation from the normal spontaneous movements of babies may alert to the diagnosis and justify mutation testing (Burford & Kerr 2003, Einspieler et al 2005).

During the regression period there may be confusion with a number of metabolic conditions including Batten's disease (Hagberg & Witt-Engerstrom 1990) however the continued deterioration of metabolic disorders contrasts with the stabilisation that is seen in the child with Rett, usually within a few months.

From the early descriptions of the condition Rett syndrome has been compared to autism and many cases have been given a tentative diagnosis of autism before being correctly diagnosed. There are undoubted similarities. Both are developmental and pervasive disorders. Both may present in late infancy or early childhood with a crisis marked by regression (Kerr 2003a). Both display multiple stereotypies and are prone to unexplained agitation.

There are major clinical differences too. The person with Rett is characteristically profoundly physically and intellectually disabled whereas most autistic people are not. Epilepsy is common in Rett and much less so in autism. Above all the person with Rett relates well to people, demonstrating a capacity for relationships that seems to be completely lacking in autism. Some would still include Rett in the 'autistic spectrum' whereas most clinicians working in Rett prefer to explore the similarities and differences between these clinically distinct states. Although both clearly affect the finer processes of thought and understanding and there are likely to be some underlying mechanisms involved in both (Shibayama et al 2004). Significant neuropathological differences have also been demonstrated (Casanova et al 2003, Samaco et al 2004).

Unlike autism and like Rett, Angelmann's syndrome is associated with a specific genetic configuration. As in Rett the child deviates subtly from normal and may develop stereotypies but the irregular breathing seen in Rett has not been described. A developmental regression is unusual. The degree of intellectual disability is usually less although as in Rett, speech is often absent. As in Rett the child is sociable. Reduced expression of UBE3 and GABRB3 has been reported to be due to *MECP2* deficiency suggesting a basis for some of the similarities between Angelmann and Rett syndromes and an association with epileptic disorders. (Samaco et al 2005).

1.5 Neuropathology, Biochemistry, physiology of the Rett brain

Rett and his colleagues were impressed by the relatively normal appearance of the brain, which although small appeared to be well formed, but it was noticed that the basal ganglia were pale (Rett 1966, 1977, Jellinger & Seitelberger 1986). Baumann indicated that the neurones were smaller and more closely packed than normal (Baumann et al 1995). Armstrong used silver staining to study the dendritic development in cortical neurones and showed a lack of normal branching, particularly in frontal, inferior temporal and parietal areas (Armstrong 1992,1995, 1998, 2000, 2002). Using immuno-fluorescent

techniques she and her colleagues also demonstrated hugely increased density of receptors for serotonin in the brain stem (Armstrong & Kinney 2001) and reduced substance P (Deguchi et al 2000). Still more recently this group has shown severe deficiency of serotonin transporter protein in the dorsal motor nucleus of the vagus (Paterson et al 2005). Blue and Johnston found increases in NMDA receptors for glutamate in the cortex during early childhood with reduction below normal by 10 years (Johnston et al 1995). Wenk and colleagues found evidence of cholinergic disturbance in the basal forebrain (Wenk et al 1999) Kaufmann found specific lack of Microtubule Associated Protein-2 (MAP2), a substance which is normally present in the base plate before the migration of neurones to the cortex and is important for the maintenance of dendritic structure (Kaufmann et al 1995, 1997, 2001). Using confocal microscopy Belichenko demonstrated partial development of the speech area in Rett (Belichenko et al 1997). Casanova distinguished the appearance of the brain from that in autism in a study of the mini-columns that surround the cortical neurones (2003). Evidence from the direct study of the brain thus seems to indicate a developmental disorder which without preventing neuronal emplacement subtly interferes with brain development with particular impact on neuronal connectivity and the synapse (Johnston 2005).

Physiological investigation revealed early disturbance of the sleep rhythms suggestive of prenatal monoamine disturbance (Nomura et al 1984, Nomura & Segawa 1990a & 1990b), relatively normal conduction in the long motor and sensory tracts with indications of central processing difficulties (Eyre et al 1990, Hagne et al 1989) and disturbed regulation of respiratory and cardiac rhythms (Sekul et al 1994, Johnsrude et al 1995, Julu et al 1997, Guideri et al 1999). Electroencephalographic (e.e.g.) records show normal or immature patterns before regression and by the end of regression bursts of slow waves with or without spikes are commonly present, exacerbated in sleep (Glaze et al 1987, Cooper et al 1998)

1.6 Genetic discoveries

The existence of monozygotic twins with the disorder suggested a genetic origin and a huge preponderance of females indicated the X chromosome. An affected young mother with male and female offspring and another family of three cases narrowed the search to Xq28 (Schanen et al 1997, Xiang et al 1998, Sirianni et al 1998) and in 1999 Amir and colleagues, in the laboratory of Huda Zoghbi located the affected gene *MECP2* (Amir et al 1999).

MECP2 had already been recognised as an important 'housekeeping' gene (Nan et al 1993, 1997, 1998). It consists of 3 known exons, of which exon 3 is the largest, spanning 1084bp and encoding a 486 amino acid protein (D'Esposito et al 1996). *MECP2* is widely expressed and alternative polyadenylation in the 3'UTR results in a highly expressed 10.1 kb transcript in the foetal brain (D'Esposito et al 1996, Coy et al 1999). The protein MeCP2 contains two known functional domains, an 85 amino acid methyl-cytosine-binding domain (MBD) and a 104 amino acid transcriptional repression domain (TRD). The MBD binds to 5 methyl cytosine residues in symmetrically positioned CpG dinucleotides located in gene promotor regions that are subject to transcriptional silencing after DNA methylation (Lewis et al 1992, Nan et al 1993). The TRD interacts with histone deacetylase and SIN3A, a transcriptional co-repressor. Interaction between this transcription repressor complex and chromatin-bound MeCP2 causes deacetylation of core histones resulting in transcriptional repression (Nan et al 1998, Jones et al 1998)

Thus through transcriptional repression and possibly in other ways, *MECP2* plays a role in regulating the expression of other genes. It transcribes into at least two forms of the MeCP2 protein (Mnatzakanian et al 2004, Samaco et al 2004) and these are dynamically controlled in response to local tissue requirements (Matarazzo & Ronnett 2004, Mullaney et al 2004). Interactions with other genes and substances important for the growth and maintenance of the body are still being explored. These include *UBE3*, *GABRA3* (Samaco et al 2005), *BDNF*

(Riikonen 2001, 2003), *DLX5* (Horike et al 2005), also *FKBP5* and *SGK* - already known to be stress-responsive genes involved in glucocorticoid metabolism (Nuber et al 2005). *MECP2* mutation affects an imprinted gene cluster on Chromosome 6, including *DLX5* and *DLX6*, which regulates the production of enzymes synthesizing gamma-aminobutyric acid (GABA). Although the *MECP2* gene is active throughout the body it is in the brain that its role appears to be most important, affecting the neurones as they become mature (Armstrong et al 2003) and specifically active at the synapse (Johnstone et al 1995, Mullaney et al 2004). That it is important in prenatal development is clear from its expression in the Cajal-Retzius cells and other subcortical and brain stem elements before the cortical neurones are emplaced (Armstrong et al 2003).

Genetic research has made rapid recent progress due to the development in Scotland (Guy et al 2001) and the USA (Akbarian et al 2001) of mice with *MECP2* mutations. These Rett models have already proved remarkably useful because the gene is highly conserved (Hendrich 2000) and the symptomatology in the mouse to some extent parallels that in the human.

Over 300 sites of mutations have been located on the *MECP2* gene leading to clearly recognisable Rett syndrome. There is general agreement that early truncating mutations most effectively prevent production of MeCP2 protein and so lead to more severe disease than missense or late truncating mutations that allow partial production (Cheadle et al 2000). However the clinical profile of the disease is remarkably constant within a wide range of severities (Kerr & Witt Engerstrom 2001, Charman et al 2005).

The presence of two X chromosomes in all female cells and the random inactivation of one of these (XCI), protects the woman from the effects of a mutation in one of her X chromosomes. When one X chromosome is used more than the other (skewed X inactivation) the disease is more or less severe according to which X chromosome is used most. At present there is still

uncertainty as to how common such skewing may be in the Rett population. One study has found significant skewing in 43% of cases with truncating mutations or mutations affecting the MBD (Weaving et al 2003). Other investigators found no significant skewing in the brains of 10 cases (Shabazian et al 2002, Gill et al 2003). In a study with mouse models of Rett disorder, Young and Zoghbi found that, at the single cell level, XCI favoured the wild type (healthy) allele because these cells survived as those with the mutation did not. No mice had non-random XCI favouring the mutant allele. This study seems to indicate the importance of MeCP2 for neuronal viability (Young and Zoghbi 2004).

A mutation in *MECP2* seems to arise most frequently during cell divisions of the sperm and since the paternal X determines female offspring it is a daughter who is affected (Miltenberger & Laccone 2003). Such cases appear sporadic, as they arise from a fresh mutation and usually fail to be transmitted to offspring of the affected female due to the severity of her condition (Shabazian & Zoghbi 2001). However the condition is a fully penetrant X-linked dominant and the uncommon situation has been recorded in which the female receiving the mutation is favourable skewed to such an extent that she is unaware of the condition and bears children, in which case there is a 50% risk to both male and female offspring (Schanen & Franke 1989, Kerr& Belichenko et al 2001). Germ line mosaicism has also been described in the female, leading to more than one offspring being affected - male or female (Gill et al 2003).

Few males have been found with the condition, presumably for the reasons explained above. Of those recorded, some have been very severely affected, presumable because their only X chromosome carries the mutation. Interestingly the clinical profile in such cases appears to be the same as in more classic cases (Kerr et al 2003). In Klinefelter's syndrome (Schwartzmann et all 1999), with one or more additional X chromosomes and in somatic mosaicism (Clayton Smith et al 2000) when only one portion of the cells contain the

mutated X, the male may present the same profile as the female with classic Rett disorder.

A start has been made in explaining some previously unrecognised disorders that share clinical features in common with Rett and may have been reported as 'aytpical Rett'. Two mutations have already been identified, remote from *MECP2*, responsible for such conditions. The gene *STK9 (CDKL5)* (Kalscheuer et al 2003) is associated with some 'atypical' cases dominated by severe early epilepsy (Weaving et al 2004). Similar neurochemical disturbance which may underlie similarities between Rett and other developmental disorders is being explored. Hitchins et al (2004) found no *MECP2* mutations in 24 sporadic cases of *UBE3* negative Angelman syndrome. However in a study comparing Prader Willi, Angelman, autism and Rett with age matched controls, Samaco et al (Samaco et al 2004) reported that whereas different transcriptional and post transcriptional mechanisms are present in these disorders all are associated with altered levels of the MeCP2 protein.

At present, with high quality research proceeding throughout the world, the development of effective treatment seems within reach at the genetic level and at the pharmacological level. Strategies being now being discussed include some for alteration of the pattern of X inactivation, insertion of *MECP2* gene or MeCP2 protein and the replacement or reduction of key neuroactive substances.

1.7 The origin and objectives of the thesis studies

The studies described here commenced late in 1982 when in response to my offer to carry out research in his department Professor John Stephenson invited me to investigate the Rett syndrome at the Fraser of Allander Unit in Glasgow (Kerr & Stephenson 1985). At that time only the publication by Rett was available but Dr Stephenson had just attended a lecture in Oxford at which Professor Bengt Hagberg had presented cases of the disease, describing the signs and demonstrating the characteristic hand movements. From Dr Stephenson's

diagnostic register of the referrals to the unit, we were able together to identify 19 cases presenting with developmental difficulties compatible with a diagnosis of Rett Syndrome and to establish an initial estimate of prevalence. At this time Rett syndrome was commonly regarded as a rare and enigmatic disorder that began with the abrupt regression and continued on a relentless downward course.

Concern to examine affected people in order to understand the disorder and the concern of families for their children's problems to be understood, led to my collaboration with the newly founded support associations and I was offered a unique opportunity to meet and examine a very large number of people with Rett at all ages, over a long period of time. From the resulting cohort have developed the many research studies reviewed in this thesis. I have given most space to those to which I have contributed most.

From the first cases and their families it was clear that the disorder was already present before the regressive episode and that there was little if any change in the level of intellectual disability after the regression period (Kerr and Stephenson 1985, 1986, Kerr et al 1987). I wished to investigate the early period in which the disease became manifest. I was impressed also by periodic disturbances in behaviour, hand stereotypies, hyperventilation, breath holding, agitation and periods of interrupted awareness and wished to discover how these related to bursts of slow wave seen on the electroencephalogram (e.e.g.). These research questions remained central to my investigations. Facilities could not be provided for extensive neurophysiological research in the Children's hospital and I was invited by Dr John Laidlaw, head of the Quarrier's Homes Epilepsy Centre and Dr James Minto its director to base the work there on the western side of Glasgow, collaborating with Mrs Patricia Amos, a highly experienced e.e.g. technician (1986-1995). In 1995 I was invited by Professor Colin Espie to join the University of Glasgow Department of Psychological Medicine (1995-2005).

Section 2

Subjects and methods – general

Introduction

The research subjects in these studies were selected from the cohort, which developed from my investigation of Rett Syndrome, beginning in November 1982. This cohort became formalised as the British Isles Survey (BIS) for Rett Syndrome in 1990-1, when the British Paediatric Surveillance Unit agreed to circulate my description to over 800 paediatricians in the UK. The collection and recording of data and the conduct of the survey has been solely by myself. The description in this section applies to the subjects in the BIS cohort and the methods that I have used in recording their health data. The subjects and methods for the individual research projects that follow are described in the later sections. Some very large genetic studies presented in section 7 have included cases from other countries and cohorts.

Ethical approval for BIS has been provided by the appropriate ethical committees at each stage in its development, by the medical board at Quarrier's Epilepsy Centre, the ethical committee of the Glasgow Royal Hospital for Sick Children and most recently the Multi-centre Research Ethics Committee for Scotland (MREC) ref MREC/03/0/42. The existence of notified cases has always been recorded. Detailed health data is held when the family/carer has given informed consent for that. Each research project arising from BIS has obtained separate, appropriate ethical approval. Families and carers have provided fully informed consent for all projects. Very few people with Rett are capable of giving informed consent due to their profound intellectual disability and these few have also consented. **Appendix E** shows typical information sheets and consent forms.

2.1 Subjects

The subjects of these studies (n=1236) have been reported or referred to me since 1982 as suffering or probably suffering from the Rett Syndrome. A note on the terminology that I have adopted is at the end of this section. The dataset in **Appendix B** indicates for all the reported cases their status with regard to the criteria for classic Rett syndrome, dates of birth and death and mutation test results as far as is known to me. A note on the present state of mutation testing is at the end of this section. Separate lists in **Appendix C** indicate mutation status for people included in each individual research study with further data relevant to that study. As a paediatrician, my initial contact was with children, however my long association with the disorder and the caring Associations, the concern of families to remain in touch with research developments and requests for advice on management by colleagues has led to many adults being reported and referred to me. Awareness in the medical profession has been slower to develop in adult care than in paediatric care and this is reflected in the relatively small number of adults in BIS. If the suspected diagnosis of Rett disorder has not been confirmed, or if another diagnosis has been made, the case is not removed from the database. This is in order to facilitate comparison with other conditions that have some features in common with Rett syndrome. Many families have found it supportive to keep this contact. Therefore about 6% of people in the survey are considered not to have Rett disorder although they have presented with some of the same signs and been reported as possibly Rett. In the database these are designated 'not Rett' with a record of any other condition that has been diagnosed. Status 'unknown' in the database indicates that I have not had an opportunity to examine the individual and have insufficient information to form an opinion on clinical status.

2.2 Survey methods

Data collection

Health data was gathered from family histories, reports from colleagues, direct examinations by myself of more than 800 people, many on several occasions,

and health questionnaires completed by families (750 people, many completing several over some years), providing valuable retrospective and prospective health data. A copy of the BIS health questionnaire is shown at **Appendix D**. The questions were chosen to provide the most robust and objective information for use in research studies and in preparing advice for families and professional colleagues. Every family completing a health questionnaire is offered a copy as a home held record, to be copied and shared at the family's discretion.

The Rett Syndrome Association UK and the Rett Syndrome Association Scotland invited me to offer consultations at family referral clinics organised by them in different parts of the country, extending my contact with families and professional colleagues, providing a wealth of clinical experience and data and ensuring that what is learned from research is shared with families and professional colleagues. No charge was made for my advice. Although families came for consultation at their own request they were advised to discuss their attendance with their medical advisers who frequently sent accompanying information. Treatment was never prescribed or undertaken by me at such clinics. Consultations lasted 30 minutes and as many as 40 families have been seen by me during these 2-3 day events. Following each consultation my summary letter was sent to the physician and other professionals as requested by the family, with a copy to the family.

With the agreement of families I recorded video during consultations, for over 400 people, many on several occasions. This has provided valuable additional clinical data and teaching material for other families and professionals.
In response to my concern to understand the earliest signs of the Rett disorder, 78 families have donated copies of cine- or video records which they made during the early days and months of life of the child with Rett. These have provided invaluable insight and have been used in the research described in section 3. Parts of the video record are also included in a teaching DVD for

physicians, 'Understanding the Rett Disorder' completed in 2005, a copy of which has been placed in the back pocket of this thesis.

Database organisation

A list of the data fields designed to store health information is provided and explained in **Appendix D**. In the data fields which record locomotor ability, hand use, use of speech, understanding of speech, feeding difficulty, scoliosis and epilepsy, data is recorded separately, as a single digit, in every 5 year period throughout life. The first such period refers to the period before regression in cases in whom regression has occurred and to the first 5 years of life in cases where no regression has occurred. This system provides a useful and robust longitudinal record that is in part retrospective and in part prospective.

A simple score reflects the severity of the disease and another reflects the health of the individual. Charting severity and health separately in this way allows some distinction to be made between aspects of the disease that are inherent (severity) and aspects, which have much to do with circumstances and may be more amenable to health management.

The Severity Score is calculated from the items: - predominant abnormality in muscle tone, feeding difficulty, ability to walk without support, presence of epilepsy and perceived severity of the scoliosis. The Health Score is calculated for the 12 months preceding the report or assessment, from the items: - weight, frequency of episodes of epilepsy, chest infections or aspirations, episodes of other illnesses and the parent's opinion of the individual's state of health. The scoring system is shown in **figure 2.2.1**.**Appendix A** When a death has occurred, in addition to available reports on the events surrounding the event and the recorded cause of death, the type of death is classified as relating to severe epilepsy (S), debility/ frailty (F), general causes (G) or sudden and unexpected (U).

2.3 Notes on BIS criteria, terminology and mutation testing status:

Note on Criteria:

BIS uses the criteria for classic Rett syndrome as agreed by international consensus in 1987 (Diagnostic Criteria working group 1988) and modified in the recent International Guidelines (Kerr et al 2001) **(figures 1.3.5 & 7)** as discussed in section 1.3 (Development of diagnostic criteria).

Note on terminology

In BIS and this thesis the term **Rett Syndrome (RS)** indicates the observed clinical profile usually associated with a mutation in *MECP2*.

The term **Classic Rett syndrome (CR)** indicates the presence of all the main clinical features and the absence of any other features of possible aetiological significance. The term **'incomplete Classic Rett' (inc CR)** indicates that the case appears classic but not all the evidence is available, due either to the young age of the individual or to the lack of early developmental history.

The term 'Rett syndrome **non classic**' ('R non C', '**atypical Rett syndrome**') indicates the presence of some but not all of the 'Rett' features, sometimes with elements not usually associated with Rett syndrome yet within a context that is suggestive of Rett disorder. The term '**Rett disorder**' is used for the situation when the mutation and the clinical condition are present and the process is being discussed. The recently introduced term '**RTT**' does not allow for these distinctions and is currently in use to describe both the disorder and the syndrome. This term is not used in this thesis for that reason.

Note on mutation testing status:

Mutation testing became possible in 1999 and is not universally available. In some areas it is still regarded as a research procedure. Although more than 300 mutation sites have been found in the *MECP2* gene, the entire gene has not yet been explored and previously unidentified pathological mutations are still being found. We presume that the Rett syndrome may follow failure to express MeCP2

protein for reasons other than a *MECP2* mutation, but so far the expression of MeCP2 is not routinely measured. For these reasons, although identification of a mutation on *MECP2* is firm evidence of the presence of the disorder, failure to identify a mutation is not good evidence of its absence.

Many people involved in these studies have not had mutation testing and some who have been investigated have not had a mutation identified. Since close to 90% of carefully examined cases with classic Rett syndrome have been shown to have a mutation, clinical status is still considered to be the most reliable guide to the presence of the disorder. Among people with 'atypical' Rett (Rett non classic) up to 40% have been found to have a *MECP2* mutation. These mutation positive 'atypical' cases include many mild cases that are not 'classic', having experienced no regression event, and having better brain growth and better skills than are expected in the classic syndrome. Others are so severe as to be judged 'non classic' due to skills never having been developed so that the abnormality was evident to all at birth and there has been no obvious regression. Weakness may be so severe that stereotypies cannot be sustained. The mutation status of those people who are included in this account remains unknown for many. The dataset in **Appendix C** shows which individuals have been included in each study as far as possible and the extent and results of mutation testing when that has been reported.

Section 3

Epidemiology

Introduction

As with many other newly discovered disorders the Rett syndrome was at first presumed to be rare but has proved relatively common among females with severe and profound intellectual disabilities. Estimates of prevalence have varied depending on how and where they have been gathered (Kerr & Stephenson 1985, Asthana 1990, Hagberg & Hagberg 1997) with general agreement at present, for the childhood figure, of not less than 1 in 10,000 females, male occurrences being quite rare. The first cohort of cases brought for my advice on diagnosis and management provided the opportunity to provide the first estimate of the prevalence and to form a concept of the nature of the condition.

3.1 West of Scotland Study:

This first estimate of prevalence was made at the invitation of and in collaboration with Dr John Stephenson at the Glasgow Royal Hospital for Sick Children. The work began in November 1982, was presented locally, in January 1985 at the annual British Paediatric Neurology Association conference and then by invitation at the European Congress of Child Neurology in Siena in April 1985 (Kerr & Stephenson 1985).

The aim of the study was to provide for the available group of patients, a detailed history and examination with video recording and to draw conclusions as to the nature and prevalence of the condition in the West of Scotland, the area served by the hospital. I was the chief investigator and provided the reports.

For 5400 referrals to the Fraser of Allander Assessment centre over 12 years, a record had been kept of diagnostic categories that included those in whom a diagnosis had not been possible. From these records we identified 42 males and

females who had been seen for an undiagnosed condition with apparent onset around 7-24 months.

Among these cases, 19 females, age range 3-15 years, were identified as fully compatible with the written descriptions by Rett (Rett 1966) and a demonstration given by Professor Bengt Hagberg during a British Paediatric Neurology Association conference in Oxford, earlier in the same year. These people were invited for a 36-hour admission and investigation. In Andreas Rett's early investigation blood ammonia had been found to be raised but Bengt Hagberg and his colleagues had found no biochemical abnormality. The aim of our initial investigation was to confirm as far as possible, without unduly invasive investigation, that no other abnormality was present which might explain the severe neurological deficits - including structural, vascular, neoplastic, metabolic, toxic, traumatic and genetic disease. A full history was obtained from the families and the following investigations carried out:- examinations of blood and urine, estimations of blood gases, concentrations of urea and electrolytes, including copper and zinc, fasting ammonia and activities of creatine phosphokinase, aldolase and leucocyte enzymes, high resolution prometaphase banding of X chromosomes. Urine tests were performed to estimate excretion of amino acids, glycosaminoglycans, oligosaccharides, organic acids, hydroxymethylmandelic acid and 3-methoxy 4-hydroxy-phenyl glycol. Waking and sleeping e.e.g. and radiography were performed and in some cases computed tomography, nerve conduction studies and electromyography.

The chief positive results are indicated in the table (**figure 3.1.1**). Calculating from the Department of Health and Social Security figure of 40,000 births annually in the referral area of the hospital, the estimated minimum childhood prevalence for Rett syndrome was 1 in 15,000 females.

In three past generations no other case of Rett Syndrome was identified in families with affected individuals. Mean maternal age at birth of the affected

child was 25 years (16-40), paternal 27 years (21-40). There were 17 male and 18 female siblings and 9 miscarriages. The mother and maternal grandmother of one child were diagnosed as schizophrenic. At birth mean gestation was 40 weeks (38-42), mean birth weight 3.2 Kg (2.1-4) and mean occipito-frontal circumference 34 cm (32-36). **Figure 3.1.2** indicates the trend in OFC growth. All had received immunisation, with febrile reactions in two but no seizures. No consistent relationship was found between dates of immunisation and onset of regression. However 7 families had considered immunisation to be the likely cause of the disorder. The onset of the disorder was seen in the pattern of early development with slight delay in initial skills, smiling and sitting alone and the late acquisition or failure in reaching to grasp, walking alone and speech. Every child had regressed (mean age 16 months, range 10-24 months). The onset of regression was commonly marked by screaming and repetitive hand movements. Regression led to 12 children being described as autistic. After a period of decline in walking, manipulation and speech, mental age was considered to be around the 6-12 month level with little change thereafter. **Figure 3.1.3** indicates the pattern of developmental progress. Individuals related well to the human face. The lower limbs were initially hypotonic and became increasingly stiff with time. Deep tendon reflexes were increased but the Babinski response was not present. On the basis of the invariably disturbed muscle tone subtypes were distinguished, a hypotonic (usually early) subtype (subtype1), an ambulant dystonic subtype, some of these markedly wasted but others not wasted (subtype 2) and a non-ambulant, usually older hypertonic subtype (subtype 3). Repetitive involuntary movements were a feature in all cases affecting all parts of the body. Apparent panic attacks were noted in all cases and hyperventilation in all but one. The electroencephalogram was abnormal in all with bursts of slow waves in four, two per second spike and wave in five and featureless recordings with much 3-4 Hz theta in five. Sleep organisation was poor with REM apparently increased at the expense of stage II sleep. Computed tomography reported the brain to appear normal in 5 and compatible with mild atrophy in 3. Biochemical investigations produced results within the normal range.

Each of these children had been previously examined by Dr Stephenson, an acute investigator who had already excluded likely alternative diagnoses. Having recorded video of each patient, I was now able to study the behaviour of these children - aged from 3 to 13 years - as a group, while considering afresh their remarkably similar histories and the results of our investigations. Many already known conditions were excluded by the results of the laboratory tests and the combination of negative findings on family history, gestation and birth history with the subsequent progress of these children, whose state had clearly stabilised after slow initial progress and a rather selective developmental regression, their present good health and their obvious enjoyment of human contact. Taken together, these findings excluded many conditions responsible for early hypotonia such as Prader Willi Syndrome, birth injury, congenital myopathies and cerebral palsy of prenatal origin; many causes of regression including degenerative and epileptic disorders, such as Batten's disease and conditions associated with stereotyped behaviour such as autism. All the cases clearly matched the detailed description provided by Rett (Rett 1966).

Conclusions

It was clear from this study that the disorder is not rare, that it is clinically manifest before the onset of the regression period at which time development is already delayed, that it is accompanied by involuntary movements affecting more than just the hands and that the prevalence at age 14 is not less than 1 in 15,000 females.

3.2 Study of the natural history of Rett Syndrome in 23 girls

This second study was an extension of the first, in preparation for an invited presentation at an international meeting in Baltimore USA in 1985, to discuss and plan research into the disorder (Kerr & Stephenson 1986). I conducted the investigation.

Subjects were as in the first study with the addition of four new cases and possibly two more identified from records, who could not be contacted at that time, all conforming to the pattern for Rett syndrome as described by Rett (Rett 1966). Ages ranged from 11 months to 22 years. One family provided a cine film taken by a grandparent, from the first week of life and during the first year, before the parents were aware of the child's difficulties

With a confirmed group of 23 cases within a well-defined area the estimated minimum had now risen to 1 in 12,500 females at 0 to 14 years.

Cases were examined as in the previous study and detailed developmental histories elicited. It was clear from the developmental histories that progress had been suboptimal in these children from at least 6 months and probably earlier, until the onset of the regression episode. Even when children were still being considered as within the normal range with regard to developmental progress, imitation was absent and hand use poor. In 13 cases the first sign leading to medical referral had been failure to walk independently.

The donated infant film showed the child as a very quiet and inactive baby, a cheerful ten months' child with ill-directed movements when reaching for toys and poor hand-eye coordination, displaying difficulty in rolling over and achieving forward movement moving by creeping with the legs dragged behind. At one year she was cruising unsteadily and in reaching for the conveniently placed handle of a toy her fingers alternately grasped and released the object. Although the child did not regress until some months later it was evident that her mobility was already compromised with a suggestion of stereotyped movements in the arms and hands.

From these 23 cases it was clear that muscle hypotonia was an early sign of the disorder, preceding the increased muscle tone and contractures observed in older people. Presentation subtypes were again described according to the

predominant abnormality of muscle tone, hypotonic (type 1), dystonic but walking (type 2), hypertonic (type 3) and less mobile (**figure 1.3.9, Appendix A**). We did not find evidence of continuing dementia, the understanding of girls after regression and later in life appearing to be little less than the state before the onset of regression.

It is of interest that one child included in this study as 'incomplete Rett' at age 2 years (BIS 495), thereafter failed to regress and her skills improved steadily although she remained without speech, stereotypy decreased and further investigation led to the diagnosis of mutation positive Angelman syndrome (del 15), which has since emerged as one of the cardinal differential diagnoses for Rett.

We concluded that these children were already affected by the disorder and had reached a developmental 'ceiling' before the onset of the regressive period. It appeared that the regressive event was in part due to exacerbation of an already existing involuntary movement disorder. We found no evidence of continuing dementia after the regressive event. Prevalence was confirmed at no less than 1 in 12,500 females.

3.3 British Paediatric Surveillance Unit study

(Kerr, 1991 - published in the fifth annual report of BPSU)

The British Paediatric Surveillance Unit BPSU <bpsu@rcpch.ac.uk> (http://bpsu:inopsu.com) by this time an established part of the British Paediatric Association aimed to support approved research into the prevalence of rare disorders, by circulating all willing paediatricians with the researcher's invitation to report appropriate cases and providing a monthly postal card on which to register that such cases had been identified. It was then for the researcher to contact the doctors who had reported cases and to complete the research project.

In this way in 1991 the BPSU assisted my launch of the British Isles Survey for Rett syndrome. No direct funding was received but my description of the disease was circulated to all willing paediatricians in Britain and the Republic of Ireland.

An invitation was issued on three consecutive months to report new cases of Rett syndrome or suspected Rett syndrome, male or female, born in or after 1975, with the result that 104 paediatricians reported 247 cases and the number of known cases throughout the British Isles increased to 383. Questionnaires which I sent to responding physicians resulted in 169 cases being sufficiently described to indicate that the classic syndrome accounted for 150 (88%). All these were females although the circulated literature had not excluded the possibility of male cases. The numbers of cases reported in each birth year suggested a minimum prevalence in childhood of 1 in 10,000. However patchy reporting suggested that many new cases were still being overlooked. From this result it could be confirmed that the syndrome was strongly associated with female sex and that a mutation in the X chromosome was likely to be the cause of the disorder.

3.4 Report of the British Longitudinal study & Survey 1982-1991

In this report it was possible to confirm that with 30 cases reported in the 10 year old group and a steady flow of new reports arriving, the prevalence at this age was probably not less than 1 in 10,000 females. The range in ages was from 3 to 42 years. There were very few reported males, apparently none classic.

In this report a pair of monozygotic twins was described, one of whom was clearly classic and severe while the other, although recognisably Rett was much less severely affected, could walk, feed and help to dress herself and to sing little songs, quite close to the pattern described by Hagberg as 'formes fruste' (Hagberg & Witt Engerstrom 1986, **figure 1.3.10**). This occurrence was convincing evidence that the same genetic disorder underlay a range in severity and was present in both twins (Kerr 1991).

Comment on the research in this section

In addition to providing an early estimate of prevalence, the results of these studies indicated that clinical signs are present before the regression period, that involuntary movements and respiratory irregularity are regular features of the

condition and that subtypes could be recognised according to the predominant abnormality of muscle tone. We found no evidence of deterioration in intellect after the end of the regression period. The involuntary movement disorder led to the suggestion, according with observations reported by Segawa and Nomura (Nomura et al 1985) that the basal ganglia and monoamines were in some way involved in the manifestations of the disorder. Sporadic mutation on the X chromosome seemed a likely cause. A Scottish workshop organised jointly with Mrs Susan Allan, founder of the RSA Scotland, brought Professor Rett, 60 leading members of the medical professions, 52 children with Rett syndrome, and 130 parents to meet in a clinic environment at the Royal Hospital for Sick Children in Glasgow (May 1986). My observation of the many people with Rett at all ages during that event led me to suspect that although epilepsy is present in many people with Rett, there were other interruptions of awareness which could not be attributed to cortical epilepsy, that might relate to the highly irregular respiratory rhythm and bizarre fluctuations in mood. I was impressed also by the ability of these physically disabled people to use their hands purposefully when strongly motivated (Kerr 1987, Kerr et al 1987).

Experience of a growing number of cases led me to adopt concepts that were not yet generally accepted at that time. Namely that these people did not appear autistic as they related well to the human face although with limited understanding; they did not appear to have been truly normal before the regression period in spite of their attractive appearance and some developmental gains; evidence was lacking to support the idea that they suffered continuing intellectual deterioration after the end of the childhood regression period. That the Babinski sign was absent in our cases suggested that the long motor tracts were intact and the problems of movement were proximal. These observations informed the design of the following studies.

In compiling and editing the invited report of the 1986 clinical workshop I described the many conditions to be distinguished from Rett Syndrome, as falling into three main categories, in the following way (Kerr 1987):-

* Firstly there are those who having presented with regression and hand stereotypy proceed to follow a steady downhill course without the Rett syndrome plateau. These are likely to have a degenerative metabolic disorder. Commonly before regression such children demonstrate more skill than is apparent in pre-regression Rett Syndrome but during regression they may appear identical.
* Second are the children with profound cognitive disability but without the severe motor difficulties of Rett Syndrome. Their hands appear to be the obedient servants of a severely restricted intelligence. Characteristically these children do not have a history of regression but only of slow development.
* Third are autistic children who give the impression of an intelligence which is less impaired, who do not make good personal contact, and whose repetitive hand movements are deft, under voluntary control and apparently perfomed to give some gratification.

Since discovery of the genetic mutations, which lead to the syndrome, it has been possible to estimate the prevalence of mutation positive cases, rather than only the prevalence of the clinical syndrome. Within the survey cohort classic cases now constitute about 75% of cases considered to have Rett syndrome and atypical cases to constitute 15%. Among those so far mutation tested, 80-90% of cases with classic Rett and 30-40% of those with atypical (non-classic) Rett have proved positive, maintaining the rough estimate of prevalence at about 1 in 10,000 females for the disorder. However it has not been possible to carry out a thorough search for cases and a steady flow of new cases at every age indicates that more are to be found, especially among adults with milder disease.

Section 4

Clinical Observations

Introduction

Lack of obvious abnormality in the newborn infant and some early developmental progress led to a common assumption that the child was normal before the onset of the regression event (Hagberg et al 1983, Hagberg et al 1985). For a proper understanding of the origins of disorder it was clearly most important to establish when the first signs of the disease might be detected. This might be investigated from detailed pre-regression developmental histories and from early family videos.

The loss of skills, which occurred during regression, led to a general assumption that deterioration continued and that the disorder is progressive (Hagberg et al 1983). This could be best investigated by observing the change in many individuals over time.

The stereotyped hand movements provided one of the cardinal features of the Rett syndrome and it was a common assumption that the child chose to indulge in these. However my impression was that she had little if any control over them and that the rhythms were centrally generated. One way to investigate this was to characterise and measure the hand activities and to observe their emergence in early childhood.

The following studies aimed to characterise the early developmental deviations and to apply objective measures to the stereotyped hand movements seen later.

4.1 Hands and Mind in Rett syndrome

A total of 40 children were included in this study. The developmental histories of 20 children were recorded in detail. Family films taken before the onset of

regression were available for 4 children. Serial filming was carried out for 19 people repeatedly over a 4-year period following regression and at single sessions in a further 14. Four children were videoed weekly for six months during music therapy sessions. Those 23 presented in most detail are indicated in **Appendix C**. (Kerr et al 1987)

Two tables **(figure 4.1.1 and 2)** provide the results of the study. The pre-regression film appearances were suggestive of hypotonia in two cases. Between 2 and 11 months there appeared to be an excess of patting or waving activity of the arms in association with jerky incoordination. Three cases showed abnormal opening and closing of the fingers and twisting movements of the wrists. Hand use was clumsy and hand skills were not demonstrated beyond the 10-12 month level some months before the onset of regression. When regression began children appeared confused and withdrawn. In each of these four cases parents had not noticed anything wrong until onset of the regression event.

The twenty pre-regression histories similarly indicated that parents considered their children normal at the pre-regression stage or were concerned only at the slow rate of progress. However the level of recorded hand skill as judged by the cleverest manipulative achievements and language development suggested failure to achieve more than a 10-12 month level of skill regardless of the age of onset of regression. There was a lack of imitative and imaginative play. Interestingly families who watched the recordings with me spontaneously recognised the early expression of later abnormalities of movement.

From the post regression videos it could be seen that the stereotyped hand movements consisted of repeated quite simple and essentially clumsy movements, which incorporated the actions, tapping, rubbing, clasping or squeezing. Each hand moved as a whole or with a wave like activity passing across it. The hands came together in most younger children but were often apart in older people. Each hand followed a distinctly different pattern to its partner.

The hands were rarely watched unless they came where they could not be ignored. The stereotyped activity continued even when it was clear that the child wanted to eat and food was within her reach and she would lean towards the food with her mouth open. Agitation or contact with a surface appeared to increase the hand activity. Holding the hands reduced but did not abolish the activity. A few children could finger feed but for most the hands seemed incapable of voluntary action with the notable exception of musical interactions during which the therapist and child were in close physical contact and the instrument presented an easily accessible means to respond to a musical stimulus. In this situation with the child interested and strongly motivated the hands were used to strike the instrument in a poorly coordinated jerky and impulsive fashion. The achievement seemed to give great satisfaction as evidenced by intimate eye contact and smiling. There was increasingly effective use of the hands in music therapy sessions although this remained jerky and poorly coordinated. Because of the possibility of bias in interpretation of such video we invited comment from colleagues with wide experience of young children and found ourselves in agreement.

4.2 Early Clinical Signs in the Rett Disorder:

This review examined the progress of people with Rett disorder during the period from birth and through the regression period, using information from more than 600 cases then in BIS, the records from their families, physicians and my own direct examinations (70% of the cases over a period of 12 years) with many video recordings made during consultations (Kerr 1995). 42 donated videos were available for this research, taken by families during the early period before during and after regression, often begun before any recognition of the child's problem and a video library had been accumulated of healthy babies with which the Rett material could be compared.

The aim of the study was to observe the natural evolution of the disorder and so to gain a clearer understanding of its origins and character. Over 85% of the

reported and examined cases displayed the features of classic Rett syndrome. There had been 19 deaths. In collaboration with neuropathologist Dr Dawna Armstrong it had been possible for donated tissues to be examined from 6 people (**see section 9.1 for these reports**).

Developmental histories indicated very early problems. Young parents without experience of other children assumed that their baby was normal until they began to notice failure to walk or to interact positively with other children or until loss of skills occurred, however they described the infant as 'very good', 'very placid', implying a lack of complaint or demand unless the child was in pain. Experienced parents or older members of the family perceived differences from their healthy children from birth, reporting them as inattentive, 'floppy' or 'stiff' in posture and 'jerky' in their movements. However if the child was making any developmental progress and did not appear unwell parents usually received reassurance from the health professionals. Parents who expressed early concerns were sometimes reproved or considered neurotic, and this attitude generated frustration and anger as the severity of the condition became evident.

The video records of the babies with Rett usually showed them to be placid and poorly mobile from birth by comparison with healthy babies of the same age. There was a lack of normal exploratory behaviour by these babies and they responded poorly to play opportunities. In some children there was an excess of repetitive movement of the limbs and trunk. Small twitching movements of the eyes were seen in some as early as 2-3 months. Particularly striking was the repeated opening of the hand with which the child grasped an object. These signs appeared to indicate that the young infant was already disabled in terms of her understanding, her postural tone and her capacity for controlled movement. Head circumferences began to drift off the birth centiles in some children as early as 2 months and in a few cases were already below 2SD at birth. While there was a range of severity in the Rett condition it was clear that the pathological process was already active in the brain at the time of birth and

although the child was making some developmental progress the higher centres appeared already incompetent. Developmental histories suggested that few children with Rett acquired skills beyond the 9-12 month stage after which stagnation supervened or there was a fluctuating course, the acquisition of a skill being closely followed by its loss. It appeared that within the pre-regression period the child was slowly reaching a developmental ceiling at or below the 12-month stage.

As the regression event supervened, skills were lost, particularly any speech and fine hand skills that had been acquired, sometimes dramatically but sometimes gradually. Although the child was frequently agitated and distressed she did not appear unwell. Muscle tone became more obviously reduced and stereotyped movements of the hands, limbs and face became more marked. The stereotypies and agitation with loss of interpersonal contact led to some being regarded as autistic. In terms of what was known about the growth of the brain during this period and the neuropathological findings in Rett, I drew up a list of factors which seemed likely to contribute to the regression event **(figure 4.2.1)**. The irregular respiratory pattern, which was a feature of the condition, appeared towards the end of the regressive period in most cases and seemed likely to be responsible for the short interruptions of awareness common to many people with Rett, which lacked the characteristics of epileptic seizures. I proposed a model, which related the behaviour of the child with Rett to a disorder of central processing of cognitive and motor activity **(figure 4.2.2)**.

In order to investigate further the early abnormalities of babies with Rett a video was produced in which a sequence of edits was arranged showing Rett and normal babies in random order but arranged serially at each month throughout the first year of life. Copies of this video were made and circulated among colleagues to explore the possibilities of enlisting collaborators with adequate resource and skill to apply objective measures to the movements seen in these babies, the aim being to explore the possibilities for screening infants with

developmental delay in order to reach an earlier diagnosis and provide earlier support to the child and parent.

Three different lines of investigation developed from this initiative, leading to the three studies recorded below:

1) Dr Bronwen Burford, a psychologist with special experience in measurement of intuitive responses of care workers agreed to collaborate in recording the responses of experienced nursing staff to normal and Rett babies from birth to one year **(study report at section 4.3)**.

2) Professors Einspieler and Prechtl agreed on a joint project to analyse video of babies with Rett using their well established and standardised objective methods for the assessment of the spontaneous movements of babies (for these methods see Prechtl 1984, Einspieler, Prechtl et al 1994, Einspieler et al 1997, Prechtl 1997, Prechtl 1999, Prechtl 2001, Einspieler et al 2005a). Their aim was to characterise the spontaneous movements of these babies. For this purpose video was produced to show all the available recordings of 10 babies with Rett. This material was arranged for viewing at every month during the first year of life **(study report at section 4.4)**

3) Colleagues at the Virtual Environment Centre in Edinburgh that provides a service in gait analysis (Ed Vec) agreed to provide three dimensional studio analysis of the stereotyped hand movements of one girl and to compare their physical characteristics with the hand movements recorded in the same girl by informal 2D video at a consultation during early childhood. **(see section 4.6)**

In each of these studies, I invited the collaboration, recruited the subjects, supplied the clinical data and videos, was involved in planning the protocols and contributed to writing the reports. My colleagues conducted the assessments.

4.3 Nurse recognition of early developmental deviation in home videos of infants with Rett disorder

This study was planned with Dr Bronwen Burford, psychologist to record the intuitive responses of experienced nurses to the activities of babies with Rett (Burford et al 2003).

Subjects and methods

The study used early video material donated by families of children with Rett for this research. Dr Bronwen Burford, a psychologist with special interest in movement and non-speech communication had previously developed a method for recording the responses of experienced observers while they viewed interactions between carers and severely disabled people on video (Macleod et al 1993). The observer pressed a button, accurately marking the recording whenever an event of significance was felt to have occurred on the video. After the first viewing, the selected points were revisited and the viewer gave reasons for selecting each point or deselected it if preferred. The viewers own words were recorded. The children included in this study are listed in **Appendix C 4.3**.

Thirty-six experienced volunteer health visitors (26) and midwives (10) were invited to view randomly arranged clips of the donated home videos at each month of life which had been recorded for 11 normal and 14 Rett infants. Midwives viewed videos of babies from birth to 26 days, most being within 14 days of birth. Health visitors viewed them from birth to one year. Rett syndrome was not mentioned but they were told that some of these infants were later found to have a developmental disorder and they were asked to indicate by pressing the button whenever the behaviour of an infant raised a suspicion of developmental deviation. After the viewing session each button press point was played back and the viewer was invited to describe why suspicion had been aroused or to cancel the earlier indication. The viewer used her own words to describe her reactions which were recorded. An independent rater confirmed the classification of the comments.

Statistical advice was independently provided in planning and in the analysis of the results by H.A.Macleod, lecturer in the University of Edinburgh department of Community and Higher Education. For all the health professionals the number of button presses as a proportion of the total number of viewings (button -press ratio) was calculated for Rett and control infant groups and subjected to Wilcoxon signed-rank tests.

Results & conclusions

Figures 4.3.1-6 provide the results. From the first month of life and throughout the first year the infants with Rett received more button presses than controls (46%, 361 out of 778) in comparison with the control group (12%, 67 out of 558 viewings).

Figure 4.3.1 shows the total number of viewings by health visitors of all samples which led to one or more button presses and those which did not, for both groups of infants at all ages Rett infants 45.7% v controls 10.9%. Different samples of two infants with Rett and two controls at the same age on different videotapes produced comparable responses and no order effects were observed. Three different compilations of videotapes produced similar results. The median button-press ratio for health visitors was 0.4 for the group with Rett and 0.1 for the control group ($p<0.0001$) indicating recognition of normal development and suspicion about infants with Rett.

Figure 4.3.3 indicates the confidence of the midwives in recognizing normal development and uncertainty about infants with Rett. The median button -press ratio was 0.5 for the Rett group and 0.1 for the control group ($p<0.01$).

The consistent nature of the comments made by the viewers made it possible to classify the comments into those about appearance of the infant, posture, movement and personal contact. **Table 4.3.4** shows these categories. An

independent rater, blind to the nature of the study, allocated a random selection of the comments (60%) to the chosen categories. A kappa 0.81 was obtained between the rater and primary researcher, indicating a good level of agreement.

The control group received 58 comments from health visitors and most of these were mild or tentative (e.g. - it might be the angle of the camera' or ' foot seems turned out but `I could check if I was there'. The babies with Rett received a total of 438 comments and in contrast to comments about healthy control babies most of these were emphatic, concerning distinct abnormality. All ten infants videotaped at 4 months or less received such comments. **Figure 4.3.5** gives the percentage of comments in each category and age group. For example 33% of all comments by health visitors at 0-4 months were on appearance. Appearance attracted the greatest share of comment in the two earlier age groups. The share of comments on movement increased steadily throughout the first year. All the infants received the comment that they 'might have a syndrome', including those who received the fewest button presses. Hands were mentioned in 10% of all comments by health visitors on Rett infants and appeared in every category and at every age. These comments referred to hand posture, lack of reaching and grasping and poor general hand use. In the 9-12 month age group some viewers remarked on infants repeatedly putting the hands in the mouth.

Midwives made 16 comments about control infants, all of which were tentative. Rett infants received 110 comments from midwives. Emphatic mention of the hands accounted for 23 of 37 comments on posture and nine of 30 on movements. Seven of the Rett infants received such comments as ' hands are very unusual', 'strange praying position of the hands' and ' hand movements are strange'. **Figure 4.3.6** compares the spread of midwife comments between the two groups.

This study not only indicated the presence of early signs of the developmental deviation in infants with Rett but also showed that experienced nurses might

detect the problem from informal videos. All these Rett infants had been passed on routine developmental assessments, some as late at 9, 12 or even 18 months, suggesting that such screening procedures may be inadequate for the detection of children with Rett.

4.4 Abnormal general movements in Rett babies

Collaboration was invited with Heinz Prechtl and Christa Einspieler whose work on the characterisation of the spontaneous movements of babies before birth and in the first months of life has provided a valuable means of objective assessment (Einspieler et al 1997). These scientists agreed to apply their methods to the early home videos of babies with Rett in order to describe and as far as possible to characterise any deviations from normal development (Prechtl 1984, Einspieler, Prechtl et al 1994, Einspieler et al 1997, Prechtl 1997, Prechtl 1999, Prechtl 2001, Einspieler et al 2005a). For full details of the methods of detection and analysis used in these Rett studies see Einspieler et al 2003, and 2005.

The two observers HP and CE analysed the videos separately with an inter-scorer agreement of 96%. In addition the first author re-analysed all the recordings again after an interval of 18 months and again found 96% agreement. This study aimed to describe the normal and abnormal spontaneous movements, posture and behaviour of babies with Rett.

Initially Einspieler and Prechtl viewed video from 22 children with classic Rett syndrome throughout the first 6 months of life. The clinical characteristics of these babies are shown in the data set **C 4.4 Appendix C** The fullest available selection of videos was supplied showing 10 babies with Rett Syndrome at each month of age throughout the first year.

Movements, posture and behaviour were assessed in a detailed frame-by-frame analysis. All signs which deviated from the normal standard were meticulously recorded paying special attention to the face, the hands and the body

movements. This analysis clearly demonstrated an abnormal quality of general movements (100%) tongue protrusion (62%), postural stiffness (58%), asymmetric eye opening and closing (56%), abnormal finger movements (52%), hand stereotypies (42%), bursts of abnormal facial expression (42%), bizarre smile (32%), tremor (28%) and stereotyped body movements (15%).
These results are shown in **Figure 4.4.1, Appendix A.** The presence or absence of the clinical signs did not correlate with the later severity of the condition.
This was the first study to be able apply standardised measures for early spontaneous movements to infants with Rett syndrome, proving conclusively that the disorder is manifest within the first six months of life, although the signs were not necessarily considered to be specific for Rett.

In a further study of the videos of 14 infants with Rett (Einspieler et al 2005) Einspieler and Prechtl studied the period from birth to 4 months in order to judge the character of the general movements (GMs) which are normally seen during that stage in development. A detailed analysis clearly demonstrated that none of the infants had normal GMs. The abnormal movements and their individual developmental trajectories differed from those seen in babies with acquired brain lesions. However no specific pattern was detected which might characterise the disorder at this stage. The **figures 4.4.3-4** show the quality of the GMs and their trajectories.

4.5 Analysis of hand movements in Rett Syndrome

Collaboration was invited with Roy Middleton, Marrietta Van Der Linden and Mark Wright of the Edinburgh Virtual Environment Centre of the University of Edinburgh in order to provide objective measures of the stereotyped hand movements in fully developed Rett syndrome, to see if the same characteristics might be detected in earlier video recordings and so to reach a better understanding of the origins of these movements and to explore the possibility of detecting the movement aberration in early life. The hand movements of a 10-year-old girl were subjected to accurate three dimensional computerized motion

analysis and compared to 2 dimensional video analysis of the same girl at 10 and at 3 years of age (Wright et al 2003).

The 3-D computerised motion analysis revealed regular patterns with strong coupling between the hands **(figure 4.5.1)**. Frequency analysis showed a dominant frequency at 1.2 Hz with a higher component at 2.4 Hz **(figure 4.5.2)**, which may relate to the activity of basic rhythm generators in the brain. The same coupling characteristics were extracted from standard 2D video made at the same time and from 2D recordings made of the same girl when she was aged 3 years **(figure 4.5.3)**.

The study has shown that informal 2D video reflects the same movement characteristics seen on accurate 3D analysis and that the movement patterns of this 3 year old child are retained at the older age of 10 years. The appearances are those of an automatic rhythm, generated centrally and under minimal if any control by the individual. A parallel is suggested with the tremor of Parkinsonism in which, like Rett the movement cannot be voluntarily controlled but in certain highly charged situations it can be interrupted allowing purposeful activity. That it has been possible to record and characterise the movement of the hands in Rett suggests that it may prove possible to develop screening which could detect the movement pattern in young children using simple 2D video and automated analysis.

Comment on the research in this section

These studies have established beyond doubt that the disorder is clinically manifest from birth, indicating the possibility of earlier diagnosis and therefore of earlier support for the child and family. Experienced parents frequently voice anxieties about their infants with Rett syndrome and deserve to be listened to. Mutation testing offers a way to confirm the diagnosis when it is suspected.

The study of hand movement has demonstrated objectively the distinct pathological pattern of hand movement and has shown that it remains stable over

many years, suggesting a rhythm which is physiologically driven. The stereotypy is one feature which has led to Rett disorder being compared to autism. **Figure 4.6.1**. (Kerr 2000) was prepared for a discussion on behaviour in Rett and comparison with that seen in autism. It suggests how behaviours aseen in Rett syndrome might be compared with those seen in autism and cerebral palsy. The **figure 4.6.2** produced for the same discussion (Kerr 2000), speculates on how prenatal subcortical influences on the developing cortical neurones set the patterns for sensorimotor feed back relationships in the mature brain, patterns which fails to develop normally in the infant with Rett disorder, producing an inflexible tremor instead of action that can be sensitively controlled according to requirements. My concept was based in the knowledge that flushes of neuroactive substances produced in the developing thalamus and base plate, including MAP2, - already known to be reduced in Rett - are known to be in contact with the immature cortical neurones as the pass through the base plate on their way to the cortex and seem likely to play a part in the essential 'servo-mechanism' linking receptive and expressive activities (Kaufmann et al 1997). The early infant studies by Einspieler and Prechtl indicate disruption of early spontaneous movement patterns. These spontaneous movements can be detected in the normal infant before birth and are believed to be generated by brain stem oscillators (Prechtl 1999). This too supports the presumption of a prenatal developmental role for the gene *MECP2*.

Section 5

Investigations I: Cardio-respiratory & e.e.g.studies

Before regression the child with Rett is often described as placid. However at the time of regression, behaviour becomes marked by sudden changes - parents have described this 'as if a switch had been turned'. Normal quiet breathing may change to deep breathing or breath holding. There may be unexplained extreme agitation with panic or screaming. The hands may suddenly engage in exaggerated squeezing or clapping, together or in the mouth or hair. Interest or engagement may be suddenly interrupted by flushing, pallor or cyanosis with loss of attention or fainting. Short bursts of slow waves, with or without spikes are seen in the electroencephalogram (e.e.g.) unaccompanied by clinical epileptic seizure.

Both Rett and Ishikawa described the hand movements as stereotyped and the breathing as periodic with agitation (Rett 1966, Rett 1977, Ishikawa et al 1978). Lugaresi and colleagues also described these features as characteristic of the Syndrome (Lugaresi & Cirignotta 1982, Lugaresi et al 1985). At this time it was still commonly assumed that the child wished to engage in these activities. It was also commonly believed that the interruptions of awareness or faints were due to epilepsy. I questioned both assumptions. I proposed to explore the nature of the bursts of abnormal activity which could be seen to affect the e.e.g., respiratory movement and the mood and awareness of the individual. I planned to investigate the time relationships between these events, using objective physiological measures in order to reach a better understanding of their origins.

5.1 A low cost method for simultaneous video recording of ambulant subject and electroencephalograph: the Quarrier's system.

A system was developed in collaboration with Mrs Pat Amos at Quarrier's Epilepsy Centre, near Glasgow and support by physics staff from the Royal Hospital for Sick Children. By this means an awake and active subject could be videoed over several hours while the electroencephalograph tracing was

superimposed on the video recording and continuously viewed on a monitor, allowing correlations to be observed between behaviour, appearance and e.e.g. signals (Kerr et al 1988). The signal from a medilog (ambulatory e.e.g.) system was passed through a time code generator and video mixer and so superimposed in real time on the monitored view of the subject as well as being recorded on paper. I led this development. The arrangement we developed allowed us to begin to explore the relationships between these variables **(Appendix A, figure 5.1)**.

5.2 Hyperventilation in the awake state.

After having developed the above techniques we became aware of the respiratory studies being carried out by Dr David Southall and invited collaboration in order to add objective measures of respiration to our investigation. I led the investigation and participated in all except the analysis of the taped respiratory and e.e.g. recordings and biochemical estimations (Southall et al 1988, Kerr et al 1990). This was a descriptive project, aiming to determine the pattern of the spontaneous respiratory disorder in Rett and measure its consequences for levels of oxygen and carbon dioxide. A control group of healthy boys and girls aged 4-15 years had already been recruited by Dr Southall as part of a separate prospective study of respiratory function.

The clinical characteristics of the Rett subjects for this and the following study, which used the same records to correlate behaviour and e.e.g. are shown in the **Appendix C, dataset 5.2.** Families attended with each subject and gave informed consent.

Respiratory inductance plethysmography (Respitrace, Studley Data systems) was used to record chest movements during breathing; measures of expired CO2 were made using an Engstrom Eliza constant sampling infrared analyser; Transcutaneous CO2 measurements were made using a Hewlitt Packard machine and beat-to-beat oxygen saturation was measured with a Nellcor Respox 2

machine. In order to synchronise the recordings a continuous time code was included and the monitors showing the physiological recordings were kept within the view of the video camera. The entire procedure was continuously recorded on VHS video and the result was simultaneously shown on a monitor screen so that the investigators and the families could observe the proceedings. Thus it was possible to analyse real time relationships between the actions of the child and the physiological measures. The recordings of respiratory movement and respiratory gases were also printed out on continuous paper, as was the e.e.g. recording so that real times could be matched precisely. A diagrammatic representation of the arrangement is shown in **Appendix A, figure 5.2.1.** In 10 cases with markedly abnormal breathing, radial arterial blood was taken for measurements of electrolytes including ionised calcium and arterial pH. The **Appendix.C, dataset 5.2** provides further background data for cases included in these studies.

Over 4 weeks we monitored 18 people with Rett syndrome, 11 during overnight recordings and all in day time using our combined techniques to measure activity by video, e.e.g., respiratory movement, expired and transcutaneous CO2, arterial oxygen. **Appendix A,Figure 5.2.2** gives the clinical details of the 18 people with Rett syndrome. **Appendix A, Figure 5.2.3** gives the physiological data for the group. **Appendix A,Figure 5.2.4** gives the biochemical data for 10 cases.

Ten of the Rett subjects (56%) but none of the controls hyperventilated. Hypocapnia was present during hyperventilation and arterial pH values ranged from 7.47 to 7.6. The hyperventilation was interspersed with periods of apnoea during which there was hypoxaemia (in 47% of apnoeas). All but one of the subjects with Rett had periods of apnoea. Sections of the paper printouts from the recordings are shown in **Appendix A, figures 5.2.5 - 8.**

Hypokalaemia and hypocalcaemia were found in cases who hyperventilated at great intensity and tetany was recorded in one child.

We suggested that the hypocapnic alkalaemia and hypoxia might contribute to cerebral impairment in Rett syndrome and that therapeutic intervention might be possible. During this study we observed several abnormal rhythms of breathing, shallow, deep with hyperventilation, breath holding, failure to take a breath and Valsalva-like breathing. We noted that many interruptions of awareness were not associated with epileptic manifestations on e.e.g. Only one epileptic seizure was shown on e.e.g., witnessed after a period asleep when the child woke and hyperventilated with such intensity that the carbon dioxide and oxygen levels fell steeply. A short epileptic convulsion occurred during which the CO2 levels recovered.

5.3 Correlation of electroencephalogram, respiration and movement in Rett Syndrome.

In a further study in collaboration with Southall, Samuels, Cooper, Mitchell and Amos a detailed analysis was made of daytime video, e.e.g. and respiration, establishing exact time relationships between episodic behaviours, e.e.g. changes, breathing rhythm, blood gases and stereotyped movements, observing differences between different age groups in order to gain insight into the nature of the breathing dysrhythmia and the non-epileptic vacant spells (Kerr et al 1990). I organised the project, determined its objective, enlisted the patients and controls and was directly involved in the recordings. The detailed study to relate the behaviours to the changes in e.e.g., respiration and respiratory gases was carried out by myself from the continuous paper recordings. E.e.g. comment was provided by Mrs Amos and Dr Rosemary Cooper.

Dr Jane Mitchell, senior lecturer in mathematics, was invited to provide the independent statistical analysis of the results.

Subjects were 14 girls indicated in the **dataset 5.2 (Appendix C)** aged 6 to 17 years (mean 7 years). Controls were 12 healthy, volunteering girls, sisters and friends of the people with Rett similarly recorded over the same period. Parents

always attended with their children. The materials used were the same as in the above project. The recordings were made over about one hour in daytime. In cases with Rett syndrome showing severe hyperventilation a period of re-breathing was introduced in order to raise the level of CO2. This was done by placing a light transparent hood over the head, resting on the shoulders of the child as can be seen in the **figure 5.3.3 Appendix C.**

No recording from a healthy control showed any abnormalities of breathing, transcutaneous respiratory gases or e.e.g record.

Data for the people with Rett is shown in **Appendix A, figure 5.3.1.** Three girls with Rett syndrome had minimal respiratory dysrhythmia and showed no correlation between e.e.g., respiration and movement. The other 11 RS girls (6-17 years) had severe awake respiratory dysrhythmia, ten showing hyperventilation with hypocapnia alternating with breath holding - one showed only breath holding episodes. All had some periods of awake regular breathing with normal respiratory gases. In these girls the e.e.g. showed non-epileptic generalised slow activity some of which was paroxysmal. **Figure 5.3.2 Appendix C** shows the typical electroencephalograms in three cases. Short periods of e.e.g. slowing occasionally followed prolonged apnoeic pauses. In two cases brief partial complex seizures occurred but these were quite distinct from the non-epileptic events.

In the six youngest girls, non-epileptic paroxysms of e.e.g. slow activity occurred at 1.5 to 4 Hz. These paroxysmal e.e.g. disturbances were associated with periods of normal breathing (with normal pCO2 levels) whether the girls were alert, drowsy or asleep, but were uncommon during episodes of hyperventilation (with hypocapnia). In these youngest girls discrete episodes of disturbance - in respiratory rhythm, e.e.g. and intensified stereotyped movement, allowed direct comparisons to be made of the time spent in each and the relationships between them. Interruption-free periods were selected for these

measurements. Within these selected periods significant hypoxia - <50% saturation was recorded on one occasion without alteration in e.e.g. or behaviour. **Figure 5.3.4** compares the time occupied by the non-epileptic e.e.g. paroxysms during periods of normal and of dysrhythmic breathing. Chi-squared tests were carried out in cases 1,2 and 5 to compare durations of regular discrete e.e.g. paroxysms in the various periods of breathing. There was a clear difference in the number of bursts during respiratory dysrhythmia (low) and normal breathing (high), p=0.001 for this difference. The number of bursts occurring during alert and asleep periods of normal breathing (with normal pCO2) was not significantly different. In cases 1,2,4 and 5 the e.e.g. paroxysms occupied 1-3% during respiratory dysrhythmic periods and 8-100% during alert normal breathing periods (p=0.001 for this difference). The episodes of stereotyped movement involved the face, trunk, limbs and hands and were graded as very energetic (++), moderately so (+) and minimal or absent (-). In cases 1,2,4,5 and 6 episodes of stereotyped movements (++ & +) occurred during the periods of respiratory dysrhythmia and diminished (+ & -) during periods of normal breathing. The percentages of ++ activity for the nineteen continuous periods recorded were compared using a non-parametric test (Kruskal Wallis) that assumes the various periods to be independent. This test shows a significant difference in the amount of intense stereotyped movement (++) during periods of dysrhythmic breathing (high) and normal but alert breathing (low) (p= 0.01)

In the older girls (aged11-17) the stereotyped hand movements did not fluctuate with the periods of respiratory dysrhythmia. Fairly persistent generalised, largely unreactive theta activity at 4-6 Hz was present in all these girls and in one tended to increase at the end of apnoeic pauses.

Six children had attacks of vacancy and staring not associated with e.e.g. changes. Two of these girls also each had one minor complex epileptic seizure with ictal activity recorded on e.e.g. Both the non-epileptic and the epileptic events occurred after periods of intense hyperventilation with severe hypocapnia

and were associated with apnoeic pauses with or without a valsalva-like manoeuvres. Pulse oximetry indicated subsequent but not prior hypoxaemia. All the girls with RS showed abnormality on e.e.g. Nine of the fourteen RS girls showed some epileptogenic activity in the form of single or grouped spike and sharp wave discharges or slow spike and wave, distinct from the episodes of paroxysmal slow activity.

Striking observations during this study were a clear association between the bursts of paroxysmal slow waves on e.e.g. and the periods of normal breathing, contrasting with the periods of severely dysregulated breathing and hypocapnia during which the e.e.g abnormality was less marked. It was clear that the dysregulated breathing was closely associated with agitation and increase in the hand stereotypy, especially in the younger children. Alerting of the child after a period of rest was almost always accompanied by the onset of disturbed respiratory rhythm. There were several types of disturbed respiratory rhythm and characteristically the pattern of breathing switched between these in the same child. Although epileptogenic e.e.g. and clinical epileptic seizures occurred during monitoring, non-epileptic vacant spells which were also recognised to be a feature of the disorder. Breathing while asleep was usually regular with normal blood gases unless it was obstructed.

5.4 Functional Evidence of brain stem immaturity

Certain aspects of the appearance and behaviour of people with Rett suggested problems of autonomic regulation. These included unexplained episodes of agitation with flushing, and almost invariably small cold feet, which had been noted to grow and become warm following sympathectomy carried out in the course of corrective surgery for scoliosis. Constipation was common. Sleep was disturbed. The source of the very abnormal respiratory rhythm was unknown and the brain stem was suspect. At this time I was invited to take a room at the University of Glasgow in the department of Psychological Medicine and met Dr Peter Julu who had recently set up a unit for the investigation of central

autonomic function at the nearby Glasgow Southern General Hospital. With colleagues he had already developed the NeuroScope, a piece of equipment to measure non-invasively the response of the brain stem cardio-respiratory neurones to changes in arterial blood pressure as shown in the change in heart rate. (Julu 1992, Julu et al 1993, Julu et al 1996). Dr Julu agreed to assess one child with Rett and this led to an extensive collaboration, investigating the abnormality of cardio-respiratory control (Julu et al 1997, 1998, 2001, Julu 2001). The equipment which we had developed at Quarrier's Epilepsy Centre was combined with that developed by Dr Julu.

The study was approved by the ethical committee of the Southern General Hospital and received fully informed parental consent. I planned the project, recruited the subjects and was involved in all the procedures, interfaced with the families, prepared the reports and assisted my colleagues in the assessments as required. Dr Stig Hansen managed the equipment, Dr Peter Julu conducted the assessments and analysed the recordings, and Mrs Flora Apartopoulos recorded the e.e.g.s,

In this preliminary study we investigated seven girls with Rett syndrome for whom background clinical data is shown in the **Appendix C. dataset 5.4.** Volunteer sisters and friends acted as controls. Parents were always present throughout the assessments.

Breathing movements were measured by a plethysmograph placed around the chest at the level of the xiphisternum, recording movement in the chest and abdomen. Sympathetic activity was monitored by measuring the arterial blood pressure (Finapres TM). Cardiac parasympathetic activity was monitored by measuring the cardiac response to baroreflex using the NeuroScope a recent invention, which outputs a measure of cardiac vagal tone (CVT) in units on a linear vagal scale (LVS) (Julu 1992). The P-P interval is continuously recorded from the electrocardiogram providing the measure of heart rate. The rate of

response by the brain stem cardio-respiratory neurones to changes in blood pressure is reflected on a beat-by-beat basis in the subsequent adjustment to heart rate. E.e.g. was recorded continuously using a cap and was time locked with the other recordings. Transcutaneous oxygen and carbon dioxide were measured as in the previous studies. A continuous video recording was made showing each subject throughout the assessment. Setting up usually took 30 minutes and then a recording was continued throughout a full hour. During recordings the girl sat in her preferred chair and parents had full access to her to entertain, offer drinks and snacks. Frequently a parent took over the task of holding one finger still enough for the recording of blood pressure to continue uninterrupted.

A more complete explanation of the methods employed, produced in collaboration with my colleagues Drs Stig Hansen and Dr Peter Julu is provided in the **section 5.5**.

The **figures 5.4.1-9, Appendix A** illustrate the findings in this study. The people with Rett were all able to breathe normally while asleep and at rest **(figure 5.4.1 Appendix A**). However while awake and alert, each girl had 6 or more abnormal respiratory rhythms, switching between these apparently at random. **Figure 5.4.2 Appendix A** shows the abnormal rhythms recorded during this study. At rest the respiratory rates and heart rates of people with Rett did not differ significantly from those of controls **(figure 5.4.3 & figure 5.4.4, Appendix A**).

Figures 5.4.5 & 5.4.6, Appendix A compare a Rett and a normal recording during quiet breathing and demonstrate how in the normal subject's record, a rise in BP is promptly controlled by a fall in heart rate **(figure 5.4.5). Figure 5.4.6**, demonstrates how in the normal girl vagal tone rises sharply to control a rise in blood pressure. Such prompt corrective action was not seen in the Rett recordings.

Resting cardiac vagal tone during periods of quiet breathing in Rett was significantly reduced $p<0.001$, 3.6 +-0.7 units in the linear scale as compared to normal controls (10.5 +-0.9). The level in Rett is close to that of the normal neonate (Halley et al 1995) **(figure 5.7, Appendix A).** Heart rate and blood pressure were under normal parasympathetic control during hyperventilation in the normal girls but not in Rett where the cardiac vagal tone (CVT) was invariably withdrawn at the height of sympathetic activity during both hyperventilation **(figure 5.4.8)** and breath holding **(figure 5.4.6)**, leading to sympatho-vagal imbalance with the risk of sudden death. Sympathetic control of heart rate and blood pressure was adequate during voluntary breath holding in normal controls but in Rett there were oscillations and rebounds **(figure 5.4.9, Appendix A).**

From this study the near neonatal level of cardiac vagal tone, the poor central autonomic regulation and the multiple breathing dysrhythmias indicated immaturity of brainstem cardio-respiratory control in Rett. This immaturity constitutes a potential hazard, risking fatal cardiac arrhythmias. The study provided new insight into the Rett disorder and into other developmental or acquired disorders that interfere with central cardio-respiratory regulation. It raised new possibilities for intervention and demonstrated a robust means of objective assessment in evaluating such treatment.

5.5 Characterisation of Breathing and associated central autonomic dysfunction in Rett disorder

This second study of central autonomic cardio-respiratory control was a continuation of the first with larger numbers. Families were being referred for assessment from physicians and health authorities in all parts of the British Isles because it was useful in management, assisting in distinguishing epilepsy from the vacant spells due to central failure of cardio-respiratory regulation and providing advice on management.

The clinical details of the British subjects included in this study are given in the **dataset 5.5, Appendix C.** There were also several additional Swedish subjects for whom data is not held in BIS. All subjects were female, male cases were not excluded but are exceptionally rare. Control values came from 11 female volunteers, family and friends of those with Rett. Fully informed consent and ethical approval was provided for all the procedures, consent always being from the parents, who always attended with their girls.

Patients were assessed as in the previous study, by synchronous, continuous, non-invasive measures of autonomic and respiratory function, time locked to video and e.e.g. Subjects sat in a chair with a parent close by. Each recording lasted one hour during which the individual could eat or drink and be entertained as required. The procedure is painless. Respiratory movement was recorded by a stretch sensitive resistance plethysmograph at xiphisternal level recording the amplitude of thoracic and abdominal breathing movements in arbitrary units. A TCM3 monitor (Radiometer Copenhagen Denmark) recorded partial pressures of oxygen (P02)and carbon dioxide (PCO2) transcutaneously. A finger photo plethysmograph (FinapresTM, Ohmea USA) recorded digital arterial blood pressure in wave forms for calculation of beat by beat systolic, mean and diastolic blood pressure. The central autonomic (brain stem) control of cardioinhibitory activity was monitored by means of the NeuroScope TM (Medifit diagnostics, London, UK), which calculates cardiac vagal tone from e.c.g. R-R intervals. The cardiac vagal tone was expressed in arbitrary units on a linear vagal scale.

Explanation of the NeuroScope method of assessment of central autonomic function (for further details see Julu 1997. Julu et al 2001)

Excitation of the baroreceptor combined with the rise in arterial pressure caused by ejection of blood from the left ventricle, inhibits firing of the sinoatrial node, delaying the onset of the following cardiac cycle, as reflected in the R-R interval. As blood is ejected into the arteries at every cardiac cycle, stimulating

the baroreceptors, there are rapid and quantifiable pulse synchronised changes in R-R intervals. These are measured continuously via the NeuroScope TM. Baroreceptor signals are the main source of excitation for the cardiovagal motor neurones in the medulla. The cardiac vagal tone is the end result of impulses carried in the vagus nerve and regulated through integrative processes in the nucleus of the tractus solitarius, nucleus ambiguus and bulbar reticular formation. Being the only inhibitory output of the cardio respiratory integrative system, cardiac vagal tone is very important in rapid cardiovascular responses and is a major contributor to integrative inhibition in the system. The normal mean value in healthy young supine adults breathing quietly is 10 arbitrary units in the linear vagal scale (LVS), falling to zero at full atropinisation. The cardiac vagal tone is a more direct indicator of central cardiovascular parasympathetic output than the surrogate index respiratory sinus arrhythmia. The cardiac sensitivity to baroreflex is the increase in pulse interval per unit change in systolic blood pressure. It is calculated by quantifying cardiac responses to ejection pressures in each cardiac cycle as delta RR/delta SBP where delta RR is the difference between present and previous e.c.g. R-R intervals and delta SBP is the difference between the systolic blood pressure values in two preceding cardiac cycles. The cardiac sensitivity to baroreflex indicates the overall gain in the negative feedback in the baroreflex system set up in the nucleus tractus solitarius and the nucleus ambiguus.

Breathing movements, levels of blood gases and blood pressure wave forms were transmitted through an interface – the MedullaLab (Medifit diagnostics) and joined the neuroscope data in a common microcomputer. The VaguSoft soft ware (Medifit diagnostics) simultaneously recorded e.c.g., heart rate, cardiac vagal tone, systolic, mean and diastolic blood pressure, blood gases and cardiac sensitivity to the spontaneous arterial baroreflex. The e.e.g was recorded on a 16 channel PL-e.e.g. in the UK (Walter Graphtec UK, West Sussex) and on an 8 channel paper machine (Nihon Ohden, Tokyo, Japan) in Sweden. Breath by Breath analyses of 47 cases excluded all interruptions.

Baseline function was defined as autonomic activity during normal breathing with normal levels of blood gases. Control subjects voluntarily hyperventilated and held their breath in accordance with our demonstrations.

Statistical values were given as mean (SEM). Statistical differences were assessed using analysis of variance (ANOVA) with a two sided Student t test for probability (p) values, using Minitab for Windows 11.21.

The respiratory and autonomic results are shown in **figure 5.5.1 Appendix A**. No control subject showed spontaneous respiratory dysrhythmia. All Rett subjects had some normal rhythm while awake but also showed 5-11 (mean 8) types of abnormal rhythm **(see figures 5.5.2-6)**. Valsalva breathing occurred in 26 of 47 subjects tested (59%), Biot's breathing in two, and Cheyne-Stokes respiration in 12 subjects with inadequate breathing.
Breathing patterns and levels of vagal tone differed in the different age groups (fig 7 and table 1**(figure 5.5.7 & 8)**. Most forceful breathers were under 5 years and most normal and Valsalva type breathers were older. Combined percentages of breathing dysrhythmias in the 0-9 years age groups were higher than in the older age groups)$p=<0.005$. The percentage of Valsalva breathing in the over 19 year age group was higher than in the youngest group ($p=<0.01$) or in the 6-9 year age group ($p=<0.05$). Inadequate breathing was most commonly seen under 18 years of age, where Cheyne –Stokes breathing was also seen. This was the same pattern as was seen in the 1987 study. Since it was already shown that more severely affected people were likely to die earlier (Kerr et al 1995) it seemed possible that the different patterns at different ages reflected the longer survival of the least affected people.

Ventilatory efficiency in Rett cases

Blood gases were adequately recorded transcutaneously for detailed analysis in 27 subjects. Carbon dioxide fell during intense hyperventilation and rose during inadequate breathing as oxygen levels fell. Mean lowest and highest PCO2

values were 4.12 and 5.43 kPa (31 and 41 mm Hg) respectively. In two of 27 feeble breathers (7%) P CO2 exceeded 7.98 kPa (60mm Hg). Repeated apnoea or valsalva breathing was always associated with a PO2 below 10.64kPa (80mm Hg). Valsalva breathers did not have raised PCO2. Oxygen levels fell below 6.65 kPa (50mm Hg) in 14 of 27 Rett subjects (52%).

Baseline autonomic function

Baseline brain stem autonomic function was analysed in 48 females aged 2-35 years, mean 13.2 years and in 11 controls ages 5-28 years (mean 10.2). There was no significant difference in mean resting heart rate (mean SEM): Rett 101 (3.6) beats/min) or mean arterial blood pressure (Rett 79 (5.3) mm Hg, controls 86 (7.1) mm Hg). Mean cardiac sensitivity to baroreflex was lower in Rett cases than in controls (Rett 3.4 (0.4) ms/mm hg; control 6.2 (0.9) ms/mm Hg; $p<00.01$). Mean cardiac vagal tone was also low in Rett cases: (Rett 4.5 (0.4) units; controls .2 (1.2) units in the linear vagal scale; $p<0.002$).

Vacant spells and associated events

Epileptiform e.e.g features increased in sleep and diminished on alerting. Monorhythmic theta waves increased with age. Epileptiform discharges were rarely associated with clinical seizures or vacant spells. Valsalva breathing was sometimes accompanied by 4-5 Hz theta wave activity and prolonged apnoeas caused e.e.g. flattening. Many vacant spells in 48 of 56 subjects were associated with involuntary movements and dystonic postures and appeared during shallow breathing, long breath holds, central apnoeas, apneusis and Valsalva breathing.

Effects of breathing dysrhythmias on autonomic function

Voluntary hyperventilation, invited in control subjects, was accompanied by increased mean blood pressure, promptly countered by increased cardiac vagal tone with a consequent decrease in heart rate bringing the blood pressure under control, after which heart rate was restored to normal (**figure 5.5.9**). Vagal tone was maintained raised during hyperventilation and was withdrawn when

hyperventilation ceased. During the spontaneous hyperventilation occurring in Rett subjects **(figure 5.5.9)** cardiac vagal tone increased transiently but was withdrawn and reinstated only after the hyperventilation ended. The increase in the mean blood pressure started by the onset of hyperventilation was thus uncontrolled. In control subjects, both cardiac vagal tone and cardiac sensitivity to baroreflex reflecting parasympathetic control were withdrawn at the beginning of the voluntary breath hold and restored immediately at the end. The cardiovascular system was thus under the sole influence of the sympathetic system at that time **(figure 5.5.10)**

In the Rett cases, breath holding caused prompt withdrawal of cardiac vagal tone and cardiac sensitivity to baroreflex, as in the controls but the increase in sympathetic activity at the beginning of breath holding caused oscillation of the blood pressure ('ringing'), indicating poor negative feedback regulation **(figure 5.5.10, Appendix A)**.

Risk factors identified in Rett

Five Rett subjects developed a progressive decrease in blood pressure with diminishing cardiac vagal tone and cardiac sensitivity to baroreflex. Mean arterial blood pressure approached 40mm Hg, the level associated with spinal transection; cardiac sensitivity to baroreflex and cardiac vagal tone came close to zero and heart rate approached the intrinsic rate of the sinoatrial node, suggesting lower brain stem shutdown (**see figure 5.5.11**). The e.e.g. showed very low voltage or flat recordings and the transcutaneous oxygen levels fell. These episodes followed repeated or prolonged periods of Valsalva manoeuvres, hyperventilation or poor ventilation. The longest such shutdown lasted 3 minutes.

A background of feeble breathing with low P02 and raised PCO2 can lead to repeated episodes of exaggerated simultaneous increases in cardiac sensitivity to baroreflex, cardiac vagal tone and blood pressure (**see figure 5.5.12**). The term 'brain stem storm' seems appropriate for this event as the functional indices of the whole brain stem – rostral, caudal and dorsal – were simultaneously and

momentarily increased. Such large sudden increases in vagal tone with poor ventilation, raise CO2 and hypoxia carry a risk of cardiac arrest.

Episodes of brain stem activity were observed which did not conform to the expected physiological activation of the neurones involved. Normally output from autonomic neurones is continuously adjusted through reflexes or pacemaker neurones according to the body's requirements. The term 'brain stem epilepsy' while controversial, seems appropriate to describe this brief widespread aberrant activation of the brainstem neurones although no epileptiform activity was recorded at the cortex in these cases during the study (**figure 5.5.13)** This event differed from brain stem storm in that the known predisposing factors – low PO2, high P CO2 were absent. Epileptic involvement of the respiratory neurones may be a hazard in Rett.

From this study a number of important conclusions could be drawn.

Brainstem function, including breathing rhythm, cardiac sensitivity to baroreflex and cardiac vagal tone, which are maintained by complex integrative inhibition, are affected in the Rett disorder, whereas the baseline sympathetic tone, which is maintained by pacemaker activity, is preserved. The normal baseline arterial blood pressure in Rett cases indicates normal sympathetic function in the brain stem. The oscillation of blood pressure during breath holding in Rett indicates lack of parasympathetic restraint of the sympathetic system because the cardiovascular system is normally restrained through a parasympathetic negative feedback system. Whereas healthy people can cope with the reduced negative feedback in the parasympathetic system during a breath hold, this manoeuvre is precarious in Rett. That Rett subjects did maintain normal breathing while asleep may reflect improved inhibitory integration in the brain stem during sleep. The breathing dysrhythmias while awake may suggest poor integration at higher centres such as the hypothalamus and the limbic cortex where wakefulness drive of breathing is significantly modulated.

The apneusis (protracted inspiration) seen in the youngest girls suggests a serotonin related defect (-HT) in the brain stem as 5H-T1A receptors play a major part in the initiation of expiration (see section 8.1)).

In the Valsalva breathing that is seen most in older people, the forceful expiration against a closed upper airway contributes to aerophagy and abdominal distension, a frequent and sometimes painful problem in these people. This deserves further investigation. It appears possible that the Valsalvas are due to poor coordination between the expiratory effort and the upper airway.

The shallow breathing and inadequate ventilation seen in some cases is easily overlooked in everyday life. Its absence among older people suggests an association with more severe disease and shorter survival. The weak respiratory drive may lead to rising CO2 and falling O2. That combination stimulates the peripheral chemoreceptor and combined with poor central respiratory drive leads to maximal cardiovagal excitation such as was seen in the brain storms. (**figure 5.5.12**)

Brainstem shutdown may be due to post activation or post ictal neuronal quiescence after the severe brain stem activation following forceful breathing (**figure 5.5.12**).

Epilepsy originating in the brain stem may not be unique to Rett and might be looked for in other conditions.

The labile respiratory rhythms, low baseline vagal tone and cardiac sensitivity to baroreflex which is comparable to that of neonates and the signs of the inability to restrain sympathetic responses in Rett suggest brain stem immaturity and a lack of integrative inhibition. These failures may explain many vacant spells and some sudden deaths and strongly support the concept of a prenatal origin in this disorder.

5.6 Critical examination of serial e.e.g. with video monitoring

At this stage in the investigation of Rett syndrome we had monitored the e.e.g. as part of the autonomic assessment finding abnormalities, sometimes with epileptogenic features but seldom witnessing an epileptic seizure. Dr Rosemary

Cooper, senior neurophysiologist recently retired from the North Staffordshire hospital, agreed to review a number of e.e.g.s recorded before, during and after the regression period to provide insight into the evolution of the e.e.g. abnormality and its relationship to suspected and diagnosed epilepsy. I invited and organised this study and provided contact with the physicians of known families. Dr Cooper requested the e.e.g.s and reported them. The paper was written jointly.

We examined data relating to epilepsy from the BIS and 150 e.e.g.s, paper recordings from 78 cases including 23 with prolonged synchronous recordings of e.e.g. respiration and movement whose assessments we had conducted for the studies reported in sections 5.2 and 5.3. The physicians who recorded e.e.g. for cases in BIS were invited to send them to Dr Cooper for review. Of particular interest were recordings made before during and soon after the regression event. Further clinical data for the subjects is supplied in **Appendix C, 5.6.**

The **figure 5.6.1 Appendix A** provides the main results of the study. The proportion of abnormal records increased from 6 of 18 (33%) during the first 7 months to 44 of 59 (75%) in the later period to 6 years, the increase in abnormality following rather than preceding the onset of regression. In young girls the abnormality increased in sleep but decreased during episodic hyperventilation and breath-holding. Epileptogenic activity was commonly present without clinical seizures. Eleven vacant spells were directly monitored during assessments in the department and these were not epileptic but related to the breathing abnormality. Without e.e.g. monitoring, these vacant spells might well have been assumed to be epileptic in origin.

This study indicated the value of monitoring when interruptions of attention or consciousness are occurring which raise the possibility of epilepsy. In Rett the intermittent e.e.g. abnormality and the behavioural changes indicate abnormal fluctuating arousal, possibly of midbrain or brainstem origin. **Figures 5.6.2 & 3, Appendix A** show the e.e.g.s in two cases. Data provided by families for BIS

made it possible to compare their reports of breathing abnormality, epileptic seizure and non-epileptic vacant spells in 191 girls. A diagram at **Figures 5.6.4, Appendix A** shows the occurrence of these three types of disturbance in BIS indicating that whereas 46% were subject to all these abnormalities (87 of 191) only 7% appeared to have epilepsy alone without the non-epileptic attacks and noticeable respiratory irregularity. 61% (116) reported both breathing irregularity and non-epileptic vacant spells. Only 6% reported none of these problems.

Comment on the research in this section

These studies led to consolidation of a concept of how the Rett disorder arises, indicated in the diagram **(figure 5.6.5, Appendix A)** and of the factors that contribute to the vacant spells seen in Rett syndrome **(figure 5.6.6, Appendix A)**. The early studies of the dysrhythmic breathing in Rett indicated involvement of the brain stem in the disorder and led to consultations with Professor DW Richter of Gottingen who had carried out extensive research into the control of cardiac and respiratory rhythms in the brainstem. Richter came at our invitation to observe several assessments. Serotonin was agreed as a likely neurotransmitter to be implicated in the apneustic breathing seen most frequently in the youngest children with Rett since through its 1A receptors it normally initiates the expiratory effort. For this reason we approached Dr Dawna Armstrong (Texas Children's hospital) who, with others had already carried out estimations of several neurotransmitters in the brain, to enquire if the status of Serotonin receptors had been considered. In fact estimations had been carried out but not as yet reported, as they had not been the focus of that investigation. Receptors for Serotonin were found to be greatly increased in the brain stem and specifically in the areas involved in regulation of respiratory rhythm (Armstrong & Kinney 2001). All these findings combined to focus the research on the brainstem and its role in early brain development as well as in the regulation of later cardio-respiratory rhythms. An international autonomic workshop was therefore held at the Swedish Rett Centre at Froson and provided

an opportunity for a small number of research colleagues to view the autonomic assessments and discuss the evidence it provides on early brain stem involvement in the Rett disorder. (Witt Engerstrom & Kerr 1998). Still more recently reports have indicated lack of serotonin transporter in the dorsal motor nucleus of the vagus nerve which might be expected to relate to the autonomic problems we have demonstrated (Paterson et al 2005).

Several early researchers investigated the cardio-respiratory and autonomic problems in Rett (Lugaresi 1985, Cirignotta 1966, Verma et al 1986, Johnsrude et al 1995, Nomura et al 1997, Guideri et al 1999). However the studies described here brought understanding to a new level with regard to the poor central autonomic control in Rett disorder and the frequent occurrences of non-epileptic vacant spells that are suffered by these people. These abnormalities constitute one of the most difficult problems in management and are very disruptive for the individual and family. They are almost certainly responsible for some of the sudden and unexpected deaths (Kerr et al 1997). When they are misinterpreted as epileptic excessive amounts of ineffective medication may be prescribed.

Section 6:

Investigations II:

6.1 Neurophysiological observations on corticospinal projections to the upper limb in subjects with Rett syndrome.

The severely disordered control of movement in Rett and the changes with age, from early hypotonia to later hypertonia gave rise to the suspicion of lesions at the level of the corticospinal tracts that increased with time (Hagberg et al 1986, Hagne et al 1989). However accounts and observations of individuals who displayed full and useful movement in limited and highly motivated situations in spite of their evidently poor control of voluntary movement led me to search for a way to investigate these tracts as I suspected that the tracts were intact and the problem arose in the higher centres. Professor Janet Eyre was already using the method of transcranial electromagnetic stimulation of the cortical neurones in a study of cerebral palsy and I invited collaboration. We agreed to investigate the excitability of the cortico-spinal neurones and the integrity of their projections to the alpha motor neurones through the corticospinal tract in subjects of different ages with Rett Syndrome. (Eyre et al 1990)

My contribution to the study was to set the research agenda and invite families to bring their girls or women, selecting a range of ages and levels of severity of the disorder and to provide the clinical assessment. The experimental methods were those of my colleagues in Newcastle. Informed consent was obtained from parents and the University of Newcastle Ethical committee approved the study.

The study was performed in 8 subjects with classic RS whose clinical characteristics are indicated in the **dataset 6.1, Appendix C.** Further neurophysiological details relevant to the study are given in the **figure 6.1.1, Appendix A.** The neurophysiological data from these subjects was compared with those from 350 healthy subjects from birth to adulthood examined as part of

Professor Eyre's earlier researches. Electromagnetic stimulation of the motor cortex and the cervical motor roots was used to evoke motor action potentials in the biceps brachii and hypothenar muscles. The phasic stretch reflex in the biceps brachii was also recorded to study the excitability of the spinal alpha motor neurons.

Electromyograms were recorded with surface mounted standard e.e.g. electrodes placed on the belly of the right biceps brachii and over the right hypothenar muscles. The signals were amplified by a Nicolet amplifier (CA 1000) and filtered with a bandpass – 3dB at 5Hz and 1.5 kHz.

An electromagnetic stimulator (MagStim 200, Novametrix) was used to excite the motor cortex. The stimulating coil was held tangential to the scalp and positioned to obtain motor action potentials in the biceps brachii and hypothenar muscles. To excite the cervical motor roots the coil was positioned in the coronal plane dorsal to the cervical spines C5 to C8 and stimulus intensity reduced to obtain the longest latency to the onset of motor action potentials in the relaxed biceps brachii and the hypothenar muscles.

In all 8 subjects with RS including those less than nine years, motor action potentials could easily be evoked by stimulation of the motor cortex in both the biceps and hypothenar muscles when they were relaxed, indicating a lowered threshold for activation. Normally these cannot be evoked unless the muscle is contracted (**figure 6.1.2**). The values for latency of onset of the evoked motor action potentials in the relaxed muscles following cortical stimulation are shown in **figure 6.1.3.** In Rett subjects these lie below the lower interquartile range for relaxed muscle indicating shortening of the latency. Since the shorter latency in Rett might be due to the shorter stature of these people the values were also plotted in relation to the C5 spine to the mid-point of biceps brachii with the results shown in **figure 6.1.4** and it can be appreciated that the shortening of latency in the Rett subjects is real. The durations of the motor action potentials are shown in **figure 6.1.5** as related to age of the subjects. The durations of the

motor action potentials lie well above the normal range and it can be seen that this does not alter with age.

In the Rett subjects the phasic stretch reflex was also readily evoked in relaxed biceps indicating a lowered threshold of activation (**figure 6.1.6**) Normally this reflex cannot be evoked in relaxed muscle after age 2 years. The latency of onset of the phasic stretch reflex in relation to the ages of the Rett subjects is shown in comparison to normal controls in the figure (**figure 6.1.7**). **Figure 6.1.8** relates the latency of onset of phasic stretch reflex to arm length, confirming the finding that latencies are genuinely reduced. The durations of the phasic stretch reflexes in the Rett subjects were longer than normal (**figure 6.1.8**) and remained so in the older people (**figure 6.1.9**). In contrast to the findings related to cortical responses, direct electromagnetic stimulation of the cervical motor roots, which was carried out in 5 subjects, resulted in responses of normal latency and duration.

The ability to evoke motor action potentials following brain stimulation in Rett subjects implies integrity of the corticospinal tracts. The short latency indicates that either the largest myelinated fibres of the corticospinal tract conduct with faster velocities than normal or that the time for bringing the corticospinal neurones and or spinal alpha motor neurones to firing threshold is diminished. The conduction delays of the peripheral efferent and afferent components of the phasic stretch reflex are likely to be normal as indicated by the normal onset latencies and durations of the motor action potentials following electromagnetic stimulation of the cervical motor roots in the five Rett subjects examined.

Taken together with the clinical and pathological evidence on the brain in Rett, the results of this study suggest that the defect lies 'upstream' from the outflow of the motor cortex. This procedure has since been repeated in people with Rett, with the same result (Heinen et al 1996) and later studies of the neuropathology of the condition indicate the major impact of the *MECP2*mutation on the

synapse (Armstrong 1992).

6.2 Short fourth ray in Rett Syndrome

The presence of a short fourth ray was first observed by me in the feet of a British case and again in a girl with Rett syndrome during an international workshop and clinic in Baltimore in 1985 when I brought it to the attention of Professor Opitz who was collecting such observations of minor anomalies from all the clinicians taking part (Opitz 1986). Opitz later noticed and reported the same defect in more cases (Opitz 1987). This minor dysmorphism was of interest as throwing light on the developmental nature of the condition at a time when that was still being debated. As special clinics for people with Rett syndrome became established in Britain the opportunity arose to test the association in a large number of people. A letter to the Archives of Disease in Childhood (Kerr et al 1993) drew attention to the observation and permission was also given to examine the feet of adults resident in a Scottish institution for people with learning disability.

The aim of the study was to test the hypothesis that this defect is present in more people with Rett syndrome than is expected in the healthy population. The anomaly is referred to below as 'short fourth toe' although it is indeed the metatarsal which is also affected as shown by later radiographic studies (Leonard et al 1999). I observed that the hands were similarly affected but considered that the abnormal movements of the hands in Rett might be considered to contribute to that abnormality and so concentrated attention on the feet. Comparison could be made with the findings of Ray and Haldane who investigated the anomaly in a healthy population and found it in 3 of 2500. They proposed autosomal dominant inheritance with incomplete (27%) penetrance (Ray & Haldane 1965).

I conducted this study. The methods, results and conclusions were discussed with the co-authors and statistical advice supplied by Jane Mitchell. Permission

to examine cases at a large Scottish institution for people with learning disability was given by the consultants concerned and ethical approval provided by the institution's ethical committee. Residents gave their spoken agreement. People with Rett were examined at the request and with the permission of the families attending Rett clinics. (Kerr et al 1995)

Two cohorts were included in this study:
Cohort 1 included 137 consecutive cases of classic Rett syndrome over 5 years of age examined by me at the Rett clinics organised by the Rett Associations. The 91 cases which have been recorded in BIS are listed with other relevant clinical characteristics **(Appendix C 6.2).**
Cohort 2 included 526 people with learning disability who were resident in an institution.
The examination was a simple observation of each bare foot, around which I drew a line. The abnormality was considered to be present when the 4th toe was of the same length as the fifth toe and substantially shorter than the 3rd toe. I examined the feet of people in the institution with the agreement of each one. Only one individual was unwilling to participate and was omitted. No other measures were employed for the entire cohort. The diagnosis of the neurological conditions was ascertained as far as possible from the case records. In cases highly suggestive of Rett syndrome families were invited to attend and supplied additional histories. The co-authors met to study the recorded outline of each foot and to agree on which were to be considered to have the short 4th toe. If there was any disagreement that foot was not rated as affected.

Cohort 1: Twenty-eight of 137 (20%) consecutive cases of Rett Syndrome aged over 5 years and 24 of 96 (25%) cases over 10 years had this minor dysmorphism indicating that it became more evident with increase in age.
Cohort 2: The short 4th toe anomaly was found in 19 of 526 residents in the institution (3.6%). Among 14 people with probable Rett syndrome 4 showed the anomaly (28%). Among 49 people with Downs Syndrome 8 showed the

anomaly (16%), Only one woman with short 4th toes did not have features suggestive of either Rett or Down's syndrome. Six men with the anomaly had suffered a variety of prenatal genetic or environmental insults. One man had signs suggestive of Rett syndrome but permission for further investigation was not provided. With two exceptions the cases of probable Rett syndrome had received no earlier neurological diagnosis. The photographs at **Appendix A, figures 6.2.1. and 6.2.2.** show the abnormality.

A strong association was demonstrated between the anomaly and Rett syndrome and a less strong association between the anomaly and Downs syndrome. The statistician considered that further statistical tests were not appropriate since the normal adult prevalence of 3 in 2500 (1 in 800) is vastly different from that in adults with Rett (more than 1 in 5) and in Downs (more than 1 in 6) and the significance is clear.

The presence of the anomaly is highly suggestive of a prenatal defect which manifests as the individual grows, affecting both brain and limb development. A flow diagram (**figure 6.2.3**) was constructed to show the stages at which a postulated genetic deficit might be expected to influence growth of the organism in these ways. The number of previously undiagnosed people with signs suggestive of Rett syndrome in this adult institution should alert physicians responsible for the health of these people to be more aware of this diagnosis. It seems highly probable that such adult cases are still overlooked.

Following this study a further radiological investigation by colleagues in Australia confirmed the presence of the anomaly in both hands and feet (Leonard et al 1999).

6.3 Visual function in Rett Syndrome:

Professor Daphne McCulloch and her optometrist colleagues from the Caledonian University had worked with me in a project examining the vision of

close to 600 people with learning disability in a large institution and were highly experienced in such visual assessments (Kerr 1994). They agreed to conduct this study. I recruited the subjects to represent a range of ages and severities of classic Rett Syndrome, supplied the clinical data, contributed to planning of the protocol, visited the project and participated in the writing of the paper (Saunders et al 1995). However I did not participate in the actual assessments or analysis. Statistical analyses were provided by Professor McCulloch, comparing results in people with Rett with established normal values.

People with Rett Syndrome seldom have useful speech but families find them very responsive to visual stimuli and educational approaches frequently use the presentation of objects pictures or cards with written words to provide choice to the individual. It was agreed to carry out ophthalmic assessments in order to see if vision is adversely affected by the disorder and to provide families with information on any minor optical corrections, which might improve vision. Previous studies had carried out tests using visually evoked potentials (VEPs) but visual acuity had not been systematically investigated by this means.

The eleven subjects with classic Rett syndrome were aged 4.8-24.3years. Their clinical characteristics are indicated in **Appendix C. 6.3**. They attended for an outpatient assessment with their parents who gave informed consent. The control subjects were 18 developmentally normal people aged 6.4 to 21.2 years who formed part of a cohort in other studies at the Caledonian University.

Each subject was refracted using a non-cycloplegic near retinoscopy technique (Mohindra 1975) and examined by direct ophthalmoscopy. Ocular posture and pupil reflexes were assessed and gross visual field testing was attempted. Binocular VEPs were recorded using pattern onset checkerboard and grating stimuli. Subjects were placed 43 or 85 cm from the stimulus screen which subtended 29.2 by 34.9 degrees visual angle at 43 cm and 15.8 by 19.4 degrees angle at 85cm. Grating stimuli ranged in size and the threshold was regarded as

the finest grating size to which a reproducible VEP could be elicited. An observer situated behind the stimulus display attracted the subjects' attention by talking, singing or jingling keys. A second observer ensured that the VEPs were recorded on while the individual was fixating the screen. Each VEP recording was the average of between 40 and 50 epochs initiated by the pattern presentation. An artefact rejection programme eliminated trials with amplitudes exceeding plus or minus 50 microvolt. VEP traces were judged to be reproducible if the most prominent peak occurred within 20 ms in two successive trials. Episodes of intense hyperventilation were noted as these might affect the attention or response of the individual.

10 Rett subjects and all the control subjects succeeded in completing all aspects of testing - one failed to cooperate long enough for a VEP threshold to be estimated. In general people with Rett were found to cooperate well with VEP testing, sitting quietly and attending to the visual stimuli. However poor or intermittent attention to Keeler and Cardiff cards made attempts to perform preferential looking tests unsuccessful in all cases. The range of eye movements was full although following a visual target was intermittent. No subject had nystagmus but one had exotropic strabismus. Two girls with Rett had corneal conditions. One girl had keratoconus in both eyes and one had a scarred cornea due to recurrent infection. Among the 22 eyes 11 had astigmatic errors of at least 1.5D (1.5-5D, mean 1.76D). Axes were all within 20 degrees of vertical. The mean level of ametropia was +1.57D (-3.75 - +5.75) among the seven subjects with this defect (**see figure 6.3.1, Appendix A**). Anisometropia was present in seven subjects and absent in five.

To analyse the VEPs, p100 latency was measured in the control subjects and the mean derived. The mean latency was 92.62 (SD 22.46) ms. A 95% confidence interval, ranging from 45 to 140ms was thus established for the latency of the positive component. In Rett subjects the largest reproducible peak within this 95% confidence limit was regarded as the p100. Both its latency and its

amplitude were noted. The latency and amplitude of negative components on either side of this p100 were also noted. Negative peaks before and after p100 were termed N60 and N120, respectively.

Subjectively the VEPs for 60'check stimuli from subjects with Rett syndrome appeared different from those of control subjects (**see figure 6.3.2, Appendix A**). The latency of the second negative component (N120) tended to occur earlier ($p<0.1$) and to be larger than in the controls subjects. The p100 component in Rett subjects tended to be earlier and smaller than in controls. The amplitude difference was significant at the 10% level. Despite the subjective impression of difference between the Rett and control responses no significant difference could be demonstrated at the 5% level either in latencies or amplitudes, possibly reflecting the small sample size. **see figure 6.3.3, Appendix A**).

Estimates of VEP acuity thresholds were calculated in all subjects. There was a significant difference between the VEPs of the Rett subjects and those of controls, The Rett group demonstrating significantly smaller amplitudes of positive and negative components (p100, $p=0.004$; N60, $p=0.05$; N120, $p=0.032$. The latencies of the p100 and N120 were significantly delayed ($p=0.019$ and $p=0.002$ respectively. These differences could not be accounted for by refractive errors in Rett subjects nor by accommodation difficulties.

This group of people with Rett syndrome showed a low incidence of strabismus and nystagmus and had relatively good visual acuity as compared to data from other studies of people with severe learning disability. The visual pathways do appear to be spared in Rett by comparison with other equally severe intellectually disabling disorders. All the Rett subjects appeared to use their vision and attend to a visual stimulus albeit with a short attention span. The increased p100 and N120 latencies at finest grating size suggest that Rett subjects were closer to threshold than control subjects at this stimulus size.

Although the sample size was small it would appear that, in common with other disabled populations these people with Rett have a high incidence of large refractive errors. Spectacles were indicated and prescribed for five of these subjects after discussion with the parents and proved to be well tolerated and apparently benefited the individuals, with improved participation, sociability and enjoyment of their surroundings while wearing the spectacles.
Neuro-anatomical studies of the brain in Rett have also found that the occipital cortex is relatively spared in Rett as compared to frontal and temporal areas (Armstrong 1992).

6.4 Urinary Pterins in Rett Syndrome: Messahel et al 2000

I invited colleagues to conduct this study, recruited the subjects to represent a range of ages and severities of Rett Syndrome, supplied clinical data for the British subjects and participated in the writing of the paper. However I was not involved in the laboratory aspects of the study. Ethical approval was obtained by the principal investigator.

There is increasing evidence that abnormal immune responses may contribute to neurological disease (McGeer et al 1001). However investigation in vivo is complicated by the fact that most of the mediators are biologically labile compounds that bind to target cells and disappear from the circulation soon after their release. An indirect approach to monitoring immune reactions is to quantify biochemical changes that are induced by cytokines. The macrophage is an important effector cell of the immune system and activated by cytokine interferon gamma produces large quantities of the unconjugated pteridine, neopterin that is relatively stable and can be measured in body fluids including urine (Fuchs et al 1993). Neopterin is therefore a clinically useful although non-specific marker of immune activation and high levels have been found in the urine in a number of neurological disorders (Anderson et al 1992).
Reduced biopterins are essential for biosynthesis of the monoamine neurotansmitters, noradrenalin, adrenalin and serotonin, which are probably

involved early in the course of Rett disorder (Nomura et al 1985). The **figure 6.4.1** shows the relationships between these substances. Bolthauser et al and Sahota et al found normal levels of biopterin derivatives in serum and urine of people with Rett (Bolthauser et al 1986) but Zoghbi et all found total biopterins to be raised in CSF (Zoghbi et al 1989). In Rett disorder a disturbance in serotonin metabolism is indicated by the large increase in serotonin receptors in the brain stem (Armstrong & Kinney 2001). The age of the subjects was not considered in these studies and we suspected that the disturbance might differ in young and older people with Rett.

This study measured urinary neopterin and biopterin by high-performance liquid chromatography in 40 subjects with Rett syndrome, eight of their healthy sisters and 29 female control volunteers (age range 2-54 years). The 28 subjects recruited from the BIS are listed with relevant clinical data in **Appendix C, 6.4** Data were analysed using Student's t test and Mann-Whitney non-parametric test.

The results were subdivided on the basis of age. Urinary neopterin was significantly higher in the under 6-year old Rett group compared with their control group ($0.05<p<0.025$) As the age of Rett girls increased the values returned to normal values until no significant difference was seen over 21 years. The sisters of girls with Rett syndrome had neopterin values intermediate between their Rett sisters and the controls ($p>0.05$ in all cases). There was no overall significant difference in urinary biopterin levels in young girls but levels in Rett remained low while control values rose. After 11 years there were significant reductions in the levels of urinary biopterin in Rett compared with normal controls (6-10 years RS vs 6-10 years controls $p>0.05$, 11-20 years RS vs controls $0.005<p<0.001$, over 21 years RS vs controls $0.05<p<0.025$. The group of sisters under 6 years showed an intermediate value for urinary biopterin and did not differ significantly for the age-matched Rett group or control group ($p>0.05$). The sisters of Rett patients also failed to show an increase in urinary

biopterin with age and so differences were observed between the older sisters and their corresponding controls. The results of the study and p values are shown in **Figures 6.4.2-3, Appendix A.**

The results of the study confirmed earlier preliminary findings that urinary neopterin levels are raised in a proportion of young girls with Rett syndrome but not in older women. In contrast urinary biopterin levels are not different from controls in the youngest children but while control values increase with age these remain low.

These findings may indicate immune activation during the regression phase of Rett syndrome which might reflect stress or another disease related change. They also raise the possibility that an inherited fault in tetrahydrobiopterin metabolism may increase the risk of developing the disorder, a matter that would require further investigation. The findings have still to be explained in terms of the results of the genetic mutations in *MECP2* that interacts with other genes and neuroactive substances including serotonin, which is chemically related to the biopterins and found in the same pathways.

Comment on the research in this section

The investigations described here indicate abnormalities but also a degree of normality in Rett syndrome, confirming the view that this disorder, while pervasive and profoundly damaging to function of the brain does leave some areas of function virtually intact. This is of importance to the scientists' understanding of the role of *MECP2* in the brain and the essential nature of this disorder - also to the therapist looking for means to assist learning and improve the quality of life. Vision and hearing are intact and clearly enjoyed by people with Rett disorder (Elefant 2002). The view of families is supported that these people can and do make use of their vision. That the defects shown in section 6.1 do not increase with age agrees with our observations that older people with Rett may live long in good health and may continue to learn throughout life.

Section 7:

Genetics

Introduction

The almost complete restriction of the Rett syndrome to females indicated the probability that this was a genetic disorder due to a mutation on the X chromosome. However its sporadic occurrence increased the difficulty of locating the affected gene and it was not until the rare occurrence of an affected brother and sister in one family (Schanen et al 1997) and three affected siblings in another (Amir et al 1999) that the first mutations on the gene *MECP2* were identified in 1999 (Amir et al 1999). Since then it has become clear that there are over 300 different mutation sites and several types of mutation, any one of which may lead to Rett syndrome. It has also become apparent that the severity of the disorder is influenced by the site and type of mutation and in the female by skewing of X inactivation. It is expected that in some cases the gene *MECP2* will be found to be intact and that lack of expression of the protein MeCP2 causes the disorder.

The presence of the distinctive classic Rett syndrome makes the diagnosis easy and mutations have been found in over 85% of such cases, but the Rett disorder may also manifest in such mild or severe forms as to fit the syndromic descriptions 'atypical', ' non-classic' and 'variant' Rett, in whom mutations on *MECP2* have so far been found in about one third. Recently mutations have been identified in other genes accounting for some such non-classic cases and a cluster of different diseases is thus coming to be recognised for the first time, each of which must be presumed to have its impact on the neuronal infrastructure for cognition, fine hand use and speech, presumably involving synaptic structure and neurotransmission and so presenting some of the same features which have been associated with

Rett disorder. One gene in which a mutation can lead to a Rett-like disorder is CDKL5(STK5), which appears to be associated with severe early epilepsy which causes a regression (Kalscheuer et al 2003, Weaving et al 2004. Evans et al 2005)

It has been reported that certain mutations on *MECP2* may present a distinctly different clinical phenotype and evidence for this is still emerging (Clayton-Smith et al 2000, Meloni et al 2000, Orrico et al 2000). There are also people who receive a diagnosis of another disorder because the physician is unaware of Rett disorder. Experience from the BIS has indicated that the diagnostic labels autism and Angelman syndrome are commonly misapplied to Rett.

7.1 Long-read sequence analysis of the *MECP2* gene in Rett syndrome: correlation of disease severity with mutation type and location.

This study was planned and executed mainly by others and my part was to supply clinical data from the British survey, advise on its use and participate in writing the parts of the published paper representing that material (Cheadle et al 2000).

This study recorded the *MECP2* mutations in 48 females with classical sporadic Rett, seven families with possible familial Rett and five sporadic females with features suggestive but not diagnostic of Rett. Long distance PCR coupled with long-read direct sequencing was employed to sequence the entire *MECP2* gene coding region in all cases. Mutations were identified in 44/55 (80%) of unrelated classic and sporadic and familial patients but only 20% of those with suggestive but not diagnostic features. Twenty-one different mutations were identified (12 missense, four nonsense and five frame-shift mutations) 14 of these were novel. All missense mutations were located either in the methyl-CpG binding domain (MBD) or in the transcription repression domain (TRD). Nine recurrent mutations

were characterized in a total of 33 unrelated cases (73% of all cases with *MECP2* mutations). Milder disease was noted in patients carrying missense mutations as compared with those with truncating mutations (p=0.0023), and milder disease was associated with late as compared to early truncating mutations (p= 0.0190). The individual mutation results from this study for British patients are integrated into the BIS database (**Appendix B)** and shown also in **dataset 7.1, Appendix C**. A map of the *MECP2* mutations in the patients with Rett disorder is shown at **figure 7.1.1.Appendix A.**

7.2 Mutation analysis of the MECP2 gene in British and Italian Rett syndrome females.

This study was planned and mainly executed by others and my part was to contribute to the aims of the study, supply clinical data from the BIS and participate in writing the parts of the published paper containing that material. (Vacca et al 2001a, Vacca et al 2001b).

Subjects were 62 patients half from the UK and half from Italy all but two (Italian cases) being classic, for whom cells had previously been taken for mutation testing with fully informed parental consent. The UK subjects are listed in **dataset 7.2, Appendix C** and further data can be found in the main database **Appendix B**

DNA was extracted from probands and when indicated from parents and siblings. The MECP2 coding region was studied by direct sequencing and by SSCP and CSGE analysis followed by direct sequencing of shifted and/or heteroduplex fragments. Published mutation results from other centres were also reviewed.

Diagrams of the gene and mutations and of the frequency of mutations are shown in **figures 7.2.1 & 2, Appendix A** including mutations reported in previous studies. The overall mutation rate in this study was 71% for UK

cases and 67.5% for Italian cases. Seven mutations were identified which had not been previously recorded. All the mutations were de novo and heterozygous. Among the point mutations all but five were C-T transitions. Eight cases had frame-shift mutations due to deletions in exon 3 (severe cases) or an insertion in exon 2. The majority of mutations were restricted to the functional MBD and TRD domains of the *MECP2* gene and the six most common mutations accounted for 62% of the total. However deletions were also detected in the 3' coding region from base pairs 1116 to 1165 outside the MBD and TRD domains and these appeared to be quite common. This observation led to the suggestion that a new functional domain exists on the MeCP2 protein. This region of MeCP2 shows a homology of 35% identity and 50% positivity in a 75 amino acid stretch with two other brain specific factors, brain specific factor 1 (BF1) and fork head 4 (FKH4) (Murphy et al 1994). Such relationships between different genes may underlie observations of a number of conditions - different from or atypical for Rett which may be associated with *MECP2* mutations (Meloni et al 2000).

From these results and the review it was clear that function of the MeCP2 protein is essential for the Rett phenotype as mutations are spread throughout the entire length of the protein. It was also obvious that the frequency of mutations clusters in certain areas. Previously unknown mutation sites were added to those already recognised and there was speculation as to how different mutations may interfere with the function of MeCP2.

7.3 Mutation analysis in the MECP2 gene and genetic counselling for Rett Syndrome.

This study was planned and executed mainly by others and my part was to supply clinical data from the British survey and to participate in writing the parts of the published paper representing that material (Gill et al 2003).

The study reported 11 families with more than one member with non classic or classic Rett Syndrome. In one British family the same *MECP2* mutation, R133C was present in two sisters with clinical Rett syndrome (BIS 148,149) and in their healthy mother see **figure 7.3.1, Appendix A**. In a second British family girl (BIS 22) has classic Rett syndrome with an R294X mutation. Her younger sister (BIS 399) had mild developmental difficulties at 7-11 months, with reduced speech and social interest and it was feared that she might have Rett disorder but by five years she was clearly functioning normally and has been shown to have normal *MECP2.* In a third British family a girl with classic Rett and an R294X mutation (BIS 322) has a non-dysmorphic maternal aunt with moderate developmental difficulties and a history suggestive of social withdrawal at 27 months. No mutation has been identified in that lady. Among the other eight families only people with definite clinical signs of Rett syndrome were shown to have *MECP2* mutations.

It was concluded that family recurrence of Rett syndrome is unusual and that other causes should be carefully considered in developmentally delayed siblings of a person with Rett syndrome. However since the disorder may be inherited the sisters and mothers of affected individuals should be offered *MECP2* gene testing. This study also indicates that the clinical signs of Rett syndrome are a very useful guide to the disorder and that severe developmental difficulties in families with a person with Rett should have other diagnoses considered in addition to Rett as the are less likely to have the Rett disorder.

7.4 Dimensional phenotypic analysis and functional categorisation of mutations reveal novel genotype-phenotype associations in Rett syndrome.

This study was planned and for the main part executed by others and my part was to supply clinical data and measures of severity and typicality for Rett and to participate in writing the parts of the published paper representing that material (Charman et al 2005).

The study aimed to explore genotype-phenotype correlations in Rett syndrome in terms of the typicality and severity of the clinical manifestations, adopting a multi-dimensional approach.

Included in the study were 190 mutation tested people reported to have Rett syndrome including 5 males (140 classic,and 50 non-classic (atypical) Rett syndrome). Mutations had been identified in *MECP2* in135 of these cases. Data was contributed from BIS (BIRS) and reports from other centres in the UK. In all cases the parents/ carers gave fully informed consent. Typicality was judged from the presence of the necessary and supportive features of the syndrome and BIS severity scores were adopted (**Figure 2.2.1 Appendix A** and Kerr 2003). The RSBQ hand score is a behavioural measure derived from the intensity of hand stereotypy (Mount et al 2001). **Figures 1.3.5 and 1.3.7** show the diagnostic and supportive criteria in early and modified forms. Diagrams showing the mutations on *MECP2* can be seen at **Figures 7.1.1 &7.2.1.**

Statistical analysis: (further details are provided in Charman et al 2005)
For those cases with identified *MECP*2 mutations, group mean scores on the dependent variables were compared using analysis of covariance (ANCOVA), covarying for age. The group mean scores for dependent variablesin cases with common individual mutations were compared using

Kruskal-Wallis and Mann-Whitney nonparametric tests, appropriate for small group sizes. Categorical comparisons were conducted using the X2-test. Alpha was set at $p< 0.05$ (two-tailed) throughout, with appropriate Bonferroni corrections for multiple comparisons being employed in *post hoc* tests (Carman et al 2005).
Probability values, 'p' are indicated in the legends for the figures.

Results are shown in the **figures 7.4.1-6 Appendix A**. **Figure 7.4.1** shows the percentages of people with mutations identified among classic and atypical Rett groups Among classic cases personally diagnosed by AK in BIS (BIRS) 89.5% had mutations (non classic Rett cases 20%). In cases reported as classic in other centres 78% had mutations identified (non-classic Rett 40%) Overall 82.9% of reported classic cases and 38% of reported non-classic Rett cases had mutations
Figure 7.4.2a shows that a mutation is more likely to be identified when a regression occurs between 6 and 30 months and when the age at the first seizure is reported after 12 months.
Figure 7.4.2b indicates that cases in which a mutation is not identified are more likely to have had some other event or illness to explain the neurological disorder and are more likely to be dysmorphic.

In **Figure 7.4.3a** the typicality of cases with early truncating mutations, believed to interfere most with the production of the protein MeCP2, is compared with the typicality of cases with mutations believed to have a milder effect - missense and late truncating mutations. It can be seen that there is some difference ($p=0.05$)

Figure 7.4.3b indicates that the presumed severity of the different categories of mutation is reflected in the BIS (BIRS) clinical severity scores ($p< 0.001$, maximum severity score =10), and to a lesser extent relates to

the reported intensity of the RSBQ hand stereotypy score ($p< 0.01$) (maximum severity of hand stereotypy=12).

Figure 7.4.3c For those cases with a *MECP2* mutation this figure indicates the association between early truncating mutations (presumed to have a more severe effect) and the onset of regression or of seizures before 6 months.

Figure 7.4.4 illustrates how the numbers of necessary and supportive criteria relate to the common individual mutations, indicating the less classic presentation of R133C and R168X. One reason for this difference is shown in **Figure 7.4.5** where BIS (BIRS) severity scores are shown for the same group of mutations and R133C and to a lesser extent R306C can be seen to be milder than the other mutations. **Figure 7.4.6** shows the later age at onset of regression associated with these two mutations relative to the more severe mutations R168X, R 255X, R270X and T158M.

This study employed mutation test results, the BIS (BIRS) severity scoring system from BIS (BIRS) and the hand stereotypy score (RSBQ) to examine the reliability of the clinical diagnosis when the classic criteria are present, to explore situations in which the presentation is less typical and to relate type of mutation to clinical presentation. Early truncating mutations were shown to be associated with more severe disease than missense or late truncating mutations. The mutations R133C and R306C are associated with less severe disease and later onset. More severe disease with earlier onset of regression and of reported seizure is associated with R270X, R168X, R255X and T158M. Presentation may be less classic in the mild disorder. In the comparison of 6 common mutations (**Figure 7.4.4-6)** the BIS (BIRS) severity score differed significantly ($p <0.001$) and Manley-Whitney *post hoc* comparisons showed that cases with R133C had a significantly lower

severity score than those with R255X and T158M. Across the six groups the RSBQ hand score did not differ significantly.

7.5 Large genomic rearrangements in *MECP2.*

This published study was planned and for the main part executed by others (Ravn et al 2005). I supplied clinical data from the British survey for five subjects and participated in writing the parts of the paper representing that material. Subjects were profiled using the international guidelines (Kerr et al 2001). UK subjects are shown with data in **Appendix B.** BIS codes 791, 915, 605, 550, 398.

At the time of this study it had become clear that 80-90% of people with clinically classic Rett syndrome have mutations in *MECP2*, leaving some classic cases unexplained. This study used the Multiplex Ligation dependent Probe Amplification technique MLPA to screen 45 patients with Rett syndrome who had previously tested negative for mutations in the coding regions of *MECP2*, 19 of whom were classic. The method determines the number of copies of each *MECP2* exon. With this approach seven patients were detected with genomic deletions not previously found. These included the subjects in BIS 550 and 398. These people with large rearrangements which had not been previously detected all had classic Rett syndrome, thus the detection rate among classic cases who had previously been reported mutation negative was 37% (7 of 19). The seven deletions detected in this study spanned from 15kb to approximately 80 kb and together covered the whole gene *MECP2*. In three of these cases the mutations also affected part of the adjacent IRAK 1 gene. However these patients did not display additional clinical features.

The pattern of X inactivation was determined and was considered to be skewed if more than 80% of either X chromosome was inactivated. One

case was found to have skewed X inactivation without obvious clinical consequences.

Comment on the research in this section

The studies in this section have progressed understanding of the nature of the Rett syndrome and disorder in several ways. There is clearly some correlation between the type and position of the mutation on *MECP2* and the clinical presentation but how much of the variety is due to the pattern of X inactivation is still to be explored. It is clear that whereas the classic Rett syndrome is almost always found to be due to mutations in *MECP2* there are still cases in which one has not been identified. It seems possible that in at least some of these the fault lies in failure to express the MeCP2 protein rather than a *MECP2* mutation per se. To understand the relationship between the gene and the clinical presentation will require further work and may lead to new and perhaps more efficient ways of making the diagnosis.

The situation as regards non-classic Rett is complex and has only begun to be explored. It is to be expected that more than one disease process may lead to a particular constellation of clinical signs so we should expect that mutations elsewhere in the genome or indeed other early neurological insults will produce some of the symptomatology associated with Rett. Also it should be expected that some mutations in *MECP2* will lead to unexpected presentations due to their position or to other epigenetic factors. Adjacent genes may be affected and translocation may involve other areas in the genome. In this next stage of investigation it will be important for the cases under discussion to be clearly described (Kerr, Nomura et al 2001).

Advice to the family of the person with Rett syndrome has improved with these and similar studies. If a mutation is found in one person it becomes possible to offer testing to sisters and mothers with the likelihood of being able to remove or greatly reduce the fear of recurrence, although we still

know little about any factors which might predispose to germ line mutation. The situation for the family is more difficult when a mutation is not identified and many people find it hard to live with the uncertainty even if the clinical diagnosis is clear.

Section 8:

Management in Rett syndrome

Possibilities for specific intervention in Rett disorder have grown with the discovery of the affected gene in 1999 and the development of methods, albeit still in the early stages, for the introduction or release of the normal gene in the cells of the affected individual. Improved understanding of the pathogenesis has indicated possibilities for pharmacological treatment and recognition of the earliest signs of the disorder raises the hope that it may become possible to treat the young infant soon after birth, before the onset of the regression period. However these possibilities are still for the future and the approaches described here reflect a pragmatic, damage limiting approach.

8.1 Serotonin and breathing dysrhythmia in Rett Syndrome.

I selected the individual for treatment (BIS 712, **Appendix B**), conducted the clinical examinations, organised the autonomic assessments and arranged the meetings with international collaborators. The autonomic assessments were carried out with a collaborative team consisting of the physicist Dr Stig Hansen, e.e.g. technician Mr Apartopoulos and Autonomic physiologist Dr Peter Julu and myself. Ethical approval was from the Southern General Hospital (Kerr et al 1998)

The family gave informed consent and the pharmaceutical firm agreed to the named patient prescription. No funding or other inducement was received.

Our observations of the abnormalities of breathing and cardiac rhythm in Rett (see neurophysiological investigation) led us to the conclusion that central autonomic control remains close to the neonatal level in Rett disorder, with relatively normal sympathetic drive but inadequate parasympathetic restraint when the individual is awake and active. Among the several different patterns of breathing recorded in

Rett it is an apneustic pattern, which predominates in the youngest children in whom there is an abnormally long inspiratory phase. Serotonin provides an important component for initiation of the normal expiratory effort. In studies of donated Rett autopsy material Professor Dawna Armstrong and colleagues demonstrated that the receptors of serotonin are greatly increased indicating a problem in serotonin production or use. Following a report of the successful treatment of patient with damage to the brain stem inspiratory centre using buspirone, a specific serotonin 1A agonist (Wilken et al 1997) and after discussion of their result with Professor Richter and Dr Wilken the authors, we agreed to offer this treatment in the case of a relatively able girl with Rett syndrome and particularly severe apneustic pauses which led to faints.

The subject presented to me because of her extreme apneustic breathing and faints. Her parent and physician requested advice on treatment and agreed to a trial of buspirone. The methods which we had developed for continuous non-invasive time-locked measurement of respiratory and cardiac rhythms, blood pressure, e.e.g., and blood gases with video allowed us to measure the abnormality of respiratory rhythm before and after the introduction of buspirone.

The recommended dose was 5mg daily increasing in stages of several days to 20 mg daily. Two days after beginning treatment the family noticed benefit in that the girl became less agitated and had fewer attacks. A reassessment 2 months after the introduction of treatment indicated a decrease in the percentage of apneustic breathing. The girl continued to be maintained on this medication. **Figure 8.1, Appendix A** shows the percentages of respiratory rhythms before and after two months of treatment. There was a marked improvement in the amount of apneustic breathing. There were no unwelcome effects of the treatment. The family and their physician have since chosen to continue this treatment.

It is of interest that after mutation testing became available a mutation was not found in this girl. Although it is acknowledged that there are people with Rett

disorder in whom mutations are present but not so far identified, however it remains possible that the subject of this study has a different disorder which is impacting on the brain stem respiratory centres and much else in the brain in a similar way to the Rett disorder.

A PhD study conducted by Dr Sami Al-Rawas under the guidance of Dr Peter Julu and with advice from myself confirmed the value of buspirone in a larger number of young children with Rett syndrome, selected as suitable because of a high proportion of apneustic breathing. The effect of buspirone was to reduce the proportion of apneustic breathing in some cases However it did not prove effective in all cases and had no effect in reducing other types of abnormal rhythm. This PhD was accepted and is in the possession of the University of London, Imperial College, and the work has not so far been published, personal communication)

8.2 Results of Surgery for Scoliosis in Rett Syndrome

This project was planned and executed by myself using the longitudinal data health data available in BIS. Comment was invited from an experienced parent and from the surgeon responsible for most of the corrective surgery in the UK (Kerr et al 2003).

In this descriptive study it was not possible to find precisely matched controls for each operated case. Statistical advice was provided in planning and in analysis by Robin Prescott, Professor of Medical Statistics at Edinburgh University who judged that the inclusion of all the available cases with sufficient data and comparable age and severity would allow useful comparisons to be made (Kerr et al 2003).

Scoliosis is a common complication of Rett syndrome and can become severe. In BIS scoliosis was present in 3% of cases before regression but by 25 years it affected 87%. In the 16-20 year age group 43% (75 of 173 cases) were reported

with severe or operated deformity. In the past many surgeons have been reluctant to operate because of the fragility and reduced lifespan of the individual with Rett and the perception that she cannot benefit from the improved posture. Developments in operative techniques and policies have reduced the requirement for immobility after surgery and with changing awareness of potential quality and length of life in Rett, more operative correction has been undertaken. Cases in the BIS cohort for whom surgery had been carried out were reviewed to compare the reports of their health provided by families before surgery and new reports of the same items of health following surgery in order to assess benefit.

In estimating the prevalence of scoliosis all individuals in the BIS with classic Rett and sufficient data were included (**Appendix B** provides brief data on all BIS cases). In assessing the effects of surgery only those classic cases were included who had data provided before corrective surgery and at least one year after surgery (**dataset 8.2 Appendix C**). The severity of the scoliosis is considered mild if it is perceptible but appears to cause no inconvenience to the individual, moderate if it is marked with some perceived effect on balance or posture and severe if that effect is considered severely disabling, The opinions of the parent and physician are both taken into consideration. This is inevitably a subjective judgement. A photograph is invited, taken from the back with the individual seated and the spinal processes marked in felt tip pen but only a minority of families have been able to supply this. New radiographic evidence of severity of scoliosis is not requested, as that is considered unjustifiable. States of health before and after surgery are recorded on each questionnaire, using the BIS scoring system (**figure 2.2.1, Appendix A**). The questions asked in the BIS health questionnaire include items of health and function and enquire regarding the effects of the scoliosis or surgery for scoliosis on these, whether an operation has been undertaken or not (for a copy of the data held in the survey computer and the health questionnaire see **Appendix D**).

The **figure 8.2.1, appendix A** shows the prevalence of scoliosis in classic Rett in BIS within each 5-year period throughout life.
Surgical correction was reported in 91 classic cases, 50 of whom were clinically classic with adequate prospective health data collected before and after surgery. The results of the enquiry about the effects of the scoliosis and of surgery and the states of health before and at least one year after surgery are given in the **figure 8.2.2, appendix A. Dataset 8.2, Appendix C** shows all the classic cases who have been operated for scoliosis and have completed one or more health questionnaires.

Following the initial post-operative recovery families considered that the operation had improved general well-being for 84% of individuals (42 of 50 classic cases with post-operative health reports), was unchanged in 3, 6% and worse in 5 (10%).
Thirteen of these people walked independently before surgery and 12 did so after surgery. Sitting posture had improved in 82% and deteriorated in 10%. 52% had a reduction in chest episodes (infections or aspirations), 6% had more. Digestion of food appeared better in 42%, worse in 6%. Toilet function improved in only 10% and had deteriorated in 20%, two people having become incontinent.

On parents' reports there were short term complications of surgery in 48% of patients (24 of 50). In 6 cases the lung collapsed - almost unavoidable in this surgery. There were four respiratory infections and four wound infections. In two cases there was ventilator dependence for several days. Three cases were considered to suffer from continuing pain. In three parents remarked on a slow return to normal eating and in two there was excessive bleeding.
Longer term problems included movement of the stabilising rods necessitating further surgery in two cases and minor recurrence of scoliosis in 11 of 50 cases (22%). The five dissatisfied families gave five different reasons for their dissatisfaction, continuing pain, lack of post-operative support, the requirement

for further corrective surgery, poor health following collapse of both lungs at surgery and the continuing requirement for a brace after surgery. The co-author surgeon had no serious complications, supporting the general experience that the centres with most experience are likely to have the lowest complication rate.

From experience of the surgical procedure, advice was provided on the management of the admission, the surgery itself and the postoperative care. Parents were always invited to stay with the child throughout her stay in hospital and the operative and ward staff were given time to become familiar with the usual behaviour and abnormal respiratory rhythm of the patient. This was particularly important for the anaesthetist. Surgery aimed for a robust anterior and posterior fixation at two operative sessions separated by two weeks. An anterior shell brace involving most of the back was used initially after surgery to support the back and ease handling. It was important to ensure that adequate lifting aids were provided in hospital and at home post operatively. Maintaining adequate nutrition was of prime importance and the presence of a parent was of great value. Early mobilisation and effective treatment for pain were given priority.

Scoliosis is a severe complication of Rett syndrome adversely influencing posture, activity and the use of skills. Surgical correction can be of considerable benefit and in this questionnaire based study, led to improved well-being in 84%. In most cases sitting, standing, walking, digestion and toileting were either improved or stabilised. However the procedure is a major one, not be lightly undertaken. The advice from an experienced specialist scoliosis surgeon is to plan the operation with the family aiming to intervene if the angle of scoliosis is progressing past 40 degre, to ensure optimal nutrition before surgery, to plan for admission of the parent with the affected person and to ensure that the nursing and anaesthetic team is familiar with the complex behaviours and disabilities including the bizarre respiratory patterns of the person with Rett. The operative technique should ensure a very robust fixture and lifting aids should be supplied at home and in hospital post-operatively.

8.3 Individuals with Rett disorder and the role of the physician:

This paper enumerates the practical problems of people with Rett disorder based on my experience from research and service for these people and their families and indicates how the physician can arrange to monitor the health of these people and plan timely intervention. The diagnosis should be made early so that the family and child can be suitably supported. The table **8.3.3, Appendix A** shows clinical features, which may assist in distinguishing the Rett disorder in the young child from autism and Angelmann Syndrome, both of which lead to frequent diagnostic uncertainty with troublesome consequences for child and parent (Kerr 2003, Kerr et al 2003).

Comment on management in Rett syndrome

These studies have advanced management of two specific problems for people with Rett disorder which represent the pharmacological and the physical approaches. The possibilities for the pharmacological approach are now beginning to open with the growing insights from the genetic and neurochemical advances. For the present the physician is likely to be more concerned to prevent unnecessary medication - traditional or 'alternative' than to advise more prescriptions. Non-epileptic vacant spells are all too often mistaken for epilepsy and treated with medication which only adds to the problem. Central to improving this situation will be the development of adequate cardio-respiratory-e.e.g. monitoring, still available in very few centres.

Corrective surgery has a limited place and it is essential to understand the natural history of the condition in order to know if and when to operate.

Physical therapies and educational approaches are of most importance and will perhaps remain chief among the possible interventions. Music as therapy and for pleasure, swimming and horse riding with suitable safeguards are effective in promoting health and encouraging learning. Since care depends on the family it is

important that family members are welcomed if they wish to be involved in programmes. However the care of such a person is so demanding that it is essential that flexible relief is offered to the family including time off at night if sleep is regularly disturbed and holiday breaks during he rest of the family can pursue other activities.

These are people with many and complex needs for health, education and social welfare, who cannot readily indicate their problems. In this situation the caring services must monitor health and well being, assessing needs and ensuring provision on a regular basis (Kerr 1994, Kerr 2003, Kerr et al 2003).

Section 9

Prognosis in Rett Syndrome

Introduction

The reduction in skills occurring during late infancy in a child who looked normal and had been making some progress led to an early assumption that the child had been normal before regression but thereafter the disorder pursued a downward course (Hagberg et al 1984). However my experience suggested that understanding was already restricted before regression and remained little changed after that time although the physical sequele of this profoundly disabling condition might produce the impression of true degeneration (Kerr & Stephenson 1985, 1986). It was important to understand the evolution of the disorder in order to plan education and care for the individual and to assess the efficacy of any therapeutic intervention.

My opportunity to observe progress throughout the lifetime of people with Rett syndrome increased with the invitation to advise the two British Rett Syndrome Associations through family referral clinics, the establishment of the British Isles Survey BIS (Kerr 1991 and **section 3.3**) and the development of the Health Survey Questionnaire' (HSQ and coding system, attached at **appendix D**). I was thus able to store health data from willing families and physicians and from my clinical examinations of people with Rett at all ages.

9.1 Analysis of deaths in BIS

I planned this study which was carried out in collaboration with Dawna Armstrong and David Doyle who were responsible for the neuropathological examination of nine autopsies and with Robin Prescott, Professor of Medical Statistics, Edinburgh University, who provided statistical advice for the study and calculated the mortality rate. The rest of the content of the study is purely descriptive for which no truly appropriate controls could be provided however

the severities of cases who died, as reported before their final illness is presented for comparison with mean severities of cases who survived. I provided the clinical data from BIS and wrote the paper (Kerr et al 1997)

At this time of this study (February 1997) there were 805 cases reported to BIS, 631 sufficiently documented for classification, among whom 77% were classical (481), 13% non-classic Rett (84) and 9% not Rett (56). Since 1983 there had been reports of 39 deaths, 31of these in people with classic Rett. For cases known throughout each year of the study the overall mortality could therefore be estimated at 1.2 percent per annum.

The available data for all those who have died up to the present time is shown in the dataset in (**Appendix C, 9.1**) Health prior to the final illness and the cause of death are established as far as possible from reports by the attendant physician and family, death certificate and post-mortem when these are available. The dataset also displays 'type of death'. This classifies deaths as 'frail-F' when the individual was debilitated with severe contractures and nutritional problems; 'seizure-S' when it was believed that severe epileptic seizure disorder had led to death; 'general-G' when the cause appeared unrelated to the Rett disorder; 'Unexpected-U' when sudden and unexpected in an otherwise robustly functioning person with Rett. For each person an index of severity was derived from the feeding difficulty score, muscle tone disturbance, presence of seizures, scoliosis and walking ability (**see coding explanation at appendix D).** For each person an index of health was derived from data in the year preceding the death and included frequency of seizures, weight, frequency of respiratory and other intercurrent illnesses and the parent's report on state of health. Higher figures indicate greater severity and poorer health. Causes of death were determined as far as possible from reports by physicians and families and in 9 cases from autopsy.

The table (**see figure 9.1.1, Appendix A**) indicates the type of death and age of each person. It can be appreciated that the largest group of deaths (48%) occurred in 'frail' people and these deaths tended to occur in late childhood or early adult life. Mean severity for the group was 100% and mean health score 87%.

Among four with 'Seizure' type death (13%) severity was 75% and health 12%. Among four with 'General' causes of death (13%) mean severity score was 80% and health score 12%. In the 'Unexpected' deaths (8 cases, 26%) severity was 80% and health score 25%. Autopsies in the nine cases (**see figure 9.1.2**) gave brain weights between 1100 and 1200g - moderately reduced in weight but not sufficiently to be called microcephalic. The results of Golgi staining were the same in each case. There was no evidence of progressive degeneration but there was a reduction of basal dendrites in layers III and V in the frontal and inferior temporal cortex and the basal dendrites in III and apical dendrites in layer V in the motor cortex. The findings were the same in all nine cases and were judged not to explain the deaths. One case was investigated for cardiac changes (Kerr et al 1997). That death was sudden and unexpected following a breath hold during feeding in a girl who had previous severe breath holding attacks with loss of consciousness not necessarily related to feeding.

Professor Prescott calculated the mortality in BIS as 1.2 percent of known cases per annum. This figure presumes on all living cases and all deaths having been reported to the survey. In fact there was then and there still remains a steady flow of new reports for children and adults at all ages. Also deaths are likely to occur unreported, still commonly in undiagnosed individuals. This figure was thus only an estimate although one which has remained useful.

From this study we concluded that a proportion of the people with classic Rett might live into adult life, deaths being due to the same causes as affected normally developed people. It was clear that the initial severity of the disease played a part in the 15 (48%) 'frail' deaths but also that these people were in poor

health, adding a further adverse factor. The study focussed attention of the proportion of people who died unexpectedly. In this group, severity was not different from that of survivors in the same age band and health was not particularly poor. Cardiac immaturity may have been a factor in one person. Having already observed the unstable central autonomic regulation underlying the characteristic irregular respiratory rhythm and non-epileptic vacant spells in Rett, we suggested that brain stem immaturities contribute to the vulnerability of these people and may lead to sudden deaths.

9.2 Predictive value of the early clinical signs in Rett disorder

This published study was conducted and the paper written by myself with independent statistical advice in planning and analysis of the results from Robin Prescott, Professor of Medical Statistics, Edinburgh University.
(Kerr & Prescott 2005)

By the time of this study mutation testing in Rett was becoming accepted although not universally available and it was already clear that *MECP2* mutations are usually found in classic Rett cases (80-90%) less often found in less typical cases (30-40%) and that in some atypical cases mutations in other genes might be responsible for the condition. The number of reports to BIS was 1159, with the health of many recorded throughout life. The aim of the study was to establish the stability and predictive value of an early severity score for people with clinical Rett syndrome.

Cases included were all those with clinical Rett syndrome, classic or non classic whose families had agreed to have data stored in BIS (**see Appendix B** for selected data for all cases). Severity scores were calculated from predominant muscle tone, locomotor ability, feeding difficulty, scoliosis and epilepsy. For the calculation of severity scores (**see Appendix A, 2.2.1).** The scores are expressed here as %, 0% being the least and 100% the most severe. This simple and robust information came from parent completed health questionnaires, supplemented by

physician's reports and my own clinical examinations (see **Appendix D for items and coding system**). From the available data a score was given for every five-year period throughout life, highest scores indicating greatest severity. When regression had occurred the first period referred to the pre-regression period and when regression had not occurred it referred to the period up to five years of age. The second period reported severity in the years after regression or five until 10 years.

The statistical methods and conclusions were provided by my co-author, Professor Robin J Prescott (Kerr & Prescott 2005). It is unavoidable from the nature of data collection that data is incomplete for most individuals. The approach adopted in this analysis uses all data as fully as possible, although this has the result that analyses directed at different questions are based on different numbers of individuals (for an account of this method see Brown & R.J. Prescott 1999). The tables **9.2.1-2** indicate the numbers on which the different analyses are based. The Kaplan-Meier survival curves that are shown are calculated for classic and non-classic cases and estimates are made of survival for those with the full range of pre-regression severity scores (**see Appendix A figures 9.2.1-2 and figures 9.2.3-4**).

The Figure (**Appendix A 9.2.1**) shows the cumulative survival for the classic Rett population in bands according the levels of pre-regression (birth to regression) severity. The Figure (**Appendix A 9.2.2**) shows cumulative survival for the classic Rett population in bands according to the levels of immediately post-regression (5-9 years) severity. It can be seen that while the 5-9 year-old severity scores more accurately predict later survival, the scores before regression also provide early and relevant indications of the later outcome. In the group of 65 subjects with a pre-regression severity of 40% or more there were 6 deaths, with Kaplan-Meyer estimates of survival at 10, 20, and 30 years of 96.3%, 87.5% and 77.8% respectively. In contrast among non-classic Rett cases there were no deaths registered in 69 subjects with a pre-regression severity

score of 30% or less and a median follow up time of 9.8 years and a maximum of 43 years (graph not shown). The table at **figure at 9.2.3, Appendix A** lists the latest severity scores for 59 classic cases who have died, indicating the type of death reported for each. It can be seen that those dying in a debilitated condition have higher severity scores before the final episode than those dying from general causes or unexpectedly. Similarly, in the earlier paper concerning deaths **9.1** and **Figure 9.1.1.** it can be appreciated that the severity score in the frail people who died was 100% (maximum severity) before the final illness.

For classic and non-classic Rett we related early and late severity scores for the same individuals. The Figure **9.2.4, Appendix A** shows the mean severity scores up to 29 years in 605 people with observations before regression and in at least one subsequent period, allowing comparison of three pre-regression severity bands. It can be seen that in all three bands severity indices rise sharply until about 15 years and then show some tendency to stabilise. The mildest through to the most severe show similar trends although at different levels. Those with classic Rett show much greater rises than Rett non classic subjects. Although the pre-regression severity index predicts the later severity index in all three bands the adult scores show a mean increase of around 40 points for classic subjects compared to around 20 points for Rett non-classic subjects.

The figure (**9.2.5, Appendix A**) shows how people with classic Rett and different levels of pre-regression severity fared at 10-14 years (a) and 15 to19 years (b). It is clear that while there is considerable individual variation the pre regression signs do give an indication of the progress to be expected later.
Early onset of regression was an independent predictor of greater severity later on ($p<0.01$).
At the time of this study a minority of cases in the survey had been tested for *MECP2* mutations and most deaths had occurred before it was possible to carry out mutation testing so that the mutations in each case could not be included in this analysis. The table (**at figure 9.2.6, Appendix A**) shows the mean severity

scores associated with the most common mutation sites on *MECP2* and indicates a degree of correlation between mutation and severity. It was expected that the presence of skewed X inactivation would contribute to the outcome but that could not be investigated at this time.

We conclude that the clinical signs that are present before the child regresses are of value in prognosis. Recognition of these signs and early diagnosis are important to allow the provision of early support for parent and child and because this early stage probably represents the best time for pharmacological intervention. The natural evolution of the disorder varies according to the initial severity with the longest survival in the least affected. It is important to appreciate the different trajectories in planning for any individual and in assessing the efficacy of any intervention introduced.

9.3 The R270X mutation and mortality in Rett syndrome

This joint Australian and British study was invited by Helen Leonard and mainly conducted by others. My contribution was to supply clinical data from the British Survey and to contribute suggestions on gathering and presenting the data (Jian et al 2005). The aim was to investigate the observation that cases with the mutation R270X were lacking from studies of older people with Rett although in the Australian survey it was one of the most common mutations to be identified. The hypothesis was that the reason for the lack among older cases in other studies was earlier death in cases with R270X.

524 mutation positive cases were included, 353 from the British and 171 from the Australian based survey. Survival from birth was determined using the Kaplan-Meier product-limit method, following the example of the above paper. The log-rank test was applied to evaluate variations in survival among those with the different mutation groups. The eight most frequently occurring C>T transition mutations were compared. Survival among cases with R270X was compared with survival in cases with all other mutations. Sufficient results for

skewing of X inactivation could not be obtained for their inclusion in the analysis.

The **figure 9.3.1, Appendix A** indicates the survival with R270X mutation as compared with all other collected mutations over a 25 year period. The survival for cases with R270X was reduced by comparison with all other mutations when taken together.

The **figure 9.3.2, Appendix A** shows the numbers and percentages of deaths from each of the most common mutation groups. The percentage of deaths in the R106W group is highest, followed by the percentage of deaths in the R270X group.

It is of interest to note a degree of correlation between the percentages of deaths in this study and the degrees of severity for each mutation found in the British study reported above. In both cases the mutation R133C is associated with a better outcome. Both studies suffer from the absence of the routine testing for skewed X inactivation - unfortunately a time-consuming and expensive procedure in the existing health system.

9.4 People with mutation positive Rett Syndrome who converse.

This project was carried out at my invitation. With colleagues I recruited subjects and ensured fully informed consent. I contributed clinical data and wrote the clinical aspects of the paper. The genetic work was carried out entirely by colleagues (Kerr et al 2005). Statistical support was provided by Robin Prescott, Professor of Medical Statistics at Edinburgh University.

A distinct group of people with Rett syndrome have useful speech (Zappella1992, 1997, De Bono et al 2000). Useful speech was reported to be present in 6% of people after regression in BIS among mutation positive people (20/331). This study aimed to explore the associations of this facility and to

learn from people with speech about the attitudes and inclinations of people with the condition.

The study included thirteen *MECP2* mutation positive people over 10 years of age, who had been reported to BIS or to the Institute of Medical Genetics in Cardiff, adequately documented and reputed to use clear speech in phrases or sentences in appropriate situations and on a regular basis after the regression period. The dataset is shown at **Appendix C 9.4.** The families completed the BIS health questionnaire with additional questions directed to ascertain the understanding and use of speech, also what we might learn from this person about her personality, interests and preferences. The results are shown in **Figures 9.4.1-4, Appendix A.** X-inactivation patterns were established as far as possible.

The study group differed significantly from an age matched, mutation positive control group without speech (n=110) with regard to disease severity ($p< 0.001$), feeding difficulty scores ($p< 0.001$), health scores ($p< 0.001$), epilepsy ($p< 0.001$), head circumference ($p< 0.004$), age at onset of the regression period ($p< 0.001$) - 6 in the study group did not regress, and mutation frequency (R133C $p<0.006$, C terminal deletions $p=0.014$). X-inactivation was moderately skewed in two and yielded no useful result in three, see **Figure 9.4.1.**

Speech was fragmented with a soft breathless quality and all but two had obviously irregular breathing. One person with R168X mutation preferred signing to speech. All enjoyed interpersonal contact, showing affection and preferring people to objects, clearly distinguishing the condition from autism. Ten were described as habitually anxious. Music was a source of pleasure and provided a valuable educational asset. Even in these most able people understanding was severely restricted and little initiative was shown.

While the characteristic Rett profile is present in these people (Kerr et al 2001) they are commonly not classic and the presence of speech and lack of regression may lead to missed diagnoses. A strong association was demonstrated between this milder form of the disease and R133C and C-terminal deletions. It is now accepted that when marked skewing of X-inactivation is present this can affect the severity of the condition. This group although small does indicate that favourably skewed X-inactivation need not be present in order to explain mild cases.

In 2003 Smeets et al reported predominantly autistic presentation in cases with the mutation R133C and a slower disease progression in cases with R 306 C (Smeets et al 2003). All the cases on whom we have reported with R133C are sociable and enjoy face to face communication. We suspect that this discrepancy may be due to the fact that we have used information from parents and the individuals with Rett who do retain speech. Also we have considered only those over 10 years of age. The marked hand stereotypy which is present in most people with Rett and the agitation and withdrawal which are common during the regression period may well give an impression of autism which is shown to be mistaken as that stage remits. However there are interesting similarities and the comparison is fruitful.

9.5 Mind and Brain in Rett Syndrome

The development and retention of speech is uncommon in Rett syndrome and people with these skills commonly manifested the non-classic (atypical) presentation, raising the question whether the cause was the Rett disorder or not. Some of the most severely affected people were also judged to be 'non-classic' as their skills were clearly poor from birth and regression imperceptible, again casting doubt on the diagnosis of Rett disorder. With the discovery in 1999 of the mutations responsible for the disease and the gradual spread of access to mutation testing it became possible to identify with certainty the non-classic cases who have the Rett disorder. The occurrence of a mother and her two

children each with the same mutation but with very different severity of the clinical signs and symptoms led to a full collaboration with that family in order to draw attention to the fact that the same genetic defect expressing the same profile of disability (phenotype) may show a very wide range in severity and to share the insights of a person with Rett and the ability to express her preferences and difficulties. In this study the numbers were also reviewed of people with Rett syndrome, classic and non-classic, with the ability to speak. The characteristics were compared of people with and without the ability to speak. Neuropathologist Pavel Belichenko contributed a review of his work on the neuroanatomy of the Rett brain relating to speech areas.
I invited this collaboration, contributed the clinical data, obtained the reports, reviewed the speech characteristics and wrote most of the resulting paper (Kerr Belichenko et al 2001).

The figure shown at **9.5.1, Appendix A** indicates the proportions of people with and without speech in BIS at this time. The table at **9.5.2. Appendix A** compares the characteristics of people with and without speech in BIS. Mutation testing was not yet generally available in the UK so that mutation test results could not be included.

The young woman was born to a healthy mother (source of her clinical information) who recognised the condition immediately because her own younger sister had been similarly affected. The infant fed poorly and seemed not to understand how to suck. Her developmental progress was very slow as regards movement and cognition however apart from her mother other professionals were reluctant to admit the presence of abnormalities. There was no regression and the child learned to walk, speak, count and read, always learning slowly and requiring much support. Her health and appearance were good and she married and had first one girl with classic Rett and then a boy who followed the same course but with much greater severity. Like the rest of his family his appearance was considered normal at birth. He smiled and had begun

to bring his hands together with stereotyped movements in the midline but weakness limited limb movements. It was quickly clear that breathing and feeding could not be managed at the same time and after a series of respiratory arrests he succumbed at 14 months.

Reviewing his studies of the speech areas in donated autopsy material, Dr Belichenko reported that there was no sign of abnormal migration of neurones. There was a reduction by 15-30% in the size of the largest neurones and the marker p38IR was reduced in all the speech areas examined as compared to controls. The interhemispheric difference was preserved in the motor speech areas 44 and 45. This interhemispheric difference is associated with the normal development of speech and in Rett is taken to indicate that some morphological basis for speech processing is present (Leontovich et al 1999, Belichenko et al 1996, Belichenko et al 1999, Belichenko et al 2001).

It can be appreciated from these results that a significant minority of people with Rett syndrome do have speech, which may remain useful. In the case of one family there is no doubt that a mutation is present. The characteristics of the people with speech indicate capacities for social engagement and for learning. The particular value of music is emphasised for pleasure but also as an aid to learning.

The presence of the same *MEPC2* mutation in a mild, classic and severe case demonstrates the wide range in clinical severity which may be expected in the Rett disorder, while the profile of the disease remains recognisable as Rett syndrome, classic or not.

The neuropathological review confirms that the infrastructure for speech is at least partially preserved in Rett.

9.6: Outcome in Rett Syndrome:

This invited chapter for a book (Kerr 2002) provided a description of the transition from childhood to adult life in Rett using research data not previously

published from BIS. The continuing growth of the brain as reflected in increasing occipito-frontal circumference is shown in the **figure 9.6.1, Appendix A.** Here it can be appreciated that in about half the cases OFC comes to lie below the 2SD and in the others it remains within the normal centiles although commonly suboptimal for that individual and family expectations.

The longer term changes in Classic Rett as related to the predominant abnormality of muscle tone are indicated in the **figure 9.6.2, Appendix A** The changing levels of function through life are indicated in the **figure 9.6.3, Appendix A** where it can be seen that skills in hand use, speech and locomotion tend to decline and feeding difficulties and scoliosis tend to worsen. However epilepsy was reported to be less common in older people.

The behaviours, which are associated with Rett syndrome, remain rather stable into adult life as shown (**see figure 9.6.4).**

Figure 9.6.5, Appendix A indicates how attention to each aspect of need maintains the individual in good health, regardless of severity while neglect allows her to slip into the circle of ill-health in which each element tends to lead to the next.

Comment on the research in this section

Only with a large cohort of people whose condition is monitored over a lifetime as exists in BIS is it possible to understand the natural history of a disorder. Especially in Rett disorder a brief acquaintance can be misleading. The very young infant gives little indication of the troubles which follow. During regression it is easy to imagine that the deterioration will continue. Later in adolescence improvement in contact can accompany the increasing difficulties due to growth.

Such an understanding makes it possible to advise the family and plan the necessary support for education and therapy for child and family. Schools particularly appreciated this guidance. Is walking likely to continue? What

communication aids are likely to be required? How much activity must be built into the school day?

Families need to prepare themselves for what lies ahead, in the most severely affected person whose life expectancy is likely to be shortened as well as in the mildly affected but dependent individual who may outlive her parents and will need to be found a home for her mature years.

Without this long-term perspective on the course of the disorder it is impossible to judge the efficacy of treatment. This will apply increasingly to pharmacological and genetic intervention but already it is important as decisions are made about management of a deteriorating scoliosis or feeding difficulties. The studies in this section have added to this knowledge and it is fortunate that in the investigation of Rett syndrome research and family interests have become so mutually supportive, making long-term studies such as this possible.

Section 10

Conclusions and future directions

These studies of people with Rett syndrome began in 1982 with the aim of achieving a better understanding of the natural history of the disorder and its underlying patho-physiology and with a particular focus on the early period between birth and the onset of the late infancy regression event, the abnormalities underlying episodes of agitation, breath-holding, hyperventilation and non-epileptic vacant spells and the evolving pattern of disability through out life. Each study has added some new knowledge to its topic. Each has also contributed knowledge about the development and function of the brain in health and disease.

The combination of the investigation of a severe and little known disease and a service for the population who suffer from it led to the establishment of what is generally believed to be the largest personal cohort of this type, holding and sharing a supply of clinical data that in itself is a valuable resource and that has already contributed to many investigations beyond those first planned. With the discovery of the *MECP2* mutations the British Survey data became highly relevant to the task of matching the types and locations of mutations with the clinical problems, which result. Already this research is being found relevant not only to Rett but also to such neurological conditions as autism, Downs, fragile X, 'non-syndromic MR, Angelman syndromes and others (Longo et al 2004, Orrico et al 2000, Shibayama et al 2004, Pescucci et al 2003).

The very large library of video recordings and donated early film of babies with Rett with family agreement has contributed to instruction about the disorder, has formed the basis for the studies in section 4 and is continuing to do so.

That so many people with Rett have been examined on so many occasions and that health questionnaires have been completed repeatedly and meticulously by so many families bears witness to the exceptional collaboration which has been possible with the Rett Associations and the individual families who have repeatedly demonstrated their serious commitment to research, travelling long distances to be seen and to contribute their valuable data. Donated videos have provided a unique resource. Tissues donated on the death of a person represent a costly sacrifice. Without such selfless giving none of this research could have taken place.

The studies have led to progress in several areas. The earlier widespread perception that the newborn child was normal has been replaced by realisation that signs may be detected at birth, bringing the hope that earlier diagnosis may lead to more effective support for child and family. The episodic behaviours have been traced to central autonomic dysregulation, which may be amenable to treatment at least in part. The natural history of the condition has been traced retrospectively and prospectively and demonstrated the wide range of severity within the condition. The different outcomes have been charted. All this has helped to lay a foundation for research into specific genetic and pharmacological intervention and the development of more effective physical and educational therapies. Knowing the problems directs research and understanding the natural course of the disease allows proper evaluation of any treatment adopted.

The policy of including non-classic Rett cases in the survey has aided the search for other conditions which impact on related neural mechanisms as well as the broadening understanding within the medical profession of how varied the presentation of the Rett disorder may be.

Much remains to be investigated before we can prevent and treat this condition but as the control and the actions of *MECP2* and its protein MeCP2 begin to be

understood the tasks become more clearly defined. With growing understanding have come suggestions for new strategies including attempts to replace *MECP2*, to switch female cell use to the normal X in the female cell and replacement of factors, which are found to be reduced. Perhaps as problematic is the prospect of altering the levels of substances which are being produced in excess due to the lack of MeCP2 restraint. It is clear that the problems in the brain begin early and yet much of it develops and functions remarkably normally, nothing appears to be destroyed, at least in the early years, providing hope that effective intervention may indeed be found.

If intervention is to be fully successful much earlier diagnosis will be necessary. Prenatal diagnosis although already possible (Mari et al 2005) is not universally feasible because occurrence can seldom be predicted. However the early signs detected in the studies of section 4 indicate that careful attention to the family accounts of early development and close observation of the infant can prompt mutation testing before the regression event takes hold. The characterisation of the movement disorder in infancy and the fact that as it emerges it can be detected by gait analysis techniques and by nurses not familiar with the condition suggests that routine automated video screening may in future be developed, adapting techniques already used in computer entertainment. Such routine and automatic screening for babies might alert the physician to the need for a more detailed assessment in a young child with an excess of stereotyped movement.

My hypothesis has been that close observation of the behaviour of the individual and of the changes occurring over time, through clinical and physiological studies, would provide important clues to the pathological processes underlying the Rett syndrome and would contribute to finding its origins and directing its management. This has been demonstrated to be the case. In my view a sound understanding of the nature of the disorder and its normal clinical course, based on observation, will remain essential in guiding

research and in the evaluation of intervention. It is the practical problems of the individual, which can focus research on the areas relevant to care. Further investigation is necessary of many more aspects of Rett disorder, the osteopenia (Budden & Gunness 2003, Leonard et al 1999a & b), the sleep disturbance (Segawa & Nomura1992), the growth failure (Holm 1986), the feeding difficulties (Morton et al 1997), the almost universal constipation and the scoliosis (Loder et al 1989, Kerr & Prescott 2005) to list just a few. These are problems, which are already under investigation and already have become better understood but still remain to be solved. In achieving a complete understanding of them not only will people with Rett syndrome be helped to a better quality of life but also the new insights so gained will lead to benefits in other areas of brain disorder and neuroscience.

Section 11

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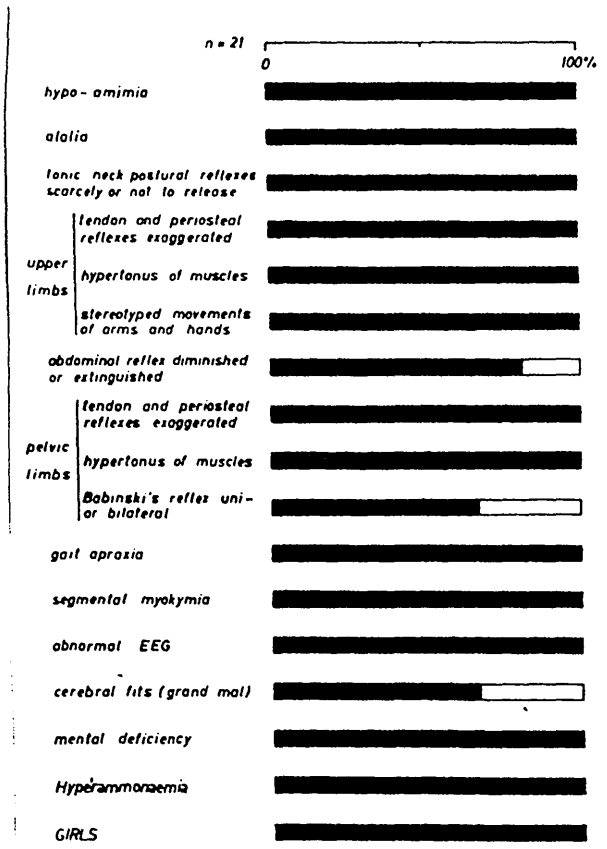
APPENDIX A: ILLUSTRATIVE MATERIAL, FIGURES AND TABLES

Section 1: Literature and Background

1.2.1 Clinical features described by Andreas Rett (Rett 1977, by kind permission of N Holland publishing company)



1.3.1 Diagnostic criteria proposed by Hagberg (Hagberg et al 1985, by kind permission of Brain & Development)

1. Female sex
2. A normal pre- and perinatal period; essentially normal psychomotor development through the first 6, often 12–18 mos of life
3. Normal head circumference at birth
   Deceleration of head growth (and therefore by interference, brain growth) between 6 mos–4 yrs of age
4. Early behavioral, social and psychomotor regression (loss of achieved abilities); development of communication dysfunction and signs of dementia
5. Loss of acquired purposeful hand skill through ages 1–4
6. Hand wringing-clapping-"washing hand" stereotypies appearing between ages 1–4
7. Appearance of gait apraxia and truncal apraxia/ataxia through ages 1–4
8. Diagnosis tentative until 3–5 yrs of age

1.3.2 Criteria for exclusion proposed by Hagberg (Hagberg et al 1985, by kind permission of Brain & Development)

1. Visceromegaly, other signs of organ storage
2. Retinopathy or optic atrophy before age 6
3. Congenital microcephaly
4. Perinatally acquired brain impairment

1.3.3 Scheme of main characteristics proposed by Hagberg (Hagberg et al 1985, by kind permission of Brain & Development)

A. Early history
   Pre-, peri- and early postnatal period uneventful
   Birthweight, length and head circumference normal

B. Onset of developmental deviations
   At 6 mos ~ 1–2 yrs of age
   Disappearance of achieved abilities
      hand skill, use of hands,
      communication,
      inner language,
      emotional contact

C. Stereotypies from onset stage
   Peculiar hand movements
      wringing,
      clapping,
      "hand-washing"
   Teeth grinding
   Body rocking – stooping gait
   Episodic "press" hyperventilation

D. Active stage of rapid deterioration
   At 1–3 yrs of age
   Period with rapid social regression
   Successively developed severe dementia
   Usually a stage of pronounced autistic behavior
   Jerky truncal ataxia/apraxia
   Epilepsy in ~ 75–80%

E. Late stage of motor disability
   Adolescents in wheel chairs or bedridden, ~ 75%
   Severe scoliosis, ~ 100%
   Hypotrophic small feet – growth retardation
   Normal puberty development otherwise
   Bilateral pyramidal tract signs

1.3.4 Criteria for classic Rett syndrome agreed in Gothenberg in 1987 (Kerr, Witt Engerstrom and Hagberg)

1. No serious complications during pregnancy, birth or the neonatal period and conforming to accepted standards during at last 4 months.
2. OFC within or close to the normal range and increasing at the normal rate for at least the first 4 months but suboptimal growth at some stage thereafter
3. Subtle evidence of slowing in psychomotor development in the first year with failure to acquire mature hand use beyond the 12 month level and speech beyond single utterances
4. Unexplained loss of hand use and skills over weeks or months, associated with social withdrawal and deterioration in non-verbal communication.
5. Characteristic repetitive hand movements consisting of hand wringing/ squeezing, clapping/ tapping, washing/ rubbing,
6. Following regression:-
    a) lack of postural control
    b) minimal and incoordinate voluntary hand use
    c) no useful speech although improved non-verbal communication
    d) mental handicap which is severe or profound and essentially static
    e) Sudden spells of agitated behaviour which may include panic, laughter or altered respiration
7. Absence of any other known disorder and of dysmorphic features

1.3.5 Criteria for classic Rett syndrome 1988 (Trevarthen et al & Rett Syndrome diagnostic criteria work group, by kind permission of Annals of Neurology)

Necessary Criteria[a]
Apparently normal prenatal and perinatal period
Apparently normal psychomotor development through the first 6 months[b]
Normal head circumference at birth
Deceleration of head growth between ages 5 months and 4 years
Loss of acquired purposeful hand skills between ages 6 and 30 months, temporally associated with communication dysfunction and social withdrawal
Development of severely impaired expressive and receptive language, and presence of apparent severe psychomotor retardation
Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and "washing"/rubbing automatisms appearing after purposeful hand skills are lost
Appearance of gait apraxia and truncal apraxia/ataxia between ages 1 and 4 years
Diagnosis tentative until 2 to 5 years of age

Supportive Criteria
Breathing dysfunction
  Periodic apnea during wakefulness
  Intermittent hyperventilation
  Breath-holding spells
  Forced expulsion of air or saliva
EEG abnormalities
  Slow waking background and intermittent rhythmical slowing (3–5 Hz)
  Epileptiform discharges, with or without clinical seizures
Seizures
Spasticity, often with associated development of muscle wasting and dystonia
Peripheral vasomotor disturbances
Scoliosis
Growth retardation
Hypotrophic small feet

Exclusion Criteria[a]
Evidence of intrauterine growth retardation
Organomegaly or other signs of storage disease
Retinopathy or optic atrophy
Microcephaly at birth
Evidence of perinatally acquired brain damage
Existence of identifiable metabolic or other progressive neurological disorder
Acquired neurological disorders resulting from severe infections or head trauma

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[a]Modified from Hagberg et al [8].
[b]Development may appear to be normal for up to 18 months.

1.3.6 Criteria circulated in the British Paediatric Surveillance unit study 1990

a) No other disease, dysmorphism or major adverse factor before, during or after birth
b) Initial development within broadly accepted limits of normal until 9-12 month level
c) Loss of acquired speech and hand use at approximately 1-2 years and withdrawal, without evident systemic illness.
d) Thereafter apparent profound stable mental handicap with minimal or no purposeful use of the hands or language
e) Prominent hand stereotypy (clapping, squeezing or patting)
f) Stiff or clumsy gait/ posture
g) OFC growth in the normal range for at least 4 months after birth with later suboptimal growth

Other characteristics: intent gaze, involuntary movements (frequently jerky) involving the face, trunk and limbs, brish tendon reflexes with ankle clonus and increasing muscle tone, in creasing lower limb deformities and scoliosis, spontaneous awake hyperventilation/ apnoea cycles, bursts of slow waves on e.e.g., seizures.

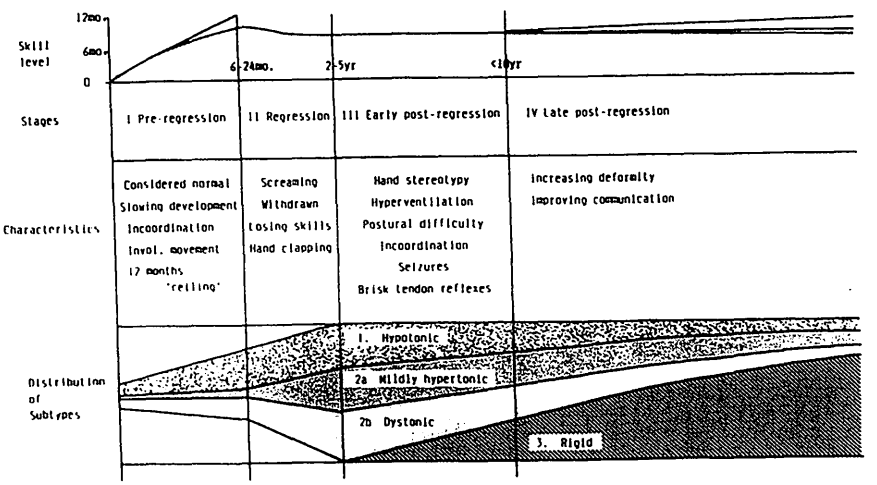
1.3.7 Modifications to the criteria in 2001 (Kerr et al 2001) by kind permission of Brain & Development

1. Apparently normal pre and perinatal period with normal head circumference at birth.
2. Suboptimal postnatal growth of head circumference [11,15–18].
3. Some early developmental progress, which may be slight, [11,16–18].
4. Skill regression in early childhood (hand use, speech, oral motor).
5. Poor intentional hand use and locomotor skills [11,18,19].
6. Stereotyped repetitive hand movements (with fixed position of the hands).
7. After regression, essentially stable severe intellectual disability [1,11,16,20].

1.3.8 Four clinical stages described by Hagberg 2002 (by kind permission of Mental Retardation and Developmental paediatrics)

Original Staging System	Later Additions
Stage I: early onset stagnation	
Onset age: 6 months to 1.5 years	Onset from 5 months of age
Developmental progress delayed	Early postural delay
Developmental pattern still not significantly abnormal	Dissociated development
	"Bottom-shufflers"
Duration: weeks to months	
Stage II: developmental regression	
Onset age: 1–3 or 4 years	Loss of acquired skills: fine finger, babble/words, active playing
Loss of acquired skills/communication	
Mental deficiency appears	Occasionally "in another world"
Duration: weeks to months, possibly 1 year	Eye contact preserved
	Breathing problems still modest
	Seizures in only 15%
Stage III: pseudostationary period	
Onset: after passing stage II	"Wake up" period
Some communicative restitution	Prominent hand apraxia/dyspraxia
Apparently preserved ambulant ability	
Unapparent, slow neuromotor regression	
Duration: years to decades	
Stage IV: late motor deterioration	*Subgrouping introduced*
Onset: when stage III ambulation ceases	Stage IV A: previous walkers, now non-ambulant
Complete wheelchair dependency	
Severe disability: wasting and distal distortion	Stage IV B: never ambulant
Duration: decades	

1.3.9 The changing trend in predominant muscle tone abnormality (Kerr 1995) by kind permission of Neuropediatrics.



(Georg Thieme Verlag KG)

1.3.10 Definition of 'formes frustes' (Hagberg and Witt Engerstrom 1986) by kind permission of American Journal of Medical Genetics.

1. Female sex; and at least 13 years old

2. Normal pre-, peri-, neonatal period.
   Development apparently normal in 1st year of life

3. Period of distict developmental decline
   - Loss of hand skill - playing
   - Loss of learned words-sentences

4. Signs in teenage years of:
   - Mental retardation - moderate or sevère
   - Apraxia (partial)
   - Dysphasia
   - Stereotypies (atypical)
   - Additional stage IV signs

5. Extensive lab. investig. unrevealing

1.3.11 Items recommended for inclusion in describing new cases relating to *MECP2* mutations: International Guideline. (Kerr et al. 2001), by kind permission of Brain & Development)

Data which allows comparison with the Rett phenotypes (classic or atypical/variant) This system scores features commonly associated with *MECP2* mutations in RS. Two points are given if the abnormality is severe, one if perceptible but not extreme and none if there is no abnormality. Age at assessment must be recorded.

Scoring for different clinical features	
A	Head circumference during the first year
2	Already below the third percentile at birth
1	Normal at birth but decelerating
0	Normal at birth with no deceleration
B	Early developmental progress (birth to 12 months)
2	No or virtually no progress
1	Suboptimal progress
0	Normal progress
C	Present head circumference - (percentile/standard deviations SD)
2	Below 3rd percentile
1	3 to 10th percentile
0	Above 10th percentile
D	Weight (kg)
2	Below 3rd percentile
1	3 to 10th percentile
0	Above 10th percentile
E	Height (cm)
2	Below 3rd percentile
1	3 to 10th percentile
0	Above 10th percentile
F	Muscle tone (also describe)
2	Severe hypotonia, dystonia or hypertonia
1	Tone mildly abnormal
0	Normal
G	Spine posture
2	Severe scoliosis
1	Mild scoliosis
0	No deviation
H	Joint contractures
2	Severe contractures
1	Minor contractures
0	None
I	Gross motor function
2	Cannot walk with support
1	Walking impaired
0	Walks normally
J	Hand stereotypy (patting, squeezing, wringing, mouthing)
2	Dominating or constant
1	Mild or intermittent
0	None
K	Other involuntary movements (eg. tremor, dystonia, chorea, athetosis)
2	Dominating or constant
1	Mild or intermittent
0	None
L	Voluntary hand use (eg. self feeding)
2	None
1	Reduced or poor
0	Hand use normal
M	Oro-motor difficulty
2	Severe (eg. feeding aversion; gagging, choking, tube/ button fed)
1	Slight (eg. delayed chewing, swallowing, on supplements)
0	None
N	Intellectual disability (= learning disability = retardation)
2	Apparent profound (infant level)
1	Any except profound
0	No impairment
O	Speech
2	Currently uses no real words with meaning
1	Currently uses some real words with meaning
0	Normal speech
P	Epilepsy
2	Uncontrolled or poorly controlled
1	Previous epileptic seizures or well-controlled with medication
0	Never
Q	Disturbed awake breathing rhythm (eg. hyperventilation, breath holding, panting)
2	Severe, with vacant spells & colour changes
1	Mild, without vacant spells & colour changes
0	Normal breathing rhythm
R	Peripheral circulation of extremities
2	Cold or discoloured with atrophic changes
1	Cold or discoloured without atrophic changes
0	Normal colour and temperature of extremities
S	Mood disturbance
2	Prominent or disruptive agitation/ crying spells
1	Abnormally prone to agitation
0	Normal
T	Sleep disturbance
2	Prominent/disruptive day sleeping or night waking
1	Present, not prominent
0	Normal sleep pattern

2.2.1 BIS Scoring system for Health, Severity and Feeding difficulty (Kerr et al 2003 by kind permission of the Journal of Child Neurology)

Score	*0*	*1*	*2*
Severity			
Feeding difficulty	0–2	3–8	9+
Tone group	Near normal	Dystonic	Hypo- or hypertonic
Locomotor skill	Solo now	Solo ever	Never solo
Scoliosis	None	Slight	Moderate/severe/operated
Epilepsy	Never	Ever	Currently
Health score			
Weight			
Child/adult	> 10th percentile/> 35 kg	3rd–10th percentile/20–34 kg	< 3rd percentile/< 20 kg
Seizure episodes	0	Infrequent	Frequent
Chest episodes	0	1	More than one
Other episodes	0	1	More than one
Wellness	Well	Fair	Poor
Feeding score			
	Shape or posture: no problem	Some problem	Severe problem
	Mouth closure: no problem	Some problem	Severe problem
	Chews well	Chews poorly	Does not chew
	Swallows well	Some problem	Severe problem
	No obstructing movements	Some problem	Severe problem
	No vomiting/regurgitation	Some problem	Severe problem
	Secretions no problem	Some problem	Severe problem
	Appetite no problem	Some problem	Severe problem
	Drinking no problem	Some problem	Severe problem
	Feeds self	Constant supervision	Totally dependent

The scores are calculated using data from the parent/carer and clinician. Feeding score is expressed in points out of 20. Severity and health scores are expressed as percentages. "Chest episodes" and "other episodes" refer to the number of significant episodes of illness in the past 12 months. "Wellness" indicates the opinion of the parent or chief carer on the individual's state of health over the last 12 months.

In some studies the severity and health scores are expressed as %, For example. 2 / 10 becomes 20%

3.1.1 Data on 19 subjects with Rett Syndrome (Kerr & Stephenson 1985, with kind permission of the British Medical Journal)

	Type I				Type II: Not wasted						Type II: Wasted			Type III					
Case No:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age examined (years)	3	3	4	4	6	6	8	9	10	10	8	13	15	8	9	9	12	12	13
Age at regression (months)	12	12	18	12	15	13	18	18	17	18	18	22	15	18	18	11	10	18	24
Occipitofrontal Circumference centile:																			
Birth-6 months	50	50-98	2-50	50-98	<50	2%	90%			50-98					98%	50-98			2%
1-2 years	2-50	50		50	50		50	50	10-50	50%	98%	>50	2-10	<2%		50	2-50	2-10	
At examination	<2	10-50	2%	2%	<2	<2%	2-50	<2%	2-10	<2%	50%	2%	<2%	<2%	2%	2-50	<2%	<2%	<2%
Developmental gain loss:																			
Responsive smile (weeks)*	6/	4/	7/	6/	8/	6/	7/	8/	7/	7/	6/	5/	6/	6/	6/	6/	6/	6/	6/
Able to sit alone (months)*	8-12	7-11	6-	15	6/	7.	7.	6/	10/	6/	6/	7/	7/	13/	9/18	7/	9/36	6/	8/
Able to walk alone (months)*			20/48		18/	14/	12/	18/	18/	17/	30/	16/	36/	15/30	13/18				
Able to pick up objects (months)*	4/	5/	9/18	9/	7/	9/	8/23	11/	10/	10/	9/	4/	5/	7/	9/18	8/10	12/36	6/	6/24
Able to drink unaided from mug (months)*	9-12	10-11	12-18		12/15	10/	9/18		10/17	10/18		12/22	12/15					18/24	18/24
Able to say da, ma, ba (months)*	9-12	9-12	10-12	8-12	8/15	10/13	9/22	12/18	10/17	12/19	10/18	10/22	12/15	9/18	8/18	6/9	12/24	9/18	
Able to speak own words (months)*	10-12	10/12		12/24	12/20	12/24	12/22	12/18	12/17	12/19	10/18	15/22	12/15	12/18	12/18	8/9	12/15	12/18	
Maximum No of words	1	12	0	1	10	4	10	1	7	5	1	6	2	6	1	5	2	8	0
Neurological findings:																			
Scoliosis	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Wasting	Yes	Yes	No	No	Slight	Slight	Slight	No	No	Slight	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Muscle tone	↓	↓	†	↓	Slight † †	†	†	†	Slight†	Slight †	†	†	†	†	†	†	†	†	†
Reflexes:																			
Brachioradialis	+	+	+	+	++	+	+	+	+	+	+	+	+	+	++	+	+	++	++
Patellar	+	+	++	+	++	+	++	+	++	+	+	+	+	+	++	++	+	++	++
Tendocalcaneus	+	+	++	+	++	+	++	+	++	++	+	+	+	+	++	++	+	++	++
Plantars	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	↓ ↓	††	↓ ↓	↓ ↓	↓ ↓
Adductor spasm	No	No	No	No	No	No	No	No	No	No	Slight	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Dislocated hips	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No
Tight tendo Achillis	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Generalised fits	No	No	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	No	Yes	No	No	No
Atypical fits	Yes	?	No	?	?	No	?	?	No	Yes	?	?	No	No	No	No	No	No	No
Panic attacks	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hyperventilation	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Involuntary movement:																			
Jerking	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Writhing	No	No	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

*Age when skill acquired/age when skill lost (if lost completely).
†Equivocal.

3.1.2 Occipito-frontal circumferences in 19 cases of Rett syndrome (Kerr & Stephenson 1985, with kind permission of the British Medical Journal)

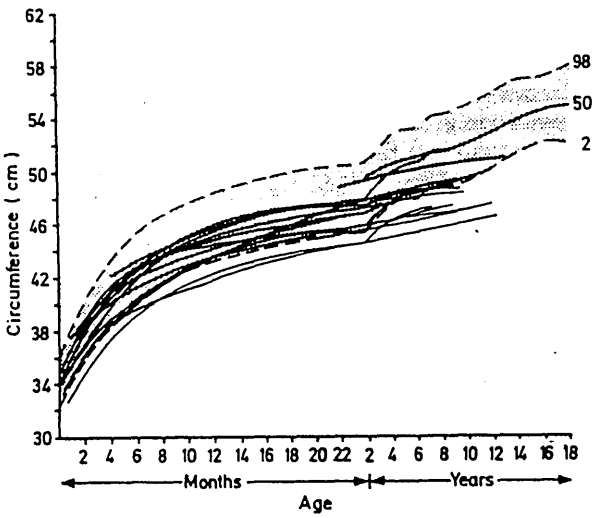
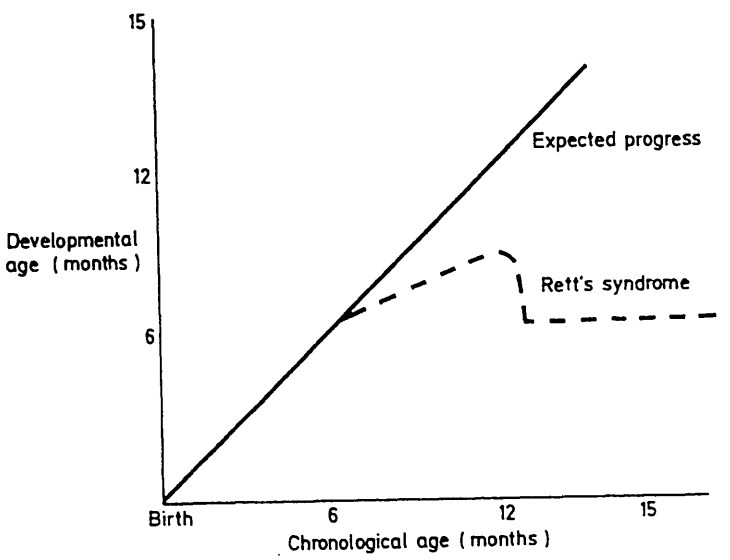


FIG 4—Occipitofrontal circumference in 19 cases of Rett's syndrome.

3.1.3. Diagrammatic representation of developmental progress in Rett Syndrome (Kerr & Stephenson 1985, with kind permission of the British Medical Journal)



4.1.1 Observations from four pre-regression films. Ages are those at which behaviour was first evident

	Hypotonia	*Excess of waving or patting*	*General incoordination*	*Abnormal alternating hand movements*	*Best hand use*	*Hands together or separate*		*Age at onset of regression*	*Age now*
						At regression	*Now*		
1	Yes	2 mos suspicious 7 mos certain	7 mos	22 mos	Grasped toy	Together	Together	24 mos	7 yrs
2	Yes	11 mos	11 mos	12 mos	Grasped toy	Together	Separate	18 mos	12 yrs
3	No	9 mos	15 mos	15 mos	Grasped and shook object	Together	Separate	22 mos	14 yrs
4	No	6 mos	15 mos	No	Picked up sweet, fingers open	Together	Together	15 mos	6 yrs

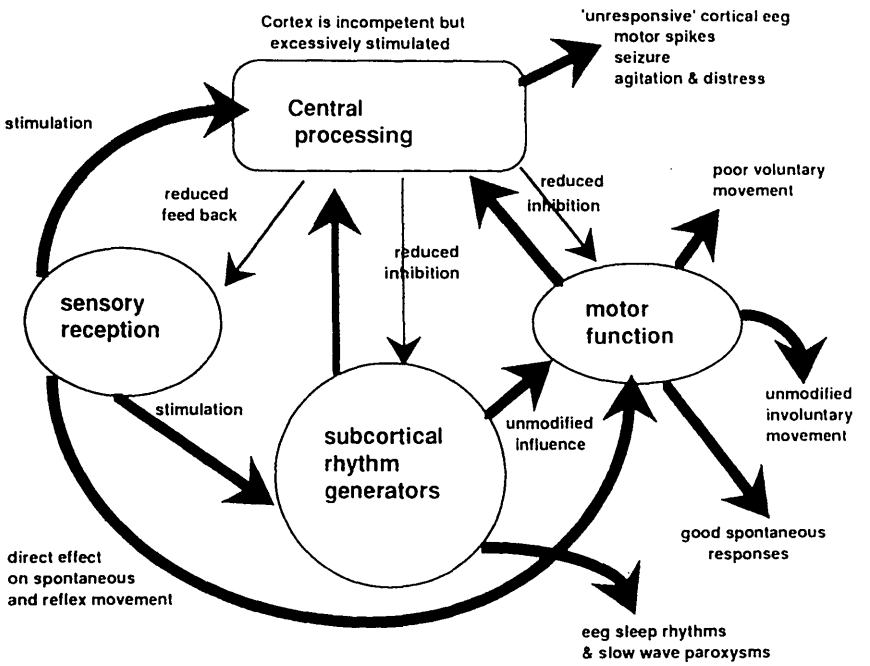
4.1.2 Pre-regression histories obtained from families in 20 girls

Patients nos	*Hypotonia*	*Jerky incoordination*	*Cleverest hand use*	*Walked alone*	*Number of words*	*2-word phrase*	*Age at onset of regression*	*Age now*
1	No	Yes	Picked up toy	No	None	No	9 mos	11 yrs
2	No	No	Flicked pages of book	No	12	No	11 mos	5 yrs
3	Yes	No	Fed with cup	No	4	No	12 mos	6 yrs
4	No	No	Held mug	No	4	No	12 mos	6 yrs
5	No	No	Turned book pages	36 mos	3	No	15 mos	17 yrs
6	Yes	No	Clapped on request	No	2	No	15 mos	14 yrs
7	No	No	Picked up feathers	48 mos	10	One	15 mos	6 yrs
8	No	No	Picked up toy	17 mos	7	No	18 mos	13 yrs
9	Yes	No	Picked up toy	No	2	No	18 mos	16 yrs
10	No	No	Turned book page	No	None	No	18 mos	12 yrs
11	Yes	Yes	Fed with spoon	No	None	No	18 mos	16 yrs
12	Yes	Yes	Fed self with spoon	30 mos	20	One	18 mos	11 yrs
13	Yes	No	Fed with biscuit	No	3	No	18 mos	27 yrs
14	No	No	Drank from can Switched on TV	13 mos	3	No	18 mos	12 yrs
15	No	No	Turned book page	24 mos	3	No	20 mos	12 yrs
16	No	No	Picked up cup	15 mos	7	No	20 mos	10 yrs
17	No	No	Opened cupboard	24 mos	6	No	21 mos	15 yrs
18	No	No	Picked up fluff Turned pages	12 mos	7	No	23 mos	11 yrs
19	No	No	Turned book pages	No	4	No	24 mos	15 yrs
20	No	No	Fed with biscuit	20 mos	10	No	30 mos	7 yrs

4.2.1 Suggested factors contributing to the Rett regression event (Kerr 1995, with kind permission of Neuropediatrics (Georg Thieme Verlag KG)

- The child has reached her developmental ceiling.
- Programmed cell death prunes early infancy neural networks.
- Myelination reveals the extent of the cortical incompetence.
- Cellular immune processes may attack abnormal neurones.
- The incompetent cortex fails to control mature subcortical rhythms.
- Subcortical movement rhythms interfere with the use of skills.
- Seizures and non-seizure vacant spells interfere with contact.
- Non-seizure EEG disturbance may interrupt neural pathways.
- Dyspraxic breathing leads to hypocarbia, hypoxia, abdominal distension and feeding difficulty.
- Agitation exacerbates repetitive movements and distress.
- Parental frustration, anxiety or rejection is felt by the child.

4.2.2 A model to illustrate the hypothetical effect of the central receptive processing defect upon patterns of behaviour in Rett disorder (Kerr 1995, with kind permission of Neuropediatrics (Georg Thieme Verlag KG)



4.3.1 Health visitors' reviews: numbers of video samples receiving button presses throughout the first year of life. (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

Group	Number of times samples viewed	Number receiving presses	Number not receiving presses	Percentage receiving presses	Percentage not receiving presses
Rett syndrome	608	278	330	45.7	54.3
Control	478	52	426	10.9	89.1

4.3.2 Health visitors' reviews: Percentage of button presses for video of Rett and normal infants in the three age bands in the first year. (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

	Age band (months)								
	0–4			5–8			9–12		
Group	Number of infants	Percentage*	Total number	Number of infants	Percentage*	Total number	Number of infants	Percentage*	Total number
Rett	9	38	262	11	35	165	11	63	181
Control	8	15	192	9	13	141	8	3	145

*The percentage of all button presses made for the infant group at the specified age band.

4.3.3 Midwives reviews: Numbers of samples receiving button presses in the first month of life (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

Group	Number of times samples viewed	Number receiving presses	Number not receiving presses	Percentage receiving presses	Percentage not receiving presses
Rett	170	83	87	48.8	51.2
Control	80	15	65	18.8	81.2

4.3.4 Categories of comment explaining button presses. (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

Category	Examples
Appearance Refers to visual impact, without need for movement; would be able to tell from a still photograph	Poor colour, head shape, snape of eyes, odd features, facial expression, ear shape or position, tongue visible (but not thrusting)
Posture Refers to way body, or part of body (e.g. hand), is held; would be able to tell from a still photograph	Floppy, rigid, way is sitting, shape of fingers – clench, cross, spread, hand position, foot position
Movement Refers to moving parts, both qualitative aspects and skill of performance Includes purposeful and spontaneous movements and reflexes	Active/inactive, jerky, jittery, wobbly, lack of movement (e.g. no foot movement), hands, tongue thrusting
Contact Refers to interest and responsiveness to people and environment (e.g. toys or sounds)	Not reaching, not engaging, not looking, not connecting, staring

4.3.5 Proportion of health visitors' comments according to the categories given in 4.3.4 (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

	Age group (months)					
	0–4		5–8		9–12	
Category	Number	Percentage*	Number	Percentage*	Number	Percentage*
Rett Group						
Appearance	48	33	35	37	53	27
Posture	35	24	17	18	40	20
Movement	22	15	19	20	52	26
Contact	41	28	23	24	53	27
Total number	146	–	94	–	198	–
Control group[†]						
Appearance	17	49	3	17	1	–
Posture	12	34	7	39	2	–
Movement	1	3	7	39	1	–
Contact	5	14	1	5	1	–
Total number	35	–	18	–	5	–

*Percentages rounded to the nearest whole number

[†]Although the number of comments ($n = 58$) on infants with normal development is small, these are presented in percentage format to allow comparison between the two groups of infants. The number of comments on infants with normal development at 9–12 months was too small for meaningful inclusion in the percentages

4.3.6 The proportion of midwives comments according to the categories given in 4.3.4. (Burford & Kerr 1995, by kind permission of the Journal of Intellectual Disability research)

	Group			
	Rett group		Control group[†]	
Category	Number	Percentage*	Number	Percentage*
Appearance	28	25	4	25
Posture	37	34	1	6
Movement	30	27	6	37
Contact	15	14	5	31
Total number	110	–	16	–

*Percentages rounded to the nearest whole number

[†]Although the numbers in the control group were very small, the percentage format is used to permit comparison.

4.4.1 The absence or presence of various signs within the first 6 months of life in 22 girls with Rett (Einspieler et al 2005, by kind permission of Pediatric Research)

. The absence (O) or presence (●) of various abnormal signs within the first six months of life of 22 girls with Rett disorder.

		General Motor Performance				The Hand			The Face		
Case	Mutation	Abnormal General Move-ments	Postural Stiffness or Slumped Posture	Tremor	Body Stereo-typies	Abnormal Finger Move-ments	Hand Stereo-typies	Asymme-tric Eye Opening and Closing	Tongue Protrusion	Bizarre Smile	Bursts of Abnormal Facial Expres-sion
		100% (N = 16)	68% (N = 19)	28% (N = 18)	15% (N = 13)	52% (N = 21)	42% (N = 19)	56% (N = 18)	62% (N = 21)	32% (N = 19)	42% (N = 19)
11	not tested	*	O	*	*	O	O	*	O	O	O
12	T158M	*	O	O	O	O	O	O	O	O	O
6	not tested	*	*	*	*	O	*	*	●	*	*
7	not tested	●	*	*	*	*	*	*	*	O	*
8	R255X	●	*	*	*	O	*	*	O	*	*
2	806delG	*	●	O	O	O	O	O	O	*	●
5	R168X	●	●	O	*	O	O	O	O	O	O
10	Q2444X	*	O	O	O	●	O	O	O	●	O
13	P152R	●	O	●	*	O	O	O	●	O	O
21	R168X	●	●	O	*	O	O	O	●	O	O
4	trunc. del.	●	●	O	O	●	O	O	O	O	●
16	not tested	●	●	O	O	O	O	●	●	O	O
3	negative	●	●	O	*	●	O	●	●	O	O
20	subst.401	●	●	O	*	●	●	O	O	O	●
22	negative	●	●	●	O	O	O	●	●	O	O
17	T158M	●	O	O	O	●	●	●	●	●	O
9	not tested	●	O	O	O	●	●	●	●	●	●
15	not tested	*	●	O	●	●	●	●	●	O	●
19	negative	●	●	O	O	●	●	●	●	O	●
18	Q244X	●	●	●	O	●	●	●	●	●	O
1	not tested	●	●	●	O	●	●	●	●	●	●
14	R168X	●	●	●	●	●	●	●	●	●	●

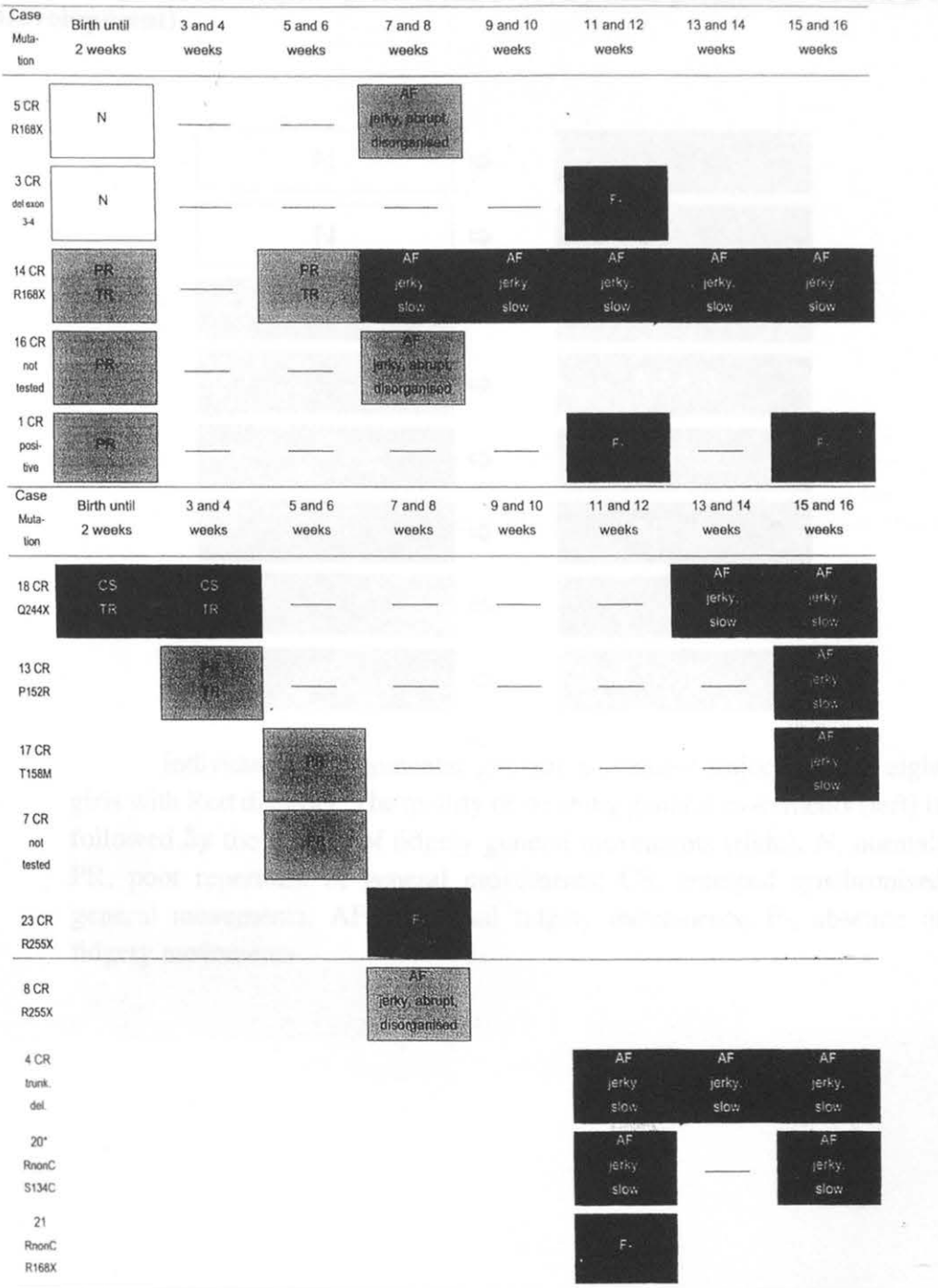
The number of infants (N) is given for whom a particular sign could be reliably assessed due to the situation video taped.
* indicates that the recording did not allow a proper assessment.
The cases are ranked according to an increasing number of abnormal signs.
trunc. del., truncating deletion 1116-1201.
subst. 401, substitution at 401 (not reported in the same format as the other cases but a pathological mutation).

4.4.2 Number of infants in 2-month epochs to show the first appearance of the various abnormal signs observed in 22 babies with Rett (Einspieler et al 2005, by kind permission of Pediatric Research)

	General Motor Performance				The Hand			The Face		
Age	Abnormal General Move-ments	Postural Stiffness or Slumped Posture	Tremor	Body Stereo-typies	Abnormal Finger Move-ments	Hand Stereo-typies	Asymme-tric Eye Opening and Closing	Tongue Protrusion	Bizarre Smile	Bursts of Abnormal Facial Expres-sion
Birth until 2 months	10	8	3	1	3	2	5	8	2	2
3 to 4 months	4	3	1	-	2	2	3	2	-	3
5 to 6 months	2	2	1	1	6	4	2	3	4	3

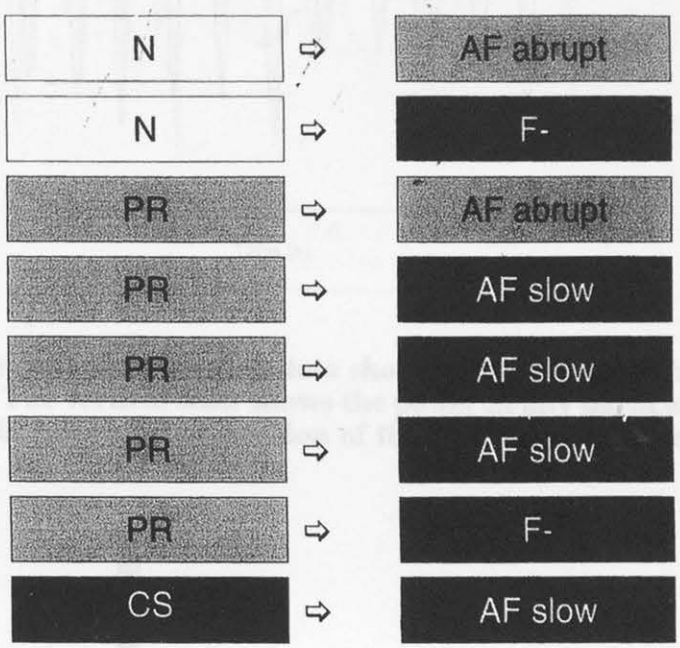
4.4.3 The quality of generalised movements in 14 girls with Rett during the first 4 months post term (Einspieler et al 2005, by kind permission of Brain & Development)

The quality of GMs of 14 girls with Rett disorder during their first 4 months postterm age (* born preterm, corrected age)



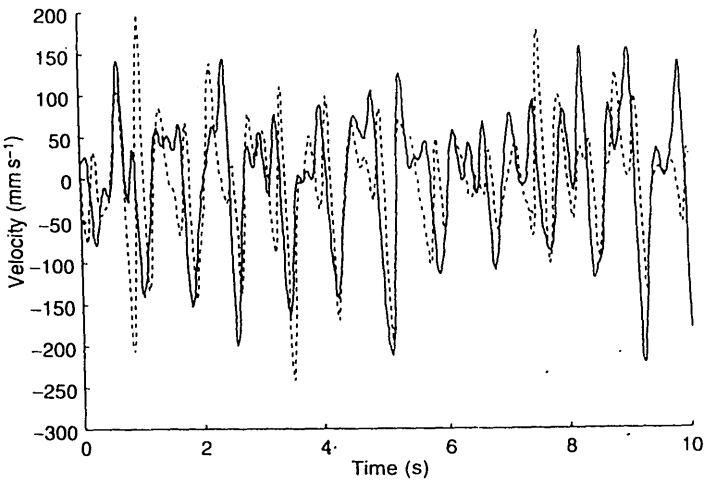
N, normal; PR, poor repertoire of GMs; TR, tremor; CS, cramped-synchronised GMs; AF, abnormal fidgety movements; F-, absence of FMs. ———, no recording; CR, classic Rett syndrome; RnonC, Rett syndrome not classic; trunc. del., truncating deletion 1116–1201.

4.4.4 Individual developmental trajectories in eight girls with Rett during the first 4 months of life. (Einspieler et al 2005, by kind permission of Brain & Development)

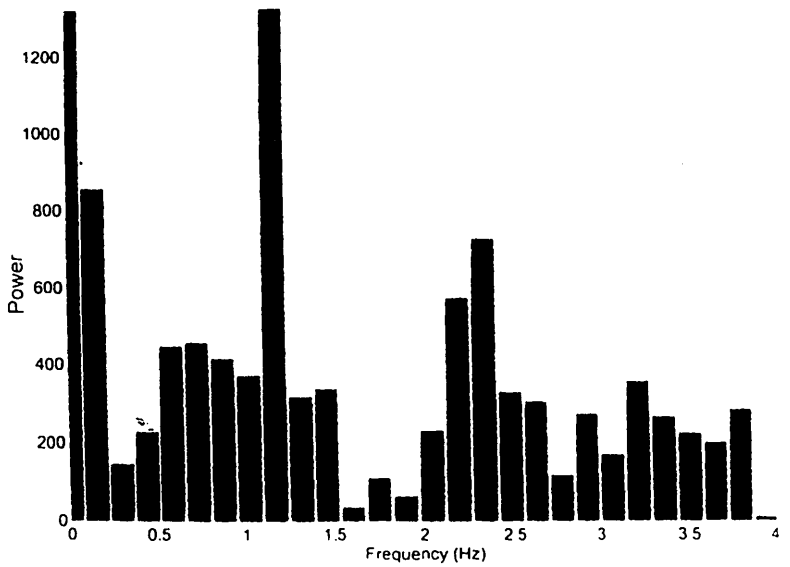


Individual developmental general movement trajectories of eight girls with Rett disorder. The quality of writhing general movements (left) is followed by the quality of fidgety general movements (right). N, normal; PR, poor repertoire of general movements; CS, cramped synchronised general movements; AF, abnormal fidgety movements; F-, absence of fidgety movements

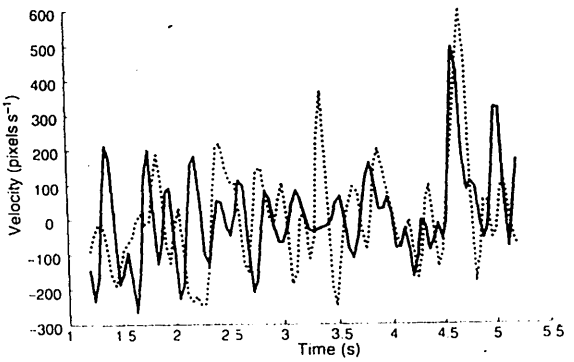
4.5.1 Stereotyped hand movements in a girl with Rett syndrome. Time curve, derived from three-dimensional motion analysis, of the markers on the right wrist (solid line) and left wrist (broken line). (Wright et al 2003, by kind permission of the Journal of Intellectual Disability Research)



4.5.2 Frequency analysis of motion data showing the dominant frequencies at 1.2 and 2.4 Hz. The vertical scale shows the power at any particular frequency. (Wright et al 2003, by kind permission of the Journal of Intellectual Disability Research)

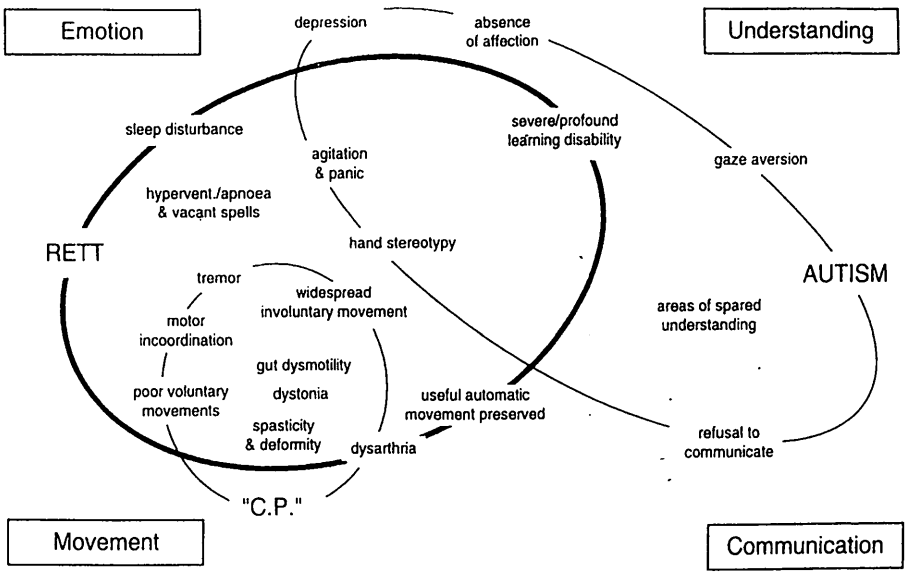


4.5.3 Two dimensional video taken from an informal video recording when the subject of 4.6.1. was 3 years old. The oscillations are well marked indicating that early video screening is informative in Rett syndrome. (Wright et al 2003, by kind permission of the Journal of Intellectual Disability Research)

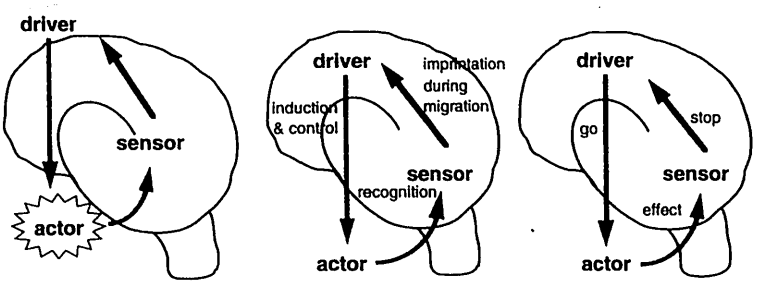


Two-dimensional (2D) video data taken from an informal video shot when the subject was 3 years of age. The oscillations are well marked, indicating that early video screening is informative in Rett syndrome.

4.6.1 How the Rett behaviours fit the 'map' of behaviours in developmental disorder . (Kerr 2000, also invited lecture RSM) by kind permission of MacKeith Press.



4.6.2 Speculation on how early subcortical influences on the developing cortical neurones may predict later functioning of the sensorimotor feedback (Kerr 2000, also invited lecture RSM) by kind permission of MacKeith Press.

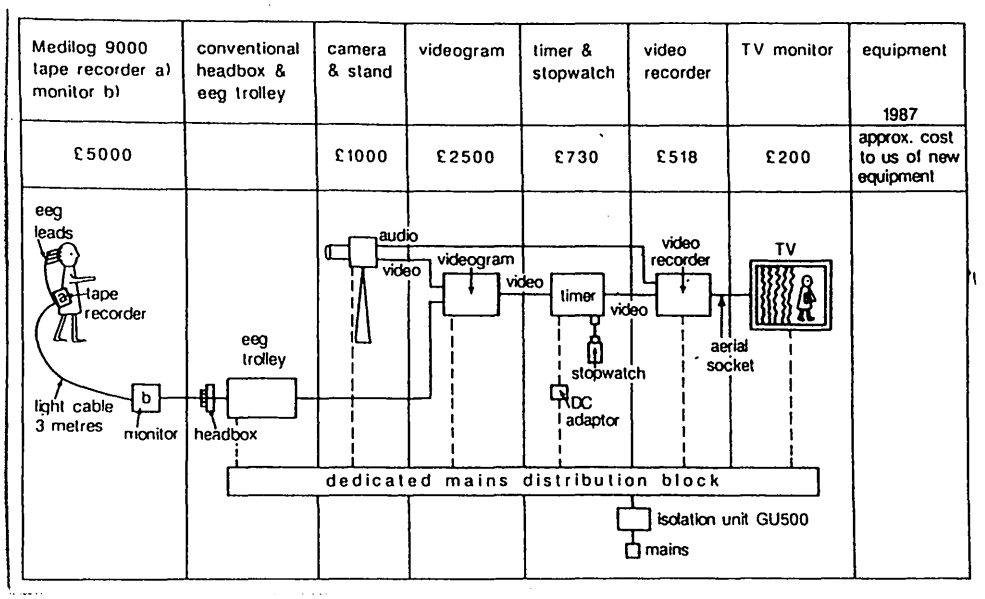


the essential feedback mechanism

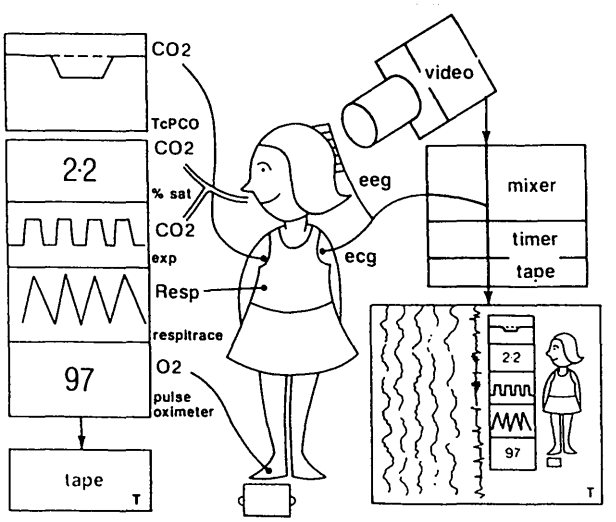
the developmental relationship

the mature working relationship

5.1. Quarrier's system for simultaneous ambulatory video-e.e.g. recording (Kerr et al 1988) by kind permission of Journal of Intellectual Deficiency Research.



5.2.1 Method for recording behaviour, respiration and e.e.g. (Kerr et al 1990) by kind permission of Brain & Development.



5.2.2 Clinical details for 18 people with Rett Syndrome in a study of respiration (Southall et al 1988) by kind permission of Archives of Disease in Childhood.

Case No	*Age (years)*	*Occipitofrontal head circumference (%)*	*Motor seizures*	*Scoliosis*	*Foot deformity*	*Gaseous abdominal distension*	*Past history of hyperventilation*	*Current treatment*
Group 1:								
1	6	3–10	Yes	Yes	Yes	No	Yes	Carbemazepine
2	12	3–10	Yes	Yes	Yes	Yes	Yes	Carbemazepine
3	11	<3	No	Yes	Yes	Yes	Yes	Salbutamol
4	10	<<3	Yes	Yes	Yes	Yes	Yes	Sodium valproate
5	7	10	No	No	No	Yes	Yes	None
6	16	<<<3	No	Yes	Yes	Yes	Yes	None
7	7	<3	Yes	Yes	No	Yes	Yes	Clonazepam, carbemazepine
8	12	<3	Yes	Yes	Yes	Yes	Yes	Carbemazepine
9*	6	10–25	Yes	No	No	No	Yes	Prednisolone
10*	6	3	Yes	Yes	Yes	Yes	Yes	Carbemazepine
Group 2:								
11	17	25	Yes	No	Yes	Yes	Yes	Carbemazepine
12	14	<3	No	Yes	Yes	Yes	Yes	None
13	16	3	Yes	No	Yes	Yes	Yes	Sodium valproate
14	13	<<3	Yes	Yes	Yes	Yes	Yes	Sodium valproate
Group 3:								
15*	6	25–50	Yes	Yes	Yes	No	No	Carbemazepine
16	7	<3	Yes	Yes	Yes	Yes	No	Sodium valproate, trimeprazine tartrate
17	14	<<3	No	Yes	No	Yes	No	None
18*	6	<3	Yes	Yes	Yes	No	No	Clonazepam

*Atypical features present.

group 1: hypotonic, group 2: dystonic, group 3:severely hypertonic

5.2.3 Selected physiological data for 18 people with Rett Syndrome in a study of respiration (Southall et al 1988) by kind permission of Archives of Disease in Childhood.

Measurement	*Case No*																		*Range in 18 controls*
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	
Duration of recording (hours)	14·3*	13·2*	12·9*	13·2*	13·8*	11·5*	14·7*	0·9	16·9*	17·1*	10·4*	0·6	0·5	0·4	14·7*	1·5	0·4	0·5	6·0 to 12·5
Lowest values when awake:																			
Transcutaneous carbon dioxide (mm Hg)	24	26	32	18	13	20	8	21	18	13	NR	42	36	51	44	46	38	37	NR
End tidal carbon dioxide (volume %)	2·2	2·2	4·2	2.1	1·4	2·0	1·6	2·4	1·8	2·0	3·8	3·8	4·2	4·4	4·5	4·4	4·8	4·0	4·6 to 5·3
Average values when asleep:																			
Transcutaneous carbon dioxide (mm Hg)	52	59	53	NR	37	32	38	NR	51	42	NR	NR	NR	NR	51	NR	NR	NR	NR
End tidal carbon dioxide (volume %)	5·4	7·2	4·6	5.8	4·2	4·0	4·8	NR	4·8	5·3	6·4	NR	NR	NR	6·2	NR	NR	NR	5·2 to 6·4
Longest apnoeic pause when awake	49	98	27	125	74	43	34	24	60	27	84	24	21	9	11	11	11	16	19*
Lowest oxygen saturation when awake (%) (below 50% oximeter inaccurate)	60	<50	92	<50	<50	66	70	92	<50	<50	80	98	95	98	94	97	98	98	96
Valsalva manoeuvres	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	None
Periodic apnoea* (asleep) (minutes/hour)	13·5	17·8	11·3	5.6	1·7	13·8	17·0	56·1	1·7	9·1	11·3	17·8	0	35·2	4·5	2·0	2·5	4·4	0 to 0·75
QTc (second)	0·44	0·40	NR	0.45	0·41	0·42	0·45	NR	0·43	0·43	NR	NR	NR	NR	NR	NR	NR	NR	NR

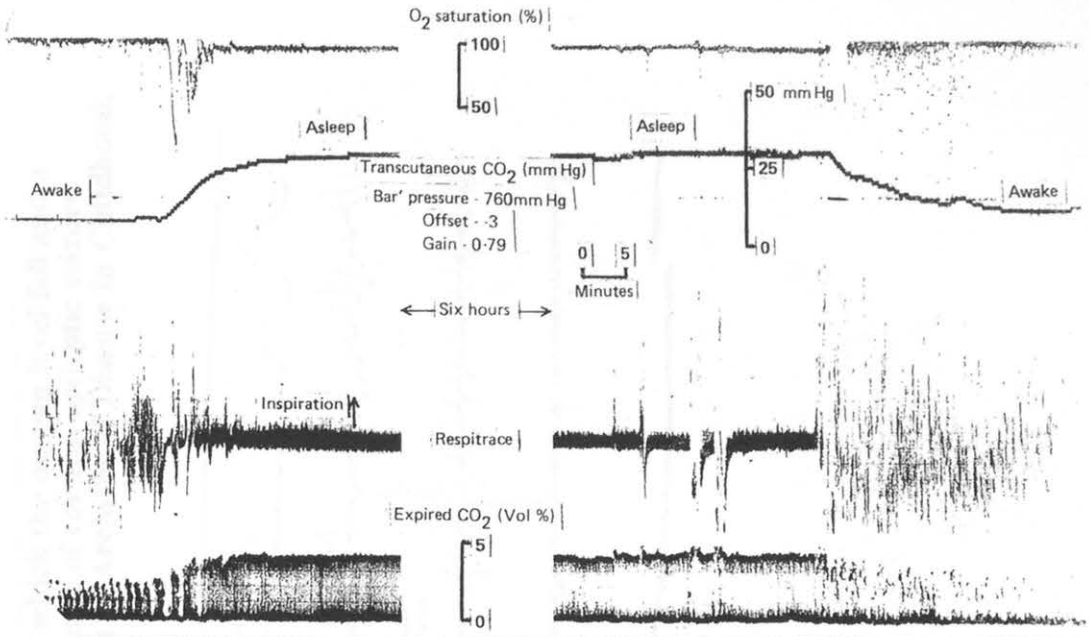
*Both day and overnight recordings; NR=not recorded.

5.2.4 Selected biochemical data on 10 people with Rett Syndrome in a study of respiration (Southall et al 1988) by kind permission of Archives of Disease in Childhood.

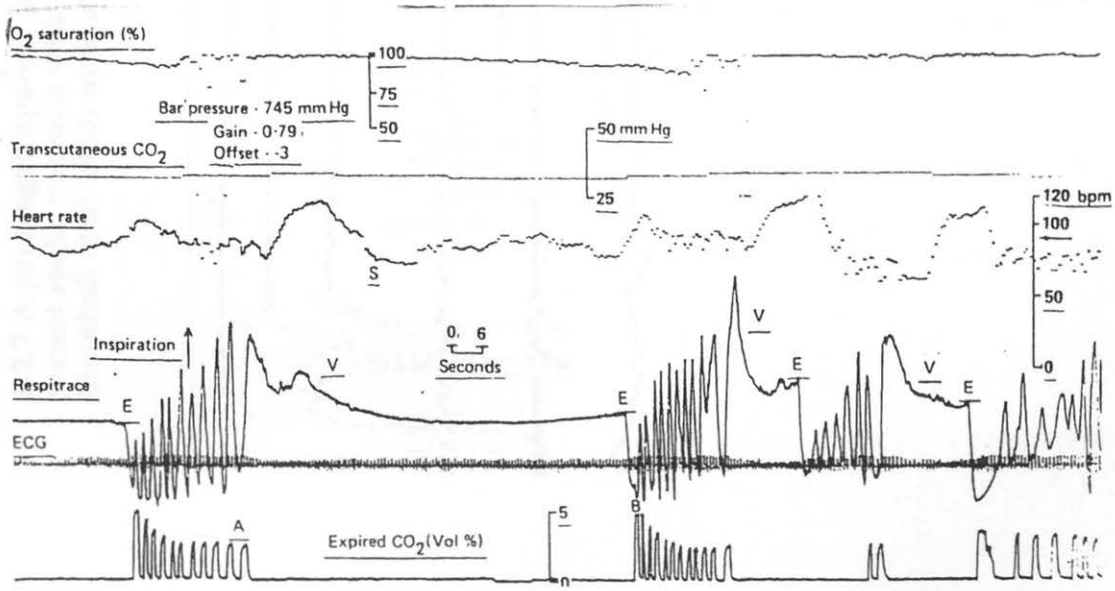
Measurement	*Case No*								*Normal range*
	1	*2*	*4*	*5*	*6*	*7*	*9*	*10*	
Plasma concentrations (mmol/l):									
Chloride	109	110	NS	110	109	110	105	NS	92–109
Ionised calcium	1·13	1·25	0·67	NM	1·24	1·26	1·24	1·19	1·19–1·31
Phosphate	1·6	1·6	1·7	1·4	1·5	1·6	1·9	1·8	0·7–1·4
Lactate	2·1	1·4	2·5	3·4	1·1	2·0	2·2	1·8	0·7–1·8
*Arterial:									
pH	7·48	7·51	7·60	7·59	7·47	7·49	7·55	NS	7·35–7·45
Bicarbonate (mmol/l)	17	22	15	13	18	20	21	NS	22–26
Carbon dioxide (mm Hg)	30	24	16	13	25	23	22	NS	35–45 mm Hg
Base excess	−1·0	−0·9	−1·5	−4·1	−2·8	−2·4	0·5	NS	−2·0–+2·0 mmol/l

*Samples taken during hyperventilation; NS=not sampled; plasma concentrations of potassium, sodium, and magnesium were all normal.

5.2.5 Interrupted printout of an overnight recording showing the transition between waking and sleeping. It can be seen that the CO2 level falls during hyperventilation. (Southall et al 1988) by kind permission of Archives of Disease in Childhood.

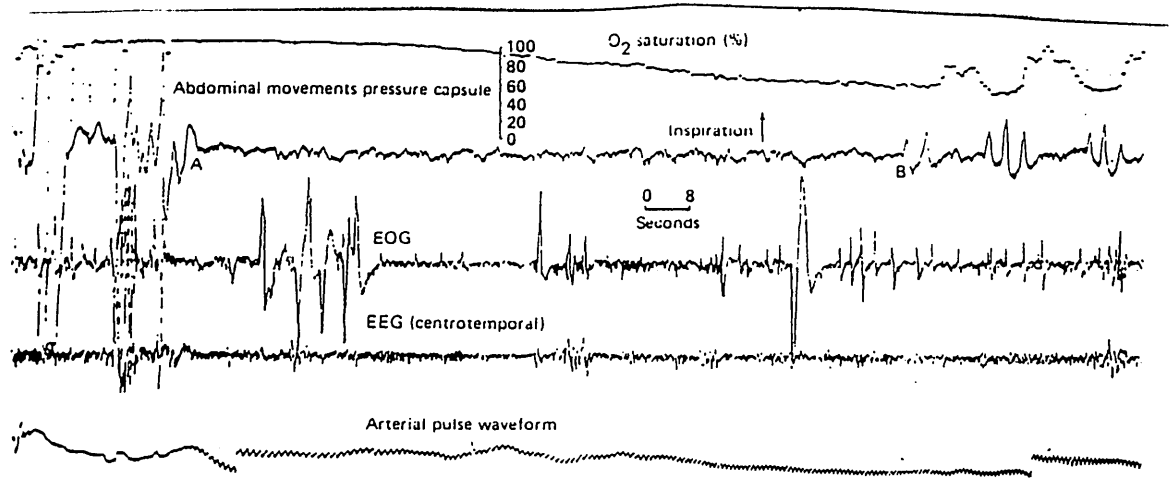


5.2.6 A section of an awake recording showing episodes of apnoea, each associated with a valsalva manoeuver. (Southall et al 1988) by kind permission of Archives of Disease in Childhood.

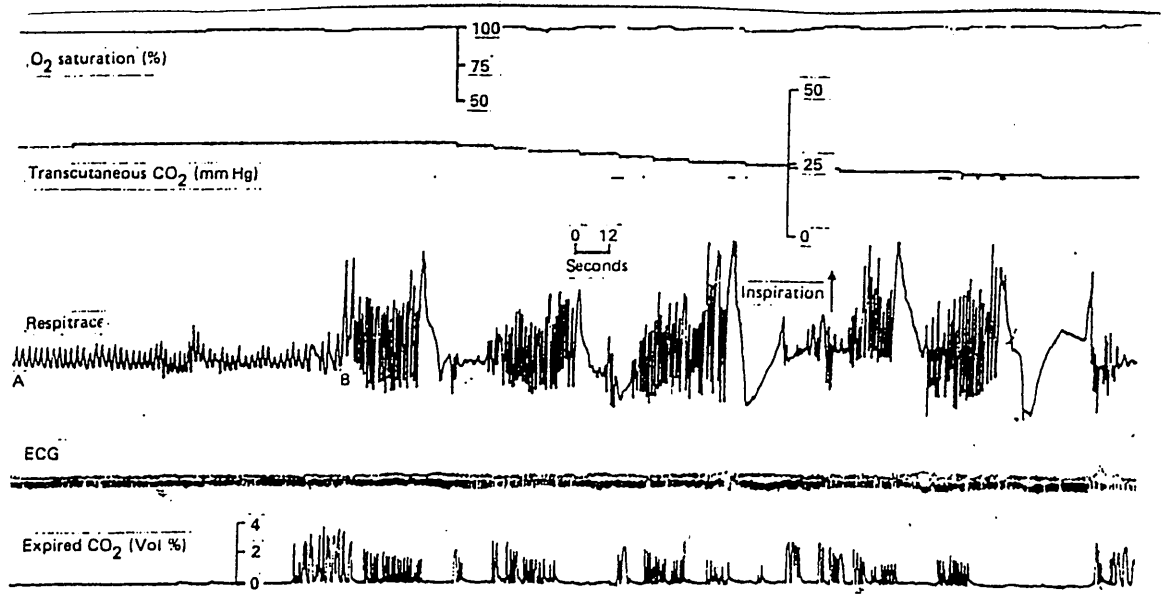


Section of recording when awake (case 2). Four episodes of apnoea each associated with Valsalva manoeuvre (V) are shown, the longest reading 77 seconds (from A to B) during which there is a small fall in oxygen saturation (to 90%). Preceding each pause the end tidal carbon dioxide is reduced by a period of hyperventilation to about 2·4 volume %. After the prolonged pause (AB) the end tidal carbon dioxide reaches 5·0 volume %. Throughout recording the transcutaneous carbon dioxide is about 32 mm Hg. Each apnoeic episode begins at end of inspiration. Lung volume is maintained (by Valsalva manoeuvres) until positions E where there is sudden expiration of gas and the immediate onset of hyperventilation. During periods of hyperventilation and the early part of the apnoeic pause (Valsalva manoeuvre) there is a comparative bradycardia. Increase in heart rate begins within six seconds of onset of the pause. About 26 seconds (position S) into the prolonged apnoeic episode (AB) the heart rate slows again.

5.2.7 A prolonged apnoeic pause during which the oxygen level fell and a vacant spells was seen without any evidence of cortical epileptic seizure. (Southall et al 1988) by kind permission of Archives of Disease in Childhood.



5.2.8 A section of day time recording in which a period of normal breathing is followed by intermittent hyperventilation. (Southall et al 1988) by kind permission of Archives of Disease in Childhood.



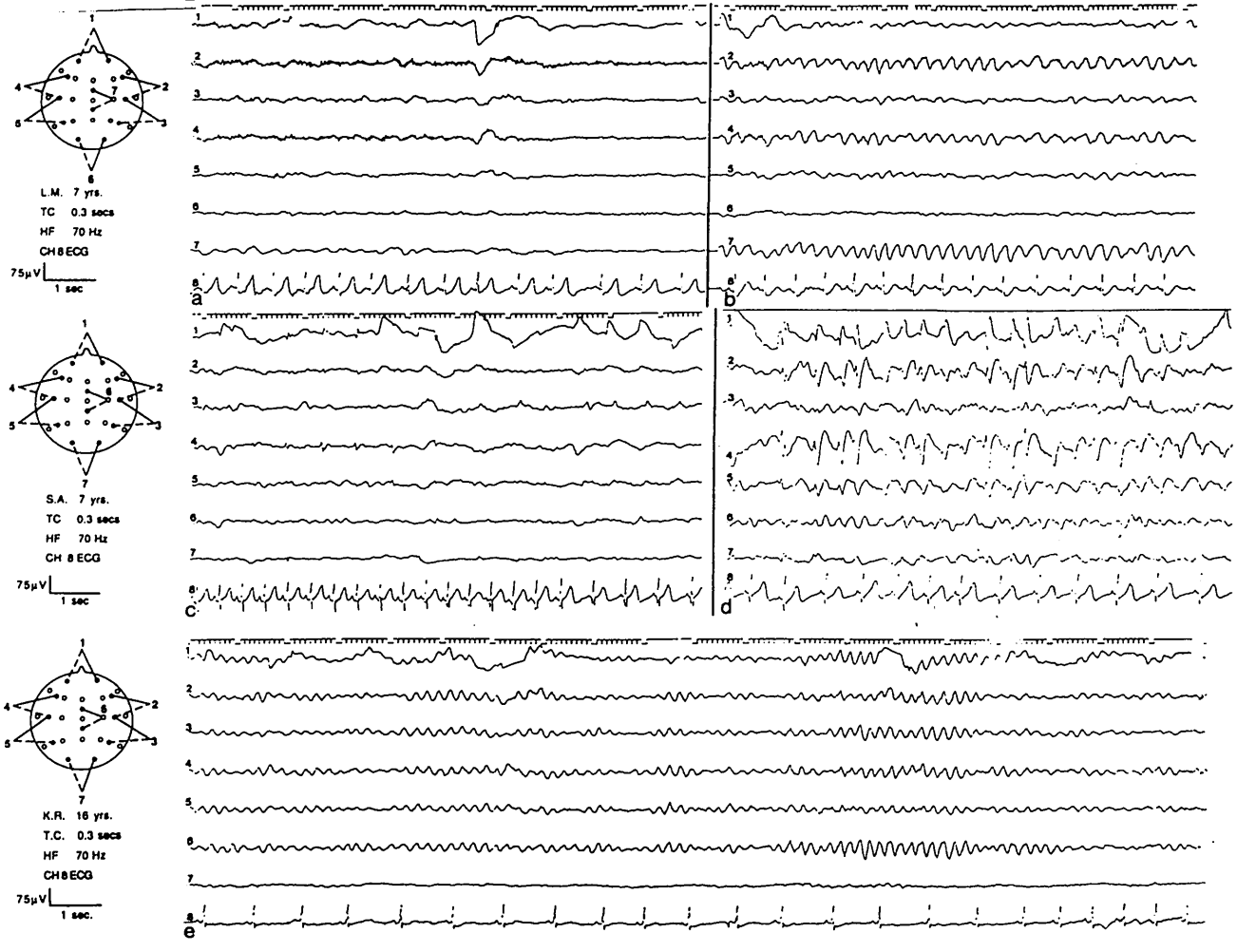
Section of daytime recording (case 5). An episode of breathing without hyperventilation (A to B) is followed by periods of hyperventilation (as shown by end tidal carbon dioxide and the increased amplitude and frequency of the breathing movements) and apnoeic pauses. Hyperventilation episodes are accompanied by a progressive fall in trancutaneous carbon dioxide. There is no evidence of hypoxaemia preceding the onset of hyperventilation (oxygen saturation 98–100%).

5.3.1 Data for 14 people with Rett is a study to correlate movement, with changes in e.e.g and respiration (Kerr et al 1990) reproduced by kind permission of Brain & Development)

Case number (*1)	*1*5* (9)	*2* (1)	*3*6* (10)	*4* (5)	*5* (7)	*6* (4)	*7* (3)	*8* (2)	*9* (8)	*10* (6)	*11* (11)	*12*7* (15)	*13*8* (18)	*14* (16)
Age (years)	6	6	6	7	7	10	11	12	13	16	17	6	6	7
Hyperventilation present	+	+	+	+	+	+	+	+	+	+	–*9	–	–	–
Lowest CO_2 recorded *2	1.8/18	2.2/24	2/13	1.4/13	1.6/8	2.1/18	4.2/33	2.2/26	2.4/26	2.2/20	3.8/NR	4.5/44	4/37	4.4/46
Apnoeic pauses present*3	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lowest oxygen recorded*4	< 50	60	< 50	< 50	70	< 50	92	< 50	92	66	80	94	98	97
EEG paroxysms at 1½–4 Hz	+	+	+	+	+	–	–	+	–	–	–	–	–	+
Increased in normal CO_2	+	+	+	+	+	–	–	–	–	–	–	–	–	–
4–6 Hz EEG activity	+ UR	+ UR	+ UR	+ R	+ UR	+ UR	+ R	+ UR	+ UR	+ UR	+ UR	+	+	+ UR
Paroxysmal 4–6 Hz activity	–	–	–	–	–	+*10	–	+	–	–	+	–	–	–
Paroxysmal limb movement with resp. dysrhythmia	+	+	–	+	+	+	–	–	–	–	–	–	–	–

*1) Brackets after case numbers give case numbers for our first paper. *2) Figure above the line is end-tidal carbon dioxide in volumes % (normal > 4); below the line is transcutaneous carbon dioxide mmHg (normal > 35 mm). *3) Active expiratory apnoeic pauses, all included Valsalva-like manoeuvers. *4) % saturation (normal > 97%). *5, *6, *7, *8) Cases with minor atypical features; *5) Better than expected use of hands. *6) Threatened miscarriage in pregnancy. *7 and *8) Earlier stereotypic hand movements had almost disappeared. *9) Hyperventilation recorded in the past. *10) Abnormality increased when end-tidal CO_2 was normal. UR: unreactive EEG, R: reactive EEG. Anticonvulsant drugs: Carbamazepine (cases 2, 3, 5, 8, 9, 11, 12), sodium valproate (cases 6, 14), clonazepam (cases 5, 13). NR: not recorded.

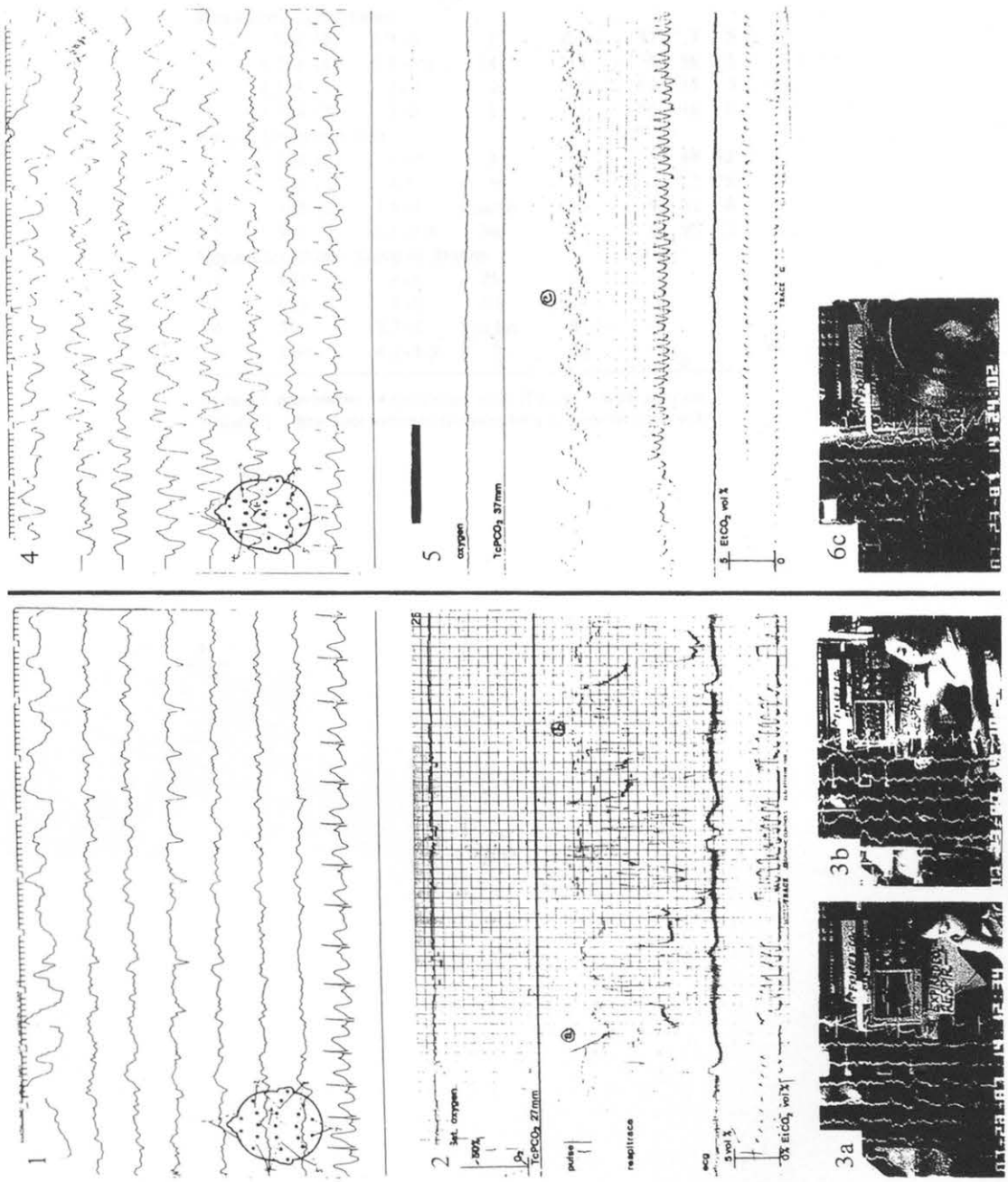
5.3.2 Encephalograms in Rett syndrome. (Kerr et al 1990) reproduced by kind permission of Brain & Development)



Electroencephalograms in cases of Rett syndrome. Examples show the EEG in cases 4 (LM) and 5 (SA) during hyperventilation a) and c); and during normal breathing b) and d). Example e) shows the theta rhythm in case 10 (KR).

5.3.3 Parallel recordings of e.e.g. breathing and behaviour in Rett syndrome. (Kerr et al 1990) reproduced by kind permission of Brain & Development)

Parallel records of e.e.g., breathing and behaviour in case 5. 1,2 and 3 are recordings during a period of respiratory dysrhythmia. 4,5 and 6 were recorded during alert normal breathing (while rebreathing). Small letters indicate respiratory activity corresponding to the photographs. In case 5 the paroxysms of movement ++ occurred not only during periods of respiratory dysrhythmia but specifically during the episodes of hyperventilation in these periods. During normal breathing, movements diminished.



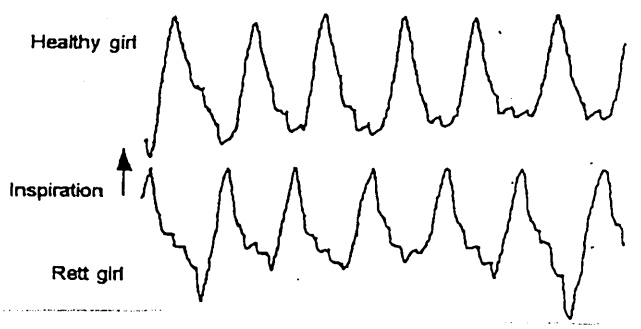
5.3.4 Comparing the occurrence of non-epileptic e.e.g. paroxysms during normal and dysrhythmic breathing. (Kerr et al 1990) reproduced by kind permission of Brain & Development)

Comparison of non-epileptic EEG paroxysms occurring during periods of normal and dysrhythmic breathing in four cases

Case	*Time sec*	*ET CO_2 vol%*	*EEG bursts*		*Movement % of time*		
			no	*% of time*	++	+	−
Respiratory dysrhythmia:							
1	741 (2)	1.9–3	1	<1	92	3	5
2	1,784 (4)	2.8–3.5	14	3	38	56	6
4	1,108 (3)	2–3	2	2	63	35	3
5	1,264 (3)	2–3	1	<1	54	46	0
Normal breathing: alert							
1	124 (2)	4–5	5	8	0	48	52
2	239 (1)	4.9	9	8	0	22	78
4	389 (2)	3.8–4	Contin.	100	0	32	68
5	985 (2)	3.1–4.4	36	57	0	98	2
Normal breathing: asleep or drowsy							
1	448	4–5	25	16			
2	623	4–5	40	24			
4	597	3.7–5	Contin.	61			
5	150	4.7–4.9	9	29			

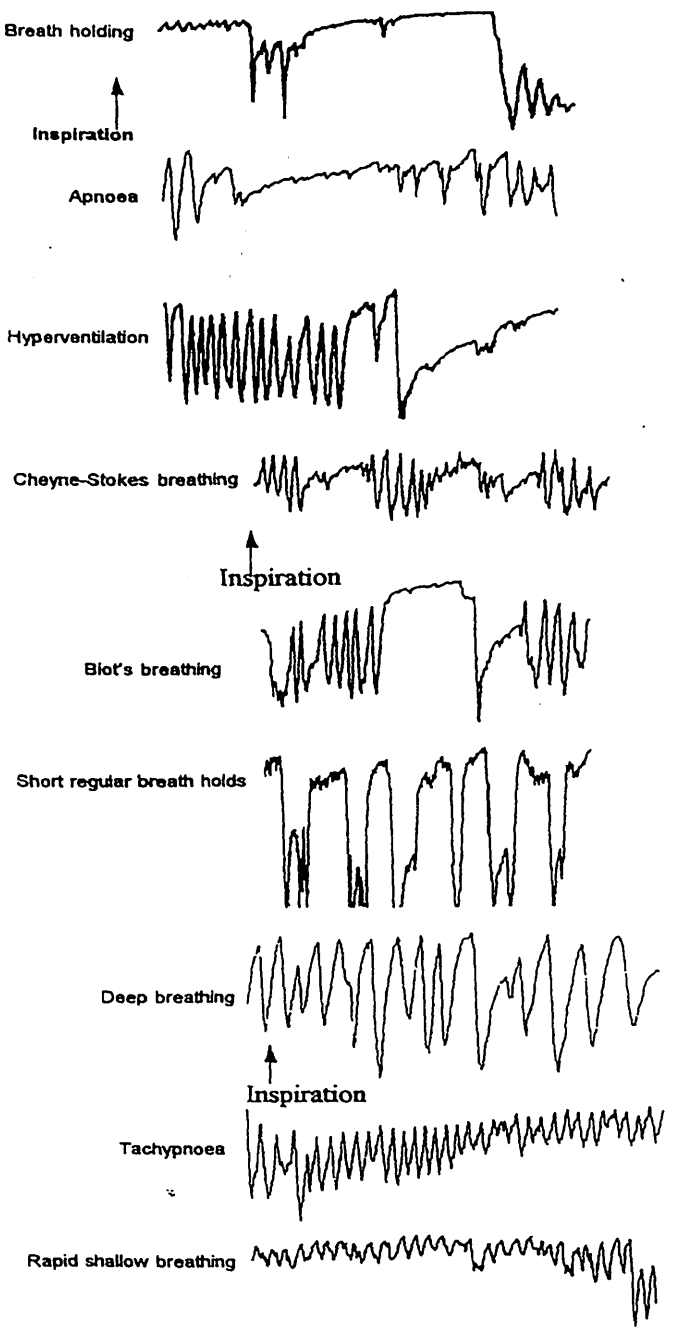
In case 5 movement ++ coincided with HV and + with apnoeic pauses. ( ) Brackets indicate the numbers of periods analysed.

5.4.1 The normal breathing pattern in a girl with Rett syndrome and a normal control. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



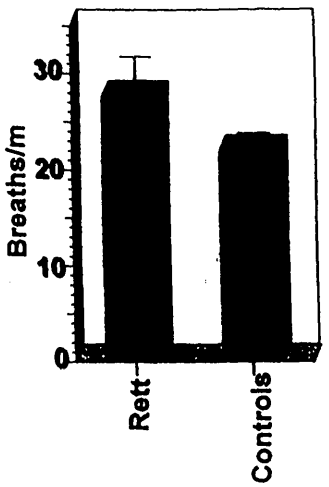
. Normal breathing pattern in a girl with Rett's syndrome and a healthy control. The depths of breathing are equal and inspirations are sharp and short, while expirations are nearly biphasic

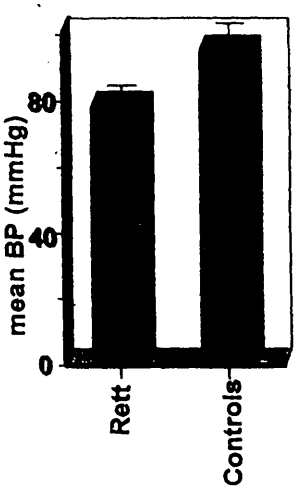
5.4.2 Breathing dysrhythmias seen in Rett syndrome. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



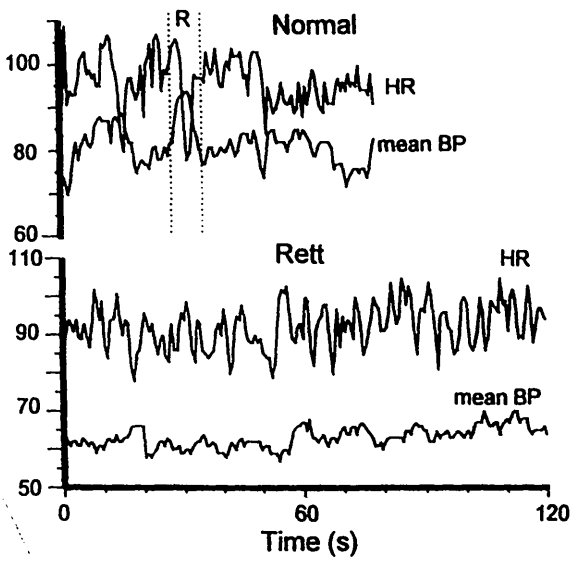
Breathing dysrhythmias in Rett's syndrome. Breath holding were often ended with a sharp burst of expiration. Central apnoea tended to interrupt normal breathing, while hyperventilation was often followed by apnoea or Cheyne-Stokes breathing. Biot's breathing and short regular breath holds were rare. Deep breathing often followed long breath holds, tachypnoea and rapid shallow breathing were interspersed among the other dysrhythmias

5.4.3 Normal breathing in Rett and controls: average rates. There was no statistical difference between these p> 0.2. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.





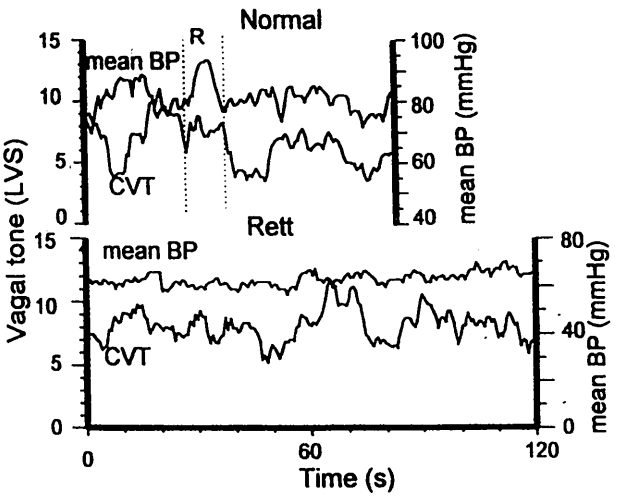
5.4.4 Compares the averages of BP in all Rett and normal girls. There was no statistically significant difference the two (p>0.1)



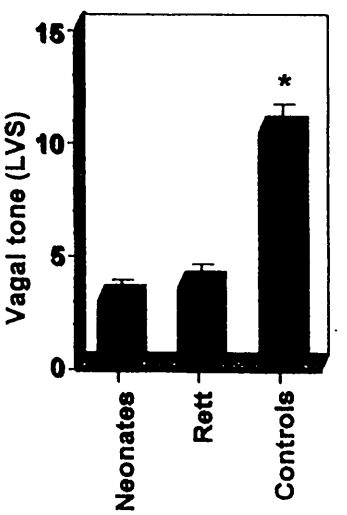
5.4.5 Continuous and simultaneous recording of heart rate (HR) and mean arterial blood pressure (mean BP) in a girl with Rett's syndrome (Rett) and a normal healthy girl (Normal) at rest and during normal breathing are shown. A sharp drop in HR at R within the vertical broken lines in the normal girl was in response to a brisk rise in BP which was successfully corrected back to the baseline level. There are no such responses in the Rett girl. The BP in the Rett girl remained below 70 mmHg while BP varied between 75–85 mmHg in the normal girl

5.4.6

(Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



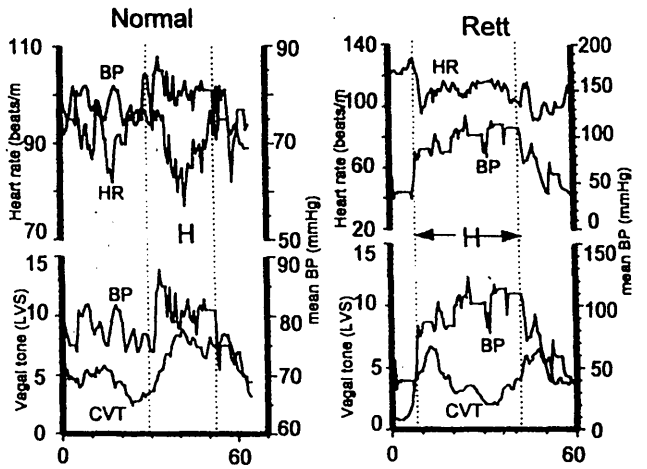
Continuous and simultaneous recording of cardiac vagal tone (CVT) and mean arterial blood pressure (mean BP) in a girl with Rett's syndrome (Rett) and a normal healthy girl (Normal) during normal breathing are shown. There was a sustained high level of CVT at R enclosed within the vertical broken lines in the normal girl in response to a sharp rise in BP, but no such responses in the Rett girl



5.4.7

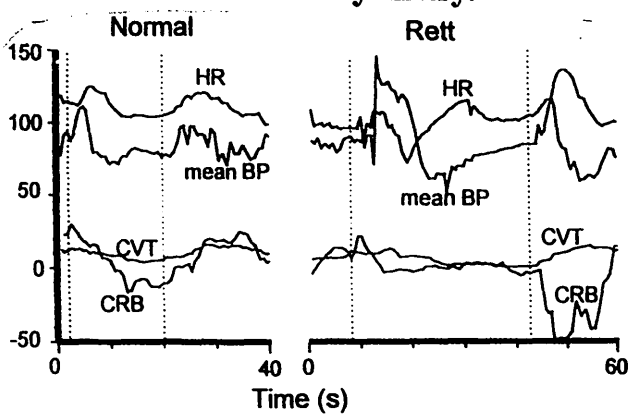
Compares the averages of the resting CVT in three groups of children. The level of CVT in the Rett girls was about equal to a previously reported neonatal level (4) and significantly lower than in controls (*p<0.001)

5.4.8 The effects of hyperventilation on sympathetic-vagal balance in Rett and normal girls. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



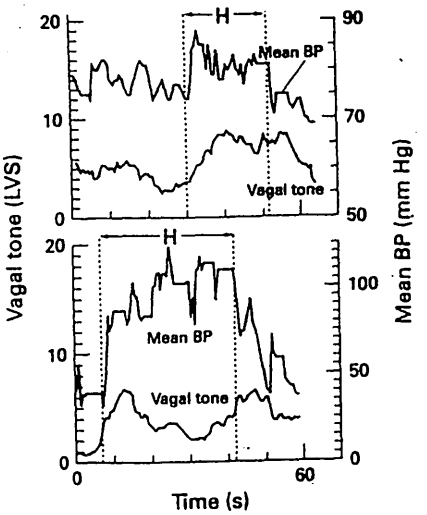
Effects of hyperventilation on sympatho-vagal balance in a normal and one Rett girl are shown. Sympathetic activity is represented by the mean arterial blood pressure (BP). Cardiac vagal tone (CVT) was measured in units of a linear vagal scale (LVS). The periods during which the two girls were hyperventilating are marked (H) and enclosed within broken vertical lines. Note the sustained increase in CVT in the normal girl contrary to vagal withdrawal in the Rett girl during hyperventilation. The heart rate (HR) dropped below 80 beats/min during hyperventilation in the normal girl, but it stayed above 100 beats/min in the Rett girl. There was agitation, distress and vocalisation as the BP peaked during hyperventilation in the Rett girl

5.4.9 The effects of breath holding on sympathetic-vagal balance in Rett and normal girls. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



Effects of breath holding on sympatho-vagal balance and baroreflex function in a normal and one Rett girl are shown. Sympathetic activity is represented by the mean arterial blood pressure (mean BP). Cardiac vagal tone (CVT) was measured in units of a linear vagal scale (LVS). Cardiac response to baroreflex (CRB) is the change in pulse interval per unit change in systolic BP and is measured in ms/mmHg. The periods during which the two girls were holding their breaths are enclosed within the broken vertical lines. Note the smooth withdrawal of CVT and CRB leaving the entire cardiovascular control to the sympathetic system during breath holding in both girls. This manoeuvre unmasked the inadequate restraint of the sympathetic system in the Rett girl indicated by oscillation of her BP and exaggerated changes in the heart rate (HR)

5.4.10 Comparing the reaction of mean arterial blood pressure (BP) and cardiac vagal tone (CVT) to hyperventilation in Rett and in a normal volunteer. (Julu et al 1997) reproduced by kind permission of the European Journal of Child and Adolescent Psychiatry.



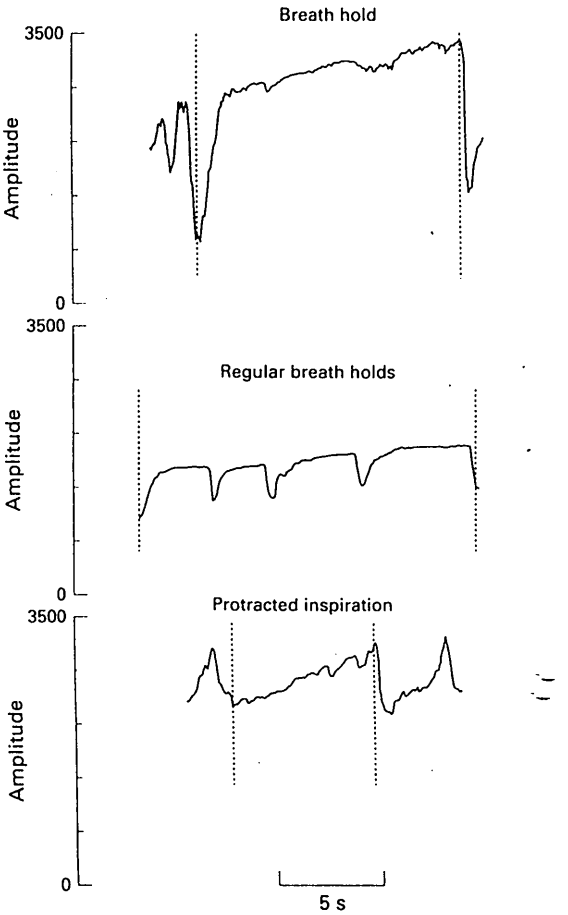
Continuous and concurrent records of mean arterial blood pressure (BP) and a measure of cardiac vagal tone expressed in units of a LVS. The upper pair of traces are examples obtained from a normal 8 year old girl to show the reaction to voluntary hyperventilation (H). The lower pair of traces are examples obtained from an 8 year old girl with Rett syndrome to show the reaction to her spontaneous hyperventilation (H).

5.5.1 Respiratory and autonomic results according to age group. (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.

Age group	*Mean age (years)*	*No in group*	*CVT LVS*	*CSB (ms/mm Hg)*	*Normal breathing (%)*	*Inadequate breathing (%)*	*Forced breathing (%)*	*Apneustic breathing (%)*	*Valsalva (%)*	*Tone type*	*Reported epilepsy*	*Pre/now walking solo*
Up to 5 y	3.6	7	3.9 (0.4)	2.4 (0.5)	26.7 (7.7)	9.6 (4.7)	24.2 (8.0)	37.0 (13.6)	0.2 (0.3)	Hypo = 1 Norm = 6 Hyper = 0 Dys = 0	2	1/2
6–9 y	7.6	13	4.2 (0.6)	3.4 (0.9)	18.7 (4.8)	14.4 (3.7)	21.4 (5.4)	32.6 (6.3)	5.8 (2.0)	Hypo = 6 Norm = 3 Hyper = 0 Dys = 4	7	8/8
10–18 y	12.3	15	3.8 (0.4)	3.0 (0.4)	26.4 (3.6)[1]	19.7 (4.1)[1]	21.3 (5.4)[1]	14.3 (2.8)[1]	10.4 (3.5)[1]	Hypo = 1 Norm = 2 Hyper = 3 Dys = 9	12	10/10
> 18 y	28.5	12	6.0 (1.2)	4.5 (1.2)	37.6 (7.2)[2]	18.4 (2.9)[2]	8.6 (1.6)[2]	13.4 (4.7)[2]	20.7 (6.6)[2]	Hypo = 0 Norm = 0 Hyper = 4 Dys = 8	9	9/7

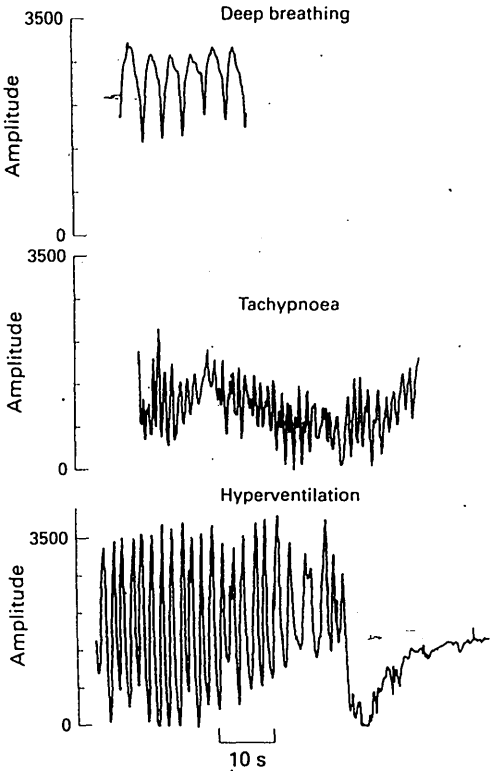
Values are mean (SEM).
[1]Number in group = 14.
[2]Number in group = 10.
Breathing rhythms: mean (SEM) per cent of monitored time spent in each rhythm.
Tone type: Number of subjects with hypo(tonia), normal tone, hyper(tonia), and dys(tonia) given.
Reported epilepsy: Number in group with reports of epilepsy
Pre/now walking solo: Number of subjects who had walked pre-regression/number of subjects who walked unaided at time of investigation.
CSB, mean sensitivity to baroreflex; $\overline{CV}$, mean cardiac vagal tone.

5.5.2 Apneustic breathing style (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



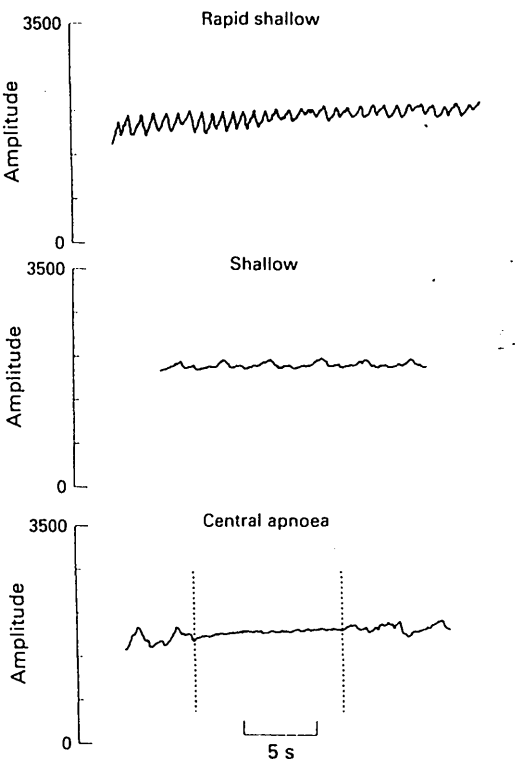
Apneustic breathing style. Top: breath hold—a single fast full inspiration followed by a delayed fast expiration. Middle: regular breath holds—episodes of breath holding. Bottom: protracted inspiration—a prolonged and continuous inspiration ended abruptly by full expiration (achieved fast, often forcefully), insufficient to obstruct venous return. Amplitude measured in arbitrary units.

5.5.3 Forceful breathing style (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



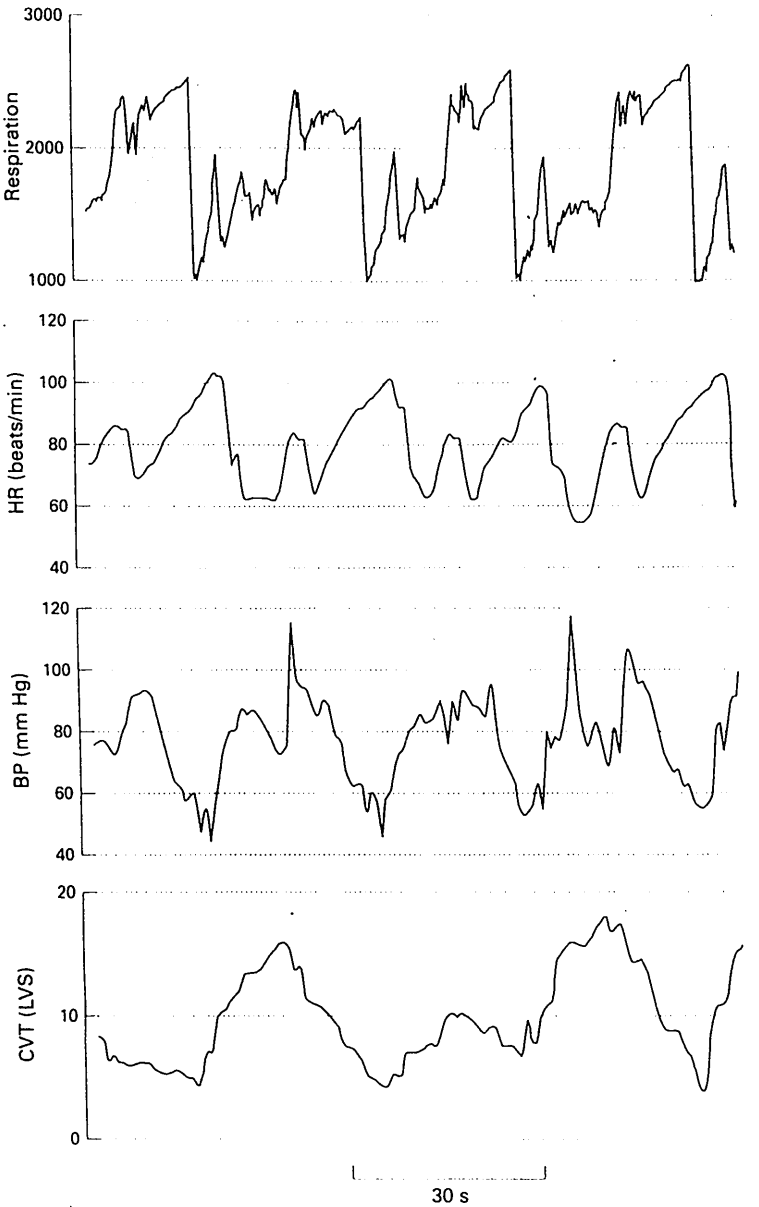
Forceful breathing style. Top: deep breathing—episode of exaggerated inspirations followed immediately by exaggerated expirations without causing central apnoea; rate below 35 breaths/min, depth must be well above average for that person. Middle: tachypnoea—episode of rapid inspirations followed immediately by expirations without causing central apnoea. Rate 35–45 breath per minute, depth average or greater for that person. Bottom: hyperventilation—episode of exaggerated inspirations followed immediately by equally exaggerated expirations contributing directly to a central apnoea. Amplitude measured in arbitrary units.

5.5.4 Inadequate breathing style (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



Inadequate breathing style. Top: rapid shallow breathing—episode of shallow inspiration followed immediately by equally shallow expiration; rate above 35 breaths/min, depth below average for that person. Middle: shallow breathing—episode of shallow inspiration followed immediately by equally shallow expiration; rate below 35 breaths/min, depth must be below average for that person. Bottom: central apnoea—cessation of breathing movement at the end of expiration. Amplitude measured in arbitrary units.

5.5.5 Valsalva breathing style(Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



) Valsalva breathing style. Valsalva manoeuvre: breath holds or protracted inspiration capable of raising intrathoracic pressure sufficiently in magnitude and duration to reduce venous return and cause characteristic blood pressure (BP) or heart rate (HR) changes (saw toothed responses with rebounds). CVT, cardiac vagal tone; LVS, linear vagal scale. Amplitude measured in arbitrary units.

5.5.6 Less common breathing styles (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.

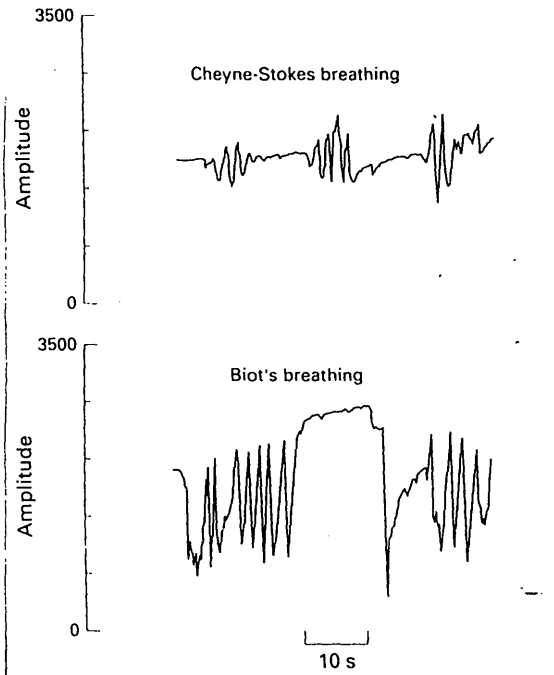
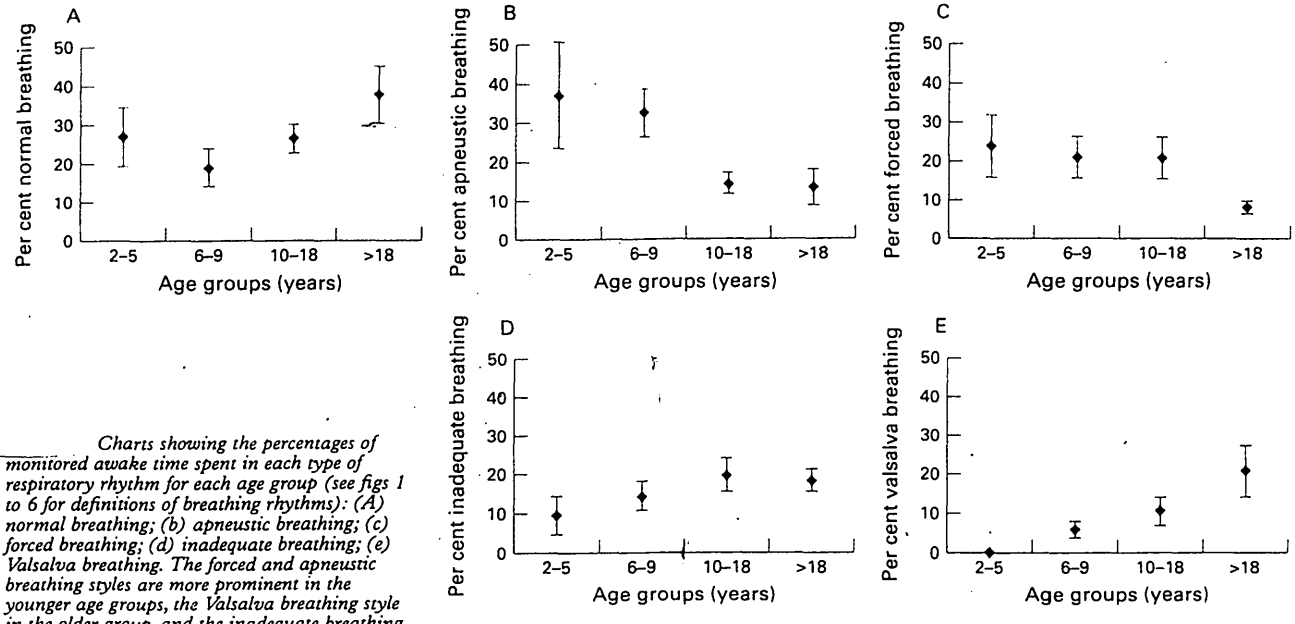


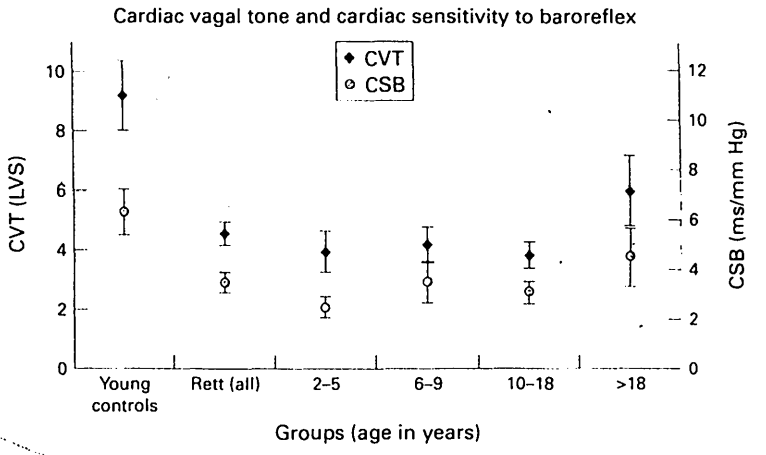
Figure 6 Less frequent breathing rhythms. Top: Cheyne–Stokes breathing—periodic breathing interrupted by central apnoea during which the breathing movements increases gradually in amplitude and decay again into apnoea. Bottom: Biot's breathing—abrupt apnoea followed by equally abrupt regular breathing in which both the apnoea and the regular breathing have variable durations. Amplitude measured in arbitrary units.

5.5.7 Charts showing the percentage of awake time spent in each type of abnormal respiratory rhythm at each age group. (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



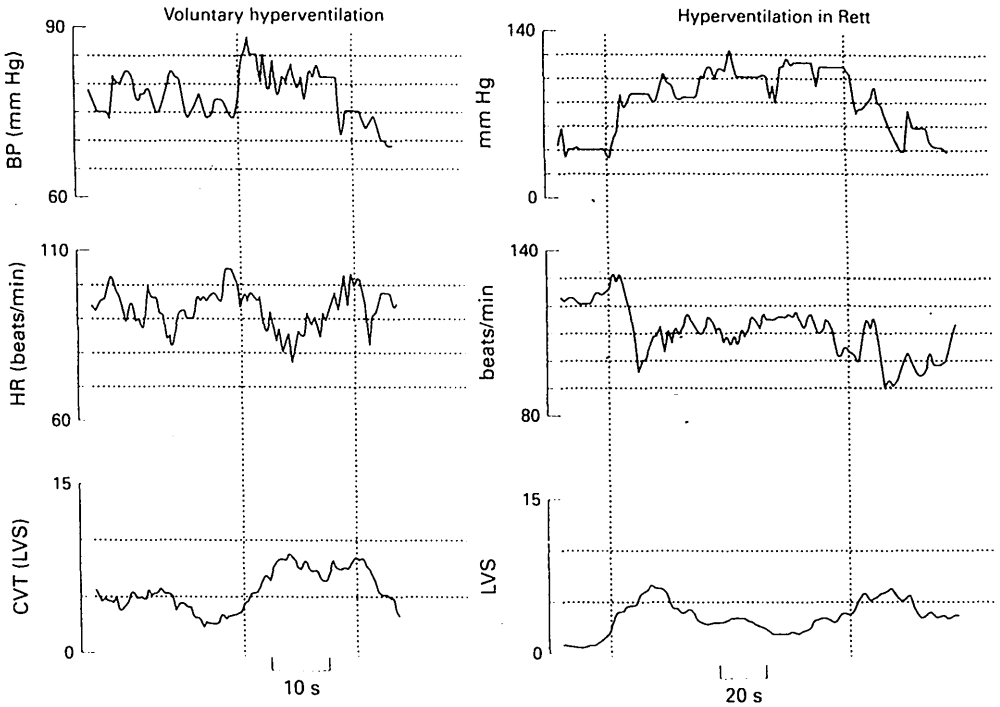
Charts showing the percentages of monitored awake time spent in each type of respiratory rhythm for each age group (see figs 1 to 6 for definitions of breathing rhythms): (A) normal breathing; (b) apneustic breathing; (c) forced breathing; (d) inadequate breathing; (e) Valsalva breathing. The forced and apneustic breathing styles are more prominent in the younger age groups, the Valsalva breathing style in the older group, and the inadequate breathing style in the 10–18 year group. Although there is individual variation and the age group differences do not reach statistical significance, except in a few instances (see text), these trends have been well maintained throughout the 56 recordings made. Values are means; error bars = SEM.

5.5.8 Cardiac vagal tone and cardiac sensitivity to baroreflex according to age of the subject. (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



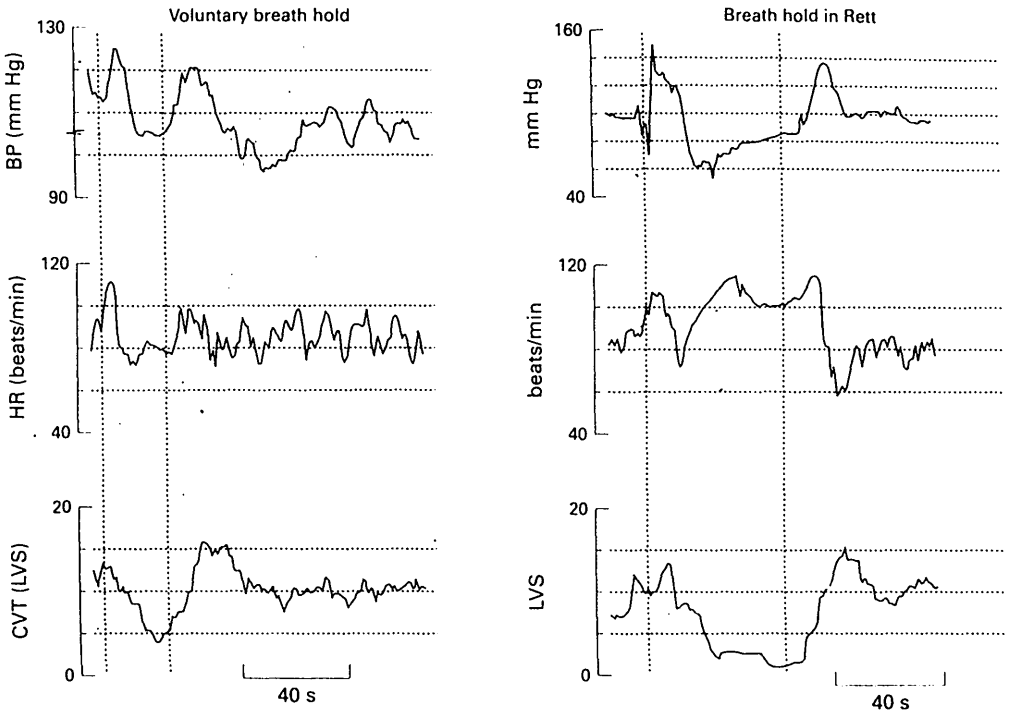
Autonomic measurements in Rett subjects and controls. The Rett subjects are also divided into age groups. Compared with controls, the mean cardiac vagal tone in the combined Rett group was reduced ($p < 0.002$), as it was in the various age groups with the exception of the over 18 group. The cardiac sensitivity to baroreflex was also reduced ($p < 0.01$) in the combined Rett group and in the age groups with the exception of the over 18 group. Values are means; error bars = SEM. CSB, resting sensitivity to baroreflex; CVT, resting cardiac vagal tone measured in the linear vagal scale; LVS, linear vagal scale.

5.5.9 Effects of hyperventilation on sympatho-vagal balance in a normal person and one with Rett syndrome(Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



Effects of hyperventilation on sympathovagal balance: control (left) and Rett case (right). The periods of hyperventilation are enclosed with broken vertical lines. Note the sustained increase in cardiac vagal tone in the normal girl, in contrast to vagal withdrawal in a Rett case. Note also the contracted time scale in the Rett diagram. BP, mean arterial blood pressure representing sympathetic activity; CVT, cardiac vagal tone (measured in linear vagal scale (LVS)); HR, heart rate.

5.5.10 Effects of breath holding on sympatho-vagal balance in a normal person and one with Rett syndrome (Julu et al 2001) reproduced by kind permission of Archives of Disease in Childhood.



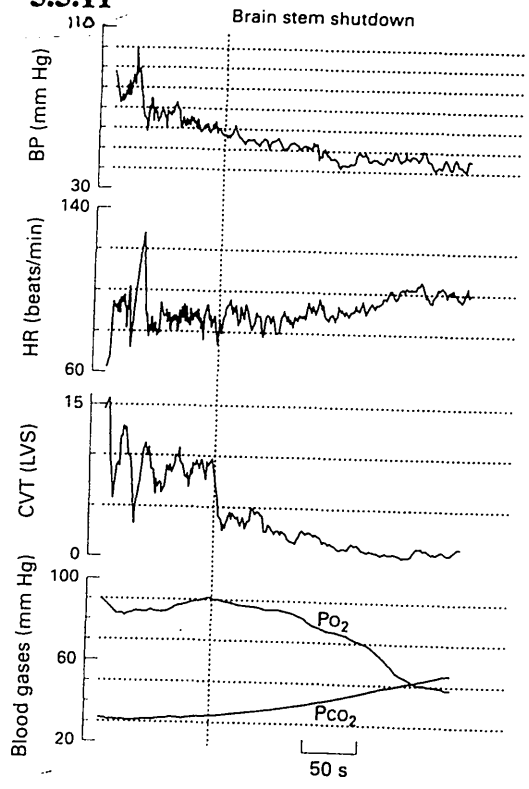
Effects of breath holding on sympathovagal balance and baroreflex function in a Rett case and a control. The periods of breath holds are enclosed by broken vertical lines. Note the normal smooth withdrawal of cardiac vagal tone and which leaves the cardiovascular control to the sympathetic system. In the Rett case, this manoeuvre unmasked the inadequate restraint of the sympathetic system, indicated by oscillation of blood pressure and exaggerated changes in heart rate. BP, mean arterial blood pressure representing sympathetic activity; CVT, cardiac vagal tone (measured in linear vagal scale (LVS)); HR, heart rate.

5.6.1 Relating abnormalities in EEG records to reported clinical epilepsy, [illegible] in the development of Rett syndrome and the waking state. (Cooper et al 1998) reproduced by kind permission of European Journal of Child Neurology

Number of patients, number reporting seizures and EEG characteristics in different phases (*note*: several patients were recorded in more than one group).

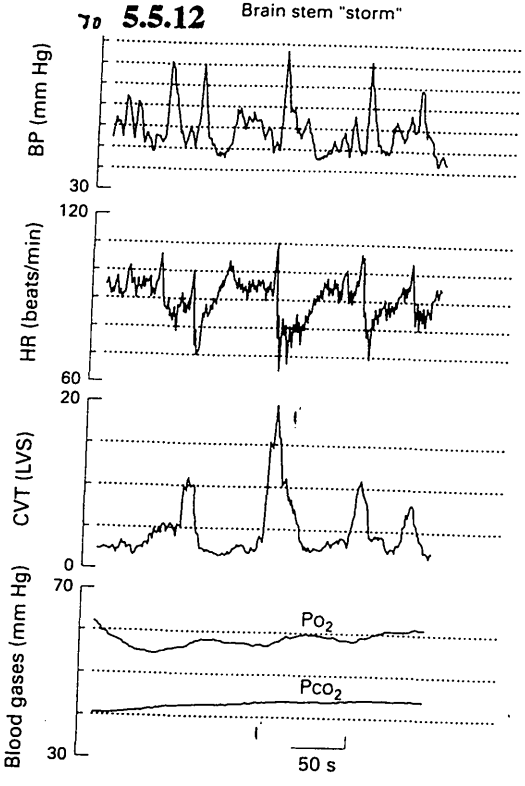
EEGs

5.5.11



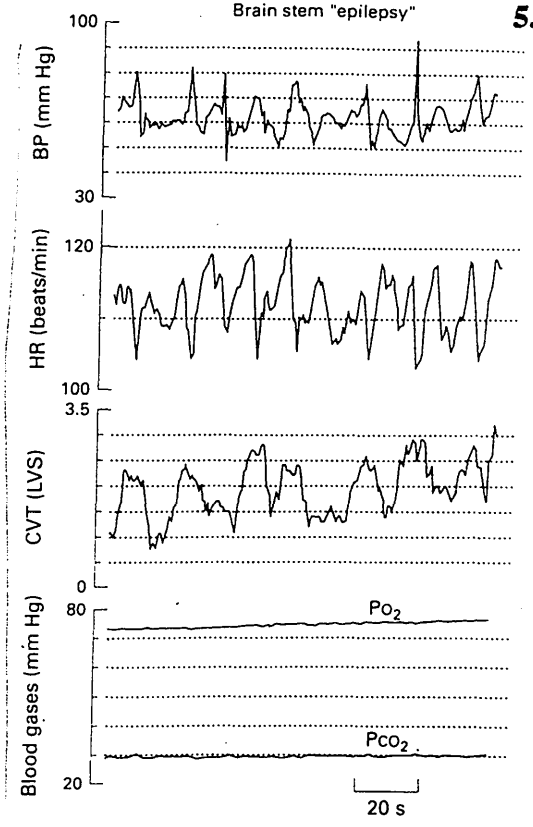
Brain stem shut down in a girl of 11 years. The vertical broken line marks the beginning of the autonomic shutdown (see text). BP, mean arterial blood pressure representing sympathetic activity; CVT, cardiac vagal tone (measured in linear vagal scale (LVS)); HR, heart rate; Po_2 and Pco_2, transcutaneous partial pressure of oxygen and carbon dioxide.

5.5.12



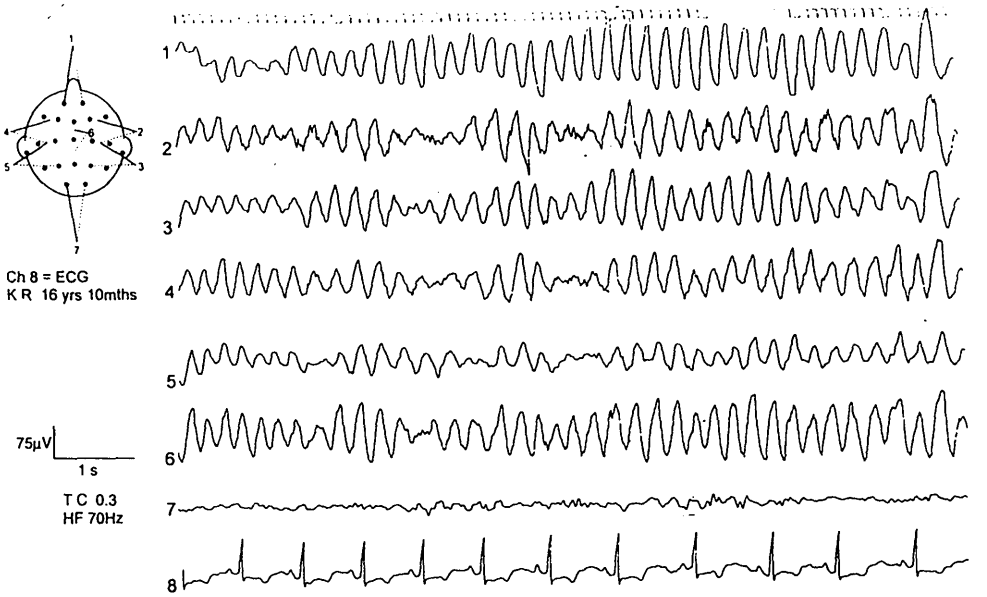
"Brain stem storm" in a girl of 11 years, illustrating spontaneous and exaggerated excitation of the brain stem during feeble breathing. Oxygen level oscillated below 60 mm Hg and at every trough there were spikes in blood pressure and heart rate. On four occasions there were spikes of cardiac vagal tone causing sharp and transient bradycardia. The exaggerated simultaneous spikes of blood pressure, heart rate, and cardiac vagal tone sensitive

5.5.13

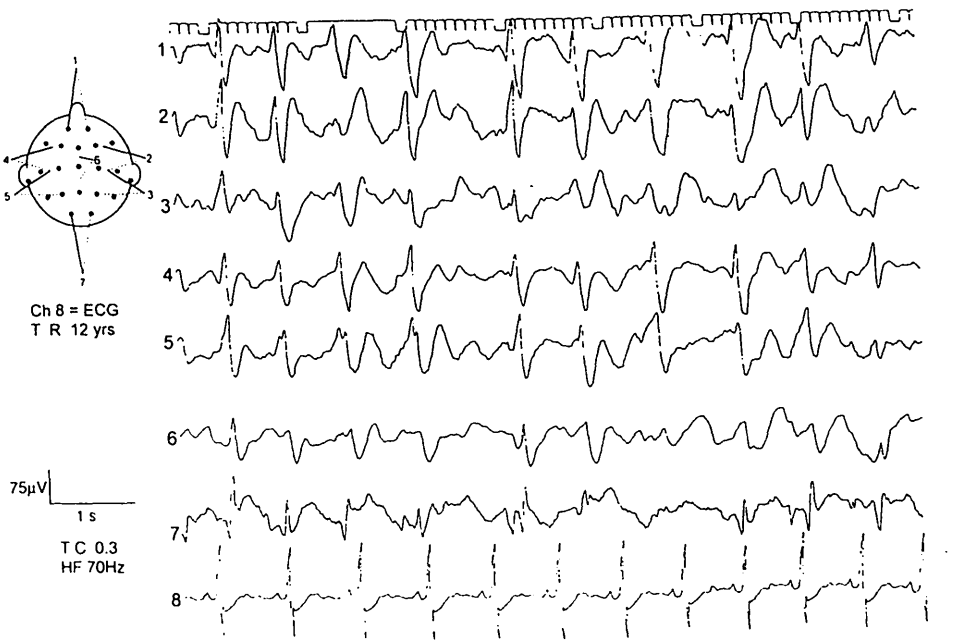


"Brain stem epilepsy" in a girl of 13 years. The breathing rhythm was normal and transcutaneous gases were within normal limits. The exaggerated and repeated simultaneous sharp increases in blood pressure, heart rate, and cardiac vagal tone—best seen at the beginning and end of the traces—represent widespread aberrant excitation of

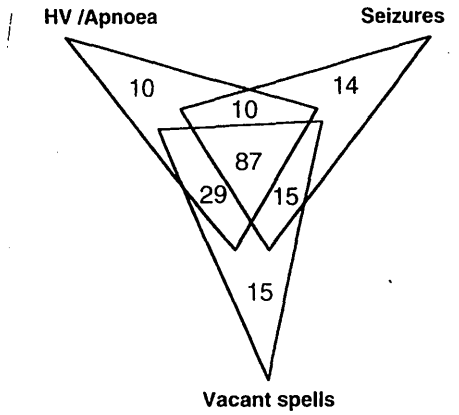
5.6.2 E.e.g from a girl of 16 years with classic Rett Syndrome showing persistent monorhythmic theta. (Cooper et al 1998) reproduced by kind permission of European Journal of Child Neurology



5.6.3 E.e.g. from a girl aged 12 years showing widespread repetitive spike discharges. (Cooper et al 1998) reproduced by kind permission of European Journal of Child Neurology



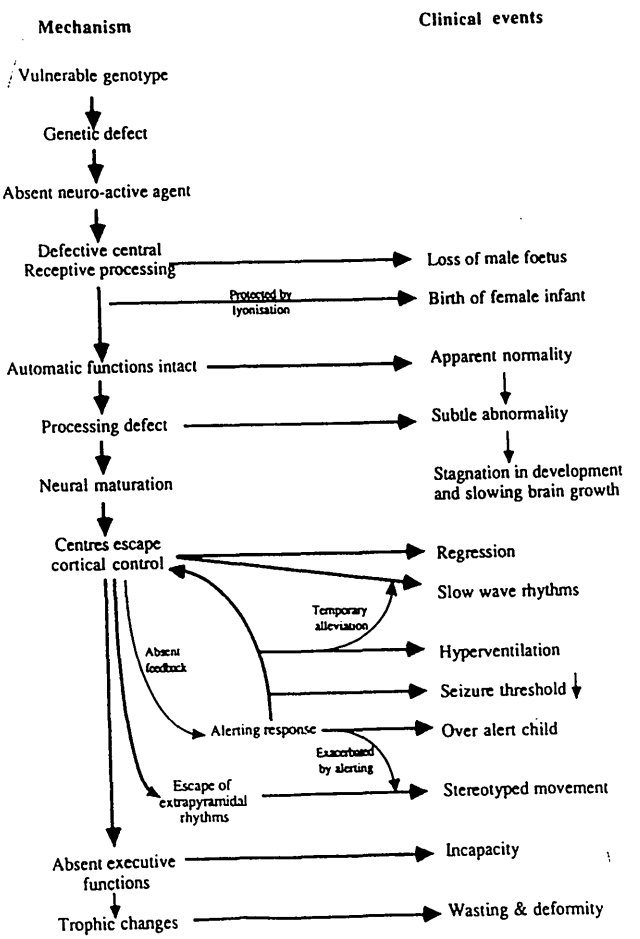
5.6.4 Diagram to illustrate the coexistence of epilepsy, non-epileptic vacant spells and respiratory dysrhythmia. (A.Kerr) (Cooper et al 1998) reproduced by kind permission of European Journal of Child Neurology



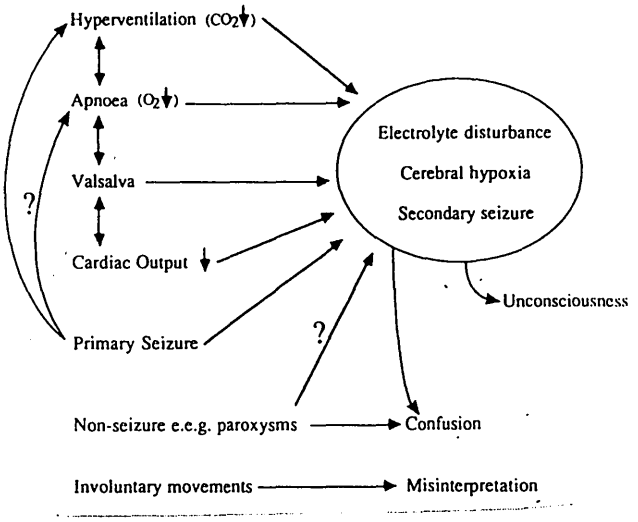
vacant spell: *brief interruption of awareness thought or shown not to be seizure*

HV-apnoea: *awake cycles of hyperventilation and breath holding*

5.6.5 A possible sequence of events in the generation of the Rett Syndrome (Kerr 1990) reproduced by kind permission of Brain & Development0



5.6.6 Mechanisms which may contribute to the vacant spells in Rett Syndrome (Kerr 1990) reproduced by kind permission of Brain & Development)



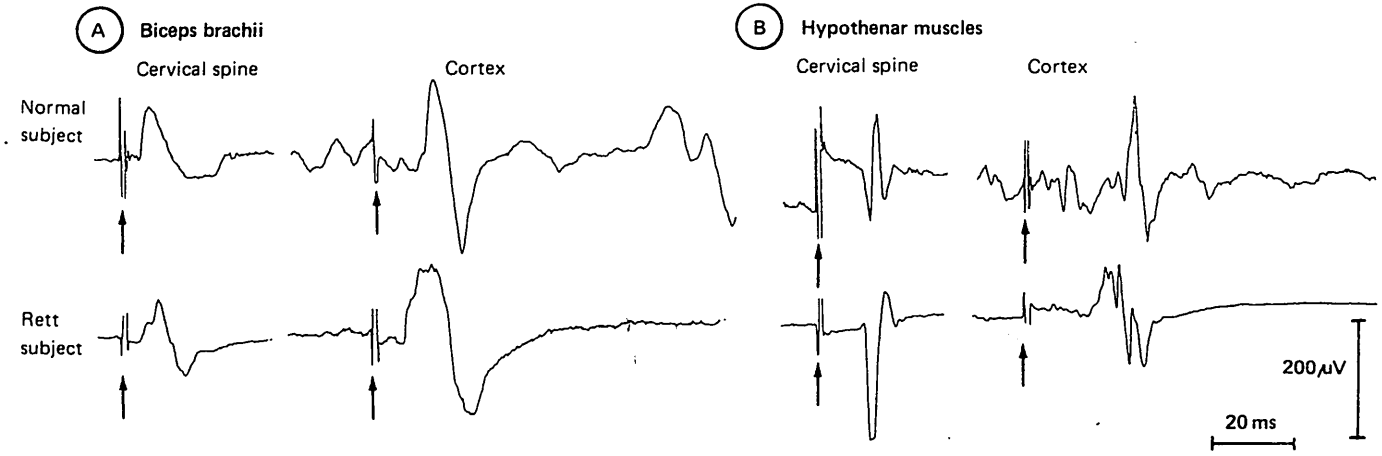
Section 6: Investigations II

6.1.1 Neurophysiological observations on eight girls with Rett Syndrome (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

Subject	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Age (years)	5	7	8	8	8	9	16	26
Height (cm)	111	108	121	121	111	116	136	152
Arm length C_5 to fifth finger tip (cm)	59	55	66	64	60	63	78	75
Length C5 to midpoint biceps brachii (cm)	19	18	22	21	20	21	26	25
Scoliosis	+	+	+	+	+	+	+	+
Hyperventilation	+	+	+	−	+	+	+	+
Walking independently	+	−	−	+	+	+	−	+
Increased biceps reflexes	+	+	+	+	+	+	+	+
Increased patellar reflexes	+	+	+	+	+	+	+	+
Increased ankle reflexes	+	+	+	+	+	+	+	+
Ankle clonus	+	+	+	+	+	−	−	+
Babinski sign	−	−	−	−	−	−	−	−
Spasticity	+	+	+	+	+	+	+	+

Definitions
+ = present
− = not present
Hyperventilation: intermittent hyperventilation and breath-holding.[24]
Spasticity: velocity dependent increase of muscle tone following stretch.[25]

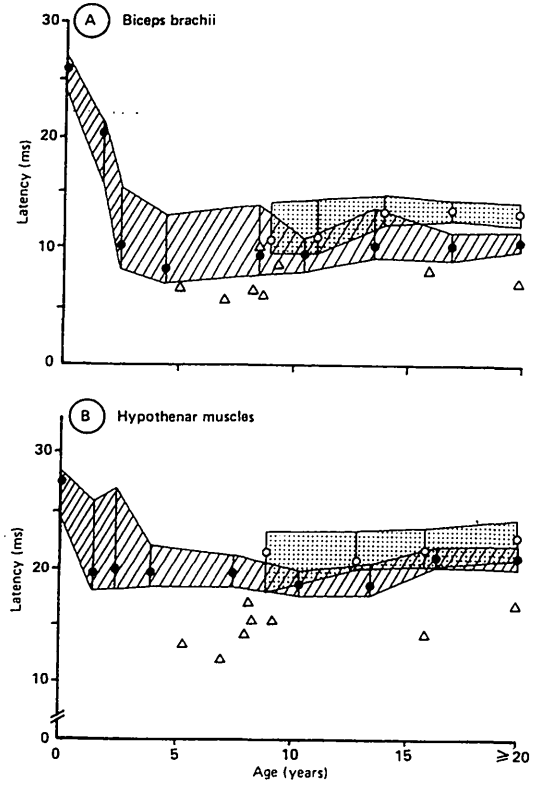
6.1.2 Motor action potentials following electromagnetic stimulation of the cervical spine and motor cortex in Rett and normal subjects (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)



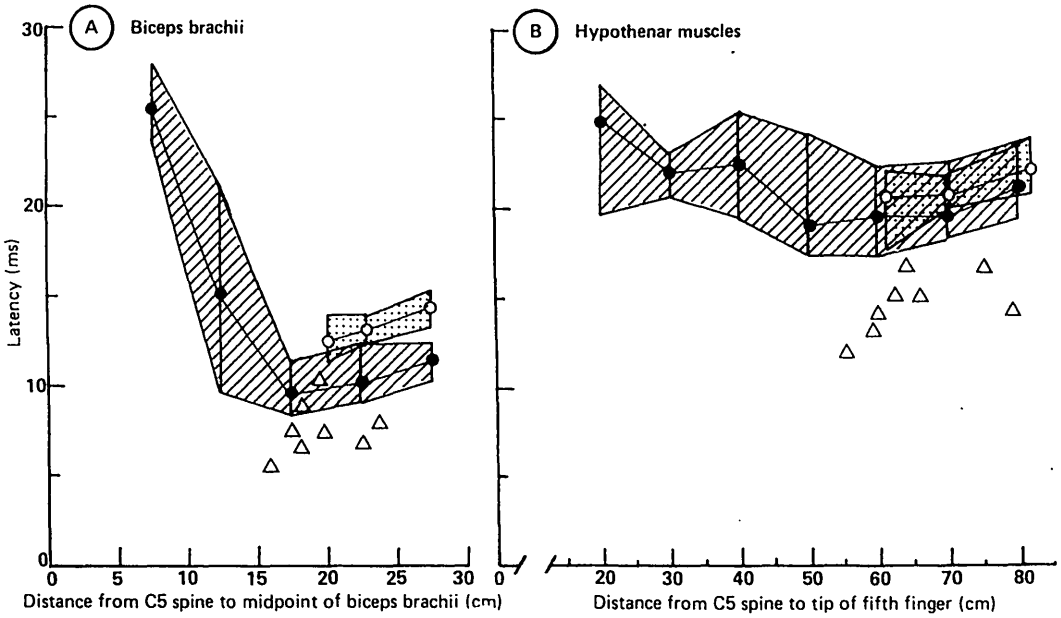
Motor action potentials following electromagnetic stimulation of cervical spine and motor cortex. Arrows indicate timing of stimulation.

6.1.3 Onset latencies of motor action potentials following electromagnetic stimulation of the motor cortex in relation to the ages of subjects (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

Onset latencies of motor action potentials following electromagnetic stimulation of the motor cortex in relation to age of subjects. The filled and open circles indicate the median values for normal subjects in contracted and relaxed muscles, respectively. The hatched area defines for normal subjects the interquartile range in contracted muscle and the stippled area the interquartile range in relaxed muscle. The triangles indicate data for the Rett subjects in relaxed muscle.



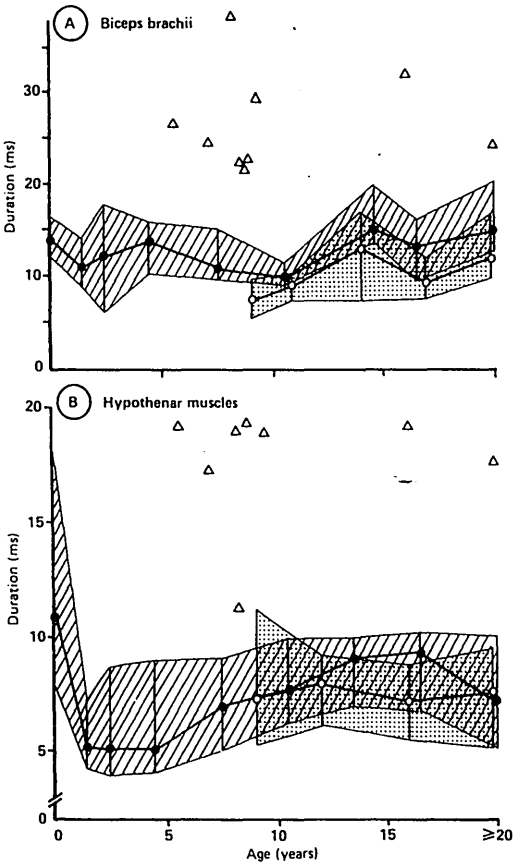
6.1.4 Onset latencies of motor action potentials in relation to conduction distance (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)



Onset latencies of motor action potentials following electromagnetic stimulation of motor cortex in relation to conduction distance. The filled and open circles indicate the median values for normal subjects in contracted and relaxed muscles, respectively. The hatched area defines for normal subjects the interquartile range in contracted muscle and the stippled area the interquartile range in relaxed muscle. The triangles indicate data for the Rett subjects in relaxed muscle.

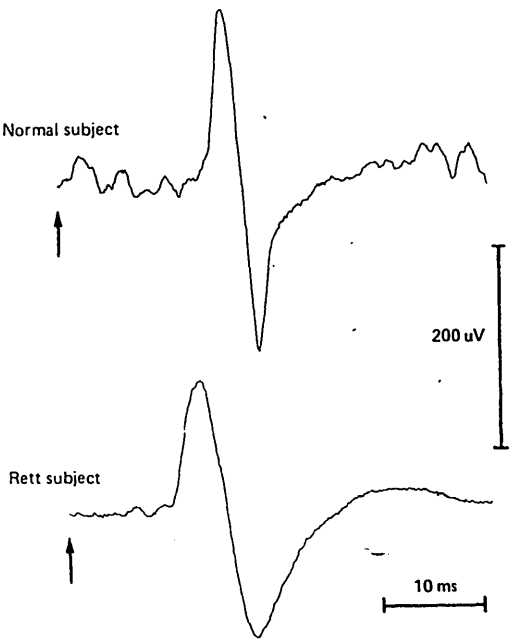
6.1.5 Durations of motor action potentials following electromagnetic stimulation of the motor cortex in Rett and normal subjects related to age (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

Durations of motor action potentials following electromagnetic stimulation of motor cortex in relation to age of subjects. The filled and open circles indicate the median values for normal subjects in contracted and relaxed muscles, respectively. The hatched area defines for normal subjects the interquartile range in contracted muscle and the stippled area the interquartile range in relaxed muscle. The triangles indicate data for the Rett subjects in relaxed muscle.

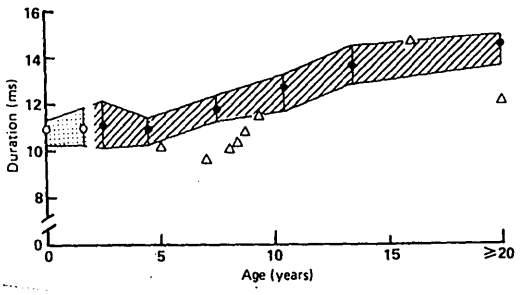


6.1.6 Recordings of the phasic stretch reflex in normal and Rett subjects. (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

Recordings of phasic stretch reflexes in a normal subject and a Rett subject, both of eight years of age. Arrows indicate timing of stimulus.

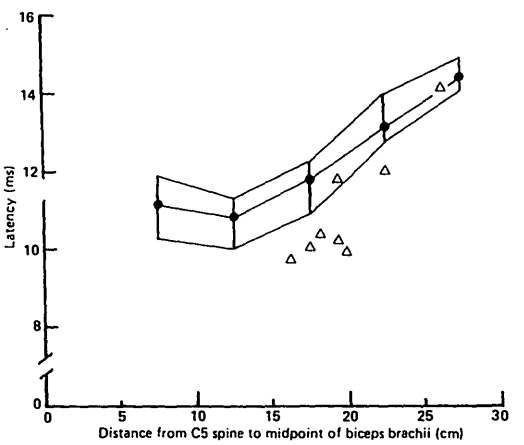


6.1.7 Onset latencies of phasic stretch reflexes in biceps brachii in relation to ages in Rett and normal subjects (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

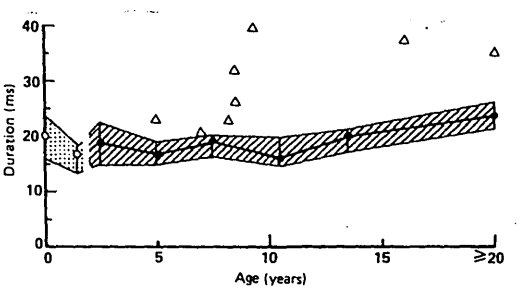


Onset latencies of phasic stretch reflexes in the biceps brachii in relation to age of subjects. The filled and open circles indicate the median values for normal subjects in contracted and relaxed muscles, respectively. The hatched area defines for normal subjects the interquartile range in contracted muscle and the stippled area the interquartile range in relaxed muscle. The triangles indicate data for the Rett subjects in relaxed muscle.

6.1.8 Onset latencies of phasic stretch reflexes in biceps brachii in relation to conduction distance in Rett and normal subjects (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)



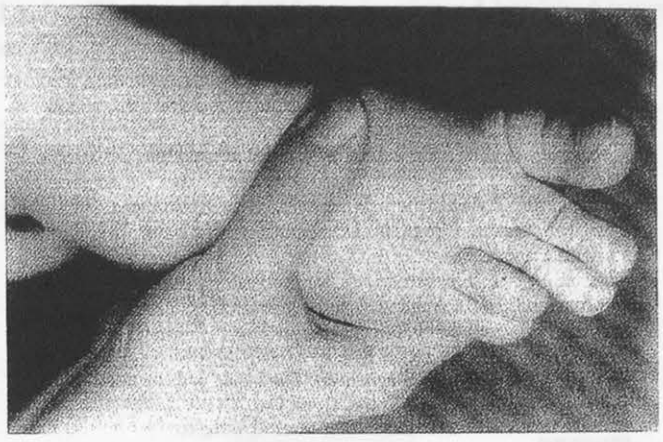
Onset latencies of phasic stretch reflexes in biceps brachii in relation to conduction distance. The filled circles indicate the median values for normal subjects. The open area defines for normal subjects the interquartile range. The data have not been plotted with respect to contracted and relaxed muscle, because of the overlap of arm length up to the age of four years. However, all the data relating to distances above 10 cm relate to contracted muscle. The triangles indicate data of the Rett subjects in relaxed muscle.



Durations of phasic stretch reflexes in biceps brachii in relation to age of subjects. The filled and open circles indicate the median values for normal subjects in contracted and relaxed muscles, respectively. The hatched area defines for normal subjects the interquartile range in contracted muscle and the stippled area the interquartile range in relaxed muscle. The triangles indicate data for the Rett subjects in relaxed muscle.

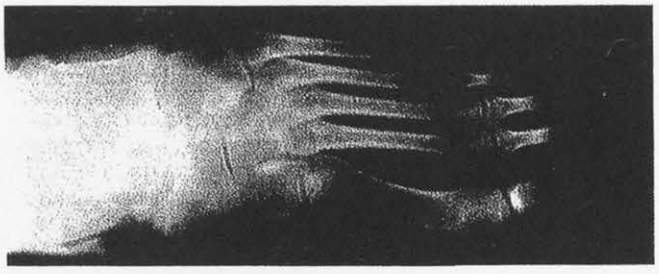
6.1.9 Durations of phasic stretch reflexes in biceps brachii in relation to age in Rett and normal subjects (Eyre et al 1990) reproduced by kind permission of Journal of Neurology Neurosurgery and psychiatry)

6.2.1 Photograph of a the foot of an adult with Rett syndrome showing the shortened 4th ray (Kerr et al 1995) reproduced by kind permission of Neuropediatrics



Photograph of the foot of a *Rett* adult with the fourth toe anomaly. The metatarsal is most clearly shortened with variable involvement of the digit. The other foot was also affected.

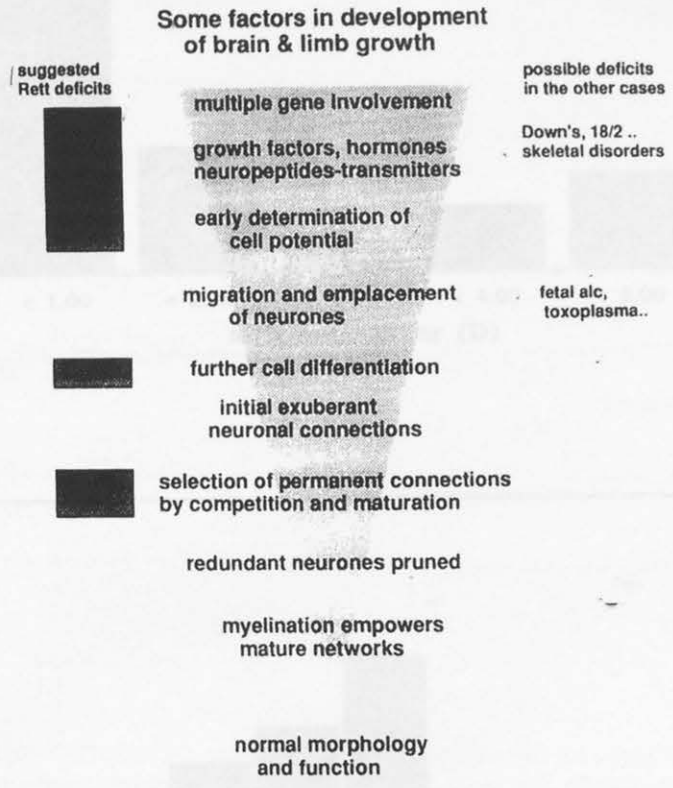
6.2.2 Radiograph of a the foot of an adult with Rett syndrome showing the shortened 4th ray (Kerr et al 1995) reproduced by kind permission of Neuropediatrics



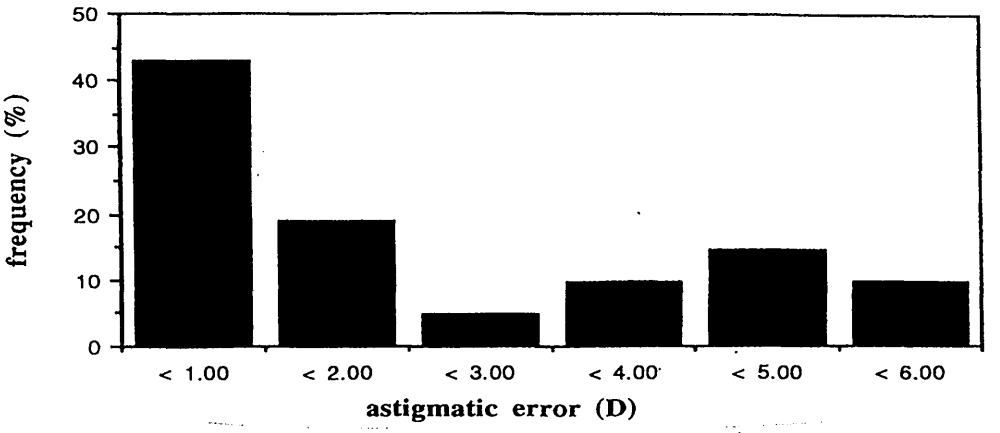
Radiograph of the foot of a *Rett* adult with the fourth toe anomaly showing shortening of the fourth metatarsal. The anomaly was present but less marked on the other foot. Surgery had been carried out for metatarsus varus (bunion).

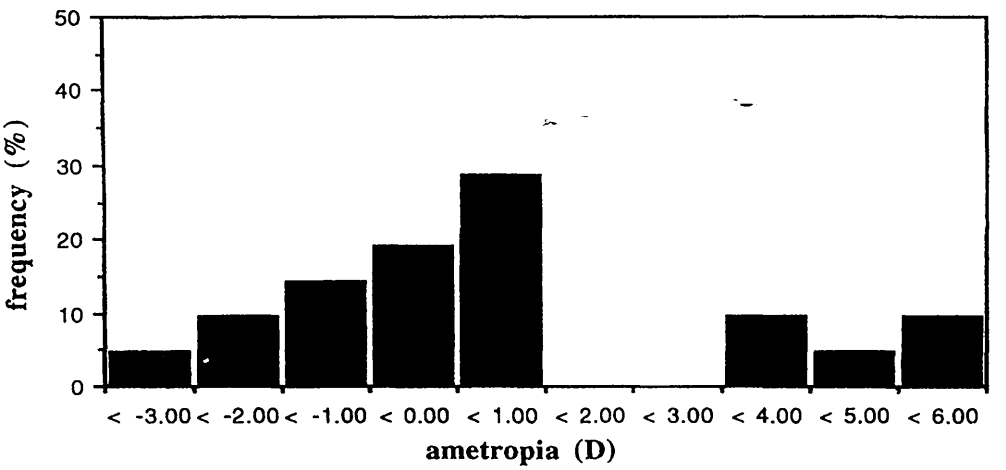
(Georg Thieme Verlag KG)

6.2.3 Diagram to indicate points at which Rett disorder, Downs syndrome and other prenatal conditions might interfere with the normal development of both brain and limbs (Kerr et al 1995) reproduced by kind permission of Neuropediatrics



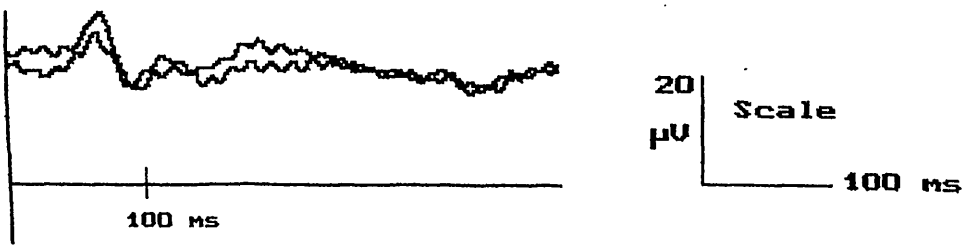
6.3.1 The distribution of astigmatic error and ametropia in subjects with Rett syndrome. (Saunders et al 1995) reproduced by kind permission of Developmental Medicine and Child Neurology.





6.3.2 Binocular VEP to 60'check pattern in normal and Rett subjects (Saunders et al 1995) reproduced by kind permission of Developmental Medicine and Child Neurology.

Representative example of binocular VEP, recorded to onset of a 60' check pattern, in a control subject.



Typical binocular VEP, recorded to onset of a 60' check pattern, in a subject with Rett syndrome.

6.3. Tables comparing latencies and amplitudes of negative and positive waveform components of VEPs in response to 60' check patterns in people with Rett syndrome and controls. (Saunders et al 1995) reproduced by kind permission of Developmental Medicine and Child Neurology.

TABLE I

Latencies (in milliseconds) of negative and positive waveform components of VEPs in response to 60' check stimuli in children with Rett syndrome and controls

	Rett		*Control*		*p*
	Mean	*(SD)*	*Mean*	*SD*	
N60	54.27	(19.17)	54.06	(12.33)	0.9705
P100	88.00	(29.13)	95.44	(17.59)	0.3963
N120	102.00	(18.85)	121.82	(25.61)	0.0819*

*Significant at the 10 per cent level.

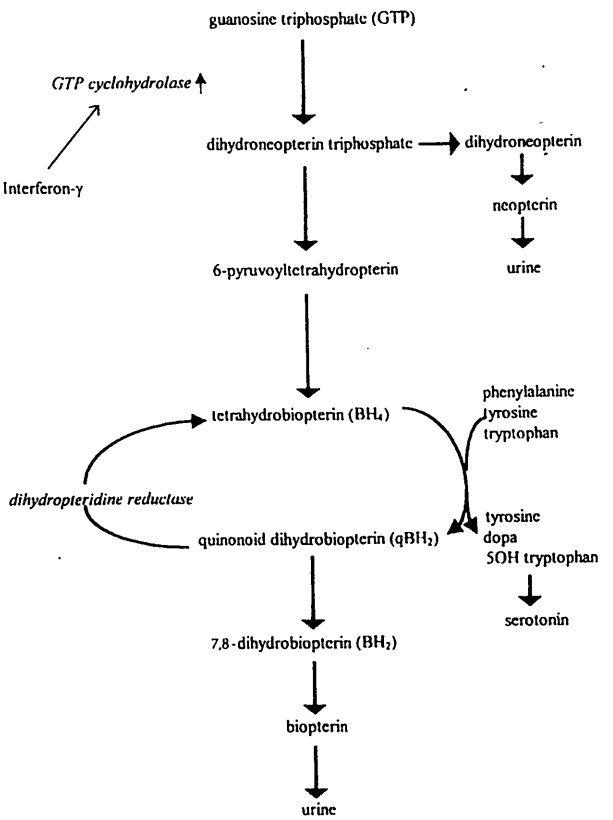
TABLE II

Amplitudes (in microvolts) of negative and positive waveform components of VEPs in response to 60' check stimuli in children with Rett syndrome and controls

	Rett		*Control*		*p*
	Mean	*(SD)*	*Mean*	*SD*	
N60	−3.78	(5.97)	−1.06	(3.01)	0.1130
P100	10.45	(6.98)	17.16	(11.11)	0.0843*
N120	−1.78	(5.49)	1.48	(5.35)	0.2123

*Significant at the 10 per cent level.

6.4.1 The biosynthesis and function of biopterin and neopterin



6.4.2 Urinary neopterin levels in Rett subjects, their sisters and controls. (Messahel et al 2000). reproduced by kind permission of European Journal of Paediatric Neurology

Urinary neopterin values in Rett syndrome subjects, their sisters and controls (μmol neopterin/mol creatinine)

Patient group	⩽5 years	6–10 years	11–21 years	Over 21 years
Rett patients	3692 ± 1086* (n = 7)	1128 ± 129* (n = 9)	1067 ± 126* (n = 12)	879 ± 152 (n = 12)
Controls	1003 ± 311 (n = 8)	668 ± 168 (n = 7)	665 ± 103 (n = 8)	534 ± 264 (n = 6)
Sisters	1482 ± 750 (n = 3)	–	1159 (n = 2)	701 ± 194 (n = 3)

Values are given as mean ± SE
*Significantly different from corresponding control group ($p \leqslant 0.05$)

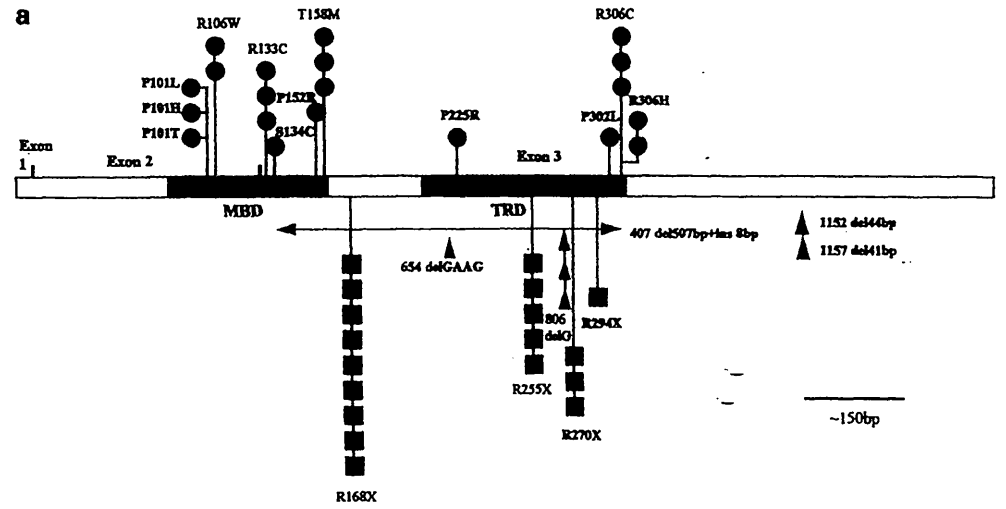
6.4.3 Urinary biopterin levels in Rett subjects, their sisters and controls. (Messahel et al 2000). reproduced by kind permission of European Journal of Paediatric Neurology

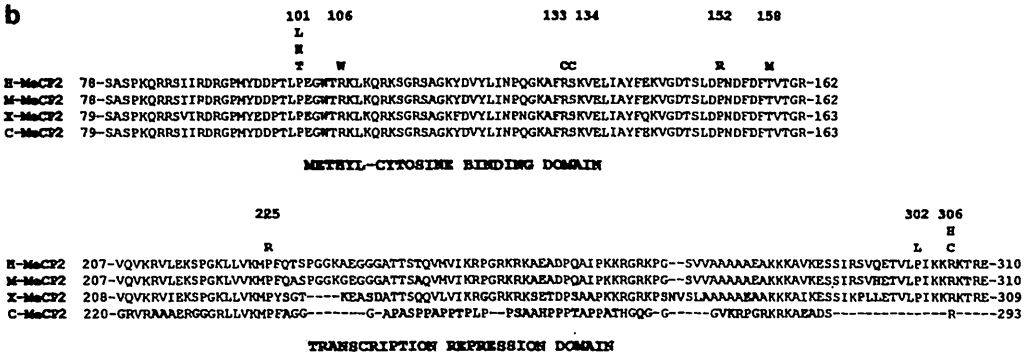
Urinary biopterin values in Rett syndrome subjects, their sisters and controls (mmol biopterin/mol creatinine)

Patient group	⩽5 years	6–10 years	11–21 years	Over 21 years
Rett patients	2027 ± 742 (n = 7)	495 ± 164 (n = 9)	456 ± 64** (n = 12)	261 ± 64* (n = 12)
Controls	427 ± 135 (n = 8)	1083 ± 320 (n = 7)	1397 ± 215 (n = 8)	1423 ± 871 (n = 6)
Sisters	792 ± 656 (n = 3)	—	168 (n = 2)	186 ± 70* (n = 3)

Values are given as mean ± SE
Significantly different from corresponding control group, *$p < 0.05$, **$p < 0.005$

7.1.1 Map of the *MECP2* mutations in people with Rett disorder (Cbeadle et al 2000). reproduced by kind permission of Human molecular genetics.

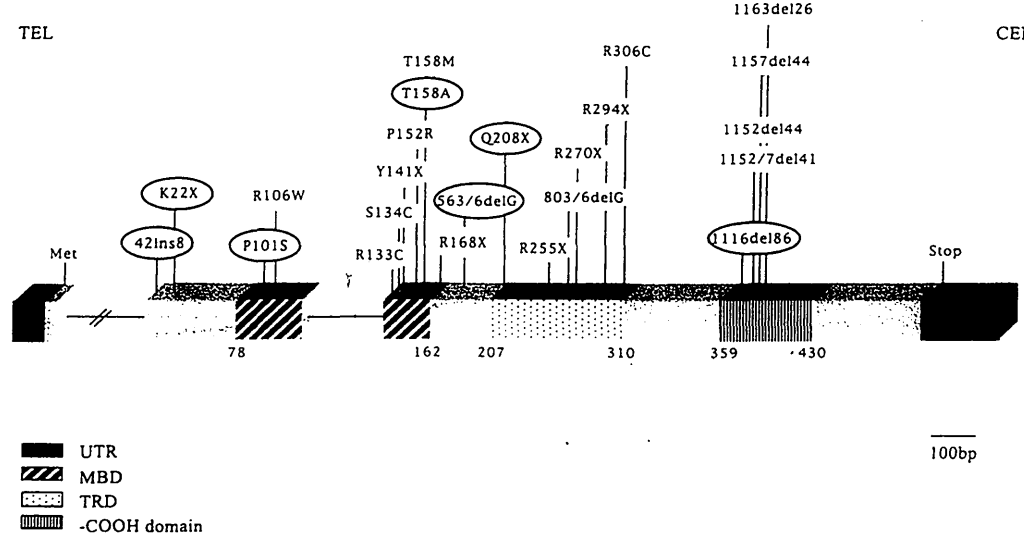




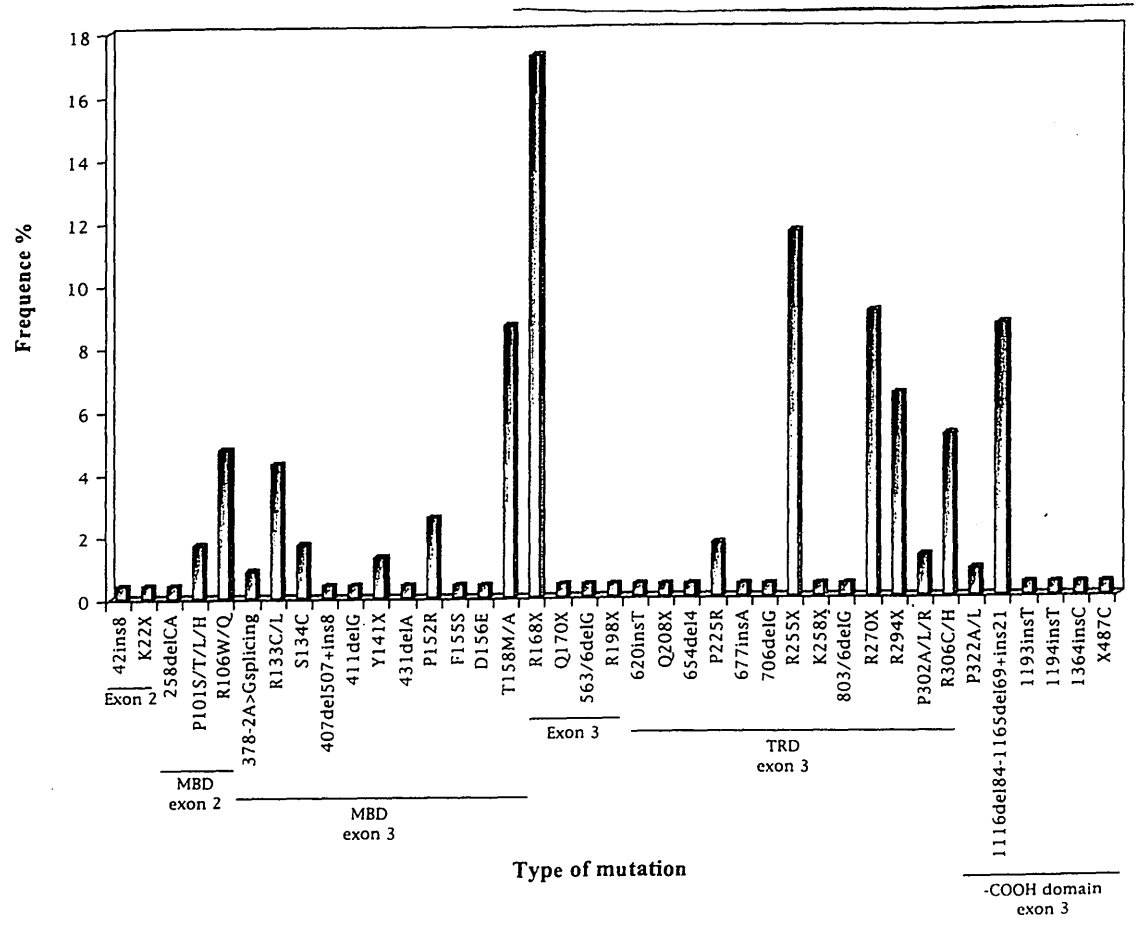
(a) Map of *MECP2* mutations in RTT patients. Missense mutations are denoted by blue circles above the gene and nonsense mutations by red squares and deletions by green arrows (indicating the region deleted) below the gene. Recurrent mutations are denoted by symbols adjoined by lines at identical positions on the gene. Novel mutations are in bold font. MBD, methyl-CpG-binding domain; TRD, transcription repression domain. (b) Detailed map of missense mutations found in the methyl-cytosine binding domains and transcription repression domains of human MeCP2 (H-MeCP2; GenBank P51608), mouse MeCP2 (M-MeCP2; GenBank AAC68880), *Xenopus laevis* MeCP2 (X-MeCP2; GenBank AAD02651) and chicken MeCP2 (C-MeCP2; GenBank Y14166). Conserved amino acids are coloured in blue and similar amino acids are coloured in red.

7.2.1 Diagram of the exon - intron structure of *MECP2* and position of mutations (Vacca et al 2001). reproduced by kind permission of Journal of molecular medicine

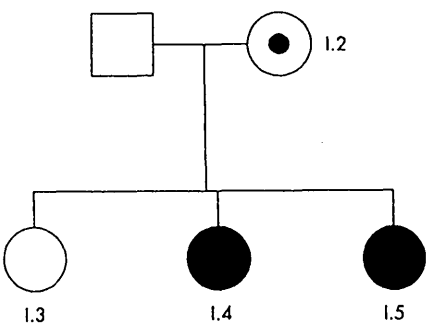
MECP2 gene exon–intron structure and mutation positions are shown. The 3′-untranslated region (*UTR*) is not to scale. Novel mutations are highlighted in a *bold oval*. Specific protein domains are *boxed* and their amino acid positions are reported at the *bottom*. A new domain of potential functional significance, rich in histidine and proline residues, is shown as a *vertically lined box*



7.2.2 The frequency of different mutations in a group of British and Italian patients with Rett disorder (Vacca et al 2001). reproduced by kind permission of Journal of molecular medicine



7.3.1 A family with two sisters with R133C mutations in *MECP2* and Rett disorder. Their mother has the same mutation shown in peripheral blood leucocytes with completely skewed X inactivation and normal intelligence (Gill et al 2003).reproduced by kind permission of the Journal of Medical Genetics



7.4.1 Proportions of cases from BIS (Glasgow) and other sources in whom mutations were identified (Charman et al 2005 in press) reproduced by kind permission of the European Journal of Human Genetics.

	N	*Have mutation (%)*	*No Mutation*
Clinical diagnosis			
Set A (Glasgow):			
Classic Rett syndrome	57	51 (89.5%)	6
Atypical Rett syndrome	5	1 (20%)	4
Set B (Other):			
Classic Rett syndrome	83	65 (78%)	18
Atypical Rett syndrome	45	18 (40%)	27
Overall:			
Classic Rett syndrome	140	116 (82.9%)	24
Atypical Rett syndrome	50	19 (38%)	31

7.4.2a) Age of onset of regression and of reported seizures in cases with and without identified mutations; b) Unusual clinical features for cases with and without identified mutations (Charman et al 2005 in press) reproduced by kind permission of European Journal of Human Genetics.

a) Age of onset for cases with and without identified mutations

	Mutation identified N (row %)	*No mutation identified N (row %)*	***Total N***
Age of onset of regression [a]			
Before 6 months	5 (33.3%)	10 (66.7%)	**15**
6 to 30 months	115 (81.0%)	27 (19.0%)	**142**
After 30 months	9 (75.0%)	3 (25.0%)	**12**
Age of first seizures [b]			
Before 12 months	3 (18.8%)	13 (86.7%)	**16**
12 to 60 months	50 (74.6%)	17 (25.4%)	**67**
After 60 months	22 (75.9%)	7 (24.1%)	**29**

b) Unusual clinical features for cases with and without identified mutations

	Mutation identified N (row %)	*No mutation identified N (row %)*	***Total N***
Event or illness that may have caused neurological deficit [c]			
Yes	11 (44.0%)	14 (56.0%)	**25**
No	120 (74.1%)	42 (25.9%)	**162**
Facial dysmorphism			
Yes	15 (55.5%)	11 (44.4%)	**26**
No	100 (73.5%)	36 (26.5%)	**136**

a) $p<.001$
b) $p<.001$
c) $p<.01$

7.4.3 Analysis of clinical features according to the type of mutation a) by number of diagnostic criteria present, b) by BIS and RSBQ severity scores (maximum severity =10); c) by age at onset of regression and of first reported seizure (Charman et al 2005 in press) reproduced by kind permission of European Journal of Human Genetics.

a) Typicality of presentation by mutation type and location

	Early truncating		*Missense*		*Late truncating*	
	Mean (SD)	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*
Number of Necessary diagnostic features present[a]	6.73 (0.62)	56	6.64 (0.63)	50	6.25 (0.93)	28
Number of Supportive diagnostic features present	4.27 (1.29)	56	4.54 (1.33)	50	4.07 (0.77)	28

b) Severity of outcome by mutation type and location

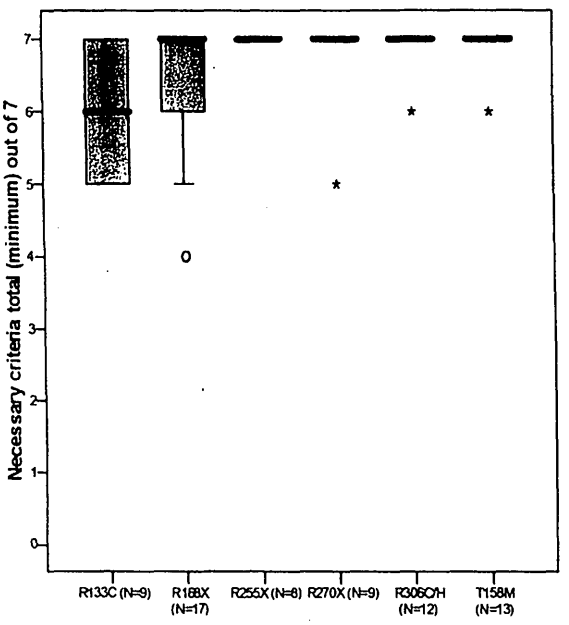
	Early truncating		*Missense*		*Late truncating*	
	Mean (SD)	*N*	*Mean (SD)*	*N*	*Mean (SD)*	*N*
BIRS severity score[b]	6.78 (2.66)	51	5.44 (2.76)	48	4.43 (2.46)	28
RSBQ Hand factor score[c]	8.89 (1.80)	52	7.93 (2.72)	42	6.76 (3.11)	28

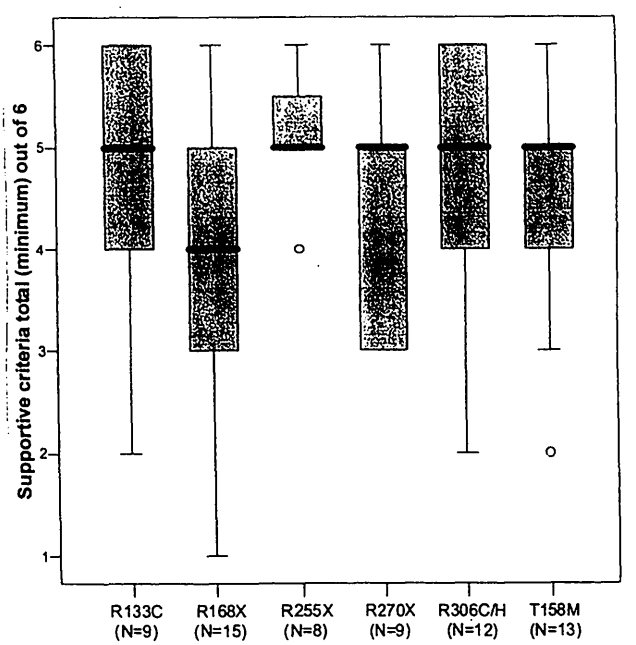
c) Age of onset for cases by mutation type and location

	Early Truncating	*Missense*	*Late Truncating*	*Total*
	N (row %)	*N (row %)*	*N (row %)*	*N*
Age of onset of regression				
Before 6 months	4 (80%)	1 (20%)	0 (0%)	**5**
6 to 30 months	46 (40.4%)	43 (37.7%)	24 (21.1%)	**114**
After 30 months	3 (30.0%)	4 (40.0%)	3 (30.0%)	**10**
Age of first seizures				
Before 12 months	2 (67.3%)	0 (0%)	1 (33.3%)	**3**
12 to 60 months	21 (42.0%)	20 (40.0%)	9 (18.0%)	**50**
After 60 months	7 (31.8%)	11 (50.0%)	4 (18.2%)	**22**

a) $p<.05$
b) $p<.001$
c) $p<.01$

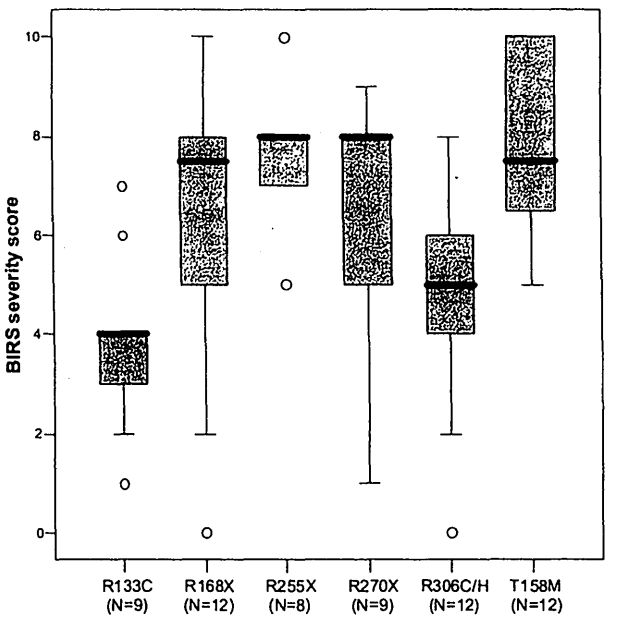
7.4.4 Necessary and supportive criteria associated with commonly occurring mutations (Charman et al 2005 in press) reproduced by kind permission of European Journal of Human Genetics.

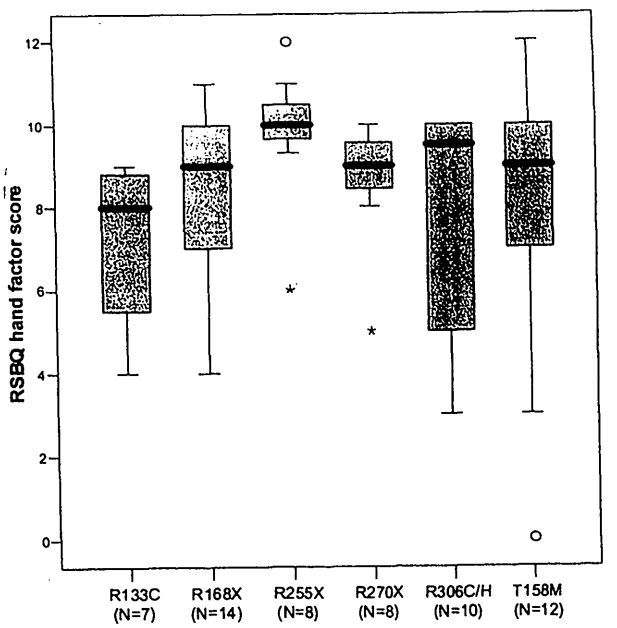




Boxplot displaying number of necessary diagnostic criteria (left) and number of supportive criteria (right) for patients with each of 6 common mutations. Shaded box indicates the interquartile range and thick black line the median of each distribution. Whiskers indicate the highest and lowest values observed, except for outliers (O = 1.5 to 3 boxlengths from the upper or lower edge of the box; * = > 3 boxlengths from the upper or lower edge of the box). N = number of patients with each mutation.

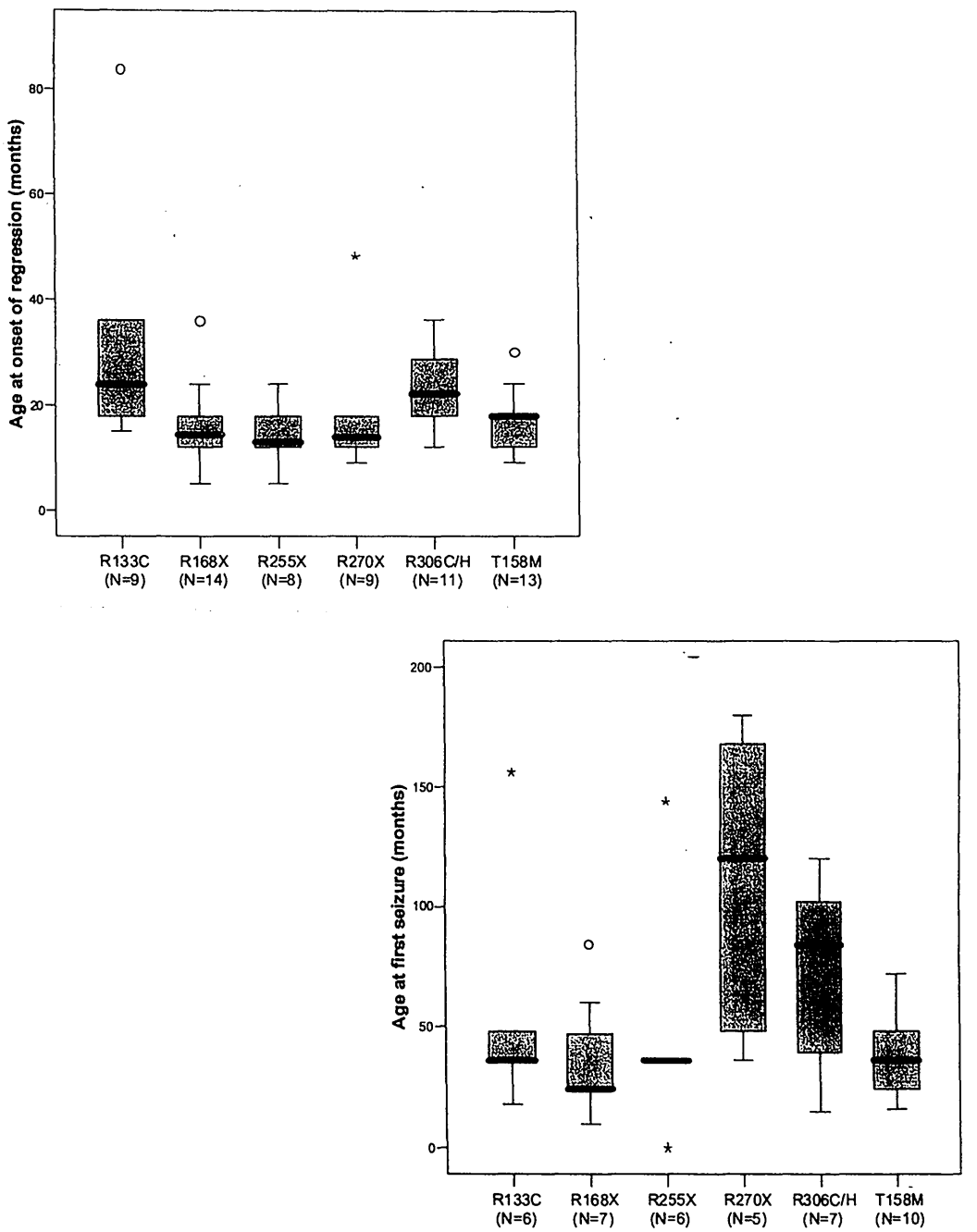
7.4.5 BIS (BIRS) severity score and RSBQ hand factor scores for commonly occurring individual mutations (Charman et al 2005 in press) reproduced by kind permission of European Journal of Human Genetics.





Boxplot displaying number of BIRS severity score (left) and RSBQ hand factor score (right) for patients with each of 6 common mutations. Shaded box indicates the interquartile range and thick black line the median of each distribution. Whiskers indicate the highest and lowest values observed, except for outliers (O = 1.5 to 3 boxlengths from the upper or lower edge of the box; * = > 3 boxlengths from the upper or lower edge of the box). N = number of patients with each mutation.

7.4.6 Age of onset of regression and age at onset of reported seizures related to individual mutations (Charman et al 2005 in press) reproduced by kind permission of European Journal of Human Genetics.



Boxplot displaying age at onset of regression in months (left) and age at onset of first seizure (right) for patients with each of 6 common mutations. Shaded box indicates the interquartile range and thick black line the median of each distribution. Whiskers indicate the highest and lowest values observed, except for outliers (O = 1.5 to 3 boxlengths from the upper or lower edge of the box; * = > 3 boxlengths from the upper or lower edge of the box). N = number of patients with each mutation.

8.1 Analysis of respiratory rhythms in TK before and two months after commencing treatment with buspirone.(Kerr et al 1998) reproduced by kind permission of Monduzzi Editori.

Type of breathing	% of total record		brief explanation of terms
	Before Buspirone	After Buspirone	
Normal	25.3	66.2	Ramp inspiration and Expiration
Atypical	11.2	2.7	unclassified
Shallow breathing	5.5	4.2	Low amplitude < 35 brth/min
Rapid shallow	2.6	3.1	Low amplitude > 35 brth/min
Tachypnoea	0.2	1.6	35-45 brth/m, no central apnoea
Deep breathing	18.4	1.5	< 35 brth/m, no central apnoea
Hyperventilation	2.5	2.3	Rapid brths with central apnoea
Cheyne-Stokes	9.5	6.9	periodic breathing
Biot's breathing	0.0	0.5	abrupt apnoea and abrupt brths
Apnoea	2.3	0.8	Cessation of breathing in expiration
Regular breath-holds	2.2	6.7	succession of breath-holds
Breath-hold	3.8	2.2	delay in expiration
Protracted Inspiration	16.4	1.2	No change in BP or pulse
Valsalva's manoeuvre	0.0	0.0	Signs of reduced venous return
Autonomic indices	**Mean resting values**		**Normal range for age**
Cardiac vagal tone (linear scale)	6.7	6.6	6-19
Heart rate (beats/m)	93	96	70-97
Baroreflex sensitivity (ms/mmHg)	5.4	4.6	5-14
Mean arterial pressure (mmHg)	82	83.6	70-120

Footnote: Breaths per minute=brth/min: expiration=exp: Transcutaneous blood gases remained in the normal range during both recordings

8.2.1 Scoliosis by age group and severity (Kerr et al 2003). reproduced by kind permission of Brain & Development

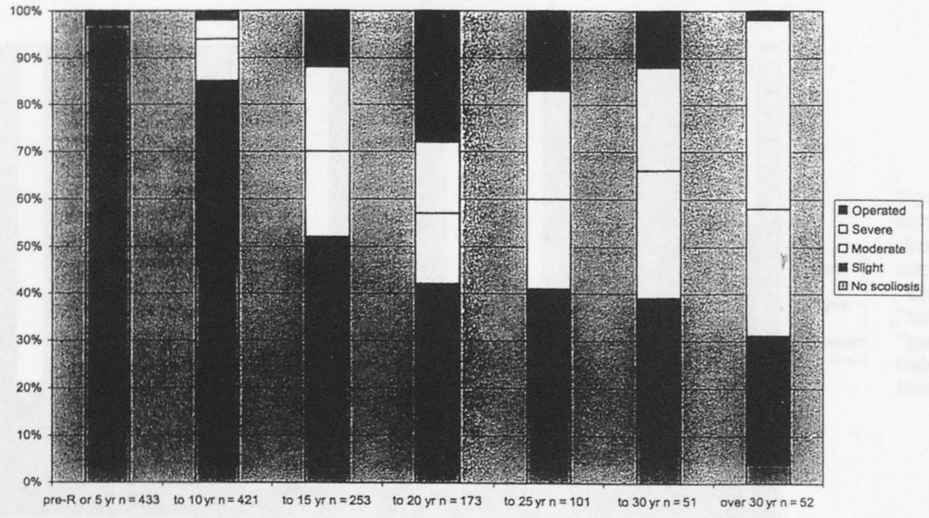


Figure 1. Scoliosis by age group and severity. Data for some people are recorded in more than one age period so that the graph shows the reported severity of scoliosis in these individuals in each age period and not the present age of all of the individuals recorded in the survey.

8.2.3 Change in function after scoliosis surgery in 50 people with classic Rett (Kerr et al 2005). reproduced by kind permission of Brain & Development.

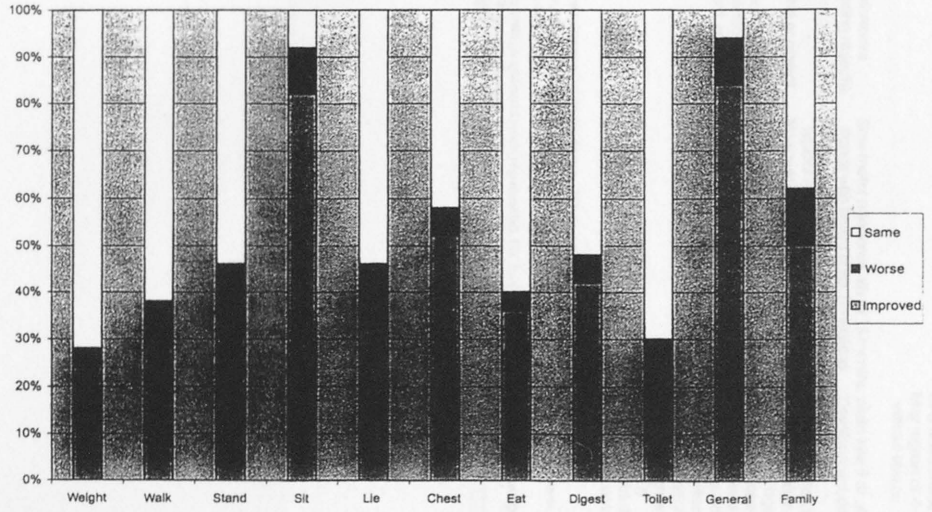


Figure 2. Change in function after scoliosis surgery in 50 people with classic Rett syndrome. Columns indicate altered function attributed by the parent to scoliosis surgery. "Chest" indicates changes in lung complaints, "toilet" indicates changes in bowel function, "general" indicates a change in general well-being, and "family" indicates effects on the family.

8.3.3 Comparing possible early signs in autistic spectrum disorder , Angelman Syndrome and Rett syndrome. (Kerr et al 2003). reproduced by kind permission of Primary Psychiatry.

Age	Autism	Angelman's Syndrome Disorder	Rett Disorder
0–6 months	Birth unremarkable Not dysmorphic OFC remains normal Placid Poor orienting, smiling, and vocalising[13] Normal response to objects[13] Abnormal movements (possibly) EEG normal	May be light compared to siblings Fair if gene deletion present Plagio/brachycephaly common Birth OFC normal, decelerating Poor feeding, regurgitation, Fails to thrive Placid, lacking babble Smiles early Trunk hypotonia, limb hypertonia Movement poor and jerky Epilepsy—salaam attacks EEG typical—bilateral synchronous 2Hz spike and wave	Birth unremarkable Not dysmorphic Birth and neonatal OFC normal, decelerating Occasionally slow feeding Usually thrives Placid but babbles Smile normal or late Responds to faces Usually hypotonia Posture and movements restricted Epilepsy uncommon EEG normal or immature
7–12 months	Rather poor response to people, aversion to touch. Developmental progress Lack of social smiling Poor orientation to name, Looking at people less, less shared attention[14] Little interest in social games Repetitive movements OFC normal	Contented A little developmental progress Smiling No babble or words Dysmorphic (small chin, wide mouth) "Commando crawl" or shuffle Jerky movements OFC decelerates Regression only with seizure	Contented until regression A little developmental progress Smiling, likes faces Babble or real words until regression Lack of exploration Not frankly dysmorphic Shuffle, rarely true crawling Increasing stereotyped limb movements OFC decelerates May regress at 4–12 months without seizure
1–2 years	Odd postures and preferences (eg, finger flicking, tasting objects). Ignores people Poor shared attention Pretend play is repetitive or absent Lack of words Regression at 15–20 months in some children with loss or reduction in speech, social contact, and affect	Slow motor milestones, sits at 13 months, stands with broad base, no walking Epilepsy problematic, status common, typical EEG No speech, quiet Inappropriate laughter OFC decelerates (microcephaly 60%) Night sleep disturbed	Walks late if at all Development stagnates until regression Acute reduction in hand use and communication usually at 1–2 years of age, without illness At 2 years of age or later: Respiration becomes irregular EEG becomes abnormal with slow wave and spikes Clinical epilepsy in some OFC growth may resume (final av. 2SD) Night sleep disturbed Unexplained crying episodes

OFC=occipitofrontal circumference; EEG=electroencephalogram; final av. 2SD=final average at second standard deviation.

Note: Not all symptoms are present in every disorder case and absence of these features does not exclude a diagnosis. However, awareness of these possible early deviations will aid detection and improve support for the child and family.

Information was supplied by Dr. Jill Clayton-Smith (Angelman's syndrome disorder), Drs. Tony Charman and Fiona Knott (Autism), Dr. Bronwen Burford (Rett disorder). This table was constructed in consultation with them.

Kerr AM. *Primary Psychiatry.* Vol 10, No 2. 2003.

9.1.1 Reported deaths among 31 people with classic Rett syndrome (Kerr et al 1997). reproduced by kind permission of European Child and Adolescent psychiatry.

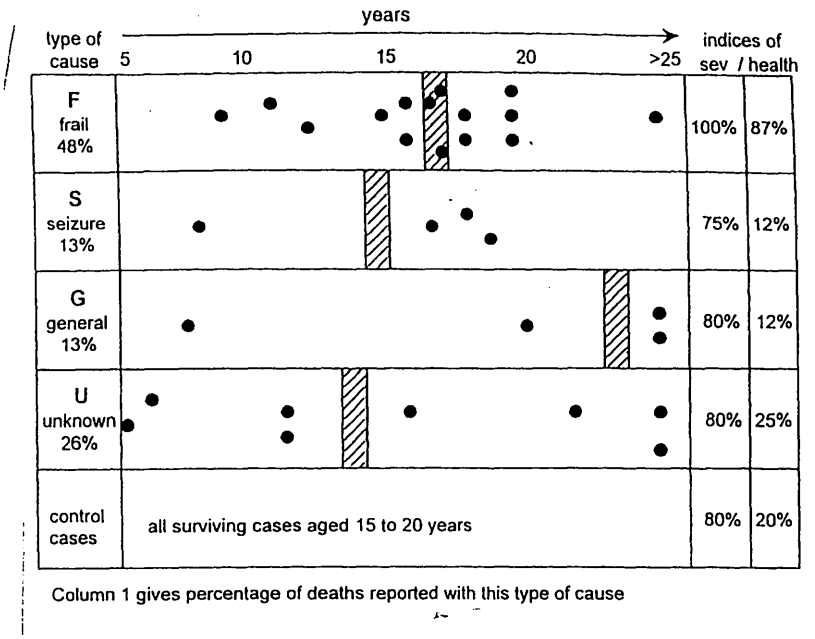


Fig. 1 Deaths among 31 classic cases by age and type of cause: 'Frail' (F)=wasted with contractures and usually major feeding difficulty; 'Seizure' (S)=associated severe seizure disorder. 'General' (G)=causes such as accident or tumour which might affect a normal person. 'Unexpected' (U)=sudden unexpected death. 'Index of Severity of RS' is derived from feeding difficulty score, muscle tone disturbance, presence of seizure and scoliosis and walking ability. 'Index of Health' is derived from reports of health over the past 12 months. Higher percentages indicate greater severity and poorer health

9.1.2 Autopsy reports in nine deaths of people with classic Rett syndrome. (Kerr et al 1997) reproduced by kind permission of European Child and Adolescent psychiatry.

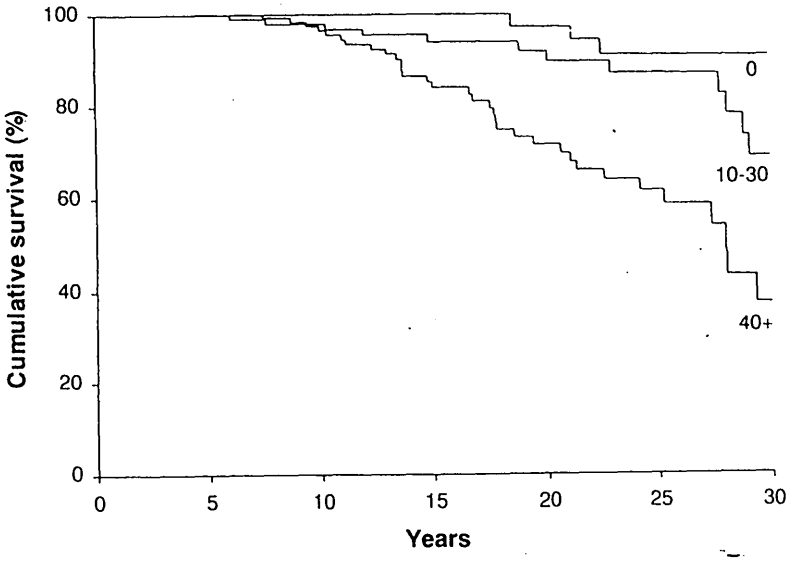
'Autopsy reports in nine classic cases

Case	Age	Circumstances	PM report	Brain Wt	Golgi
1	19	S	basal lung congestion[a]	1170 g	[b]
2	20	F	bronchopneumonia[a]	975 g	[b]
3	11	U	no abnormality	927 g	[b,c]
4	3	U (night)	no gross abnormality[a]	not given	[b]
5	11	U (night)	H Infl isolated, nil gross[a]	1120 g	[b]
6	5	U (night)	no evident cause of death	970 g	[b]
7	33	U	no gross abnormality	915 g	[b]
8	15	F	areas of atelectasis	900 g	
9	11	F	bronchopneumonia	956 g	

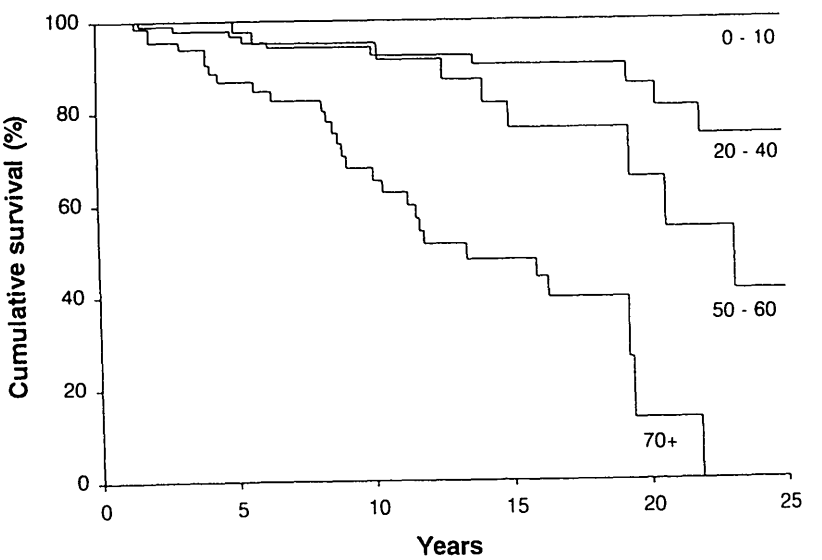
[a] pallor of S nigra commented upon
[b] golgi staining of dendritic growth in frontal, temporal, hippocampal, occipital areas (see text)
[c] fetal disperison of AV node, aberrant nodal cells, fatty infiltration of AV node and bundle of His

9.2.1 Kaplan Meyer curves for people with Classic Rett grouped by pre-regression severity. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development

Kaplan-Meier survival curves for people with classic Rett grouped according to 1) severity scores before regression and 2) severity scores at 5-9 years. The numbers of people being followed up at 0-5 (pre-regression),-10, -15 ,-20, -25 and -30 years in figure 1. are 463, 351, 257,180, 119, 78 and 33 respectively; and in figure 2. are 285, 201, 133, 87, 38 and 16 respectively.
The cases included in these figures are all 'classic' therefore the period 0-5 years describes only the period before the onset of their regression (see text).



9.2.2 Kaplan Meyer curves for people with Classic Rett grouped by early post-regression severity. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development

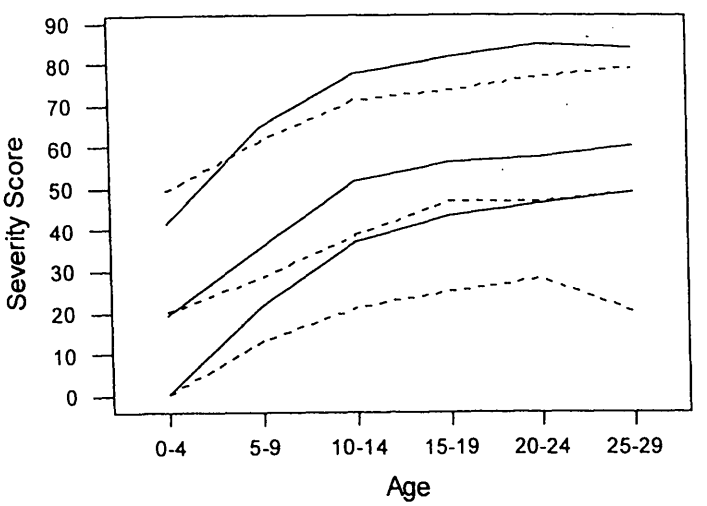


9.2.3 Deaths related to the severity before the final episode. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development

type of death	SS range	mean SS	median SS	N=59
debilitated	30-100%	90%	90%	35
Seizure related	30-100%	70%	70%	5
general	30-100%	60%	70%	7
unexpected	20-100%	71%	75%	12

| Deaths related to the severity score before the final episode
SS=severity score. It can be seen that among those who have died those who are debilitated (weak, thin and in poor general health) are in the most severe group before the episode culminating in death.

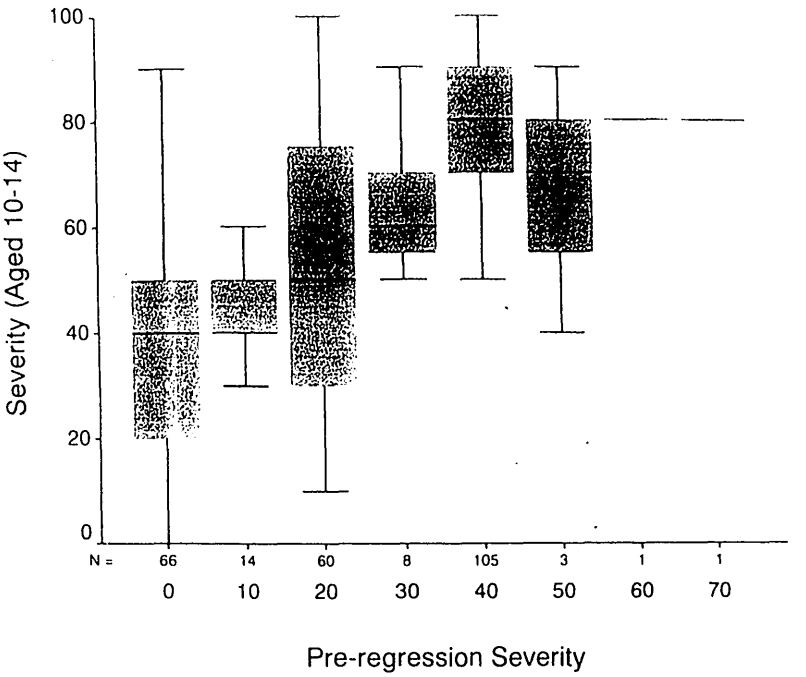
9.2.4 The change in severity scores with age in individuals with classic and non classic Rett. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development



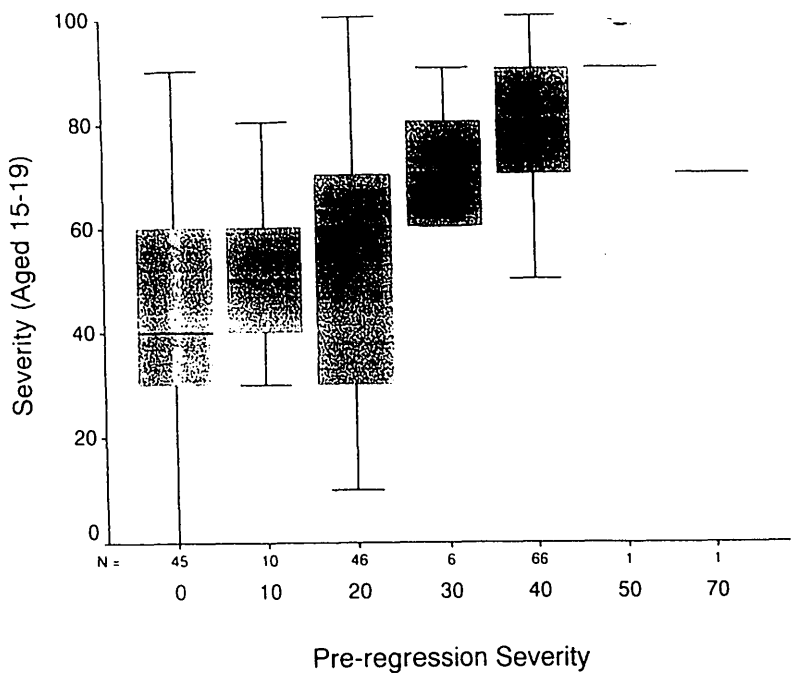
\Mean levels of severity scores with age in people with classic Rett (solid line) and Rett non classic (dotted line), grouped according to pre-regression severity scores. For classic cases the period 0-5 years describes only the period before the onset of their regression. For non-classic cases who have not regressed this interval described the situation before 5 years (see text).

9.2.5 Box plots of severity scores at age 10-14 years a) and at 15-19 years b) in relation to pre-regression severity scores in people with classic Rett. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development

a)



b)

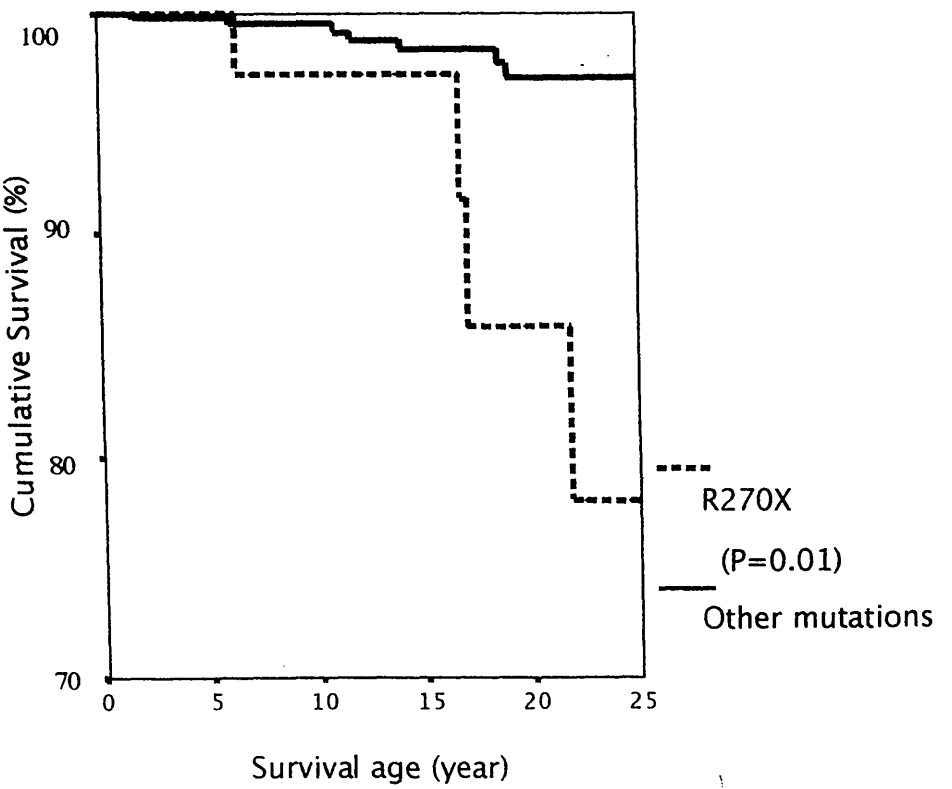


Box plots of severity scores at age 10-14 years (a) and 15-19 years (b) in relation to pre-regression severity scores in people with classic Rett. Each box represents the inter-quartile range with the horizontal line in the box denoting the median. The 'whiskers' represent the range of values after any outliers have been removed (ref 14)

9.2.6 Most frequently occurring mutations in the study population related to most recent severity scores. (Kerr & Prescott 2005) reproduced by kind permission of Brain & Development

Mutation protein	mean severity score	N=
T158M	77%	29
R255X	67%	20
R168X	66%	27
R270X	66%	21
R106W	65%	7
P152R	61%	6
R306C	53%	16
R133C	36%	18

9.3.1.Survival with R270X mutation compared with all other mutations. (Jian et al in press 2005) reproduced by kind permission of European Journal of Human Genetics



9.3.2.The distribution of 8 common and other collected mutations on *MECP2* by deceased status in Australian and UK cases of Rett disorder. (Jian L et al in press 2005) reproduced by kind permission of Eur J Hum Genet

The final figures in this table have been added to indicate the percentage of cases of each mutation who are known to have died. (Jian L et al in press 2005) reproduced by kind permission of European Journal of Human Genetics

Mutation	Age	Australian cases		UK cases		Total (%)
	Median (range)	Deceased	Alive	Deceased	Alive	
p.R106W	11.0 (2.0-27.6)	1	5	1	9	16 (3.0)
p.R133C	15.2 (4.0-41.0)	0	10	0	24	34 (6.5)
p.T158M	13.0 (2.0-40.0)	1	20	2	42	65 (12.4)
p.R168X	10.9 (2.0-42.0)	0	20	1	37	58 (11.1)
p.R255X	9.0 (2.0-40.0)	0	13	2	27	42 (8.0)
p.R270X	12.6 (2.0-30.0)	4	10	1	29	44 (8.4)
p.R294X	13.1 (2.0-40.0)	0	17	0	16	33 (6.3)
p.R306C	17.0 (3.0-39.0)	1	10	0	19	30 (5.7)
Others	12.0 (1.0-54.0)	1	61	8	132	202 (38.6)
All		8	166	15	335	524 (100.0)

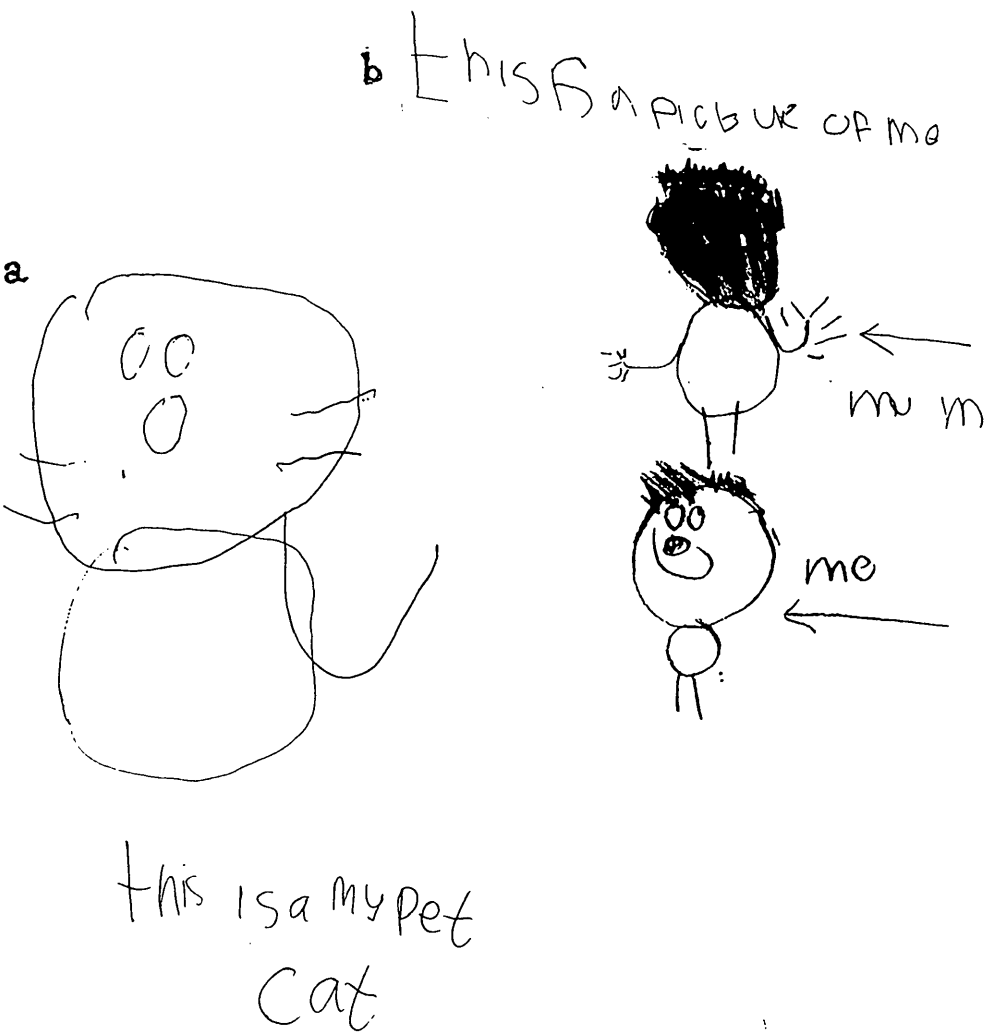
9.4.1. Mutation positive people who converse: Comparison of cases and controls. For derivation of health and severity scores see Figure 2.2.1 & Kerr et al 2003. Low scores indicate less severe disease and high scores more severe disease (maximum 10). 2- age at onset of regression, 3 ability to feed self with cup or spoon, + Wilcoxon Rank Sum Test, ǂ Fisher's Exact Test, 1 six of the 13 cases had not regressed so the upper quartile is not calculable. (Kerr et al 2005) by kind permission of Journal of Intellectual Disability Research

Variable	Cases	Controls	p-value
Mean age at update(yr) (SD)	22.4 (8.6)	20.0 (8.8)	0.27*
Mean severity score (SD)	2.2 (1.9)	6.8 (2.4)	<0.001*
Mean feeding score (SD)	1.6 (0.8)	3.2 (1.8)	<0.001*
Mean health score (SD)	0.8 (1.2)	3.2 (2.4)	<0.001*
Median age at regression (mths) (IQR) [2]	36 (6 no reg[1])	17 (12,24)	<0.001*
Centile head circumference <3 (%)	0/13 (0%)	40/95 (42%)	0.004†
Injury to self	4/13 (31%)	38/109 (35%)	1.00†
Injury to others	4/13 (31%)	19/107 (18%)	0.44†
Able to walk unsupported at 10-15 yrs (%)	11/13 (85%)	49/109 (45%)	0.014†
Able to self-feed at 10-15 yrs (%) [3]	12/13 (92%)	12/108 (11%)	<0.001†
True words before regression or age 5 (%)	12/13 (92%)	75/108 (69%)	0.014†
Epilepsy ever (%)	2/13 (15%)	81/110 (74%)	<0.001†
Vacant spells (%)	10/13 (77%)	91/107 (85%)	0.67†
Night-time sleep disturbed	7/12 (58%)	79/108 (73%)	0.44†
Handedness (Left/Right/Both)	6/2/4	34/27/18	0.49†
Classic Rett (%)	3/13 (23%)	100/110 (90%)	<0.001†
C terminal deletions	5/13 (38%)	9/110 (8%)	0.014†
R133C	5/13 (38%)	7/110 (6%)	0.006†

9.4.2. Mutation positive people who converse: Molecular Genetic Results: *MECP2* gene analysis and X-chromosome inactivation ratios for the study group. (Kerr et al 2005) by kind permission of Journal of Intellectual Disability Research

Case	Mutation (protein)	Mutation (sequence)	X inactivation ratio
1	R133C	c.397C>T	34:66
2	R133C	c.397C>T	23:77
3	P389X	c.1164-1207del44bp	28:72
4	P389X	c.1164-1207del44bp	45:55
5	R133C	c.397C>T	41:59
6	P389X	c.1164-1207del44bp	40:60
7	P389X	c.1164-1207del44bp	17:83
8	R168X	c.502C>T	not informative
9	G269fsX288	c.803delG	15:85
10	P388_393del	c.1162-1179del18bp	38:52
11	R133C	c.397C>T	insufficient DNA
12	R133C	c.397C>T	49:51
13	R168X	c.502C>T	not informative

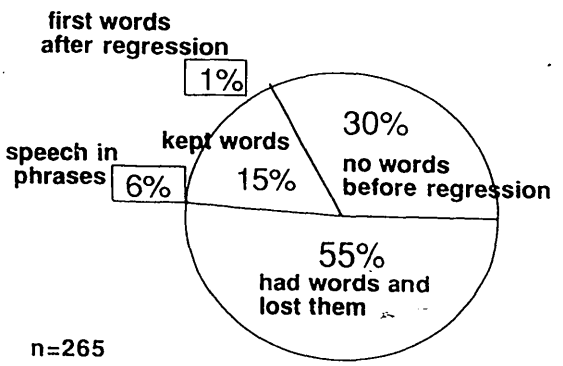
9.4.3. Drawings and writing by cases a) case 8, b) case 10. (Kerr et al 2005) by kind permission of Journal of Intellectual Disability Research



9.4.4. Reported skills of mutation positive people who can converse (Kerr et al 2005) by kind permission of Journal of Intellectual Disability Research

Skill	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13
Understand speech	Single words	Sentences	Sentences	Sentences	Sentences	Single words	Sentences	Sentences	Sentences	Sentences	Sentences	Sentences	Sentences
Obey speech	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Use words	Single	Sentences	Sentences	Parts of word	Sentences	Phrases	Single	Phrases	Sentences	Phrases	Phrases	Sentences	Sentences
Use sign language	No	No	No	Makaton	No	No	No	Makaton	N/A	No	Dinner, toilet, good morning	N/A	N/A
Answer (word/sign)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	In sentences	Yes	In phrases	Yes	In sentences
Write	No	No	No	Yes	Yes	No	No	Yes	Yes	No	Scribble	Yes	Yes
Read	No	Yes	No	Yes	No	No	No	Yes	Yes	No	Few single words	Yes, copy	Yes, romance novels
Count	No	Recite	No	Recite	Recite	No	Recites to 20	Yes	Yes	Recite	To 10, missing '5'	Yes	Yes, including money
Drawing	No	No	No	Yes	Yes (scribble)	No	No	Yes	Yes	Yes	Scribble	Yes	Yes
Affectionate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Prefers objects	No	No	No	No	No	No	No	No	No	No	No	No	No
Anxious	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Occasionally	Yes
Angry	No	No	No	Rarely	Yes	No	No	No	No	Rarely	Sometimes	No	Rarely but with reason
Distressed by	Big dog, anger	Failure, strange	Nothing	Failure, injustice	Noise, unexplained	Conflict	Anger, sad faces, noise	Crowds, noise	Crowds	Noise	Loud noise, inaction	Being told off	Being told off
Relaxed by	Bath	Music	Always relaxed	Dancing to music	Nothing	Massage	Massage	Swimming	Read, walk, pet care	Massage	Talk about nice events	Cuddles, video	Reading
Learns from	Situation	Instruction	Instruction	Instruction	Instruction	Situation	Situation	Situation	Using music	Situation	Example	Instruction	Instruction and experience
Shows initiative	No	A little	No	A little	A little	A little	No	No	Little	No	No	Little	Some
Remembers people	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Well	Yes	Yes	Yes	Yes
Remembers places	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Poor	Yes	Yes	Yes	Yes
Remembers names	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Well	Yes	Yes	Yes	Yes
Laughs at	Slapstick	Slapstick	Slapstick	Slapstick	Nothing reported	Slapstick	Silly songs	Slapstick	Simple jokes	Slapstick	Incongruity	Slapstick	Nothing reported
Entertainment	Sung to	Talking	Talking	Music	Talk & sing	Talking, music	Watching people	Swimming	Familiar company	Sit in café watching	Quiet family party	Hiking	Dancing, swimming
TV favourites	Simpsons	Mary Poppins	Harry Potter	Tweenies	Mr Bean	Sports	Sports	None	Older musicals	None	Singing	Mr Bean, various	Soap operas
Response to music	Enjoys	Enjoys	Sings	Enjoys	Enjoys	Enjoys	Enjoys	Enjoys	Enjoys	Enjoys	Enjoys if quiet	Enjoys	Enjoys sometimes
Songs	Enjoys	Recites	Sings words	Enjoys	Sings words	Enjoys	Enjoys	Sings words	Sings well	Recites	Sings well	Sings well	Sings words

9.5.1 Proportions of those acquiring speech and retaining clear words in 265 cases (classic and atypical) in BIS (Kerr, Belichenko et al 2001, by kind permission of Brain & Development)

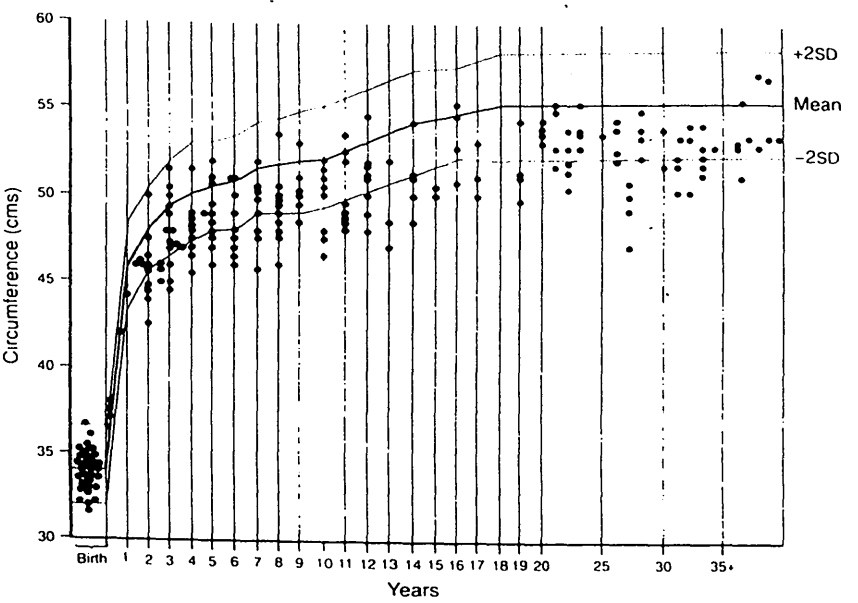


9.5.2 Comparison of the characteristics of adults with and without speech from BIS (Kerr, Belichenko et al 2001, by kind permission of Brain & Development)

Case	Status	Yr	OFC	Regr	Speech	Self F	Resp	Fsc	Tone	Walk S	Ep	Scol	S (%)	Vis	Hear	Contact	Agit	Music	Sleep
1	R**	37	55	36	Yes/Yes	Yes	Yes	1	N	Yes	No	No	0	Yes	Yes	Yes	Yes	Yes	NK
2	R**	32	56	36	Yes/Yes	Yes	Yes	2	Dys	Yes	Yes	No	30	Yes	Yes	Yes	Yes	Yes	NK
3	CR	26	53	9	Yes/Yes	Yes	Yes	9	Dys	No	Yes	Mild	70	Yes	Yes	Yes	Yes	Yes	Yes
4	CR	37	53	24	Yes/Yes	No	Yes	5	N	Yes	No	Op	30	Yes	Yes	Yes	Yes	Yes	Yes
5	CR	28	52	18	Yes/Yes	Yes	Yes	5	N	Yes	No	Op	30	Yes	Yes	Yes	Yes	Yes	Yes
6	R**	17	52	None	Yes/Yes	Yes	Yes	0	N	Yes	No	No	0	Yes	Yes	Yes	Yes	Yes	Yes
7	CR	28	53	18	Yes/Yes	Yes	Yes	3	N	Yes	Yes	Mild	40	Yes	Yes	Yes	Yes	Yes	Yes
8	R†	24	56	8 yr	Yes/Yes	Yes	Yes	5	N	Yes	No	No	10	Yes	Yes	Yes	Yes	Yes	No
9	R†	31	52	9 yr	Yes/Yes	Yes	Yes	0	Dys	Yes	No	No	10	Yes	Yes	Yes	Yes	Yes	No
10	R**	31	49	None	Yes/Yes	Yes	Yes	1	N	Yes	No	No	0	Yes	Yes	Yes	Yes	Yes	Yes
Mean		29	53					3.1					22%						
11	CR	37	52	24	No/No	No	Yes	5	Hyp	No	No	Sev	70	Yes	Yes	Yes	Yes	Yes	NK
12	CR	24	54	24	Yes/No	No	Yes	4	Dys	Yes	No	Op	40	Yes	Yes	Yes	Yes	Yes	Yes
13	CR	23	51	36	No/No	No	Yes	6	Hyp	No	Yes	Mild	70	Yes	Yes	Yes	Yes	Yes	Yes
14	CR	28	54	24	No/No	No	Yes	7	Dys	No	Yes	Mild	60	Yes	Yes	Yes	Yes	Yes	Yes
15	CR	19	49	15	Yes/No	No	Yes	5	Dys	No	No	Op	60	Yes	Yes	Yes	Yes	Yes	Yes
16	CR	32	51	15	No/No	Yes	Yes	10	Dys	Yes	Yes	Sev	70	Yes	Yes	Yes	Yes	Yes	Yes
17	CR	19	50	11	No/No	No	Yes	6	Dys	Yes	Yes	Mod	60	Yes	Yes	Yes	Yes	Yes	Yes
18	CR	37	51	18	Yes/No	No	Yes	5	Dys	No	No	Mod	50	Yes	Yes	Yes	Yes	Yes	Yes
19	CR	30	52	24	No/No	No	Yes	6	Dys	Yes	No	Sev	40	Yes	Yes	Yes	Yes	Yes	Yes
20	Rep	21	54	18	No/No	No	Yes	0	Dys	No	Yes	Mild	60	Yes	Yes	Yes	Yes	Yes	Yes
Mean		27	52					5.4					58%						

[a] Cases 1 and 11 are monozygotic twins with a mutation at 255. CR = classic Rett syndrome. R = atypical Rett. *Indicates no evidence of fall off in OFC. **Indicates no regression. †Indicates late regression. Ep (case no. 20) indicates epilepsy before regression. OFC = occipito-frontal circumference in cm. Regr = age in months at onset of regression. Speech/ indicates words used in early infancy and now. self F = able to feed unassisted with a spoon. resp = irregularity of breathing. Fsc = feeding score (see results section). tone = predominant abnormality of muscle tone at present, N = mildly increased, Dys = dystonic, Hyp = severely hypertonic. walk S = walks unassisted. Ep = epilepsy now present. Scol = scoliosis, Mod = moderate, Sev = severe. S (%) = severity score (see results section) higher% indicates greater severity. Vis: Hear = vision: hearing good. Contact indicates seeking face to face contact. Agit = agitation with severe unexplained excitement and sadness. Music = particularly responsive to selected music. Sleep = sleep disturbance, waking at night or sleeping by day. NK = not known.

9.6.1 Occipito-frontal circumference measurements for people with classic Rett Syndrome at birth and after 18 months (Kerr 2002) reproduced by kind permission of Cambridge University Press



9.6.2 Longer term changes in classic Rett related to the predominant early abnormality of muscle tone (Kerr 2002) reproduced by kind permission of Cambridge University Press

The clinical subtypes in classic Rett syndrome, before and during regression and later in life

Tone subtype	Before regression	During regression	After regression
Hypotonic (subtype 1)	Floppy and placid Few skills, lost early, no speech	Slight decline in already poor skills; remains placid	May be obese if feeding difficulties permit. Shallow, sometimes inadequate breathing; passive; prone to contractures
	Proportion of cases: 80%	Percentage falls during regression	About 5%, falls steadily
Hypertonic and dystonic (subtypes 2 and 3)	Odd postures and stereotyped movements, but skills gained	Abrupt skill loss; breathing irregularity is obvious	Walks if encouraged with dystonic posture, prone to scoliosis and contractures; extreme agitation; valsalva breathing
	Proportion of cases: 1%	Percentage rises during regression	Rises to about 70%
Mildly increased muscle tone (subtype 4)	'Good baby, placid, lacking initiative but gaining skill, often considered normal	Breathing may be less obvious; regression is less severe and later; less reduction in OFC growth	Prone to scoliosis but walks well; some hand use and speech; hyperactive with mood swings
	Proportion of cases: 19%	Percentage remains stable	Remains about 25%

OFC, occipito-frontal circumferance.

9.6.3 Changing skills with age in a cohort of adults with classic Rett syndrome (Kerr 2002) reproduced by kind permission of Cambridge University Press

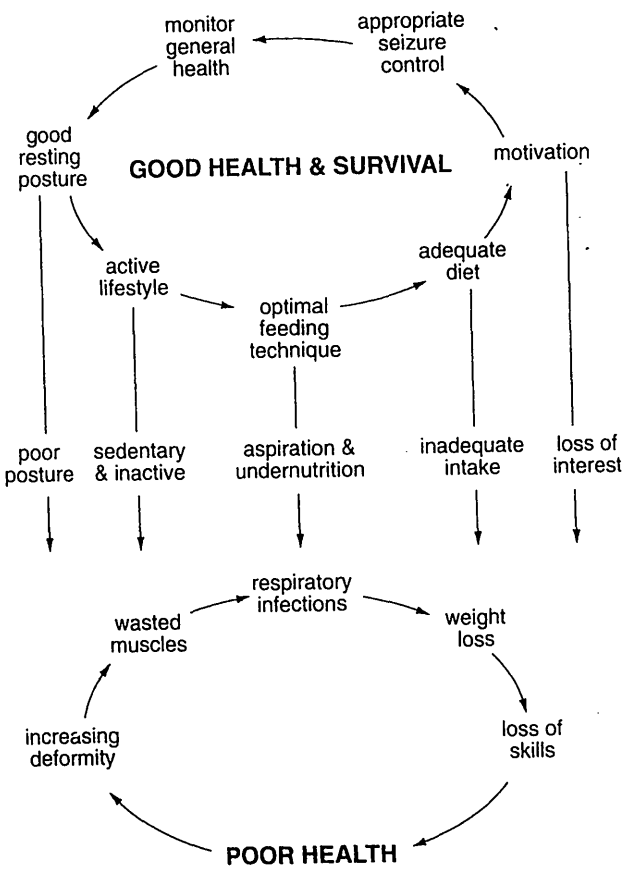
cohort aged 15–40 years with additional early childhood data

Reported skill	Pre-regression *n* = 46–80 (%)	5–10 years *n* = 17–80 (%)	15–20 years *n* = 20–64 (%)	25–30 years *n* = 15–25 (%)	35–40 years *n* = 6–9 (%)
Take spoon or cup	61	21	18	21	14
Walk alone	56	60	48	67	14
Use words	75	22	20	4	0
Understand words	91	54	50	35	25
Major feeding difficulty	6	18	35	73	67
Moderate or severe scoliosis	0	9	52	59	56
Epilepsy	0	61	73	48	38

9.6.4 Comparing behaviour in 10 people in adolescence and adulthood (Kerr 2002) reproduced by kind permission of Cambridge University Press

Reported by family/carer	Adolescent (*n*)	Adult (*n*)
Agitation	10	10
Injury to self	4	5
Injury to others	0	3
Night sleep disturbed	4	9
Day time sleep	7	7
Irregular breathing	10	9
Gaseous distension	5	9
Menstrual difficulty	1	5

9.5.5 Good and poor health circles in Rett syndrome. (Kerr 2002) reproduced by kind permission of Cambridge University Press



The diagram illustrates how attention or failure to attend to these aspects of care lead to cycles of good or poor health

APPENDIX B: SURVEY DATASET

British Isles Survey: n=1236:sources and criteria for Rett status: November 2005

BIS survey code, In general 1=yes, 2=no,3=presumed present,9=not found, AK saw=first examination, AK dates= later examination (latest not all shown), Infant V=infant video, age upd=age at update, face=face dysmorphic dyspraxdyspraxia, Herr Q=dates of completed HSQ, mut=mutation (1=present, 2=not found, no entry=not tested), CR=classic Rett, IncCR=incomplete CR, R nonC Rett =non-classic, not R=not Rett, C=latest centile OFC early crit=Rett developmental history, regres=regressed, stereo=hand stereotypy, first S=first seizure, other aet=possible other cause of problem, Items right of 'status' indicate criteria for classic Rett.

BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dyspraxx	face	stereo	regres	first S	other aet
1	1/10/1979	2	2	15	3/6/1991	21/1/1994	HSQ.'94	2	none (AC)	R nonC	>50	2	1	1	2	1	1	6wk	2
2	24/3/1981	2	1	23	24/5/1988	24/7/1987,11/6/1991	Q '86			CR	10-		1	1	2	1	1		2
3	8/5/1980	2	2	21	25/8/1983	1/11/2000	'93			CR	10t	1	1	1	2	1	1	3y	2
4	19/6/1975	2	2	20			HSQ.'95			R nonC	nk	9	1	1	nk	1	1	3mo	2
5	12/4/1977	2		0						unknown									
6	9/8/1976	2	2	18	20/7/1987	12/1/1994	Q			CR	<2n	1	1	1	2	1	1	8y	2
7	13/8/1984	2	2	22	28/4/1988		Q'86			CR	10t	1	1	1	2	1	1	nk	2
8	27/3/1987	2	1	17	6/10/1990	23/1/1991,21/1/1992,	mult '90, '94, '95 '96, '98,'04			CR	NR	1	1	1	2	1	1	non	2
9	2/2/1978	2	2	21	26/8/1987	6/6/1997	mult '95,'98			CR	<3r	1	1	1	2	1	1	9.0	2
10	15/5/1979	2	2	12			Q.'90			Inc CR	50t	2	1	1		1	1		2
11	24/1/1980	2		0			Inv	1	c808C>T;	unknown									
12	27/8/1974	2		25						unknown	nk	9	9	1	9	1	9	nk	2
13	26/1/1979	2	2	12			Q'91			CR	3rd	1	1	1		1	1		2
14	16/5/1989	2	2	0			Inv			R nonC			1	1		9	1	earl	1.thr
15	14/5/1978	2	2	18	9/1/1996		mult. '91, '95			CR	10-	1	1	1	2	1	1	non	2
16	27/2/1983	2	2	16	24/6/1966	23/1/1991	HSQ. '96	2	none(MB)	CR	<3r	1	1	1		1	1	8y	2
17	27/11/1983		2	0			Inv			unknown			9	9		9	9		
18	28/11/1979	2	2	16	4/6/1992	18/1/1995	mult. '92, '94,			CR	<3r	1	1	1	2	1	1	?	2
19	19/11/1981		2	0			Inv			unknown			9	9		9	9		
20	22/8/1977	2	2	28	24/5/1988	21/6/2000,24/10/2001,15/10/2001,	mult.'91,'94,'96,'98,'00	1	917G>A(AC)R306	CR	3-1	1	1	1	2.	1	1	4yr	2.
21	14/6/1978	2	2	18	14/6/1978	30/3/1992	mult '93,'95,'98	1	R106W(AC)106(d'	CR	10-	9	1	1	2	1	1	5y	2
22	12/7/1980	2	2	20	22/1/1992		mult.'80'94,'95,	1	c401C>G,S134C(	CR	50-	3.	1	1	2	1	1	3y	2
23	2/1/1980	2	2	0			Q '90	1	T158M (WGH)	CR	<3r	1	1	1		1	1	13m	
24	29/3/1987	1	2	5	12/6/1991		Inv			CR	10-	3	1	1		1	1	non	2
25	29/7/1980	2	2	13	23/1/1991	29/1/1993	Q'91			CR	25t	1	1	1		1	1	2y	
26	13/2/1976	2	1	27	16/10/1989	12/10/2002	HSQ '98	1	R168X(AC)(d'E168	CR	25t	3	1	1	2	1	1	non	2
27	23/11/1974	1	2	24	16/10/1989		mult.'95,'98			CR	<2n	3	9	1	9	1	9	5y	2
28	22/7/1980	2	2	25	18/1/1993	1/10/1999, 12/10/2002	mult. '96, '98,	1	c808 C>T;R270X	CR	10-	1	1	1	2	1	1	10y	2
29	21/5/1970	2	2	35	14/7/1987	28/1/1988,16/5/1992, 1/6/1998,	HSQ. '98	1	P152R (MB)	CR	3-5	1	1	1	2	1	1	3.0	2
30	3/9/1977	2	2	19	1/5/1986	1/1/1987,1/10/1992,1/10/1994,	HSQ '98	1	R255X and	CR	<3r	1	1	1	1	1	1	6y	2

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
31	28/3/1987	2	2	7	8/6/1993		HSQ			CR	<3r	1	1	1	1	1	1	non	2
32	2/10/1985	2		0			Q '91			R nonC		1	2	1		1	2		2
33	15/7/1973	2	2	25	26/10/2083		mult'93,'95,'98			CR	10t	1	1	1	2	1	1	non	2
34	10/12/1975	1	2	21	1/6/1989		Q			CR	50t	1	1	1	2	1	1	2.6	2
35	27/8/1952	2	2	46			mult '93,'98	2	none (AC)	R nonC	50t	2	1	1	2	1	1	2yr.	2
36	30/7/1977			0						unknown									
37	13/6/1986	1	2	19	28/10/1989	23/1/1991, 8/6/1994,	mult.'93. '94'03	1	P302L(AC)	CR	<3r	1	1	1	2	1	1	8y	2
38	27/4/1973	1		0			Inv			inc CR									
39	18/12/1981	2	2	16	5/2/1992	17/1/1995, 10/1/1996, 15/1/1997	HSQ.'96	1	c473C>T; T158M	CR	<3r	1	1	1	2	1	1	9yr	2
40	12/5/1978	2		0	1/10/1987	28/10/1989	Q			CR		1	1			1	1	2y	
41	16/5/1978	2	2	21	1/10/1987		HSQ '98			CR	10-	1	1	1	2	1	1	4y	2
42	18/8/1976	2		27	1/10/1992	18/6/1997,	mult. '97,'98,'02	1	K352fsX366	CR	50-	9	1	1	2	1	1	3y	2
43	12/9/1984			0			Q'90,			inc CR		9				1	1		2
44	23/8/1982	2	2	16	22/1/1991	22/1/1991; 29/1/2001	HSQ'98	1	c880c>t;R294X	CR	10-	3	1	1		1	1	3-4	2
45	20/5/1980	1		19	1/10/1991		mult'93,95,'97			CR	NK	1	1	1	2	1	1	2y	2
46	2/2/1982	2		18	1/10/1990		HSQ,'99	1	c316C>T;R106W	CR	NR	9	1	1	9	1	1	NK	2
47	22/5/1984	2		19	1/1/1987	1/10/1991,1/10/1994,1/11/1995,1/2/20	mult '98,'00			CR	25-	1	1	1	2	1	1	12y	2
48	27/3/1981			10			Q '90			CR	<10	1	1			1	1		
49	25/8/1981			0			inv			R nonC									
50	20/1/1976	2		0	5/5/1983	12/12/1987	mult			CR	2nd	3	1	1	2	1	1	4.6	2
51	21/10/1976	1	2	19	1/4/1989					CR	<3r	1	1	1	2	1	1	9y	2
52	7/6/1976	1	2	20	1/10/1989	1/10/1991	HSQ			CR	NK	3	1	1	9	1	1	3y	2
53	6/8/1971	2		0			Inv			unknown									
54	14/9/1987	2		0			Q'90,	1	S68X (WGH)	CR	3rd	1	1	1		1	1	5y	
55	2/6/1985			0			Inv	2	none(AC)	unknown									
56	20/9/1969			0						unknown									
57	9/2/1983			18	15/10/1993	15/6/1994, 26/6/1998	Inv			CR	3rd	3	1	1	2	1	1	?	
58	19/3/1986			0						unknown									
59	4/7/1982	2		18	21/6/2000		HSQ. '00	2	AC none	CR	2-5	9	1	1	2	1	1	non	2
60	28/10/1960	2	2	34	13/6/1994		Inv			CR	nk	1.	1	1	2	1	1		2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
61	23/9/1976			0	20/6/1996		Inv			unknown									
62	21/2/1975	1	1	24	19/10/1991		HSQ '90,'98			CR	3rd	1	1	1		1	1	5y?	2
63	3/2/1980	2	2	16			mult '90,'96			CR	<3r	1	1	1	9	1	1	non	2
64	16/7/1975			14	1/1/1987	1/4/1989	Inv			CR	<3r	1	1	1	2	1	1	nk	2
65	25/9/1984		2	14	31/1/1992	14/6/1994, 1/11/1995,16/6/1998	Inv			CR	>3r	1	1	1	2	1	1	?	2
66	26/7/1984			0			Inv			unknown									
67	14/2/1971	1		22						Inc CR	<3r	1	1	1	2	1	1	NK	2
68	10/3/1962	2	1	34	29/10/1988		mult.'94,'95,'98	1	1157del141bp (d'E	CR	3rd	1	1	1	2	1	1	4.y	2
69	14/5/1973	1	2	20			Q'92			CR	NR	1	1	1	2	1	1	3y	2
70	4/2/1963	2	2	38	1/1/1990	22/1/1991,	mult'95,'96,'98,'00		(MB) awaited	CR	<3r	1	1	1	2	1	1	7y	2
71	21/6/1983	2		19			Q '90	2	AC not found	CR		1	1	1		1	1		2
72	23/5/1967			0			Inv			unknown									
73	13/9/1974	1		18			Q'91	1	c654-657delGAAG	CR	NR	1	1	1		1	1		2
74	25/3/1986			0			Inv	2	AC none found	unknown									
75	28/2/1985	2	1	13	1/10/1989	1/10/1989	HSQ '97			CR	<3r	1	1	1	2	1	1	2yr	2.
76	19/1/1983	1	2	11	1/5/1987		mult '93,'95	1	168d'E)	CR	<3r	1	1	1	2	1	1	3.0	2
77	18/7/1982	2		15			Q '90			CR	3rd	3	1	1	9	1	1		2
78	14/8/1979	2	2	12	20/6/1991		Inv			CR	25-	3	1	1	2	1	1	7y	2
79	13/2/1987	1	1	12	6/10/1990	1/10/1994,	mult. '93,'94,'96,'99	1	T158M	CR	25t	1	1	1	2	1	1	4.0	2
80	16/9/1980	2		21	11/6/1991	17/6/1995,	mult '95, '96,'97, '00			CR	<3r	1	1	1	2	1	1	non	2
81	10/8/1980	2	2	12	21/1/1992		Q '91	1	c502C>T;R168X	CR	25t	1	1	1	2	1	1	8y	2
82	13/7/1973	2	2	27	1/5/1986	22/1/1991,1/10/1991,15/10/1993,23/1/	mult'94,'98,'00		MH?	R nonC	2nd	1	1	1	2	1	1	3mo	2
83	27/7/1977	2		14	23/7/1991	20/6/1999	Inv			R nonC	<3r	1	1	2	2	1	1	9mo	1.
84	19/12/1987	2		9	22/1/1991	1/10/1991,1/10/1996,	Q.'90			CR	10-	1	1	1	2	1	1		
85	19/8/1988	2	2	5	9/6/1993		HSQ'93			CR	3rd	1	1	1	2	1	1	2.6	2
86	1/11/1978	2		12			Q '91			Inc CR		3	1	1		1	1	NK	2
87	12/8/1977	2		19	20/10/1983	8/4/1986, 5/12/1987, 11/6/1994,	mult '93, '94,'95			CR	25t	1	1	1	2	1	1	non	2
88	14/10/1985	2	2	10	1/4/1989	26/6/1993	HSQ. '95	2	not found (MB)(AC)	CR	2-5	1	1	1	2	1	1	5.0	1.2
89	11/9/1980	2		23	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1	mult.'85, '93, '03	2	none (MB)	CR	<3r	1	1	1	1	1	1	4y	2
90	17/1/1983	1	2	13	21/1/1992		mult '94,'95			R nonC	<3r	1	2	1	2	1	1	3-4	2

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BIS	d of birth	Infant V died		age upd	AK eaw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
91	16/12/1985	1	2	8	7/6/1993		Inv			CR	<3r				2			non	2
92	20/1/1986	2	2	8	8/6/1993		HSQ '93			CR	nk		1	1	0	1	1	non	2
93	29/7/1984		2	9	8/6/1993		Q'90			CR	<3r	1	1	1	2	1	1	?	2
94	13/6/1984	2	2	32			HSQ '95			CR	nk	1	1	1	9	1	1	6	2
95	23/4/1985	2	2	12	19/1/1993		mult '95,'97			CR	50t	9	1	1	2	1	1.	9y	2
96	6/6/1987	2	2	32	4/6/1992		mult			CR	2nd	1	1	1	2	1	1	7.0	2
97	22/1/1987	2		3	3/6/1989		Inv	1	c502C>T; R168X	inc CR	10t	3	1	1		1	1		2
98	20/12/1984	2		0	1/10/1991		Q '91	1	c916C>T;	CR	25-	1	1	?		1	1		2
99	7/7/1982	2	2	15	14/1/1997		mult.'95,'98	2	none(Wallis,	CR	25-	1	1	1	2	1	1	10y	2
100	13/4/1975	1		22	24/5/1984		mult			CR	2-5	1	1	1	2	1	1	1y	2
101	29/5/1981	2		18	1/1/1988		HSQ '98	2	none (AC)	CR	3rd	1	1	1	2	1	1	4y	2
102	3/9/1987	2		5	12/6/1991		Q '91			Inc CR	10t	3	1	1		1	1	non	2
103	20/4/1973	2		30	17/1/1995	14/1/1998	HSQ. '95,	1	missense T158M	CR	<3r	1	1	1	2	1	1	6y	2
104	26/2/1981	2	2	23	11/1/1994		mult.'93,'94,'95,'98,'00	1	R133C(d'E)(MB)	CR	10-	9	1	1	1	1	1	3y	2
105	21/11/1982	2		16	1/5/1986		HSQ.'98	1	R168X (AC)(MB)	CR	10-	9	1	1	2	1	1	2y	2
106	29/9/1978	2		15	9/2/1981	10/5/1984,1/1/1985, 2/12/1987	Q			CR	25t	1	1	1	2	1	1	8y	2
107	5/8/1977	2		19	1/5/1986	1/4/1989	mult.'94,'95	1	L386fsX389(MB)	CR	<2n	1	1	1	9	1	1	4.5	2
108	6/8/1975	2		28	1/10/1989		HSQ '96			CR	nk	9	1	1	9	1	1	8y	2
109	9/10/1983	2		17	1/10/1990	11/6/1991,1/6/1994	HSQ '00	1	A133C(d'E,MH)	R nonC	90t	2	1	1	2	1	1	5-6	2
110	22/5/1981			10	23/1/1991		Inv			Inc CR			1			1	1		2
111	28/7/1996	2		5	19/6/2001		HSQ. '01		awaited	CR	25-	9	1	1	2	1	1	non	9
112	12/3/1985	1	2	4						CR	<2n	1	1	1	2	1	1	non	2
113	5/5/1977	2	2	17	20/6/1991	11/1/1994	HSQ, '94	1	c763c>t;R255Xd'E	CR	<3r	1	1	1	2	1	1	11y	2
114	1/8/1978			0			Q '02			CR		1	1			1	1		2
115	24/4/1970	2		27	19/6/1996		mult '95,'6			CR	<2n	1	1	1	9	1	1	nk	1
116	24/11/1967	2	2	27	20/7/1994	13/11/1991, 14/6/1994	Q.'91			CR	<3r	1	1	1	2	1	1	3y	2
117	11/2/1972			0			Q'90			CR		9	1			1	1		
118	17/3/1985	2	2	9	8/6/1993		HSQ '93	1	c808C>T;R270X(A	CR	3rd	1	1	1	2	1	1	5y	2.
119	4/6/1990	2		7	10/6/1993	11/1/2004	HSQ			CR	25t	3	1	1	2	1	1	4y	2
120	10/5/1978	2		0				1	c502C	Inc CR									

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
121	8/12/1984	2		15	1/4/1989	10/6/1992,17/6/1995,16/6/1999,	HSQ. '99	1	c502C>T;	CR	50t	9	1	1	2	1	1	5yr	2
122	8/10/1975	2	2	28	19/1/1993		mult.'90,'96,'98,'03			CR	<3r	3	1	1	2	1	1	3y	2
123	10/11/1986	2	2	12	7/7/1993	27/6/97, 3/10/1997, 1/11/1997,	Q .'97	1	T158M (MB)	CR	3rd	1	1	1	2	1	1	5.0	2
124	3/3/1949	1	2	39	3/6/1987		HSQ			CR	2nd	3	1	1	2	1	1	10y	2
125	21/9/1973			30			HSQ '03			CR	nk	9	1	1	9	1	1	4y	2
126	5/5/1979	2		20	23/1/1991	5/2/1992	mult.'94,'98			R nonC	50t	2	1	1	2	2	1	non	2
127	21/6/1980	2	2	0	7/7/1986	22/6/1987,25/11/1988,12/5/1992,1/6/1	Q '86-'96			CR	<3r	1	1	1	2	1	1	3y	2
128	13/9/1975	2	2	22	18/4/1984		mult Q,HSQ'97			CR	25t	1	1	1	2	1	1	non	2
129	16/6/1987	1		7	17/3/1994		inv			CR	<2n	3	1	1	2	1	1	2y	2
130	22/4/1985	2	1	20	1/10/1991	17/6/1995, 22/6/1999,	mult '91, '94,'95,'97,'04			CR	10-	1	1	1	2	1	1	12y	2
131	16/7/1983	2	2	17	1/10/1989	11/1/1994,21/6/2000,4/4/2001	mult.'90,'93'95'98'99'00	1	1157del144bp (CS)	CR	<3r	1	1	1	2	1	1	15	2
132	28/6/1978	2		18			HSQ '95			not R		9	2	1	1	1	1	10y	1.
133	8/1/1982			0	1/10/1991	17/6/1997	Q '91,			CR	<3r	1	1	1		1	1	12m	2
134	14/5/1971	1	2	26	19/1/1993		HSQ			CR	<2n	1	1	1	2	1	1	7y	2
135	16/1/1982	1		5	1/5/1986	1/1/1987	Q inv			CR	<2n	1	1	1	9	1	1	nk	2
136	9/2/1972	2		30	1/11/1987	11/2/2000,29/1/2002.	mult.'95'98'00'02	1	c763 C>T; R255X	CR	3rd	1	1	1	2	1	1	3y	2
137	2/4/1974	2	2	16	10/11/1983	10/11/1983, 21/6/1990	Q '83			CR	<3r	3	1	1	2	1	1	1.6	2.
138	7/1/1969	2		28	1/1/1989	22/1/1991	HSQ'96			CR	<2n	3	1	1	2	1	1	9yr	2
139	16/4/1972			18	1/6/1989		inv			Inc CR		9	1	1		1	1		
140	4/9/1983	2		12			mult '92, '95			R nonC	50-	2	1	9	2	1	1	non	2
141	9/3/1987	2	2	13	25/5/1992		Q '92	1	R168X(AC)(168d'E	CR	10t	1	1	1		1	1	?	2
142	12/10/1975	1	2	0	21/6/1984		Q			CR	50t	1	1	1	1	1	1	5.0	2.
143	11/7/1986			0			Q			unknown									
144	29/11/1977	1		0						R nonC	10t	1	1	9	9	9	1	8mo	1
145	22/2/1987	2		4	1/10/1990		Q '91	1	c473c>t; T158M	Inc CR		1	1	1	2	1	1		
146	2/6/1984	2	2	19	26/5/1993		mult'95,'96,'03	1	1157-1197del.41b	R nonC	50t	2	1	1	2	1	1	non	2
147	28/2/1994	2		0				2	AC none found	unknown									
148	25/4/1981	2		17	30/6/1988	1/1/1989,5/6/1992,13/6/1995,30/11/19	Q.'92	1	c397C>TR133C(A	R nonC	10-	1	1	1	2	1	1	non	1
149	10/4/1985	2		13	6/6/1991	30/11/1997, 12/10/2002,1/10/2003	Q.'91	1	c397C>TR133C(A	R nonC	50-	2	1	1	2	1	1?	3y	1.
150	6/11/1978	1		22	22/6/1987	1/10/1989	mult. '91,'99	1	c316C>T; R106W	CR	<3r	1	1	1	2	1	1	14	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
151	5/9/1977			0						unknown	nk	2	1	9		1	1		2
152	19/10/1970	2		28	1/6/1989	12/6/1991	mult. '93,'95,'98	2	d'E not	CR	2-5	9	1	1	2	1	1	6y	2
153	15/1/1983	2		9	22/1/1991	18/10/1991	Q '90,			CR	<3r	1	1	1		1	1	NK	2
154	29/8/1974	2		28	29/9/1983	17/12/1995,13/3/1996, 5/10/2001	mult.'94,'96.'98	1	P152R (Glasgow)	CR	<2n	1	1	1	2	1	1	3y	2
155	8/9/1969	2	2	28	1/10/1992		mult.'94,'96,'98,'99	2	(AC)(d'E)not found	CR	2nd	1	1	1	2	1	1	non	2
156	18/2/1970	2		30	1/1/1989	11/6/1991	mult.'93,'95,'96,'98,'99	2	none(AV)	CR	10-	1	1	1	2	1	1	7y	2
157	6/12/1985	2		10	18/1/1995		Q.Inv	1	G252fsX287(MB)	CR		1	1		2	1	1		2
158	13/4/1973	2		28	1/5/1986	17/6/1995, 20/6/2000	mult.'86,'95.'98	1	R255X(MB)	CR	3-1	1	1	1	2	1	1	12.	2
159	23/3/1973	1		0	22/1/1991		Inv			CR		9	1			1	1	3y	1.toe
160	17/5/1988	1		6	12/6/1991		inv			CR									
161	10/9/1982	2		16			mult.'92,'95,'98	1	none(MB)168(d'E)(	CR	nk	9	1	1	1	1	1	non	2
162	14/9/1986	2	1	15	1/9/1991	29/4/1992, 17/7/1998, 1/6/2000,	mult. '90, '98,	1	R133C (MB)	CR	3rd	1	1	1	2	1	1	4yr	2
163	21/1/1977			15			Q '91			Inc CR	3rd	1	1	1	9	1	1		
164	5/4/1974	1		0			Inv			unknown	nk	9	9	3	9	9	9	nk	9
165	29/10/1990	2		1	7/11/1995		Inv			CR	3rd	1	1	1	2	1	1	4y	2
166	5/10/1972			0			Inv			unknown	nk	9	9	9	9	9	9	nk	9
167	20/3/1988	2		14	20/6/1999		HSQ.'93			CR	3rd	1	1	1	2	1	1	5y	2
168	8/11/1972	2		30	14/6/1994	25/6/1998	mult.'94,'98	1	T158M (Glasgow)	CR	50t	9	1	1	2	1	1	16	2
170	27/6/1970	2	2	25	11/1/1994		mult '94,'95,'98			CR	<2n	1	1	1	2	1	1	14y	2
171	19/6/1974	2		25			mult.'95,'96.'98			CR	nk	9	1	1	9	1	1	non	2
169	31/3/1993	2	1	6	15/6/1995	18/6/1996, 1/10/1999,	mult. '95, '96, '98	1	Q244X (MB)(MH)	CR	10-	1	1	1	2	1	1	1.3	2
172	30/6/1984			0						unknown									
173	3/3/1987			18			HSQ'04	2	none (AC)	R nonC	75t	NK	2	1	1.wl	1	17	non	1.
174	5/7/1979	1	2	17	3/6/1989	17/6/1995	HSQ. '95			CR	25t	9	1	1	2	1	1	9y	2
175	13/5/1982			0			Q '90			CR		1	1	1		1	1		
176	1/9/1981		2	14	1/10/1989	1/1/1993	HSQ '95			CR	10-	3	1	1	2	1	1	7y	2
177	7/10/1975			16			Q'91			Inc CR	nk	9	1	1	9	1	1	nk	2
178	23/3/1977			0			Q'92			CR			1			1		22	
179	21/9/1974			15						CR	nk	9	1	1	2	1	1	nk	2
180	5/4/1987	2		16	12/6/1991		HSQ '02		awaited	R nonC	25t	3	1	1	2	1	1	8mo	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
181	18/3/1988	1		3	1/10/1990		Q'90			inc CR	50t	1	1	1	1.sl	1	1	2y	2
182	26/8/1988	1	2	12	1/10/1991	30/1/1992,10/11/1997,15/10/2001	mult.'94,'95,'97,'98,'00			CR	<2n	1	1	1	2	1	1	yes	2
183										unknown									
184	6/7/1975			16			Q			CR	nk	1	1	1	9	1	1	nk	2
185	3/3/1980	2	2	19	11/6/1991	14/6/1994	HSQ.'98	1	1152-93.del.41(M	CR	NR	NR	11	1	2	1	1	8yr	2
186	25/9/1976	2		23			mult '96,'98			Inc CR	nk	9	1	1	9	1	1	17y	2
187	23/5/1986			0			Q '91			R nonC	10-		1			2	1		1.
188	3/6/1985	2		15	1/10/1992		HSQ '00	1	c473C>T; T158M &	CR	3rd	1	1	1	2	1	1	3y	1.sm
189	6/5/1979	2	2	23	17/6/1998	1/6/2002	mult '98.'02	1	R168X	CR	<2n	1	1	1	2	1	1	12y	2
190										unknown									
191	18/7/1974	2		25	1/4/1989	23/4/1999	Inv	1	c808C>T;R270X,	CR	<3r	1	1	1	2	1	1	7yr	2
192	2/4/1972		2	27	1/11/1985		mult '94.'98			CR	2nd	1	1	1	2	1	1	2.3	2
193	6/10/1972		1	13	1/10/1985					CR	2nd	3	1	1	2	1	1	8y	2
194	7/7/1985	2	2	16	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995,	mult '93,'94, '97, '98,'00,	1	916C>T(AC)R306C	CR	10-	1	1	1	1.	1	1	2.6	2
195	25/9/1973	1		0			Inv			unknown									
196	12/10/1984	2	1	13	24/6/1987	18/6/1997,21/6/2000	Q '92,			CR	<3r	1	1	1		1	1	non	2
197	18/5/1964	2	2	40	22/2/1991		HSQ'04	1	c763CC>T;R255X(	R nonC	50t	2	1	2	2	1	1	6y	2
198	18/5/1964	1	2	29	20/2/1991		Q	1	c763C>T;R255X(A	CR	3rd	1	1	1	2	1	1	6.0	2
199	1/7/1983	2	2	12	19/1/1993		HSQ '94	1	c316 C>T; R106W	CR	<3r	1	1	1		1	1	2.0	2
200	27/6/1982			8	1/1/1990					unknown									
201	6/7/1976	2		19	31/1/1995	18.1.1995	Q '90			Inc CR	3rd	3	1	1	2	1		0?	2
202	9/5/1975	1		16			Q'90			Inc CR	nk	9	1	1	9	1	9	nk	2
203	8/11/1975	2		20			HSQ			R nonC	10t	9	3	1	1	1	1	12	1
204	19/10/1979			10	1/4/1989		Q'90			R nonC		1	1	1		1	1		
205	9/11/1977	1	2	19			HSQ.'95			CR		1	1	1		1	1	7y	2
206	14/10/1982	2	2	20	1/10/1986		mult. '95.'96.'98.'02	1	T158M(MB)	CR	nk	1	1	1	2	1	1	3.y	2
207	14/6/1980	2	2	18	23/7/1991		mult '94 '95,'96,'98	1	T158M (TW)	CR	<3r	1	1	1	2	1	1	7.0	2
208	7/6/1983	2		18	13/6/1991		mut.'94,'95,'98	2	del 1p	not R	25t	2	2	2	1	2	2	0.1	1.1p
209	26/1/1989	2	1	15	11/6/1991	17/1/1995	mult.'91 ,'03	1	T158M	CR	3rd	1	1	1	2	1	1	16	2
210	21/10/1978	1	1	20	1/10/1987	21/1/1992	mult.'94,'98,'02			CR	<2n	1	1	1	2	1	1	10y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	text	status	C	OFC fall	early crit	dysprax face	stereo	regres	first S	other aet
211	7/5/1975			15	1/6/1989		Inv			CR	25-	3	1	1	2	1	1	nk	2
212	13/7/1983	2	2	17	1/10/1990	21/1/1993,1/10/1994,	HSQ'95	1	101d'E)	CR	10-	3	1	1	2	1	1	5y	2
213	15/1/1981			13	1/5/1986	15/10/1993, 17/6/1995	Q'90			CR	<3r	1	1	1		1	1		2
214	10/5/1978			0			Inv			inc CR			1			1	1		
215	30/11/1978			13	1/5/1986		Q '86			inc CR	<3r	1	1	1		1	1		
216	8/12/1978	2		17	17/1/1995		HSQ'94			CR	<3r	1	1	1	1.	1	1	18y	2
217	10/7/1986	2	2	13	1/10/1991	10/6/1992	mult. 93,'98,			CR	10-	9	1	1		1	1	5y	2
218	19/9/1980	2	2	23			HSQ '92.'03	1	R306H (MB)	CR	nk	3	1	1	1	1	1	15m	2
219	1/2/1986	2	2	8	8/6/1993		HSQ '93	1	c.808delC	CR	<3r	1	1	1	2	1	1	3y	2
220	31/10/1986	2	2	10	22/1/1991	1/10/1992, 21/1/1993	mult. '93, '95,			CR	25-	3	1	1	2	1	24-	non	2
221	28/8/1972	2	2	30	1/4/1986	28/7/97	mult'93,'01			CR	10t	1	1	1	2	1	1	non	2
222	8/5/1978	1	1	0	12/11/1987	1/6/1998	Q			CR	<2n	1	1	1	2	1	1	2.y	2
223	1/10/1965	2	1	39	22/12/1987	1/11/2000,19/9/2004	HSQ'00			inc CR	<2n	3	1	1	2	1	1	16y	2
224	4/9/1981			0			Q '90.Inv			CR		1	1	1		1	1		
225	4/2/1980	2		4	1/6/1989	1/10/1992	Q '90			CR		9	1	3	2	3	1	6y	2
226	10/10/1980	2		8	14/6/1984	18/7/1987,16/3/1988,	Q'84-'88			CR	10h	1	1	1	2	1	1	3y	2
227	17/3/1974	1		21	28/7/1986		HSQ			CR	<2n	1	1	1	2	1	1	6y	2
228	4/3/1963	1		32	3/6/1989	15/10/1993	HSQ'93			CR	nk	9	1	1	9	1	1	2.6	1.bla
229	27/6/1974	1		0			Q			CR	3rd	1	1	1	9	1	1	4y	2
230	27/5/1982		2	12	7/6/1993		Inv			CR	<3r	3	1	1	2	1	1		
231	23/6/1982	2		17	1/5/1986	1/1/1987	HSQ '98			CR	nk	1	1	1	2	1	1	non	2
232	3/3/1981	2		17	1/1/1987	1/1/1989,	Inv			CR									
233	28/1/1981	2		22	1/4/1989		mult. '98, '02			CR	3rd	1	1		1	1	1	17y	2
234	24/6/1980	2	1	20	1/10/1986	28/8/1988, 1/6/1989, 12/6/1991,	mult '91,'94,'98	1	c763C>T;R255X(A	CR	10-	1	1	1	1	1	1	2	2
235	28/3/1964	2	2	35	11/1/1994	31/1/1995	mult '92,'93,'95,'97,'98,			CR		9	1	1	2	1	1	non	2
236	24/6/1949	2	2	50	4/10/1996	4/10/1996	mult '96,'98			CR	50-	9	1	1	2	1	1	non	2
237	9/1/1972	1		0	15/6/1994					CR	<2n	1	1	1	2	1	1	nk	2
238	18/10/1981			0			Inv			unknown									
239	7/7/1979	1	1	13	1/9/1988	10/6/1992,8/4/1999	Q '89	2	(AC) not found	CR	<2n	1	1	1	2	1	1	<9y	2
240	3/1/1979			0	1/10/1987		Q'91			CR	90t	1	1			1	1		2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
241	8/5/1973	2		31	15/6/1994		mult'94,'04	1	1133d'E)	CR	10-	1	1	1	2	1	1	4.0	2
242	1/2/1969	2		23			Inv			unknown	<3r	1	1	1		NK		NK	1.
243	14/5/1956	2	2	48	27/11/1990		mult'97,'98,'04			CR	3rd	3	1	1	2	1	1	non	2
244	25/10/1982			0			Q '91			inc CR	3rd	1	1	1		11	11		
245	8/2/1984		2	9	1/1/1987	1/4/1989, 4/6/1992	Q'90			CR		1	1	1		1	1		2
246	8/4/1984			6			Q'90			CR		1	1		9	1	1		2
247	20/10/1984			17	23/1/1991	3/2/1992,	Q.'91	1	positive	CR	10-	1	1	1	2	1	1	3y	
248	21/3/1984			3	1/5/1988					inc CR									
249	31/10/1983	2	2	18	20/1/1993	1/10/1994, 19/6/1995	mult. '93, '94, '95, '01,	2	none(d'E. MB.AC)	CR	3rd	1	1	1	2	1	1	10y	2
250	7/10/1983	2		8	3/6/1989	11/6/1991	Inv			CR	10-	3	1	1		1	1	2.0	2
251	2/9/1980	2		15	7/6/1995	30/3/2001,21/6/1995	Q '86.Inv	2	neg(AC)	CR	<3r	3	1	1	2	1	1	NK	2
252	23/3/1977	2	2	26	23/1/1991	11/6/2002	mult '95,'98,'00	1	c.695delG(AC)	CR	<3r	1	1	1	2	1	1	20y	2
253	7/10/1980	1	2	9	6/6/1986		Q			CR	2nd	1	1	1	2	1	1	nk	2
254	5/5/1988	2		16	25/6/1990		mult.'90,'94,'95,'96,'98.'04	1	Y141X(Aberdeen)	CR	3rd	1	1	1	9	1	1	non	2
255	22/11/1984	1		6			Q			CR	2nd	1	1	1	1	1	1		1.dy
256	20/3/1985	2	2	18	1/10/1992	16/1/1995,31/1/2001,	HSQ '02	1	473C>T(AC)	CR	<3r	1	1	1	2	1	1	3y	2
257	6/5/1980	2	1	21	1/10/1986	21/7/1987,28/3/1990,19/2/1991,21/6/2	mult'93,'95,'00	1	c473C>T; T158M &	CR	3rd	1	1	1	2	1	1	2y	2
258	7/1/1967	2	2	30	1/6/1983		mult'96			CR	<2n	1	1	1	2	1	1	5.0	2
259	24/7/1959	2		43	7/2/1986	30/3/2001,19/4/2002	Q '86			CR	<2n	1	1	1	2	1	1	12y	2
260	9/3/1983			0			inv			not R									
261	16/6/1982	2	2	10	14/5/1992		inv			CR	10-	1	1	1		1	1	5y	2
262	4/4/1985	2	1	20	1/10/1987	19/9/2004	mult	1	R168X(AC)(WGH)	CR	<3r	1	1	1	2	1	1	3.4	2
263	14/10/1971	2		29	24/5/1986	1/1/1987,2/9/1988,19/6/2001	HSQ'01	1	158(d'E)	CR	<3r	1	1	1	2	1	1	4y	2
264	29/10/1969		2	22			Q			inc CR		9	1	1		1	9		9
265	25/9/1975			15						unknown	nk	9	9	9	9	9	9	nk	9
266	25/12/1985	2	1	0	26/7/1990		Q'01			CR			1	1		1	1		
267	25/12/1985	2	1	0	26/7/1990		HSQ			CR			1	1		1	1		
268	8/7/1978	2		18	1/11/1995		HSQ.'93	1	(306d'E)	CR	<3r	2	1	1	2	1	1	5.	2
269	16/10/1988	2	2	23	12/6/1991		Q '91			R nonC	>50	2	1	1	2	1	1	7y	2
270	19/12/1974	2		24			mult. '95,'98			CR	nk	3	1	1	9	1	1	9y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC	fail	early crit	dysprax	face	stereo	regres	first S	other aet
271	31/7/1978			0			Inv			unknown										
272	21/8/1990			0			Inv			unknown										1
273	21/11/1989	2	2	29	1/4/1989	4/9/1989	HSQ	2	(AC) none found	R nonC		9	1	1	2	1	1	2yr	2.
274	31/5/1980	2	2	23	1/1/1987	1/10/1989,14/6/1994,1/10/1996,11/6/2	mult.'94,'02	1	c.880C>T.R294X(	CR	<2n	1	1	1	2	1	1	12y	2
275	8/8/1976	2		28	22/6/1991		HSQ'03			CR	>2n	1	1	1	2	1	1	2y	2
276	9/12/1987	2	2	15	22/6/1991		mult. '94,'95, '98	2	not found (MB)	CR	2-5	1	1	1	2	1	1	4yr	2
277	1/8/1969	2	2	31	23/1/1991	10/1/1996,15/2/2000	mult.'95,'98,'00			CR	25t	3	1	1	2	1	1	30y	2
278	7/8/1977	2		22	14/1/1998		mult,'98,'99			CR	<2n	1	1	1	2	1	1	10y	2
279	10/9/1982	2	2	16	15/10/1994	1/11/1995, 1/10/1996,1/10/2001,	mult '95, 96, '98	1	495-1164del869.	CR	<3r	1	1	1	9	1	1	non	2
280	17/6/1977	1	2	19	1/10/1991	10	HSQ.'96,'02			CR	nk	9	1	1	9	2	1	13	2
281	16/6/1986			0			Q '91			inc CR		1	1			1	1		
282	3/7/1981	2	1	17	24/7/1987	1/1/1989,1/1/1992,	mult.'92'93,'95,'98	1	107in frame	CR	3rd	1	1	1	1	1	1	4y	2
283	23/7/1982	2	2	19	16/9/1987		HSQ '95			CR	<3r	1	1	1	2	1	1	?	
284	14/3/1983	2	2	11	22/6/1991	11/1/1994	Q'90,	1	c302C>A;P101H(A	CR	2nd	3	1	1	2	1	1	nk	2
285	14/10/1978			13			Q'91			CR		1	1	1		1	1		
286	9/2/1971	1		30			mult '95,'98,'00			CR		9	1	1	9	1	1	16.	2
287	1/4/1978	2		26			Inv	2	none(AC)	R nonC	10-	2	1	1	9	1	1	non	2
288	12/6/1978			0			Q'90			CR		1	1			1	1		
289	15/9/1976	1		0			Inv	2	AC) none found	unknown										
290	11/7/1975			15			Q'90 HSQ Inv			inc CR	25t	2	1	1	9	1	1	nk	1.po
291	4/7/1990	2	2	5	2/2/1995		mult. '94, '95, '97,	1	c877delG,I293fsx	CR	50-	3	1	1	2	1	1	non	2
292	11/8/1989	2		7			HSQ '96			R nonC	25t	1.st	1	1	9	1	1	non	2.?a
293	9/5/1964	1		0						not R										
294	15/8/1989	1		4	8/6/1993		Inv			CR	<2n	1	1	1	1	1	1	yes	1.
295	17/6/1982	1		15			HSQ '93			CR	<2n	3	1	1	2	1	1	16m	2
296	6/5/1988	2	2	6	8/6/1993		HSQ'93			CR	3rd	3	1	1	2	1	1	4.6	2
297	8/6/1976	2	2	23	1/6/1993		mult '95, '98	1	P152R(MB)	CR	3rd	1	1	1	2	1	1	14y	2
298	14/12/1979	1	2	14	8/6/1993		Q '93			not R	<3r	3	2	1		2	2	non	1.
299	14/12/1979	2	2	25	8/6/1993	7/7/1993, 11/1/2004	Inv	1	IVS3-3C>G(mosai	R nonC	nk	3	1	1	2	1	1	4y	1.pre
300	19/6/1985	2	1	14	23/1/1991	22/1/1993	mult. '93, '98,	1	R270X (MB)	CR	3rd	1	1	1	2	1	1	4y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dyspraxi	face	stereo	regres	first S	other aet
301	8/11/1974	1	1	22	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1	HSQ			CR	10t	1	1	1	2	1	1	9.0	2
302	28/9/1979	2	2	13	25/5/1992		Q'91	1	c502C>T; R168X	CR	<3r	1	1	1	2	1	1		2
303	30/9/1970	2	2	27	9/11/1983	16/5/1992	mult '86,'96			CR	<2n	1	1	1	1. L	1	1	non	2
304	3/2/1980			0						unknown									
305	17/11/1966	2		0			Inv			unknown									
306	13/8/1976	2		19	13/9/1976	1/4/1991	HSQ.'95	1	R270X(MB)	CR	<3r	3	1	1	2	1	1	pre	2
307	15/3/1964	2	1	34	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/19	mult.'93,'95,'97	1	806delG(AC)	CR	<3r	1	1	1	2	1	1	10y	2
308	30/5/1959	1	2	0	1/5/1988		Q			CR	<2n	3	1	1		1	1	11y	1 ,30
309	4/12/1984	1		8	12/6/1991	1/10/1992	Inv			CR	10-	3	1	1	2	1	1	3y	2
310	11/8/1985		1	7	23/1/1991		Q'91			CR	<3r	3	1		2	1	1		
311	28/3/1987	2	2	7	24/6/1993		mult '93,'96			CR	10-	1.	1	1	2	1	1	0.9	2.
312	9/2/1970	2	1	22	1/10/1989		Q'91 inv			CR	nk	1	1	1	2	1	1	ons	2
313	6/6/1973	1		17	1/10/1989					CR	nk	3	1	1	2	1	1	non	9
314	31/7/1982	2		12	20/6/1991	1/10/2003	HSQ.'93	1	R255X(TW)	CR	3rd	3	1	1	2	1	1	5y	2
315										unknown									
316	26/2/1971			0			Inv			unknown									
317	1/1/1975			0						unknown	nk	nk	nk	nk	9	nk	nk	nk	nk
318	16/3/1960	1		0						unknown									
319	18/6/1987	2		12	21/1/1994		mult.'94.'97,98	2	neg(AC)	CR	2nd	1	1	1	0	1	1	3.0	2
320	12/2/1985	2	1	12	18/10/1991	1/2/2000, 18/10/1991,	mult '90 '96,'00			CR		1	1	1	9	1	1	4y	2
321	10/3/1977	2		22	1/7/1994		mult'94,'98			CR	25-	9	1	1	2	1	1	13y	2
322	4/3/1983	2	2	11	21/1/1992		mult .'94	1	880C>T;R294X(AC	CR	25-	9	1	1	2	1	1	3.9	2
323	21/11/1982			0	1/6/1989		Q'91			CR	25t	1	1			1	1		2
324	26/11/1982	2	2	19	1/5/1986	31/8/1988,1/8/1987,1/6/1992,19/6/199	mult'95,01			CR	3rd	1	1	1	2	1	1	3y	2
325	21/1/1985	2		16	21/6/2000		HSQ '00	1	del exon 3	CR	<3r	1	1	1	2	1	1	4y	2
326	23/12/1982		1	5	1/1/1987		Inv			CR	3rd			1		1		6y?	
327	17/5/1981			16			Inv			unknown						1			
328	9/6/1977	2		22			mult.'90,'95,'98			CR	<2n	1	1	1	9	1	1	9y	2
329	20/6/1971	1		0	12/4/1984		Q			CR	<2n	1	1	1	2	1	1	non	2
330	7/3/1973	2		0			Q			CR	unk	1	1	1	2	1	1	5y	2

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		Infant V																			
BIS	d of birth	died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet	
331	6/2/1971	2		0			Inv			unknown											
332	4/10/1984			0	1/5/1988		Q			not R							2				
333	26/6/1988	2		8			HSQ'95			CR		3	1	1	9	1	1	2y	2	
334	13/7/1973			19			Q'92			CR	nk	1	1	1	2	1	1	nk	2	
335	25/5/1971	2		14	28/6/1984	1.9.1986,21/7/1987	Q'84			CR	3rd	1	1	1		1	1	13y	2	
336	28/4/1985	2		6			'91			unknown		1	1			1	1			
337	17/9/1979	2		19	12/6/1991		mult.'91,'98			CR	<2n	3	1	1	2	1	1	non	2	
338	7/10/1973			12			Q'85			incCR	nk	1	1	1	9	1	1	nk	2	
339	29/8/1986		2	6	25/5/1992		Inv			CR	<3r	1	1	1	2	1	1	non	2	
340	12/7/1987	2		4	23/1/1991	3/2/1992	Q.'91			CR	10t	1	1	1	3	1	1	3.0	2	
341	19/4/1963			0						unknown		9	9	9		9	9		9	
342	13/3/1968	2	2	31	1/10/1992		Q			CR	10t	9	?	1	2	1	1	non	2	
343	14/2/1968		2	28	11/6/1991		mult '94, 95			CR	3rd	3	1.	1	2	1	1	non	2	
344	1/9/1977			0			Inv			unknown										
345	14/10/1979	2	1	19	11/1/1992	21/1/1992	mult '95,'96,'98			CR	<3r	1	1	1	2	1	1	10y	2	
346	12/1/1991	2	2	5	9/6/1993	18/11/2004	mult '93,'95			CR		9	1	1	2	1	1		2	
347	30/1/1982	2	2	17	1/10/1992	18/1/1995,16/8/1996	mult. '95,96,'97,'98,02,	2	not found (Wessex	R nonC	3rd	1	1	1	2	1	1	4mo	1.sei	
348	2/10/1980	2	1	13	20/1/1993		Inv			CR	10t	3	1	1	2	1	1	NR	2	
349	18/11/1960	2	2	31	23/1/1991		mult.'91,'95			CR	<3r	1	1	1	2	1	1	4y	2	
350	8/8/1966	2	2	38	6/6/1986		HSQ'98			CR	10-	3	1	1	9	1	1	non	2	
351	21/1/1974	2		25	25/5/1986	16/5/1992,1/6/1998,9/6/2000	mult '88,'96,'98			CR	3rd	1	1	1	2	1	1	non	2	
352	2/7/1979			0	2/7/1979		Inv			unknown										
353	22/3/1974		2	22			HSQ.'95			CR	nk	nk	1	1	9	1	1	7y	2	
354	17/7/1986	2		5			Q '91			CR		1	1	2		1	1	2y	2	
355	30/9/1983	2		13	1/10/1987	1/10/1989, 15/10/1983, 1/6/1995	Inv			CR	50-	9	1	1	9	1	1		9	
356	3/9/1980	2		22	1/10/1987	1/8/1988,1/4/1989,15/10/2001,1/10/20	Q'90,'88	1	R255X	CR	<3r	1	1	1	2	1	1	3y	2	
357	29/9/1984	1	2	0			QHSQ '95			CR		9	1	1	9	1	1	3y	2	
358	29/8/1985	2	2	12	1/4/1989	1/10/1990	mult. '94, '95, '97,	1	473C>T.T158M (	CR		3	1	1	2	1	1	2	2	
359	11/8/1968	2	1	30	26/10/1987	1/6/1996,29/11/1997,1/6/1998,1/11/19	mult '93			R nonC	10-	1	1	1	2	1	1	7yr	2	
360	23/4/1969	2	2	30	26/7/1984	27/6/1997	HSQ			CR	<2n	1	1	1	2	1	1	9	2.	

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
361	18/8/1975	1		11	1/5/1986		Q '86,'95			CR	<2n	1	1	1	2	1	1	4y	2
362	22/8/1976			0			Q'90			CR									
363	13/7/1975	2		28			HSQ '98,'03			CR	nk	1	1	1	9	1	1	non	2
364	1/7/1980	1		19			mult, '90 '95			CR	3rd	1	1	1	9	1	1	3y	2
365	17/12/1980	1		12			Q '91			CR	nk	1	1	1	9	1	1	4	2
366	23/10/1981	2		17	4/2/1992	14/6/1994,1/10/1996	mult.'92,'98	1	c916C.T;R306C	R nonC	50t	2	1	1	2	1	1	non	2
367	22/2/1981	1		15	26/7/1984		mult Q			CR	<2n	1	1	1	2	1	1	13y	2
368	6/8/1982	2	2	20	1/10/1991	1/2/1992,1/10/1996,7/10/1999,24/10/2	Q.'92,			CR	10-	1	1	1	2	1	1	per	2
369	2/9/1986	1	2	10	3/8/1992	4/4/1996	HSQ.'94			CR	<2n	1	1	1	9	1	1	30	2
370	12/11/1979	2		7	14/11/1985	6/6/1988	Q			CR	<3r	1	1	1		1	1	2y	2
371	9/4/1986			10	1/6/1990	17.6.1995	Q'90			CR	75t	2	1	1	2	1	1	non	2
372	10/1/1984	1		12	1/10/1987	1/1/1989,22/6/1991, 15/6/1995	Q'91			CR	2nd	1	1	2	2	1	1	4y	2
373	12/11/1971	1	2	25	1/6/1993		mult.'93,'96,'98			CR		1	1	1	2	1	1	non	2
374	16/11/1971			0			Inv			unknown									
375	8/9/1971	2		32			HSQ'03			CR	nk	9	1	1	9	1	1	6y	2
376	3/1/1973	2		28	3/6/1992		mult.'98,'00			R nonC	nk	9	1	1	9	1	1	2.6	2
377	1/1/1979			0			Inv			unknown									
378	30/10/1973	1		17	1/4/1989	1/6/1990	Q'90			CR	<2n	1	1	1	2	1	1	6y	2
379	17/7/1978	2	2	24	1/6/1994		HSQ '02			CR	2nd	1	1	1		1	1	yes	2
380	6/2/1985	2		14	7/8/1991	26/7/1996,5/10/2001	mult. '94,'95,'96,'98	1	P302L	CR	50t	2.	1	1	2	1	1	8.y	2
381	10/11/1987	1	2	13	4/9/1991	16/5/1992,1/1/1997,13/11/1998,4/9/20	mult.'91, '94,'95,'96,'98			CR	<3r	1	1	1	2	1	2	10y	2.
382	3/8/1974	2		29	8/1/1996		HSQ'96			CR	<2n	1	1	1	2	1	1	13y	2
383	5/12/1974	2		0			Inv			unknown	nk	9	9	9	9	9	9	nk	9
384										unknown									
385	9/3/1979			0			Q'91			unknown	50t		1				1		
386	30/9/1988	2		10			HSQ '94			CR	3rd	1	1	1.	1	1	1		2.
387	27/12/1988	2		8			mult. '91,'96			R nonC	25t	1	1	2	9	2	1	4y	2
388	25/12/1979		2	14	14/6/1993		Q			CR	<3r	1	1	1	2	1	1	non	2
389	24/4/1973	1		0						Inc CR								7y	
390	8/12/1978			13			Q'91			CR	10t	1	1	1		1	1	non	

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Herr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
391	28/3/1975	2		24			HSQ '99			CR	<3r	3	1	1	2	1	1	non	2
392	28/11/1985	2	1	9	25/5/1992		mult '91,'94			R nonC	<3r	1	1	1	2	1	1	non	1.
393	7/8/1978			0			Q'91			inc CR			1			13	1		
394	8/3/1986			6			Inv			unknown		1	1			1	1	non	1.aut
395	21/8/1976	2		26	29/4/1992		HSQ'94			CR	nk	3	1	1	9	1	1	4y	2
396	18/10/1984	2		13	15/6/1994		mult '94 '95 '97,	1	T158M missense	CR	3rd	1	1	1	2	1	1	4.0	2
397	20/12/1989	2		3	19/10/1991	5/2/1992	Q			inc CR	50t	9	1	1		1	1		2
398	21/3/1971	1?	2	28	19/10/1991	1/11/1995, 21/1/1992	mult.'93,'98	1	del exon 3-4 MH	CR	<3r	1	1	1	2	1	1	10y	2
399	12/4/1991	2	1	4	3/2/1992		mult	2	(AC)(d'E) none	not R		2	1	2	2	2	1	non	2.
400	13/12/1987	1		15	1/10/1991	1/10/1992,1/10/1994,	Inv			inc CR	<2n	3	1	1	2	1	1	non	2
401	17/5/1987			8	19/10/1991					inc CR	10t		1	1		1	1		
402	12/10/1988	2	2	11	15/1/1992	25/5/1998,24/10/2001,	mult'93,'95,'96,'99			CR	10t	1	1	1	2	1	1	3y	2
403	25/2/1967			0			Inv			unknown									
404	26/8/1986	2		8	21/1/1992		HSQ '94			not R	10-	1	1	2	2	1	1	5y	2.
405	24/11/1987	2	2	15	22/1/1992		mult '95.'02	1	R306C (Wessex)	CR	<3r	1	1	1	2	1	1	4.y	2
406	7/5/1988	2	2	15	22/1/1992		HSQ. '01	2	none (AC)	R nonC	25-	1	1	1	2	1	1	18	2
407	29/10/1977	2		25			mult.'98,'02			R nonC		nk	1	1	nk	1	1	3m	1.
408	14/5/1970	1	2	29	21/1/1992		mult '95,'98			CR	2nd	1	1	1	2	1	1	15m	2
409	4/9/1989	2		7	1/10/1992	1/10/1996	Q	1	158(d'E)	CR	25-	1	1	1		1	1		2
410	15/3/1962	1	2	30	21/1/1992					CR	2nd	3	1	1	2	1	1	?	2
411	4/12/1986	2		6	22/1/1992					R nonC	10-	9	2	2		1	1		2
412	8/4/1983		2	16	21/1/1993	26/6/1998	mult '98			CR	<3r	9	1		1	1	1	non	2
413	7/1/1990			3	20/1/1992	7/2/02,	HSQ '02			CR	<3r	1	1	1	2	1	1	non	2
414	24/3/1989			13	20/6/2001		HSQ'01			CR	25-	1	1	1	2	1	1	2y	2
415	4/5/1979			17			HSQ '95			unknown			1			2	2	?	
416	30/9/1993	2		6	8/3/1999		HSQ.'99	1	c502C>T;	CR	2nd	1	1	1	2	1	1	non	2
417	26/11/1986	2	2	8	1/10/1992		HSQ '93	1	(158d'E)	CR	10t	3	1	1	1	1	1	non	2
418	28/3/1989		2	4	20/1/1993		Inv			CR	10t	3	1	1	2	1	1	non	2
419	12/3/1988	2	2	12	1/10/1992	11/1/1994	mult.'97, '98,			CR	3rd	1	1	1	2	1	1	8y	1.?ml
420	4/2/1988		2	6	8/6/1993		Inv			CR	<3r	3	1	1		1	1	non	2

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
421	20/9/1977			0						unknown									
422	16/9/1982	2		14			HSQ'95	1	c808C>T;	CR		1	1	1	9	1	1	non	2
423	16/5/1971			27	18/7/1997		HSQ'97			CR	<2n	1	1	1	2	1	1	13y	2
424	11/10/1970	2		25			mult '93,'95			R nonC	nk	9		1	9	1	2	4y	2
425	5/2/1947	2	2	55	1/10/1992	12/10/2002.1/10/2003	mult'93,'95,98,'02			Inc CR	10-	9	1	1	2	1	1	nk	2
426	27/7/1983			0						unknown									
427	28/5/1973	2	2	25	25/2/1992	19/2/1998	HSQ			CR	<2n	1.	1	1	2	1	1	6y	2
428	1/1/1947	2		0			Inv			unknown									
429	11/7/1987	2	2	13	1/10/1992	8/2/1993,1/10/1994,1/10/1996,8/2/200	HSQ.'00			CR	<3r	1	1	1	2	1	1	6y	2
430	21/1/1959	2	2	37	19/1/1993		HSQ .'92 '95		not requested	CR	<3r	3	1	1	9	1	1	non	2
431	28/10/1997	2	1	7	6/6/2001		HSQ '01	2	not found (AC)	R nonC	2-5	1	1	1	2	1	1	32	1.ble
432	24/9/1999	1		2			HSQ,'01	1	c473G>T; T158M	R nonC	10-	1	2	1	2	1	1	birt	2
433	6/9/1988	2	1	10	1/10/1992	8/2/1993,18/6/1996,	mult'94.'96,'98			CR	2nd	1	1	1	1	1	1	non	2
434	26/9/1988		2	5	8/6/1993		Inv			CR	3rd	3	1	1	2	1	1	non	2
435	12/10/1981			0			Inv			unknown									
436	5/10/1971			32	7/6/1995		HSQ'3			CR	3rd	1	1	1	2		1	14y	2
437	14/4/1963	2	2	36			mult.'95,'98			CR	nk	9	1	1	1	1	1	non	2
438	12/4/1980	1		19	17/8/1998		HSQ'98			R nonC			1	1		1	1	6mo	1.
439	17/11/1987			0						unknown									
440	5/4/1977	2		16	18/11/1992		Q	2	(AC) none found	not R	2nd	3.	1	1	1	1	2	non	2
441	26/7/1994	2		10	23/10/2001	30/1/2002	HSQ. '01,'04	1	R133C(Wessex)(C	R nonC	50-	2	1	1	2	1	1	non	2
442	27/4/1981	2		19			Inv			unknown	<3r					1		5m	
443	1/1/1994			0						unknown									
444	11/7/1965			0						unknown									
445	17/3/1973	2	2	19	18/11/1992		Q'92	2	(AC none found	not R	10t	3.	1	1	1od	1	2	non	2
446	15/2/1961	2	2	37	14/1/1998		HSQ'98	2	none (Wessex)	not R	50t	2	2.	1	2	1	2.	31y	1.
447	12/7/1990	2		7	25/5/1992	11/1/1994,17/6/1997	mult. '94, '97			CR	3rd	1	1	1	1	1	1	non	1. ?
448	31/5/1989	2	3	7	1/10/1992		HSQ '94			CR	25-	3	1	1	2	1	1	2.6	2
449	22/11/1989	2	2	9	8/6/1994	13/1/1998	HSQ.'94	1	R306C(MB)	CR	25t	1	1	1	2	1	1	8y	2
450	7/6/1989		2	4	20/1/1993		Inv			CR	25t	3	1	1		1	1	non	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC	fall	early crit	dysprax	face	stereo	regres	first S	other aet
451	18/11/1989	2		14	1/10/1992	30/1/1995	HSQ '03,Q '02	1	R270X (MB)	CR	<2n	3		1	1	2	1	1	non	2
452	23/11/1971	2		0			inv			unknown										
453	8/12/1986			6	1/10/1992		inv			CR					1					
454	19/7/1986	2	2	8	8/7/1993		HSQ '93			CR	10-	3		1	1	1	1	1	2.6	1.
455	26/10/1994	2		7	3/11/2000		HSQ	2	none (AC)	not R	50-			1		1	1sti	1	9m	1.
456	8/7/1990			0			inv			unknown										
457	30/4/1986	2		13	4/1/1999		HSQ,'99	2	none(AC)	R nonC	25t	1			1		1	2	6wk	1.sei
458	8/5/1984			13			HSQ '96			CR				1		9	1	1	18	2
459	5/6/1985	1	2	10	26/5/1992	10/6/1992, 15/6/1995	HSQ			R nonC	10-	1		1	1	2	1	1?	3m	1.
460	30/11/1993	2	2	7	15/3/1999		mult.'99,'00			CR	3rd	1		1	1	0	1	1	6y	2
461	30/4/1991	2		7			HSQ'97			CR				1	1	9	1	1	6y	1.
462	29/12/1985	2	2	12	25/5/1992	17/6/1997	mult. '94, '97,	1	R306C(MB)	CR	<3r	1		1	1	9	1	1	7y	2
463	9/7/1985			0			inv			unknown										
464	22/9/1978	2		20	12/1/1994		mult,'94,'95,'97,'98	2	none(AC)(CS)	CR	50t	1		1	1	2	1	1	15y	2
465	20/10/1978			14	1/10/1992					inc CR										
466	6/12/1994	2		7	30/1/2001		inv	1	c880C>T,R294X	CR	<3r	1		1	1	1	1	1	non	2
467	9/6/1964	2	2	30	17/1/1995	1/11/1999	HSQ.'93		awaited	CR	<3r	1		1	1	9	1	1	2y	2
468	2/6/1992	2	1	3	11/11/1995		HSQ.'95,1/10/2003			CR	10-	9		1	9	2	1	1	non	2
469	7/8/1985	2	2	16	1/10/1994	30/1/2001	mult'95,'00	1	P302R	CR	<3r	9		1	2	2	1	1		9
470	25/11/1997			0			inv		IVS2+95G<A(AC)	unknown										
471	2/10/1979	2		0			inv			CR										
472	28/8/1972			0			inv			unknown										
473	16/10/1963	2	2	32	9/1/1996		HSQ.'95			CR	25t	1		1	1	2	1	1	2.0	2
474	26/8/1994			0						not R					1					
475	25/9/1983	2		9	12/5/1992		inv			not R	25t	9		1	2		1	1	non	1.
476	3/6/1992		2	3			inv			CR	3rd	1		1	1	2	1	1		
477	1/1/1989			0			inv			CR										
478	17/5/1990			0						unknown										
479	10/12/1980	2	2	21	1/6/1990	1/11/1999,	Q.'90.	1	R133C	CR	3rd	1		1	1	2	1	1	11y	2
480										unknown										

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
481	28/12/1987			0						unknown									
482	22/6/1992			0						unknown									
483	10/5/1976	1	2	23	22/1/1991	25/1/1993	HSQ.'98,'02	1	R270X(MB)	CR	3rd	1	1	1	2	1	1	14y	2
484										unknown									
485	8/11/1984	2		14	4/11/1988		HSQ '98			not R	25t		1	1	2	2	2	4mo	1
486		2								unknown									
487	8/9/1974	2		18	6/6/1988	10/10/1990, 1/5/1992,	Q.'88.inv	1	44bpdel.1163-(We	R nonC	10-	2	1	1	2	2	1	10y	2
488	30/3/1968	2	2	18	31/10/1985		Q'85			R nonC	nk	9	1	1	2	1	1	non	1.
489	16/3/1976	2		13	23/7/1987	9/12/1988,				not R	10t	1	1	1		1	1	7mo	1.
490	6/4/1982	2		0	18/9/1990		Inv			not R	3-1	1	2		2	1	1	3da	1.
491	20/9/1970	2		27	29/7/1997		HSQ.'97,'03	2	neg(AC)	R nonC	3rd	1	1	1	1	1	2	1y	2
492	7/4/1983	2		19			Inv			unknown	10-					1			1.co
493		2								unknown									
494	29/5/1986			0						unknown									
495	16/11/1983	2		18	6/11/1984	5/1/1996	Q	de	del 15	not R	3rd	1	1	1	2	1	1	3y	1.An
496	11/7/1974	1		18						inc CR									
497	16/11/1986	2		6			Q'92	1	c763C>T;	CR	3rd	1	1	1		1	1	7y?	2
498	6/7/1984	2	2	37	1/5/1988	11/6/1991, 31/1/1995,11/6/1001,	mult. '97, '00,	1	473C>T	CR	<2n	1	1	1	9	1.	1	non	2
499	31/7/1973		2	19	4/6/1992		Q'91			CR	3rd	1	1	1	2	1	1	5y	2
500	15/10/1971	1	2	23	10/6/1992	20/1/1994	HSQ'94			inc CR	50t	1	1	1	2	1	1	4y?	2
501	29/12/1970		2	22	4/6/1992		Q			CR	<2n	1	1	1	2	1	1	7y	2
502	6/5/1989	2	2	13	4/6/1992	1/11/1997,1/10/2001	mult.'93,'94,'96,'97,'98,'01	1	1152del144bp(AC)	CR	10-	3	1	1	2	1	1	3y	2.
503	7/10/1972	1		0						unknown									
504	2/3/1985	1		3	10/3/1987					not R	10t	9	1	1	9	1	1		1.
505	2/9/1983	2		20	12/10/2002	12/12/2002	Inv	1	R294X(MH)	CR	<3r	3	1	1	2	1	3	nk	2
506	4/7/1974		2	19	19/1/1993		Inv			CR	10t	9	1	1	2	1	1	3y	2
507	11/9/1997			0	11/10/2002		Inv			unknown									
508	14/2/1976	2	2	29	4/6/1992	14/9/1993,11/6/1994,14/6/1998,1/12/1	mult '94,'98			CR	10t	3	1	1	2	1	1	10y	2
509	7/9/1972			29	20/6/2001		HSQ'01			CR	<2n	3	1	1	2	1	1	non	2
510	28/7/1989	2	2	13	5/8/1992	1/1/94,1/1/96,1/1/2000	mult.			CR	10t	1	1	1	2	1	1	2y	2

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511	18/6/1979	2	2	0	5/8/1992		HSQ '95			not R	50-	2	1	1	1	1	2	10m	1.fra
512	30/5/1989	2	2	7	9/5/1995		mult. '95,'96			R nonC	50t	2	1	1	2	2	2	non	2
513	24/10/1987		2	11	20/1/1993		HSQ'98			CR	<3r	1	1	1	2	1	1	5-6	
514	4/7/1962	2		31	1/1/1993		Inv			R nonC	50-	1	1		1	1	2		2
515	15/4/1967	1		0						Inc CR	nk	9	3	1		1	1	nk	2
516	17/7/1989	2	2	10	20/1/1993		mult'94,'95,'96,'98			CR	10-	9	1	1	2	1	1	non	2
517	13/6/1990	2		10	1/10/1996	1/10/2001, 12/10/2002	mult. '94,'96,'00	1	c763C>T;R255X	CR	<3r	1	1	1	9	1	1	3y	2
518	23/12/1985		1	17	1/10/1992	1/6/2001	mult '99.'01			CR	25t	1	1	1	1	1	1	14y	2
519	29/12/1987		2	0	1/10/1992	25/1/1993				CR	10-		1	1		1	1		
520	18/6/1990	2		7	22/12/1992	7/2/1996,31/5/1997	HSQ '97	2	none (WGH)	CR	<3r	1	1	1	1	1	1	non	2
521	22/2/1989	2		6	1/10/1992	16/1/1995, 12/10/2002,1/10/2003	Q '93			CR	10t	3	1	1	2	1	1	non	2
522	28/8/1962	2	2	35	19/1/1993		HSQ.'97			CR	10-	9	1	1	2	1	1	non	2
523	9/2/1960	1	2	41	19/1/1993		mult.'95,'98,'00	2	neg (AC)	CR	<2n	1	1	1	2	1	1	2y	2
524	15/7/1972		2	21	26/1/1993		Inv			CR	10t	3	1	1	2	1	1	7y	2
525	10/8/1990	2		6	21/1/1993	1/10/1996	HSQ. '96	1	T158M (MB)	CR	3rd	1	1	1	2	1	1	4y	2
526	31/12/1988	2	2	6	20/1/1993		HSQ. '94	1	R306C(MB)&T197	CR	<3r	1	1	1	2	1	1	non	2
527	27/4/1983		2	11	8/7/1993		Inv			CR	10t	3	1	1	2	1	1	3y	2
528	13/6/1988		2	27	1/10/1992					Inc CR		9	9	1	2	1	9		
529	6/6/1988	2	2	10	1/10/1992	23/6/1995	HSQ . '95			CR	25-	1	1	1	2	1	1	non	2
530	13/1/1988	2		6	1/10/1992		HSQ.'94			R nonC	<3r	1	1	1	1.	1	2	non	2
531	9/2/1979	2		16	13/6/1994		Inv			CR	<3r	1			2				
532	17/12/1961	2	2	37	19/1/1994		mult'93,'95,'98	1	R133C(MB)	CR	<3r	1	1	1	2	1	1	18	2
533	2/6/1952	2	2	44	26/1/1993		HSQ. '98			CR	<3r	3	1	1	9	1	1	10y	1
534	9/7/1981	2	2	16	21/1/1993	14/1/1997	mult.'93,'95,'98	2	15Q duplication	R nonC	10-	1	1	1	1.a	1	1	8m	1.
535	1/10/1978			0			Q '93			R nonC	50t	2	1			1	1		
536	29/10/1984	2		9			Q '93	1	316C>T	R nonC		2	1			1	1		2
537	29/3/1990	2		6	5/1/1995		HSQ '93			not R	10-	1	2	1	1	1	2	10	2.de
538	27/11/1984	1		14			HSQ.'98	2	none(AC)	R nonC	<3r	1	1	1	2	1	1	2y	1.
539	2/5/1972	2		27	24/5/1984	1/5/1996,26/22/1991	mult'95,'98			CR	<2n	1	1	1	2	1	1	10	2
540	1/3/1989	2	1	10	25/10/1993	1/10/1996,17/6/1998	mult.'93,'95,'98			CR	50t	3.	1	1	2	1	1	5y	2

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541	23/4/1990	2		0	26/6/1993	5/10/2001	Inv			R nonC	50t	1	1	1	2	1	1		
542	8/12/1955	2	2	38	19/10/1989		Inv			inc CR	3rd	3	1	1	2	1	1	non	2
543	16/2/1991	2	2	10	11/1/1994	1/10/1996,4/9/2000,15/10/2001,12/10/	mult '93,'94,'96,'97,'98,'00	1	Q262X(MH)	CR	<3r	1	1	1	2	1	1	non	2
544	16/5/1990	2	2.	12	2/11/1993	19/6/2001	mult.'93,'96,'99,'01			CR	10-	1	1	1	2	1	1	9yr	2
545	1/1/1974			0						unknown									
546	13/11/1991	2	1	12	28/10/1993	28/10/1993, 1/6/1995,	mult. '93,'94,'03	1	del exon 4	CR	25-	9	1	1	1.sl	1	1	non	2
547	2/2/1947	1	2	52	8/6/1994		mult '93,'98			CR	2nd	1	1	1	2	1	1	4y	2.
548	3/9/1977	2		23	1/1/2000		HSQ '00			CR	<2n	1	1	1	2	1	1	7y	1.
549	18/1/1977			26	13/6/1994	1/10/2001	HSQ '03			CR	<2n	1	1	1	2	1	1	6y	2
550	29/9/1990	2	1	13	15/10/1993	4/2/1995,4/2/1999	mult. '93,'94,'96	1	del exon3-4	CR	<2n	1	1	1	2	1	1	4.y	2
551	13/12/1990	2		4	11/1/1994	1/11/1995	HSQ '94	1	c455	CR	25-	1	1	1	2	1	1	non	2
552	28/8/1991			0	17/10/1993		Inv			CR	<3r		1	1		1	1		
553	8/5/1991	2	2	9	24/1/1994	4/4/2001, 12/10/2002	mult.'93,'00	1	R168X (MB)	CR	<3r	1	1	1	2	1	1	2y	2
554	30/9/1969	2	2	27	15/10/1993		HSQ'95			CR	<2n	1	1	1	2	1	1	7.0	2
555	8/2/1970	2	2	29	15/10/1993		mult.'93,'95,'98	1	T158M (MB)	CR	<3r	1	1	1	2	1	1	2y	2
556	15/1/1991	2		8	15/1/1991	15/10/1993	HSQ.'98			CR	10-	9	1	1	9	1	1	non	2
557	25/7/1992	2	2	7	15/10/1993		mult'93,'94,'96,'97,'98			inc CR	50-	9	1	1	2	1	1	non	2
558	12/1/1990	2		9			mult.'93,'98			CR	NK	9	1	1	9	1	1	5y	2
559	21/2/1990	2		4	12/1/1994		Inv	2	noneAC)	not R	50-	2	1	2	1	2	2	non	1.pre
560	21/2/1990	2		2	12/1/1994		Inv	2	none(AC)	not R	50-	2	.1	2	1	1	2	non	1.
561	11/5/1961	2	2	36	2/2/1994		HSQ.'96			R nonC	<3r	1	1	1	2	1	1	6y?	2
562	20/7/1981	2		13	21/1/1994		Inv	2	(AC) none found	not R	<3r		2	2	1	1	1	6mo	1.no
563	24/8/1962	2	2	37	11/1/1994		mult. '94, '95, '98,	1	R294X(MB)	CR	50t	9	1	1	2	1	1	non	2
564	14/9/1983	2	2	15	12/1/1994	15/10/2001,	mult. '94,'98	1	c397C>T; R133C	R nonC	10-	1	1	1	2	1	2	non	2
565	11/10/1980	2		20	11/1/1994	18/8/1997	mult.'94,'95,'97,'00	2	none(AC)	R nonC	<2n	1	1	1	1	1	9	12.	2
566	19/5/1989	2	2	5	11/1/1993		HSQ.'94			CR	10-	1	1	1	2	1	1	4.y	2
567	18/8/1990			4	12/1/1994		Inv			CR	<3r	1	1	1	1	1	1	non	2
568	18/8/1987	2		12	15/8/1994	26/3/1999	HSQ.'98	1	R168X(MB)	CR	<3r	1	1	1	2	1	1	5y	2
569	14/12/1965	2	2	32	15/10/1993		HSQ'97			CR	nk	9	1	1	9	1	1	NK	2
570	29/10/1990	2		4	10/1/1994		HSQ '94	2	none (Addenbr)	not R	10-	2	1	1	1 m	1	2	non	1.

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
571	16/4/1990			5	15/10/1993	1/10/1994	inv			inc CR									
572	13/9/1995			0						unknown	25t	1	1	2	1.	1			
573	7/1/1992	2	2	5	14/3/1994	1/1/2001	mult '94,'96	2	neg(AC)	CR	<2n	1	1	1	2	1	1	10	2
574	9/4/1991			0			inv			not R						1			
575	16/7/1991	2		9	17/6/1995	10/10/1999,1/10/2003	inv		del exon 3-4.1(AC)	R nonC	10-	1	1	1	2	1	1	<1y	1.
576	4/12/1990			0			inv			unknown									
577	28/7/1990	2	2	6	18/1/1995	19/6/1996,	HSQ.'95	1	502C>T(AC)R168X	CR	<2n	1	1	1	2	1	1	2y	1.ear
578	11/7/1961	1	2	39	15/1/1994		HSQ'96			inc CR	3rd	1	1	1	2	1	1	7y	2
579	27/2/1935	2	2	62	1/6/1998		mult'94,'96			not R	nk	9	1	1	2	1	2	2	9. no
580	30/11/1988	2		10			HSQ'98	1	c301C>A;	R nonC	nk	9	1	1	2	1	1	non	1.pre
581	24/5/1971	2		33	15/6/1994		mult'94,'98	2	none(AC)	R nonC	50t	2	1	1	2	1	1	5mo	2
582	19/2/1991			0						unknown									
583	19/3/1991	2	2	12	1/11/1997	1/6/1998,22/10/2001	mult '98.'02	1	1157del44(MH)	CR	<3r	1	1	1	2	1	1	non	2
584	29/4/1962	2		0	1/4/1994		inv			inc CR									
585	13/9/1947	2	2	47	1/12/1993		inv			inc CR				1					
586	28/12/1958	22	2	40	1/12/1993		HSQ'98			R nonC	nk	9	1	1		1	1	3yr	2
587	20/9/1950	2	2	48	18/3/1991		HSQ			CR	3rd	9	1	1	0	1	1	non	2
588	12/3/1961	2		0			inv			inc CR			9	1		1	9		2
589	25/6/1963	2	2	31	1/12/1993		inv			inc CR	<2n						1	nk	1.
590	18/6/1961	2	2	0	31/3/1993		inv			inc CR						1			
591	1/9/1948	2	2	45	31/3/1993		inv			R nonC	<3r	3	9		1	1			2
592	2/9/1965	2		29	1/4/1994		inv			R nonC		1		1	2	1		20y	1.
593	28/9/1988	2		13	14/6/1994	26/6/1998	HSQ.'01	2	none (where?)	CR	2-5	1	1	1	2	1	1	non	2
594	12/11/1979			19			mult.'94,'98			CR	<3r	1	1	1	2	1	1	3.6	1.1 in
595	8/9/1964	2	1	35			mult'94,'98	1	R255X	CR	50t	9	1	1	2	1	1	11y	2
596	8/12/1990	2	2	4			HSQ.'94			R nonC		9	1	1	9	1	2	17m	2
597	8/1/1991	2		5	14/6/1994	15/6/1995	inv	1	c502C>T; R168X	CR	10-	2	1	1		1	1	non	1.po
598	2/10/1991	2	2	5	14/6/1994		mult.'94,'95			R nonC	50t	2	1	1	1	1	1	non	2
599	1/11/1950	2	2	48	14/6/1994		mult'95,'98			CR	10-	2	1	2	2	2	2	non	2.
600	30/12/1970	2		28	14/6/1994	16/6/1998	mult.'94,'95			CR	25-	9	1	1	2	1	1	10y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Herr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
601	31/3/1972	2		27	13/6/1994		mult. '94,'95,'98			R nonC	<3r	1	1	1	2	1	1	2.6	1.ear
602	6/2/1973	1	2	30	14/6/1994		mult. '94, '98,	2	neg (AC)	CR	2nd	1	1	1	2	1	1	non	2
603	13/7/1983	2		11	14/6/1994		mult '94,'97,'98			not R	75t	2	2	2	1	1	1	2y	1.no
604	26/11/2003			0															
605	23/10/1977	2		21	14/6/1994	12/10/2002	mult.'94,'98	2	negative(MB?)	CR	25t	9	1	1	2	1	1	3y	2
606	29/8/1983			15	15/6/1994		HSQ '98			R nonC	<<3	3	2.v	1	2	1	2	non	2
607	4/6/1962	2	2	35	1/10/1994		HSQ.'94,'97,'01			CR	<2n	3	1	1	2	1	1	non	2
608	16/9/1989			0			inv			CR									
609	11/6/1987	2	2	15	15/6/1994	18/6/002	mult'94,'02			CR	10-	3	1	1	2	1	1	3y	2
610	4/2/1988	1	2	7	1/5/1994		HSQ			CR	nk	9	1	1	2	1	1	non	2
611	29/5/1992	2	2	5	29/5/1992	1/10/1996,15/1/1997	mult.'94,'97			CR	10-	9	1	1	2	1	1	3y	2
612	17/5/1990			0			inv			unknown	<3r		1				1		
613	20/6/1988			8	1/6/1994		inv			CR	<3r	1	1	1		1	1	3y	2
614	11/5/1990			0						CR	50t	2				1	1	12m	1. pig
615	27/9/1980			0	8/6/1994		inv			CR	25-		1			1		3y	
616	3/1/1986	2	2	9	8/6/1994		mult '94,'95			CR	3rd	1	1	1	2	1	1	non	2.
617	28/5/1986			9	8/6/1994		inv			not R	10-		1	2		1	1	7y	
618	3/2/1987	2	2	9	14/6/1994		mult.'94,'95,'96,'98	2	none(AC)	R nonC	10-	2	1	1	2	1	1	4y	2
619	7/5/1992	2	2	12	3/6/1994	1/10/1996,11/6/2002,	HSQ.'02	1	1157-1200del44bp	CR	10-	1	1	1	2	1	1	10	2
620	22/4/1964	2	2	35			mult'94,'95,'98			CR		9	1	1	2	1	1	non	2
621	1/1/1966			0			inv			unknown									
622	6/5/1991	2	1	8	16/1/1995	9/1/1996,1/10/1996,15/10/2001,	mult '94,'96,'98	1	Q47X(MH)	CR	3rd	2	1	1	2	1	1	non	2
623	12/11/1992	2	2	8	16/1/1995	10/1/1998,13/1/1998,10/2/2000	mult.'94,'95,'98.'00	1	R270X (MH)	CR	10-	1	1	1	1	1	1	3y	2
624	9/4/1982			0			inv			unknown									
625	28/12/1992			0						unknown									
626	19/9/1990	2		4			HSQ '94			CR	<3r	1	1	1	9	1	1	non	2
627	26/4/1985	2		14			mult. '94,'98		balanced inversion	not R			1	9	2	1	2	4y	1.?c
628	22/11/1989			5	1/10/1994		inv			Inc CR	<3r	3	1	1		1	3		2
629	6/12/1991	2	1	7	1/10/1994	18/1/1995, 14/10/2001, 12/10/2002	mult. '94, '98,			CR	2-5	1	1	1	2	1	1	non	2
630	10/12/1990			5	16/1/1995		inv	2	none AC)	R nonC	<3r	3	2	1	2	1	1	24h	1.

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
631	21/8/1990	2		5	5/8/1995	18/8/1996,1/11/1997	HSQ.'94	2	none(MB)	CR	2nd	1	1	1	1,a	1	1	non	2
632	18/10/1991	2	2	7	16/1/1995		mult.'94,'98			CR	10t	1	1	1	2	1	1	6y	2
633	2/4/1982	1		15	26/2/1986		Q			not R	3rd	1	1	1	2	1	1	2y	1.Bat
634	24/8/1970	1	2	28	1/10/1994		mult.'95,'96,'97,'9896			CR	<2n	1	1	1	1	1	1	23y	2
635	27/11/1991	2		5	2/12/1994		mult. '95, '96,	1	792-804del13, I	CR	10-	1	1	1	2	1	1	non	2
636	26/1/1989	2		6	1/10/1994		Inv			R nonC	3rd	1	1	1	1	1	1	2.y	1.
637	20/3/1975		2	24	1/10/1994		PSQ'95,HSQ '98			not R	50t	2	2	1	9	1	2	0.1	2
638	24/6/1988	1		0						unknown									
639	30/3/1986			9						unknown	50t		1	1		1	1?		
640	31/10/1967	2	2	28	1/10/1994	17/1/1995	Inv			R nonC	<3r	3	1	1	1	1	1wl	2mo	1.
641	9/12/1989		2	6	1/10/1994	18/1/1995	inv			CR	<3r	1	1	1		1	1	18m	2
642	2/12/1992	2	2	3	24/1/1995	14/1/1998,	mult.'95,'98			CR	<3r	1	1	1	9	1	1	rec	2
643	28/10/1992		2	3	16/1/1995		Inv			CR	10-		1	1		1	1		
644	31/10/1990	2		5	16/1/1995		Inv			R nonC	2nd	1	1	1	2		2	3y	2
645	17/5/1980	2		15	16/1/1995		HSQ '95			R nonC	50-	2	1	1		1	?	1y	1
646	7/5/1983			12	16/1/1995		inv			R nonC			1				1	4y	1.typ
647	15/12/1988			7	16/1/1995		inv			CR	<3r	1	1	1		1	1		
648	22/5/1984	2		19	17/1/1995	17/6/1998	HSQ '95,'02	1	R306C (MB)	CR	25t	1	1	1	1	1	1	9y	2
649	12/9/1992	2	2	3	16/1/1995		inv	1	c1130C.TA444T	Inc CR	25t		1	1	2	1	2	non	2
650	24/12/1992	2	2	5	24/12/1992	2/2/1995, 1/10/1996, 1/11/1997,	mult. '95, '97	1	R270X(AC)	CR	<3r	2	1	1	9	1	1	1.8	2
651	14/5/1976	2		20	1/10/1991		PSQ			not R	10t	2	2.	1	2	2	1.	y	1.
652	9/8/1989			6	4/2/1995					R nonC	90t	2	1	1		1	1	non	
653	1/3/1993	2	1	9	18/1/1995	19/6/01, 15/1/01,23/10/01,	mult '95,'96,'97,'98,'01,02	1	R270X (MB)	CR	<3r	1	1	1	2	1	1	non	2
654	11/4/1990	2		9	6/6/1995		mult.'95,'96,'98	1	yes, no details	R nonC	3rd	1	1	1	2	2	1	3y	2
655	3/5/1980			15				1	R270X	unknown	10-	1		1		1	2	9m	
656	19/1/1972			24	19/6/1995		inv			R nonC	3rd	3	1	1	1an	1	1	?	2
657	13/8/1989	2		7	17/1/1995	9/1/1996	inv			R nonC	3rd	3	1	1	1	2	2	non	1.
658	21/8/1992	2	2	3	12/1/2003		HSQ.'95	2	none '02 (Dennis)	R nonC	NK	9	1	1	9	1	1	8mo	2
659	29/4/1992	2	2	4	9/5/1995					not R	50t		1	2		2	1	13m	1.sei
660	23/9/1981	2	2	21	2/5/1995	5/10/2001	HSQ.'95	1	R133C (Ed)	R nonC	50t	2	1	1	1	1	1	3y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
661	4/6/1991	2		12	15/6/1995		HSQ.'95			R nonC	>50	2	1	2	2	2	2	non	2
662	2/7/1978	2		0						not R									
663	26/11/1974	2		15	20/10/1983	22/1/1988, 1/8/1989,				not R	>10	2	1	1	2	2	2	7y	1.
664	1/1/1964			26	1/4/1989					not R						1			
665	20/8/1971	2	2	28	19/1/1993		mult.'95'98	1	208(d'E)(MH)	CR	3rd	3	1	1	1	1	1	non	2
666	25/9/1988		2	5	24/5/1993					CR	<3r		1	1		1	1	non	
667	30/9/1986			15	31/1/2001		Inv			R nonC	50t	2	1	1	2	1	1	18	1.sei
668	6/1/2000			0			Inv	1	c.1157-1188del32	unknown	nk								
669		2						2	(d'E) none found	unknown									
670	26/7/1981			19			HSQ			CR	10-	9	1	1	2	1	1	2.2	2
671	28/8/1988			7			Inv			unknown									
672	28/5/1987			9			Inv	1		CR						1		non	
673	3/2/1983			0			Inv			unknown									1.
674	1/1/1973			23	18/6/1995					CR	<2n	1	1	1	2	1	1	non	2
675	12/6/1987	2	1	12	17/6/1995	19/6/2001	mult,'95'98	1	P376fsX400(MB)	CR	10-	1	1	1.	2	1	18	non	2
676	21/6/1967	2	2	28	5/6/1995		Inv	1	R306C	CR	10t	3	1	1	9	1	1	10y	2
677	10/7/1993	2		3	6/6/1995	10/1/1996	HSQ. '95	2	R270X(MB)	CR	<2n	1	1	1	9	1	1	non	2
678	14/5/1991	2	1	6	21/8/1995	18/6/1996,1998	mult. '95,'96	1	c502C>T;R168X	R nonC	<3r	1	1	1	2	1	1	10	1.T
679	30/11/1991	2		4	7/6/1995		Inv	1	IVS2-9A>G-8nt	CR	<3r	1	1	1		1	1		
680	16/2/1991	2		8	6/6/1995		mult.'95,'98	2	none (AC)	R nonC	10-	1	1	1	1	1	1	20	2.
681	12/2/1993	2	2	9	7/6/1995	23/6/1995, 15/1/1997, 10/2/2000	mult			R nonC	<3r	2	2	1	2	1	1	1mo	1.
682	6/9/1990	2		7	17/6/1997		HSQ. '97,			CR	25t	1	1	1	2	1	1	non	2
683	2/6/1970	2	2	26	25/7/1995		HSQ '95			CR	2nd	1	1	1	2	1	1	2y	2
684	11/10/1991	2		5	9/1/1996		HSQ. '96,	1	R106W (MB)	CR	3rd	1	1	1	2	1	1	non	2.
685	21/3/1982	2		16	17/6/1998		HSQ.'98			CR	25-	9	1	1	2	1	1	6y	2
686	17/8/1971			24			HSQ'95			CR	nk	1	1	1	9	1	1	3y	2
687	7/2/1987	2	2	9	1/11/1995	9/1/1996	HSQ.'95			R nonC	<3r	1	1	1	2	1	1	4mo	1.
688	13/7/1986		1	9			Inv			unknown								non	
689										unknown									
690	13/11/1993	2	1	5	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002	mult. '95, '97, '98	1	R168X(MH)trunc	CR	3rd	1	1	1	2	1	1	non	2

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dyspraxic	face	stereo	regress	first S	other aet
691	13/11/1991	2		5	27/11/1995		Inv	2	none(AC)	R nonC	<3r	1	1	1	1	1	1	7-8	1.ear
692	13/11/1991	2		5	27/11/1995		Inv	2	none(AC)	R nonC	10-	1	1	1	1	1	1	7-8	1.
693	20/9/1993			5			HSQ '98			unknown		1	1	1		1	1	6mo	1.'dif
694	19/11/1993	2	2	6	11/11/1995	5/2/1996,23/10/2001,12/10/2002	mult. '95,'98,	1	R255X (MH)	CR	3rd	1	1	1	1	1	1.	non	2
695	14/5/1991	1		6	17/6/1996		Inv	2	none(AC)	R nonC	<3r	1	1	1	2	1	1	1y	?
696	29/12/1981	2		21	9/1/1996	13/1/1998, 14/10/2001,29/1/2002	mult'95,'97	1	c397c>t; R133C	CR	50t	9	1	1	2	1	1	3y	2
697	29/5/1988	2		8	8/1/1996		Inv	1?	no mut(Salis) yes	R nonC	<2n	1	1	1	2	1	1?	10m	2
698	26/9/1988	2		8	19/12/1995	19/12/95	HSQ '95	2	neg (AC)	R nonC	2-5	1	1	1	1	1	2	3mo	2
699	10/8/1993			0			Inv			unknown									
700	2/2/1973			31	10/1/1996					R nonC	90t	2	1	1	2	1	1	26	2
701	17/10/1968			28	14/6/1994		Inv			Inc CR		9	1	1	1	1	1		2
702	4/7/1992	2		11	11/11/1995	12/10/2002	Inv	1	exon4.3	CR	<3r								
703	26/7/1967	2	2	35	11/11/1995	30/1/2002,	mult'95,'98,'02	2	no mut (Salis)	R nonC	50t	9	1	1	2	1	1	11y	2
704	18/6/1989			0	11/11/1995					unknown									
705	19/5/1987			9	10/11/1995					unknown	25t								
706	12/12/1951	2	2	47	11/11/1995	9/1/1996,10/10/1998,12/10/2002	mult.'96,'98			CR	3rd	3	1	1	2	1	1	5y	2
707	12/12/1936	1		59	11/11/1995		Inv			Inc CR			1	1		1	9		1.
708	4/5/1983	2		21	16/12/2003		Inv	2	(AC)none	CR	3rd	3	1	1		?	1		
709	9/11/1984	2		14	1/11/1995		mult '95,'98			Inc CR	3rd	3	9	1	9	1	1	10y	2
710	28/9/1968	2		28	9/1/1996		HSQ'95			R nonC	10-	9	1	1	2	1	1	nk	2
711	2/8/1993	2		10	10/1/1996		HSQ '03	1	R255X(MB)	CR	3rd	1	1	1	2	1	1	3y	1.po
712	10/5/1984	2	2	15	10/1/1996	6/8/1997,18/8/1998,9/2/2000,1/10/200	mult'95,'96,'98	2	not found	R nonC	3rd	2.	1	1	2	1	2	16y	2
713	10/1/1968	2	2	32	18/6/1996	1/10/2001	mult'95,'98,'99	1	R306C(MB)	R nonC	50t	1	1	1	2	1	1	18y	1.
714	17/10/1993	2		5	9/1/1996	14/1/1998,1/10/1999,12/10/2002,1/10/	mult. '96,'98			CR	<2n	1	1	1	2	1	1	non	2
715	12/3/1967	2		30	18/6/1996		HSQ'95			CR	2nd	1	1	1	2	1	1	7y	2
716	1/1/1969		2	27			Inv			unknown									
717	4/11/1988			0			Inv		awaited	unknown	nk		2					4y	
718	21/9/1981	2		15	9/1/1996		HSQ. '95			R nonC	<3r	1	1	1	2	1	1	4mo	1.ear
719	4/5/1973	1	2	23	9/1/1996		HSQ.'95,			CR	10-	3	1	1	2	1	1	4y	2
720	15/9/1981			0			Inv			unknown									

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
721	17/10/1988	2		8	10/1/1996		HSQ'95			R nonC	<3r	1	1	1	9	1	1.b	8mo	1.?e
722	20/12/1993	2		4	17/6/1997		mult. '96,'97	1	del exon 3-4.1	CR	3rd	9	1	1	9	1	1	non	2
723	1/1/1989			7			Inv			CR				1	2	1			
724	25/1/1977	2	2	26	8/1/1996		mult.\96,'98,'02,'03	2	none(MB)	R nonC	50-	2	1	1	2	1	1.	non	2
725	4/3/1970	2	2	32	8/1/1996	12/2/2002	mult.'96,'02	1	del exon 4 c	CR	10t	1	1	1	2	1	1	non	2
726	30/11/1991	2		5	1/6/1996	27/3/97	HSQ.'96	1	T158M	CR	3rd	1	1	1	2	1	1	non	2
727	19/6/1993	2		5	1/10/1994	1/10/1994,18/6/1996, 13/10/1996,	HSQ. '98,			CR	3rd	1	1	1	2	1	1	non	1.
728	20/10/1993	2		4	20/10/1993		mult '96,'97			CR	3rd	1.	1	1		1	1	non	2
729	26/10/1993			0						inc CR									
730	6/1/1997	2	2	6	18/6/2002		HSQ.'02	1	c397C>T;R133C	CR	3rd	3	1	1	2	1	1	non	2
731	22/10/1992			0						unknown									
732	4/4/1987	2	2	10	14/1/1997		HSQ '96			CR	50t	9	1	1	9	1	1	0.8	2
733	15/9/1986	2	2	12	20/3/1996		mult '96,'98	1	yes (AC)	R nonC	<3r	1	1	1	2	1	1	3da	2.
734	25/4/1991	2		6	18/6/1996		Inv	1	c808C.T;R270X	CR	3rd	1	1	1		1	1	non	2
735	1/2/1989	2	2	28	17/6/1996		mult.'96,'98			CR	<2n	1	1	1	9	1	1	2yr	2
736	23/9/1981	2		15	24/6/1996	31/5/1996	HSQ.'96			R nonC	50t	1.	1	1	2	1	2	1.2	2
737	8/4/1993			3			Inv			Inc CR	50-					1	1		
738	14/4/1992	2		5	1/6/1996	30/7/1996	Inv	1	R255X	CR	<3r	1	1	1	2	1	1	4y	1.
739										unknown									
740	24/4/1984	2	2	18	18/6/1996	29/6/2001	mult '96,'01	2	none(MB)	CR	10t	9	1	1	2	1	1	2y	2
741	7/2/1980	2		19			HSQ.'98			not R			1	1	9	1	2	18y	2.
742	6/5/1984	2		15	18/6/1996		mult'96,'98			CR	10-	9	1	1	2	1	1	9	2
743	7/11/1981			0			Inv			IncCR									
744	11/9/1976			0						unknown								13y	
745	14/3/1991			0			Inv			unknown	10-		1			1	2		
746	19/3/1979			18			Inv			unknown						2			
747	27/12/1979	1		0						unknown									1.
748	22/5/1973	2		24	17/6/1996	9/10/1998	Inv	2	neg(AC)	R nonC	<3r	1	1	1	2	1	1	non	2
749	1/7/1969	2	2	27	17/6/1996		Inv	2	neg(AC)	R nonC	<3r	1	2	1	2	1	1.	non	2.mo
750	1/12/1978	2		18	17/6/1996		inv			Inc CR	<3r	1	1	1	2	1	1	18	1.par

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Herr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regree	first S	other aet
751	6/2/1985	2	2	32	18/6/1996		HSQ.'98			CR	<3r	3	1	1	2	1	1	4y	2
752	26/7/1988			28	17/6/1996					not R		1	2	2		1	2	non	
753	29/8/1985	2		15	18/6/1996		mult '98,'99	2	none (Manchester)	not R	<3r	1	1	1	2	1	1	17y	1.me
754										unknown									
755	20/12/1986	2		10	18/6/1996		Inv			CR	3rd	1	1	1	2	1	1	2yr	2
756	12/3/1994	2		8	18/6/1996	1/10/1999,1/10/2003	mult.'96, '98	1	753InsC (MH)	CR	25t	1	1	1	2	1	1	3yr	2
757	14/1/1992	2		5	18/6/1996		Inv			CR	10-	3	1	1	2	1	1	non	2
758	19/6/1994			2	16/6/1996		Inv			CR	<3r	1	1	1	2	1	1	non	2
759	4/9/1994	2		3	17/6/1997		mult. '96,'97	1	G252fsX287(MB)	CR	<3r	1	1	1	1	1	1	non	2
760	13/11/1993	2		3	17/6/1996		HSQ.'96			CR	3rd	1	1	1	2	1	1	non	2
761	21/10/1994	2		5	24/8/1999		HSQ '99			unknown	10t	9	1	1	2	1	1	2y	9
762	18/8/1961	2		35	19/6/1996		HSQ.'96	2	neg (MB)	R nonC	<3r	1	2	1	2	1	2	non	1.
763	5/10/1994	2		4	17/6/1998	13/10/1996,1/9/1998,1/10/2001,	mult.'97, '98,	1	R168X (MH)	CR	3rd	1	1	1	2	1	1	2.1	2
764	7/1/1995	2		4	13/10/1996	13/1/1998,15/10/2001,1/10/2003	mult.'76,'97,'98,'02,	1	R270X(AC)	CR	<3r	1	1	1	2	1	1	5y	2
765	28/4/1989	2		15	14/10/1996		HSQ.'96	1	c397C>T;R133C	R nonC	50-	9	1	2	2	1	1	non	2
766	17/12/1989	2		7	15/1/1997		HSQ.'96			CR	10-	1.	1	1	9	1	1	5y	2.
767	18/2/1990			0			Inv			unknown									
768	12/10/1948	1		0						not R			1	1		2	1	4yr	1.
769	24/8/1973			0			Inv			unk									
770	12/5/1959		2	43	16/6/1998	7/2/2002	mult '99,'02			CR	3rd	9	1	1	2	1	1	non	2
771	11/2/1982			0			Inv			unknown									
772	21/1/1992	2		7	16/6/1999		Inv			CR	<3r	1	1	1		1	1	18m	2
773	18/9/1990	2		12	1/10/1996		HSQ '02	1	pos(MB)	CR	3rd	1	1	1	2	1	1	2y	2
774	14/11/1957	2	2	45	14/1/1998	12/10/2002,1/10/2003	mult'98,'98,'02	1	exons 1-2	Inc CR	50t	9	1	1	2	1	1	non	2
775	1/1/1956			0			Inv			CR									
776	13/1/1972			0						unknown	nk	9	9	9	9	9	9		9
777	2/9/1984			13	12/10/1994	1/10/1996	HSQ '96			CR	<2n	1	1	1	2	1	1	2y	2
778	6/10/1987			10	16/10/1996		HSQ '96			CR	50-	1	1	1	2	1	1	non	2
779	27/10/1993	2	2	5	15/1/1997		mult.'96,'98	2	none(AC)	R nonC	10-	2	1	1	2	1	2	non	1.
780	17/2/1992	2		7	15/1/1997		mult. '96, '98	2	none(AC)	R nonC	10-	1.	1	2	2	1	2	5yr	2.

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
781	18/9/1986	2		11			HSQ. '96	1	R294X(TW)	inc CR	nk	3	1	1	9	1	1	?	2
782	26/1/1974	2		28	1/1/1982	29/9/1996, 28/10/1996	mult '02.	2	none (AC)	not R	2-5	1	2	1	1	1	1	2y	1.oth
783	14/4/1994	2		3	17/12/1996	17/12/96	HSQ'96			CR	3rd	1	1	1	2	1	1	non	2
784	31/12/1996			0				2	none	unknown									
785	28/1/1993	2		4			HSQ'96			not R		9	1	1	1	1	1	non	1.Ref
786	8/3/1990	2		7			HSQ '96			not R			1	1	2	1	1	non	1.
787	14/7/1993	2		5	21/2/1997	21/2/1997	mult.'97,'98			R nonC	3rd	1		1	1	1	1	non	2 but
788	24/5/1968			25			inv			inc CR						1	1		
789	20/1/1962	1		25						CR	nk	nk	1	1	2	1	1	non	2
790	14/6/1990			0			inv			inc CR						1	1		
791	19/4/1994	2	2	3	15/1/1997	1/10/1999,12/10/2002	mult '96,'98,'03	2	negative MH?	CR	50t	2	1	1	9	1	1	non	2.
792	23/9/1992	1		11	13/1/1998		mult.'97,'98,'03	2	none (AC)	not R	50t	2	2	1	2	1	1wlt	4mo	1.se
793	14/6/1964	2	2	33	15/1/1997		mult'97,'98			inc CR	10t	1	1	1	1	1	1	31y	2
794	5/3/1970	2		27	14/1/1997		HSQ'96			R nonC	3rd	1	1	1	2	2	2	non	2.
795	2/10/1983	2		20	14/1/1997	23/10/2001	mult. '96, '98,'03			CR	50t	1	1	1	2	1	1	18y	2
796	26/5/1995	2		4	15/1/1997		mult.'96,'97,'98			R nonC	10-	1	1	1	2	1	2	non	2
797	26/4/1991	2	1	13	15/1/1997	26/9/1997,21/6/2000,	mult. '96, '97, '98, '00,	1	1164-1207del44(A	CR	50t	9	1	1	2	1	1	6y	2
798	6/11/1992	2	2	5	15/1/1997		HSQ.'96			CR	3-1	3	1	1	2	1	1	non	2
799	5/7/1970			28	15/1/1997		mult '97,'98			CR	<2n	1	1.	1	2	1	1	non	2
800	21/4/1994	2	2	9	15/1/1997	10/2/2000	mult.'97,'98,'00.'03	2	none(AC)	R nonC	25t	1	2	1	2	1	1	6y	1.
801	23/6/1995	2	2	2	15/1/1997		inv	2		R nonC			1				2	9wk	1.
802	1/1/1993			0			inv			unknown									
803	14/6/1980	2	2	25	10/10/1997	12/10/2002	mult '97,'98,'04			CR	10-	3	1	1	2	1	1	7mo	3
804	2/1/1988	2		0						CR									
805	25/2/1972			0			inv			unknown	nk	9	9	9	9	9	9	nk	9
806	17/6/1994	2	2	7	17/6/1994	14/3/1997, 1/11/2000	HSQ. '97	1	R306C (Edin)(MB)	CR	3rd	1	1	1	2	1	1	non	2
807	9/7/1994	2		9	13/1/1998	14/1/1999	mult.'98,'02,	2	none MECP2,	R nonC	50t	1	1	1	1	1	1	7mo	1.
808	22/4/1987	2		14	20/6/2000		HSQ.'97			R nonC	10-	2	1	1		1	1	non	2
809	22/11/1994	2		3	1/11/1997		HSQ.'97			inc CR	50t	2	1	1	2	1	1	non	2
810	19/7/1994			4			mult.'97'98			CR		nk	1	1		1	1	non	2

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811	15/10/1992	2		13	17/6/1997		HSQ.'97.'04	1	1157del44bp	CR	3rd	1	1	1	2	1	1	13	2
812	29/1/1991	2		7	18/6/1997		HSQ.'97	2	none(AC)	not R	10-	1	2	1	1	1	2	10m	1
813	5/11/1988			0						unknown									
814	1/1/1989			0						unknown									
815	1/1/1972			0			inv			Inc CR									
816	20/9/1957		2	40	17/6/1997		HSQ			Inc CR	<2n	3	1	1	2	1	1	6y?	2
817	14/12/1989	2		8	17/6/1997		HSQ'97	2	none (AC)	R nonC	2-5	1	1	1	1	1	1	non	1.
818	10/9/1992	2		10	13/1/1998		mult.'98,'02	2	none(AC)	not R	25t	9	1	1	1	2	1	6y?	1.co
819	26/5/1991	2		7	18/6/1997		HSQ.'97		? awaited	R nonC	10-	9	1	1	2	1	1	non	2
820	17/5/1994	2	2	8	17/6/1997	1/10/2001, 12/1/2003	HSQ '97	1	c753delC(AC)	R nonC	50t	1.	1	1	2	1	1	7y	1.
821	12/5/1994	2		4	17/6/1997		HSQ '97			not R	10-	9	1	2	1	1	2	non	1.
822	27/6/1979	2		19	18/6/1997		mult.'97,'98,'02	2	none (AC)	not R	<3r	3	1	1	2	1	2	4mo	2
823	28/4/1995	2		3	17/6/1997		mult '95,'97	1	R255X(MH)	CR	25t	1	1	1	2	1	1	non	2
824	23/6/1996	2		1	17/6/1997		HSQ		uncertain	Inc CR		1	1	1		1	1	non	2
825	31/8/1991	2		6	17/6/1997		HSQ			R nonC	50-	2	1	1	1	1	2	non	1.
826	21/8/1991	2	1	11	18/6/1997	30/1/2002	mult'97,'98,'01	1	Cto G base 401	R nonC	>50	2	1	1	2	1	1	7y	2
827	10/8/1976			24	19/1/2000		HSQ			Inc CR	<2n	3	1	1	2	1	1	nne	2
828	15/5/1989	2		14	1/11/2000		'02	2	none(AC)	CR	<3r	1	1	1	2	1	1	4y	2
829	28/8/1989	2	0	9	1/3/1998	3/7/98	HSQ '98			R nonC	90t	2	1	1	2	1	1	non	2
830	10/11/1994	2		4	20/10/1997	14/1/1998,	mult. '97,'98			CR	25t	1	1	1	2	1	1	non	2
831	19/10/1990	1		11				1	c730C>T;Q244X	CR								4y	
832	20/8/1992		1	12			HSQ.'97,03	2	none UCLA	R nonC	50t	1	1	1	2	1	1	24m	1.sei
833	13/1/1995	2	2	6	1/11/1997	16/6/1998	inv	1	c126-127insG (AC)	CR	2-5	9	1	1	2	1	1	14	2
834	3/6/1987			11			HSQ '97			CR		1	1	1	2	1	1	12	2
835	23/11/1980	2		18			inv			not R	50t	2				1		non	1.po
836	1/7/1985		2	14	5/4/1999		inv			not R	3rd	1	2	1	1	1	2	non	1.
837	11/5/1995	2		3	13/1/1995		inv			CR		3	1	1		1	1		2.but
838	27/4/1989	2		9	13/1/1998		HSQ '98			R nonC	<3r	1	2	2		1	1	non	1
839	18/3/1991	2		7	13/1/1998		HSQ.'98		awaited	not R	10-	2	1	2	2	2	2	2mo	2
840	29/4/1970	2		34	14/1/1998		mult'98, '02,'04	1	c1164-1207del44b	R nonC	50-	2	1	1	2	1	2	non	2

British Isles Survey: n=1236 sources and criteria for Rett status: November 2005

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
841	10/7/1976	2		22	14/1/1998		HSQ '98,			not R	2nd	1	2		2	1	2	non	1.
842	21/4/1971			27	14/1/1998		HSQ'98			CR	<2n	1	1	1	2	1	1	3y	
843	30/5/1978	2		22	14/1/1998		mult '98,'01	2	(d'E)none,mutSTK	R nonC	<50	1.	2	1	2	1	1	6we	1.
844	10/10/1990	2		9	14/1/1998	20/6/2001	mult'98,'01	2	(d'E, AC)none	CR	<2	1.	1	1	2	1	1	non	2
845	30/5/1964	2		34	14/1/1998		HSQ'98			CR		9	1	1	9	1	1	non	2
846	4/2/1940		2	58			mult'98,'99			Inc CR	nk	9	9	1	9	1	9	2y	9
847	6/5/1984	2	2	14	23/1/1991	26/3/1999,14/6/1999,1/10/1999	mult '98,'99	2	not found(AC)	R nonC	<3i	1	1	1	2	1	1	6mo	1.
848	13/2/1986	2		12	24/1/1998		HSQ '96			R nonC	10-	1	1	1	2	1	1	6mo	2
849	7/8/1993	2		5	17/8/1998		HSQ.'98	1	position to come	CR	<3r	1	1	1	2	1	1	non	2
850	6/5/1995	2		4	6/11/1998		HSQ.'98	2	none (AC,MB)	R nonC	2-5	1	1	1	2	1	2	15	2
851	31/10/1994	2		5	15/6/1999		HSQ '98			Inc CR	25t	1	1	1	2	1	2	4y	2
852	6/11/1977			0			Inv	2	2 but looking still	R nonC					2	1		8mo	
853	27/9/1993	2		7	23/6/1998		mult'98,'00	1	c916C>T; R306C	CR	<3r	1	1	1	2	1	1	non	2
854	4/7/1991	2	2	11	3/7/1998	4/2/1999,22/6/1999,20/6/2000,31/1/20	mult'98, '99,	1	c1157-1200del144	CR	90t	2	1	1	1	1	1	non	2
855	1/3/1972	2		27	21/8/1998		HSQ'98			CR	10-	3	1	1	2	1	1	non	2
856	13/6/1987	2		16			HSQ.;98,'02	2	none (Belgium) MB	R nonC	<50	1	1	1	9	1	2	non	2
857	26/4/1988	2		13	16/6/1998		HSQ. '98	2	none (AC)	R nonC	<3r	1	1	1	2	1	1	15	1.se
858	26/9/1988	2	2	14	19/6/1998	7/8/1998,11/7/1998,11/6/2002	HSQ. '98	2	not found (AC)	CR	<2n	1	1	1	2	1	1	15	2
859	28/9/1995	2	2	8	16/6/1998	12/10/2002	HSQ.'98	2	negative (AC)	R nonC	50t	2	2	1	1	1	1	non	2
860	3/4/1994			5	23/6/1998					R nonC	10t	1	1	2	2	1	1	4m	1
861	10/9/1995	2		3	16/6/1998		Inv			CR	50t	3	1	1		1	1	dou	2
862	28/7/1993	2		7	17/6/1998	19/1/2000	HSQ. '00	2	polymorphismc386	Inc CR	<2n	3	1	1	2	1	1	3y	1.po
863	22/4/1991	2		13	19/1/1999	23/6/1998, 1/10/98	mult'98,'03	1	1157-1197del 41	CR	3rd	1	1	1	2	1	1	6y	2
864	24/7/1990	2		8	26/6/1998		HSQ '96	2	none(AC)none	R nonC	25t	1	1		2	2	2	?	2
865	30/12/1992	2		7	1/11/1999		HSQ.'99	1	1157del44	CR	10-	9	1	1	1	1	1	5y	2
866	26/3/1995	2		6	30/1/2000		Inv	1	c502 C>T; R168X	R nonC	<3r	1	1	1		1	2	few	1.sei
867	11/5/1986	2		13			HSQ. '96	2	none(AC)	CR		9	1	9		1	1		2
868	31/1/1992	2		7	28/8/1998		Inv	1	7bp del (WGH)	R nonC	10-		1	1		1	1	3y	
869	7/3/1995	2	2	4	1/3/1999		HSQ'99	1	R168X(AC)	CR	10t	1	1	1	2	1	1	non	2
870	12/8/1995	2	1	8	30/11/1998	1/10/1999,15/10/2001,, 12/10/2002	HSQ '99	1	c455c>G;P152R(	CR	10-	1	1	1	2	1	1	non	2

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BIS	d of birth	Infant V died		age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
871	13/10/1995			8			HSQ '03		none (AC) but del	not R	<3r	nk	1	1	2	1	1	6-8	1.
872	15/9/1991			10	19/1/2000		HSQ.'00			CR	<3r	1	1		2	1	1	2y	2
873	19/11/1996	2	1	7	14/10/1998	12/10/2002	HSQ'98	1	c473C>T; T158M	CR	10-	1	1	1	2	1	1	6-1	2
874	29/7/1965	2		35	1/10/1998	1/10/1999	HSQ'99		MH?	CR		3	1	1	2	1	1	nk	
875	10/2/1996	2		7	11/10/1998	12/10/2002,1/10/2003	Inv	1	T158M(MH)	CR	<3r	1	1	1	2	1	2	2y	2
876	26/2/1997	2	2	4	20/6/2000	20/6/2000	Inv	2	not found(AC) still	CR	50t	1	1	1	2	1	1		2.but
877	3/10/1993			0						unknown						1	2	6mo	
878	7/4/1996	2		3	7/2/2003		Inv	1	c473C>T; T158M	CR	3rd	1	1	1		1	1	non	1. R
879	13/4/1987			0			Inv	2	none (AC)	not R	75-						2	3y	
880	16/12/1995	2		8	1/11/1999		HSQ'99,'03	1	c302C>T; P101L	CR	3rd	1	1	1	2	1	1	6y	2.
881	28/4/1993			10	15/10/2001	12/10/2002	Inv			R nonC	<3n		1	1	1	1	1	9mo	2
882	30/3/1998			0			Inv			not R									1.
883	23/8/1995	2	1	4			HSQ	2	none(AC)	CR	25-	1	1	1	2	1	1	3.5	2
884	1/1/1991			0			Inv			unknown									
885	25/9/1990	2		13	20/6/2001		HSQ '01,'03	1	c502C>T;R168X	CR	<3r	1	1	1	2	1	1	?	2
886	30/9/1988	2		12	20/6/2000		mult.'99,'00	2	no mutation(MB)	R nonC	10-	1	1	1	1	1	2	8y	2
887	12/1/1987			13	16/6/1999		Inv			R nonC	25-	9	1	1	2	1	1	6y	2
888										unknown									
889	13/2/1972			28			HSQ'99			R nonC	nk	9	3	1	9	1	3	3mo	2
890	22/2/1991			9	15/6/1999					not R	25t			1		2			1.
891	3/1/1997	2	1	3	22/6/1999		Inv	1	c.865A>T;K289X	CR	10t	1	1	1		1	1		2
892	10/7/1997			0			Inv		awaited	unknown									
893	13/7/1994			6	17/3/2000		HSQ			R nonC	50-	1	1	1	2	2	1	3y	1.
894	30/10/1989			10	22/6/1999		Inv			R nonC	25-		2	1	1	1	1	10w	1.ligh
895	13/1/1988	2		12	16/6/1999		Inv	2	none (AC)	R nonC	50t	1	1	1	1	1	2?	3-4	2
896	6/5/1993			7			Inv			unknown						1		birt	
897	15/7/1974	2		26	20/6/2000		HSQ'00	1	c502C>T;	R nonC	50t	2	1	1	2	1	1	non	1.
898	1/1/1935			65			Inv			unknown									
899	28/11/1976			23			HSQ '99			IncCR	<2n	1	1	1	nk	1	1	21y	1.
900	4/6/1971	2		30			HSQ'01			CR	nk	3	1	1	9	1	1	3y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
901	1/8/1963	2		0						CR									
902	26/1/1979	2		0						CR									
903	17/11/1987	2		11	26/4/1998					CR	10t			1	1.pr			4y	
904	24/4/1982	2		17						CR	10-								
905	25/1/1991	2		0						CR									
906	17/4/1991	2		0						CR									
907	12/11/1987	2		0						CR									
908	27/4/1997	2	1	6	19/1/2000	1/2/2000	HSQ.'00	1	c502c>t;R168X	CR	3rd	1.	1	1	1	1	1	2y	2
909	11/4/1995	2		5	1/2/2000		HSQ'95	2	negative	inc CR	10-	1	1	1		1	2	1y	2
910	9/7/1993			0						unknown						1	1		
911	31/10/1995	2	2	8	19/1/2000	1/2/2000,31/1/2001,15/10/2001,	mult '99.'00			CR	<2n	1	1	1	2	1	1	2y	2
912	1/1/1998	2		5	14/10/2001	12/10/2002	Inv	1	pos (AC)	CR	<3r		1		1	1			
913	22/5/1990	2		0				2	none(AC)	unknown									
914	8/10/1989	2		0				2	none(AC)	unknown									
915	16/11/1998	2		3	30/1/2001		HSQ'00	2	negative(AC)?MH	R nonC	10t	1	2	1	2	1	1	12h	1.
916	16/2/1992	2		9	20/6/2000		HSQ.'00	2	none (AC)	R nonC	10-	1	2		1	1	2	non	2
917	4/6/1995	2		6	20/6/2000		inv	1	G269fsx19	CR		2	1	1		1	1	non	2
918	17/4/1991	2	2	12	18/6/2002		HSQ '02	1	c808C>T;R270X	R nonC	10-	2	1	1	2	1	1	12	1.
919	25/7/1997	2	2	4	19/1/2000	1/1/00,	HSQ.'00			CR	3rd	1	1	1		1	1	14	2
920	20/1/1998	2	2	3	19/1/2000	1/2/2000	HSQ'00	1	c473c>t;T158M	CR	<3r	1	1	1	2	1	1	non	2
921	23/6/1960	2		42	19/1/2000	1/2/002	HSQ.'00	1	c398g>A;R133H	Inc CR	3rd	3	1	1	2	1	1	non	2
922	9/3/1994	2		7	14/11/2000		Inv	2	none, testing for	CR	<2n	1	1	1	2	1	1		2
923	8/12/1996	2		4	19/1/2000		HSQ'00	2	none (AC)	R nonC	3rd	1	2	2	1	2	2	non	2
924	17/10/1996	2		8	20/6/2000	12/10/2002, 7/10/2005	HSQ.'00	1	exon4	CR	<3r	2	1	1	2	1	1	one	1.(ad
925	2/9/1995	2		0	9/10/1998	15/10/2001,22/10/2001	HSQ. '01	1	1157del44(MH)	CR	3rd	1	1	1	2	1	1	non	2
926	3/7/1997	2	1	5	19/1/2000	1/2/2000	mult.'00,'02	1	Q244X(MH)	CR	<3r	1	1	1	2	1	1	18	2
927	5/10/1997	2	2	6	19/1/2000	10/2/2000, 12/10/2002	HSQ. '00			CR	3rd	1	1	1		1	1	non	2
928	19/11/1988			12	19/1/2000		HSQ '00			unknown	<3r	1	1	1	2	1	1	non	2
929	15/11/1993	2		7	20/6/2000		HSQ.'00		polymorphism ?	CR	3rd	1	1	1	2	1	1	3y	2
930	2/12/1997	2		4	30/1/2001		Inv			CR			1	1		1	1		2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
931	20/3/1998	2		4	19/6/2001		HSQ'01	1	T158M (AC)	Inc CR	50t	2	1	1	2	1	1	non	2
932	11/10/1988			12	20/6/2000		Inv			CR	25-	1	1	1	2	1	1	non	2
933	11/6/1968	1		0						unknown									
934	1/8/1988			15	1/11/2002					not R	75t	2	1	2	1.	2	2	6y	1.
935	13/9/1980			20			Inv			not R	3rd	1	1		1.				1
936	11/12/1997	2		0				2	none(AC)	unknown									
937	21/6/1987	2		13	20/6/2000		HSQ'00	2	none(AC)	R nonC	10-	2	1	1		1	1	3y	1.
938	24/11/1997	2	2	5	1/9/2000	1/9/2000	Inv	1	c808C>T;R270X(A	CR	2-5	1	1	1		1	1		2
939	3/7/1994	2	2	6	1/6/2001		HSQ '00	1	c397C>T1207del4	CR	<3r	1	1	1		1	1	3mo	1.?e
940	8/6/1996	2		7	20/6/2000	12/10/2002	HSQ '01,'02	1	c.502C>T;R133C(	CR	3rd	1	1	1	2	1	1	non	2
941	13/1/1992	2		0			Inv			Inc CR									
942	14/11/1995	2	2	7	19/4/2002		HSQ. '02	1	c916C.T;R306C	CR	>50	1	1	1	1.	1	1	non	2
943	4/3/1995	2		8	20/6/2000		HSQ.'01,'02,'04	1	808delC(AC)	CR	3rd	1	1	1	2	1	1	5y	2
944	17/6/1997	2		4	29/1/2001		HSQ '01	2	none(AC) but del	R nonC	50-	2	1	1	2	1	1	18	2
945	4/6/1989	2		11	20/6/2000		HSQ.'00	1	A466fsX464(Mtcal	CR	25t	3	1	1	2	1	1	non	2
946	20/7/1979	2		21	20/6/2000		HSQ '00	2	?silentT299T (AC)	R nonC	50-	2	1	1	2	1	1	3m	1.
947	11/8/1996	2		4	20/6/2000		HSQ'00	1	1164-1207del44(M	CR	<3r	1	1	1	2	1	1	unc	2
948	23/2/1978			0						unknown									
949	3/4/1989			0						CR									
950	13/4/1977			0						CR									
951	3/4/1992			9	20/6/2000		HSQ.'00			R nonC	<3r	1	1		2	1	1	6mo	1.ble
952	28/7/1975			0			inv			unknown									
953	30/3/1992	2		10	31/1/2001	12/10/2002	HSQ.'01	1	mosaic	R nonC	3-5	2	1	1	1	1	1	5y	2
954	30/10/1983			17	19/6/2000		HSQ '0			R nonC	50t	9	1	1		1	2	5y	2
955	24/8/1997	2		6	30/1/2001		HSQ.'00.'03	2	none (AC)	R nonC	50t	2	1	1	2	1	2	non	2
956								2	no mut	unknown									
957	28/1/1998	2	2	3	30/1/2001		HSQ'01	1	1.R294X(AC)	CR	10-	1	1	1	9	1	1	non	2
958	21/9/1962			38			HSQ'00			inc CR	nk	3	1	1	9	1	1	nk	9
959	1/8/1994	2		7	1/11/2000		HSQ. '02,	1	?? none(MB)	CR	3rd	1	1	1	2	1	1	2y	2
960	19/3/1967			0						R nonC									

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
961	30/4/1993			0			Inv			inc CR	50t		1			1	1		
962	15/9/1988			0			Inv			unknown									
963	18/6/1998	2		3	15/10/2001		Inv	2	none (WGH)none	CR	50t	9	1	1	2	1	1	non	2
964	20/5/1996	2	1	5	1/11/2001	1/11/2001, 20/4/2001,6/1/04	HSQ'00	1	1116-1201del 86	CR	10t	1	1	1	2	1	1	non	2
965	9/2/1998	2	1.	7	1/11/2000	5/10/200119/9/204	mult '00,'02,'03	1	1157-1197del41(A	CR	75t	9	1	11	2	1	1	30m	2
966	6/1/1999	2		3	19/6/2001		HSQ'01	2	none(Wessex)	CR	10-	1	1	1	1	1	1	non	2
967	10/6/1975	2		26	23/2/2001		HSQ. '02	1	R270X (WGH) neg	CR	3rd	1	1	1		1	1	4y	2.
968	21/3/1986			15						not R					2	1			
969	21/10/1998	2		4	30/1/2001	12/10/2002, 12/1/2003.1/10/2003	mult.'00,'01	1	del.exon4-3prime	R nonC	<3r	1	1	1	2	1	1	14	1.po
970	29/9/1981	2		20	31/1/2001		IHSQ '01	2	none(AC) still	R nonC	2-5	3	1	1	2	1	1	13y	2
971	25/4/1975	2		26	31/1/2001		HSQ '01			inc CR	<2n	3	9	1	2	1	1	nk	2
972	15/10/1997	2		6	31/1/2001		mult '01,'03	2	not found (AC)	R nonC	50t	2	1	1	2	1	1	7mo	2
973	11/3/1993			0			Inv	2	none (AC)	unknown									
974	21/10/1998	2		4	30/1/2001		Inv	1	1150-1153delAGA	CR	10t	1	1	1	1	1	1	1yr	1.36
975	1/1/1968			0	1/1/1997					unknown									
976	10/10/1962	2		39	30/1/2001	30/1/2001	HSQ '01			CR	<2n	1	1	1	2	1	1	NK	2
977	8/8/1997	2		4	30/1/2001		HSQ'01	2	still uncertain 8.02	CR	<3r	1	1	1	2	1	1	non	2
978	14/9/1995	2	1	6	30/1/2001	30/1/2001	HSQ '01		uncertain result	CR	20-	1	1	1	2	1	1	non	2
979	18/1/1999	2		2	30/1/2001		HSQ.'01	2	none(AC)	R nonC	50-	2	1	2	2	2	2	non	2.
980	29/8/1998	2	1o	3	31/1/2001		HSQ.'01	1	c502c>t;	R nonC	50-	2	1	1	2	1	1	2.3	2
981	4/7/1997	2		4	6/4/2001		HSQ'01	2	polymorphism	R nonC			1	1	2	1	1	2mo	2
982	29/8/1998	2	1	5	19/6/2001	12/10/2002.1/10/2003	mult '01,'02,'03	2	negative	R nonC	3-5	1	1	1	1	1	2	4y	2
983	22/10/1967	2		34			HSQ'01	1	c880c>t; R294X	R nonC	50-	2	1	9	2	1	1	6y	1.
984	17/1/1975	1		27						CR									
985	16/5/1996	2		0			Inv	2	none)(AC)	R nonC									
986	10/4/1991	2		11	10/8/2001		Inv	1	291 C>A; D97E	CR	10-	1	1				1	3y	2
987	20/11/1985	2		0			Inv		awaited	unknown			1			1	1		2
988	12/5/1999	2		4	19/6/2001	12/10/2002.1/10/2003	HSQ '01,'03	1	R106W(Wessex)	CR	3rd	1	1	1	2	1	1	3..6	2
989	19/10/1998	2		3	19/6/2001		HSQ'01	1	c512C.T;R168X	CR	2-5		1	1		1	1	non	2
990	21/8/1986	2		17	20/7/2001		HSQ '01,'03	1	397C>T.R133C(AC	CR	3rd	1	1	1	2	1	1	13y	2

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC	fall	early crit	dysprax	face	stereo	regres	first S	other aet
991	3/11/1987	2		14	20/6/2001		HSQ'01	2	not found (?where)	CR	50t	1		1	1	2	1	1	5y	2
992	21/7/1992	2		9			HSQ.'01	2	none (AC)	R nonC	25t	1		1	1		1	1	14m	1.
993	7/3/1986	2		19	11/12/2001	91/9/2004	HSQ.'01	2	none	R nonC	50t	1		1	1	2	1	1	non	2
994	20/10/1988			0						unknown										
995	1/1/1997	2		6	20/7/2001		HSQ.'01			R nonC		1		1	1	2	1	2	non	2
996										unknown										
997	7/3/1995	2		7	19/6/2001		HSQ'01	1	c473C>T;T158M(A	CR	10-	1		1	1	2	1	1	21	2
998	12/1/1999	2	1	5	1/10/2003		HSQ. '02	1	R270X	CR	nk	9		1	1	2	1	1	non	2
999	3/1/1995	2		5			Inv	1	positive	CR	<3r	1		1	1		1	1		2
1000	21/9/1988			17	15/10/2001		HSQ 05	1	R294X	CR		9		1	1	9	1	1	yes	
1001	1/1/1998	2		0	15/10/2001		Inv	1	del exons 3-4(AC)	Inc CR	2-5									
1002	18/7/1992	2		9	15/10/2001		Inv	1	W197X(MH)	Inc CR				1		1	1		nk	
1003	25/8/1989			15	15/10/2001		HSQ '03	1	positive (Wessex)	CR	2-5	nk		1	1	9	1	1	12	2
1004	21/4/1996	2		6	15/2/2002		HSQ. '01,	2	none(WGH)	R nonC	<3r	1		2	2	1	1	2	non	1.
1005	1/1/2000			0						unknown										
1006	24/9/1998	2		4	29/1/2002	29/1/2002	Inv	2	none(AC)	Inc CR	50t	2		1	2	2	2	1	non	2
1007	1/1/1998	2		4	5/10/2001		Inv	1	positive R270X ??,	R nonC	25-	9		1	1		1	1		2
1008	20/4/1999	2		4	1/10/2004		mult '01, '03	1	positive (Holland!)	Inc CR	nk	nk		1	1	nk	1	1	non	2
1009	21/8/1965	2		37	29/1/2002		HSQ '01	1	530del448(MH)	CR	3rd	1		1	1	2	1	1	13y	2
1010	28/5/1998	2		5	14/10/2001	14/10/2001, 29/1/2002,	HSQ'01	1	c880 R294X (AC)	CR	25-	9		1	1	2	1	1	non	2.
1011	15/11/1997			0			Inv	1	none (AC)	unknown										
1012	15/10/1998			4	11/10/2002	12/10/2002	Inv	1	41 base del	CR	<3r									
1013	27/8/1998	2		4	29/1/2002		HSQ '02	1	c.502C>T;R168X	CR	50t	2		1	1	0	1	1	non	2
1014	24/9/1998	2		6	29/1/2002		HSQ. '02	2	none (AC)	R nonC	10-	NK		1	1	1	1	1	19	2
1015	2/6/1994	2		9	1/10/2002	12/10/2002	HSQ '01	1	c808C>T;R270X	CR	25-	9		1	1	1	1	1	non	2
1016	20/5/1995	2		7	30/1/2002	8/3/2002	HSQ.'02	1	44 base pair del	CR	50t	1		1	1	2	1	1	4y	2
1017	2/3/1999	2	1	3	29/1/2002	12/10/2002.1/10/2003	HSQ'01	1	C617delG (?Notts)	CR	3rd	1		1	1	2	1	1	non	2
1018	12/8/1997	2	1	5	29/1/2002		HSQ'02	1	'mutation 910'(?)	CR	10-	9		1	1	2	1	1	non	2
1019	23/2/1989	2		13	30/1/2002		HSQ'02	2	none(AC)	R nonC	50t	2		2	2	1	1	?	non	2
1020	17/5/1998			6	29/1/2002	29/1/2002	HSQ '02	2	none (Manchester)	not R		2		1	2	2	2	1	8mo	1.

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BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1021	8/10/1974		28	29/1/2002		HSQ			CR	<2n	1	1	1	2	1	1	3y	2
1022	4/12/1988	2	16	29/1/2002	1/10/2003	HSQ'02	1	c.502C>T.R168X	R nonC	50t	2	1	1	2	1	1	non	2
1023	26/7/1998		4	30/1/2002		HSQ			not R	<3r	9	1	2	22	2	2	non	2
1024	20/8/1997		0				1	del exon 3(DR) and	unknown									
1025	26/2/1998		0				2	c1215C>T;P405P(	unknown									
1026	9/9/1987		0				1	c473C>t;T158M(A	unknown									
1027	26/7/1978		0				1	c763C>T;R255X	unknown									
1028	2/8/1994		10			HSQ '04	1	c397C>T;R133C	CR	nk	9	1	1	2	1	1	3-4	2
1029	19/3/1999		0			Inv	1	c763C>T;R255X(A	unknown									
1030	2/2/1998		0				1	c808C>T;R270X(A	unknown									
1031	2/2/1998		5	12/10/2002	1/10/2003	Inv	1	c.808C>T;R270X(	unknown	<3r								
1032	9/1/1992		0						unknown									
1033	21/12/1996		0				1	poly IVS3+22C>G	unknown									
1034	19/3/1995		0				1	c1372C>T;R485C(	unknown									
1035	28/4/1997		0				1	c1097-1203	unknown									
1036	13/9/1990		0				1	c473C>T;T158M(A	unknown									
1037	24/6/1999		0			Q	1	no mutation?, poly	CR	10t	1	1			1	1	non	
1038	4/5/1998		0				1	c1126C>T;P376S(	unknown									
1039	21/9/1993		0				1	c897C>T;T299T(A	unknown									
1040	30/11/1989		0			HSQ	1	c311-323del13bp	unknown									
1041	23/8/1998		0				1	1168-1173del	unknown									
1042	12/12/1998	2	5	12/10/2002	1/10/2003	HSQ'02	1	c91delG (AC)	CR	10t	1	1	1	2	1	1	non	2
1043	6/9/1988		0				1	c984C>G;P322(A	unknown									
1044	21/11/1995		0						unknown									
1045	21/12/1997		0				1	c311G>A;W104X(	unknown									
1046	14/2/1999		4	11/6/2002		HSQ'03	1	c473C>T;T158M(A	R nonC	<2n	9	1	1	9	1	1	4mo	2
1047	19/11/1997		0				1	c763C>T;R255X(A	unknown									
1048	28/6/1964		39			Inv	1	del (exon 4.3DR)	inc CR	<3r	9	1	1		1	1	non	1
1049	12/4/1994		0				1	c1152del44de	unknown									
1050	6/6/1998		0				1	3'UTR-TGA+98-99(	unknown									

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BIS	d of birth	died	Infant V	age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1051	27/4/1998			0	1/10/2003			1	c763C>T;R255X&	unknown									
1052	3/8/1971			0				1	c1164-1208del45?	unknown									
1053	1/1/1998		1	0			Inv			unknown									
1054	15/5/1996			7			HSQ'03	1	c880;C>TR294X(A	CR	nk	nk	1	1	9	1	1	non	2
1055	16/10/1997			0				1	c455C.G;P152R	R nonC			1			1	2	non	
1056	24/11/1997			0				1	C1081C>G;P361A	unknown									
1057	6/9/2001			3	18/9/2003	1/10/2003	HSQ'03	1	R255X (AC)	CR	10-	3	1	1	9	1	1	non	2
1058	15/4/1993			0				1	c502C>T;R168X	unknown									
1059	19/7/1989			18				1	c397C>T;R133C	R nonC	3-1		1			1	2	4y	
1060	14/10/1996			0				1	c917G>T;R306L(A	unknown									
1061	8/7/1991			0				1	c401C>G;S134C	unknown									
1062	4/11/1996			0	1/11/2004			1	c473C>T;T158M	CR			1		1	1			
1063	30/9/2000			0				1	multiple defects	unknown									
1064	15/8/1999	2		3	18/8/2002		HSQ.'02	2	none found (AC)	CR	<3r	1	1	1	2	1	1	2.6	2
1065	15/10/1990			0				1	c1164-1207del44	unknown									
1066	22/10/1993			0				1	c316C.G;R106G(A	unknown									
1067	8/9/1988	1		14			Inv	1	c502C>T;R168X	CR		3	1	1		1	1	yes	2
1068	7/8/1996			0			inv	2	no mut (MB)	unknown									
1069	19/3/1995			0				1	c1164-1207del44	unknown									
1070	29/4/1998			8	1/10/2003		Inv	1	c916C.T;R306C(A	inc CR						1			
1071	4/12/1996	2		0				1	3'UTR-TGA+98-99	unknown									
1072	22/2/1999			5			HSQ'03	1	R168X & 7bpdel	R nonC	nk	3	2	1	9	1	2	unk	2
1073	17/8/1984			18	11/8/2002		HSQ.'02			CR	3-1	3	2	1	2	1	1	5y	2
1074	6/4/1977	1		25						unknown									
1075	28/4/1995			0						unknown									
1076	27/1/1989	2		0						unknown									
1077	31/7/1978	2		0						unknown									
1078	5/7/1983	2		0						unknown									
1079	13/4/1991	2		0			Inv			unknown									
1080	5/1/1993	2		0						unknown									

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BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1081	6/1/1999	2	4	11/6/2002	1/10/2003	HSQ '02	1	44bp del	CR	3rd	1	1	1	2	1	1	15m	2
1082	19/9/1992	2	10			HSQ '02	1	P152R (MB)	CR	nk	3	1	1	9	1	1	9y	2
1083	31/8/1980	2	0						unknown									
1084	19/1/1990	2	0			Inv			unknown									
1085	9/9/1961	2	42			HSQ '03	1	R168X	CR	nk	3	1	1	9	1	1	7y	2
1086	25/3/1989	2	14			HSQ '02	2	none (AC)	CR	50t	nk	1	1	9	1	1	8y	2
1087	2/12/1999	2	3	11/6/2002		HSQ. '02	1	502C>T (AC)	CR	3rd	1	1	1	2	1	1	2y	2
1088	16/5/1987	2	16	11/6/2002		HSQ.'02	2	negative(DR)	R nonC	50t	2	1	1	2	1	1	birt	1.po
1089	1/1/1990	2	13			HSQ.'02			not R		nk	2	2	2.D	2	11y	non	1
1090	23/2/1991	2	12	12/6/2002		Inv			R nonC	<3r	3	1	1		1	1		2
1091	25/10/1949	2	53	12/6/2002		Inv			inc CR	3rd	3	1	1	2	1	1	non	2
1092	18/7/1954	2	48	12/6/2002		Inv			inc CR	<3r	3	3	1	2	1	3	4mo	1.dia
1093	6/4/1998	2	0			Inv	2	none Huppke	unknown			1					2y	
1094	30/3/1999	2	0			Inv			unknown									
1095	29/5/1994	2	9	12/1/2003		HSQ'02	2	none (AC)	not R	<2n	1	1	1	1.	1	1	non	1.
1096	27/9/1997	2	0			Inv	1	R168X	CR									
1097	17/12/1996		0				1	no mutation, poly	unknown									
1098	27/3/1999		4			HSQ '03	1	c464b>g;F155C	CR	nk	9	1	1	9	1	1	non	2
1099	24/3/1999		3					c1491? (AC)	inc CR	50t		1			1	9	9	1.
1100	1/10/1998		0					c880c>t; R294X (&	unknown									
1101	29/10/1999		4				1	c880C>T; R294X	CR	nk	9	1	1	9	1	1	3y	2
1102	10/9/1994		0				2	del exon 3-2 kb	unknown									
1103	17/8/2000		3			HSQ '03	1	c473C>T; T158M	unknown	nk	9	1	1	9	1	1	2y	2
1104	14/8/1996		0				1	c316C>T; R106W	unknown									
1105	19/9/1990		0				1	c1234G>A; V412I	unknown									
1106	18/3/1994		0				1	c808C>T;R270X	unknown									
1107	2/5/2000	2	0	17/12/2003		Inv	1	c916C>T;R306C	CR	3rd	1	1			1	1	14	2
1108	10/8/1988		0				1	c316C>G;R106G	unknown									
1109	17/3/2000	2	4	10/10/2003		HSQ '03	1	c808C>T; R270X	inc CR	50t	9	1	1	9	1	1	non	2
1110	16/2/1996		0				1	c277 C>TP93S?	unknown									

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BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1111	11/2/1999		0				1	c1118C>G; S373X	unknown	50t	2	1			1			
1112	26/7/2001	1	2			HSQ'03	1	132 bp del	R nonC	50t	1	2	1	9	1	1	dou	2
1113	3/9/2000	2	3	12/1/2003		HSQ '02	1	positive (Aug '02)	CR	<3r	1	1	1	2	1	1	non	2
1114	13/3/1971	1	32	30/9/1993		HSQ '02	2	none (Yorkhill)	R nonC	2nd	3	2	1	2	1	1	9mo	2
1115	14/1/1988		0			inv			unknown									
1116	19/3/1967		34			Q '00	1	803delG InTRD	R nonC	50-	no?	1	1	2	2	2	non	2
1117	25/11/1999		2	12/10/2002		HSQ '02	1	?P225R not	CR	10t	1	1	1	2			non	2
1118	4/8/1999		5	12/10/2002	12/10/2003	HSQ '03	1	R106W	R nonC	3rd	1	2	1	2	1	2	non	2
1119	12/5/1998	2	7			HSQ '02			R nonC	2nd	2	1	1	9	1	2	4y	2
1120	26/10/2000		0			inv			unknown									
1121	27/9/1989		0				1	positive	unknown									
1122	16/6/1964		0				1	c.397C>T;R133C	unknown									
1123	24/1/1996		0	12/12/2002		inv			CR									
1124	6/1/1998		0			inv			unknown									
1125	30/1/1979		0			inv			unknown									
1126									unknown									
1127	7/9/1994		0						unknown									
1128	29/9/1999		4	12/1/2003		HSQ '03	1	R255X(Wessex)	CR	10t	3	1	1	2	1	1	non	2
1129	8/8/1987		16	13/1/2003		inv		awaited	not R	3rd	9	2	2	1	1	2	4mo	1
1130	27/11/2000		3	12/1/2003	1/10/2003	HSQ '3,	1	positive	CR	<3r	1	1	1	2	1	1	non	2
1131	5/6/2000		3	17/4/2003		HSQ'03			Inc CR	50t	9	1	1		1	1	non	1.
1132	1/6/2001		2				1	exon3.c316C>T.R	unknown									
1133	4/10/1985		0			inv			unknown									
1134	21/2/1952		0			inv			unknown									
1135	8/11/1989		14			HSQ'03			R nonC	nk	1	1	1	9	1	1	18	1
1136	5/8/1995		0			inv			unknown									
1137	18/11/2000		0	1/10/2003	10/1/2004	inv	1	R255X	CR									
1138	27/7/1997		0			inv			unknown									
1139	9/7/1998	2	8			HSQ'03	2	none(AC)	R nonC	nk	9	1	1	9	1	2	non	1.sm
1140	3/12/1993		0			inv			unknown									

British Isles Survey: n=1238 sources and criteria for Rett status: November 2005

BIS survey code, in general 1=yes, 2=no,3=presumed present,9=not found, AK saw=first examination, AK dates= later examination (latest not all shown), Infant V=infant video, age upd=age at update, face=face dysmorphic dysprax=dyspraxia, Herr Q=dates of completed HSQ, mut=mutation (1=present, 2=not found, no entry=not tested), CR=classic Rett, incCR=incomplete CR, R nonC Rett =non-classic, not R=not Rett, C=latest centile OFC early crit=Rett developmental history, regres=regressed, stereo=hand stereotypy, first S=first seizure, other aet=possible other cause of problem, items right of 'status' indicate criteria for classic Rett.

BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1141	29/9/1998		5			HSQ'03	1	yes in Belgrade	inc CR	nk	9	1	9	9	1	2	3y	2
1142	12/9/1993		10			HSQ '03,			CR	<2n	3	1	1	2	1	1	3y	2
1143	30/5/2000		4	1/10/2003		Inv	1	G269fsX19	inc CR	50t					1			
1144	1/4/1993		0			Inv			unknown									
1145	9/1/1991		13	18/9/2003		HSQ'03	2	P272L	R nonC	<3r	1	1	1	9	1	1	3mo	2
1146	2/5/2000		3	5/2/2000		HSQ '03	1	positive Aberdeen	CR	<3r	9	1	1	2	1	1	non	2
1147	4/8/1975		0			Inv			unknown									
1148						Inv			unknown									
1149	8/5/2000		0			Inv			unknown									
1150	3/8/2000	2	5	11/10/2003	7/7/04,	HSQ '03	1	467ins(Wessex)	CR	,3R	3	1	1		1	1	3y4	1.
1151	15/10/1990		0			Inv	1	c1164-1207del44	unknown									
1152	30/6/1987		17	11/12/2003	6/10/2005	HSQ'03	2	none (Wessex)	CR	10-	2	1	2	2	1	1	non	2
1153	20/7/2000		0			Inv			unknown									
1154	3/1/1990	2	14	1/10/2003		HSQ '03	2	negative (Bm)	R nonC	98t	9	2	1	2	1	2	3da	1.po
1155	1/5/1984		40	2/7/2003		HSQ '03	1	R306C (AC)	CR	nk	3	1	1	9	1	1	13y	2
1156	31/3/1997		7			HSQ'03	2	negative	not R	25t	9	2	1	2	1	2	2wk	1. M
1157	4/5/1985		20	2/3/2005		HSQ'05	2	none (Edin/Gla)	R nonC			2			1	2	12	2
1158	11/4/1970		34			HSQ'04	1	R306C (AC)	CR	nk	9	1	1	9	1	1	10y	2
1159	9/6/1992		12			HSQ'03			CR	nk	9	1	1	9	1	1	2v	
1160	9/7/1993		0			Inv			unknown									
1161	18/7/1978		0						unknown									
1162	21/6/1991		0			Inv			unknown									
1163	26/5/2000		0	1/10/2003		Inv	1	R168X	inc CR									
1164	4/9/1998		0						unknown									
1165	1/1/1998		0						unknown									
1166	1/1/1999		0			Inv			unknown									
1167	28/5/1989		0			Inv			unknown									
1168	9/4/2000		0			Inv			unknown									
1169	11/11/2000		0	1/10/2004		Inv			unknown									
1170	19/12/1996		0			Inv			unknown									

British Isles Survey: n=1236:sources and criteria for Rett status: November 2005

BIS survey code, in general 1=yes, 2=no,3=presumed present,9=not found, AK saw=first examination, AK dates= later examination (latest not all shown), Infant V=infant video, age upd=age at update, face=face dysmorphic dysprax=dyspraxia, Herr Q=dates of completed HSQ, mut=mutation (1=present, 2=not found, no entry=not tested), CR=classic Rett, IncCR=incomplete CR, R nonC Rett =non-classic, not R=not Rett, C=latest centile OFC early crit=Rett developmental history, regres=regressed, stereo=hand stereotypy, first S=first seizure, other aet=possible other cause of problem, items right of 'status' indicate criteria for classic Rett.

BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1171	5/8/1971		0			inv			unknown									
1172	20/1/1995		0			inv			unknown									
1173	13/7/1973		0				1	del exon2 (AC)	unknown									
1174	8/7/2001		0			inv			unknown									
1175	20/12/1998		5	16/12/2003		inv	2	del test in process	R nonC	50t	2	1	1	1pr	1	2	14m	1.sm
1176	15/8/1987	2	17	17/12/2003	7/7/2004	HSQ'04	1	1162-1172 del	R nonC	50t	9	1	1	2	1	2	non	2
1177	7/4/2000		4			inv	1	T158M	CR	25t	1	1	1	9	1	1	non	2
1178	12/12/1992		12			HSQ'03	1	positive	CR			1	1	9	1	1	4y	2
1179	28/4/1993		0						unknown									
1180						inv			unknown									
1181	15/10/1990		0			inv			unknown									
1182	24/3/1999		0			inv			unknown									
1183	5/5/1999		5			HSQ '04	1	positive (Bm)	CR	nk	nk	1	1	nk	1	1	3.1	2
1184	3/11/1998		6			HSQ'04	2	none (AC)	R nonC	nk	9	2	1	2	1	2	non	2
1185	29/8/1994		0			inv		neg (AC)	unknown									
1186	14/7/2001		0			inv			unknown									
1187	15/9/1980	2	25			HSQ	1	1157-1188del32bp	CR		nk	1	1		1	1	4y	2
1188	6/2/1992		0				2	still checking	unknown									
1189	22/12/1997		0	19/9/2004		inv			R nonC									
1190	17/12/1987		17	1/7/2004		HSQ	2	neg(AC)	not R	50t	2	1	2	1	1	2	sin	1. no
1191	15/7/1994	1	10			HSQ'04	1	R270X (J C-S)	R nonC	nk	nk	1	1	9	2	1	18	2
1192	23/1/2000		0			inv			unknown									
1193	25/11/2000		5			HSQ 05	1	del exons 1-2	unknown			1	1		1	1	2.3	2
1194	5/3/2000		0					3'end-exon4	unknown									
1195	27/3/1999		0				2	STK9 'JC gene'	unknown									
1196	28/4/1998		0	1/8/2005		inv	2	none but	R nonC	75t						2		
1197	13/12/2001		3			HSQ'04	1	R255X	CR			1	1		1	1	non	2
1198	8/5/2001		0						unknown									
1199	2/11/2000		0	7/10/2005			1	R270X	CR									
1200	13/12/2001		0	1/10/2004					unknown									

British Isles Survey: n=1236:sources and criteria for Rett status: November 2005

BIS survey code, in general 1=yes, 2=no,3=presumed present,9=not found, AK saw=first examination, AK dates= later examination (latest not all shown), Infant V=infant video, age upd=age at update, face=face dysmorphic dysprax=dyspraxia, Herr Q=dates of completed HSQ, mut=mutation (1=present, 2=not found, no entry=not tested), CR=classic Rett, incCR=incomplete CR, R nonC Rett =non-classic, not R=not Rett, C=latest centile OFC early crit=Rett developmental history, regres=regressed, stereo=hand stereotypy, first S=first seizure, other aet=possible other cause of problem, items right of 'status' indicate criteria for classic Rett.

BIS	d of birth	died	Infant V age upd	AK saw	AK dates	Kerr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1201	24/5/1989		0						unknown									
1202	17/7/1999		0			HSQ '04			unknown									
1203	31/7/2002		2	12/7/2004		Inv	1	R255X	CR	<3r	1	1	1		1	1		
1204	21/11/2000		0			Inv			unknown									
1205	11/6/2000		0				1	R168X	unknown									
1206	10/10/1996	2	5				1	positive (USA)	CR									
1207	25/3/2001		0	1/10/2004	7/10/2005				unknown									
1208	25/12/2001	2	0	1/11/2004			1	R255X	CR			1	1	2	1	1		
1209	17/5/2002		0	10/10/2004					unknown									
1210	7/5/2002		0	18/11/2004				T158M	CR		1	1	1	2	1	1	2y	
1211	8/11/1999		0	1/11/2004				R133C	CR			1	1		1	1		
1212	27/7/1952		0						unknown									
1213	29/10/1998		0				1	L386fsX5	unknown									
1214	14/4/1998		0						unknown									
1215	28/1/2001		0						unknown									
1216	11/2/1991	2	0						unknown									
1217	24/11/2000		0						unknown									
1218	31/3/1978	2	27			Inv	1	R133C (AC)	R nonC	10t		1		2	1	2	non	
1219	10/12/1996		0			Inv			unknown									
1220	1/10/1986		19			Inv	1	R133C (AC)	R nonC		2	1	1	2	1	1		
1221	4/10/1993		0						unknown									
1222	12/9/2002		3						unknown	<3r								
1223								negative							1			
1224	30/3/1999		0						unknown									
1225	24/12/2001		0						unknown									
1226	27/1/2001		0						unknown									

British Isles Survey: n=1236:sources and criteria for Rett status: November 2005

BIS survey code, in general 1=yes, 2=no,3=presumed present,9=not found, AK saw=first examination, AK dates= later examination (latest not all shown), Infant V=infant video, age upd=age at update, face=face dysmorphic dysprax=dyspraxia, Herr Q=dates of completed HSQ, mut=mutation (1=present, 2=not found, no entry=not tested), CR=classic Rett, incCR=incomplete CR, R nonC Rett =non-classic, not R=not Rett, C=latest centile OFC early crit=Rett developmental history, regres=regressed, stereo=hand stereotypy, first S=first seizure, other aet=possible other cause of problem, Items right of 'status' indicate criteria for classic Rett.

BIS	d of birth	Infant V died	age upd	AK saw	AK dates	Korr Q	mut	test	status	C	OFC fall	early crit	dysprax	face	stereo	regres	first S	other aet
1227	5/11/1997		0						unknown									
1228	3/7/1971	2	34			inv	1	R168X (AC)	R nonC		3		1	2		2	non	2
1229	9/3/2002		4			HSQ'05	2	none(Edin)	unknown	nk	nk	1	1	nk	1	1	2.1	?
1230				7/10/2005		Inv			CR									
1231	22/6/1995		0				1	R133C										
1232	31/10/2003		0				1	R255X										
1233				7/10/2005					CR?									
1234	27/1/2000		0	7/10/2005			1	missense (Oxford)	CR									
1235							1	pos										
1236				7/10/2005														

APPENDIX C: STUDY DATASETS

Dataset 3.1:West of Scotland study

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	3.1	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
3	1	8/5/1980	CR	2				'93	25/8/1983	1/11/2000
33	1	15/7/1973	CR	2				mult'93,'95,'98	26/10/2083	
50	1	20/1/1976	CR	2				mult	5/5/1983	12/12/1987
87	1	12/8/1977	CR	2				mult '93, '94,'95	20/10/1983	8/4/1986, 5/12/1987, 11/6/1994, 1/6/1996, 28/7/1997
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/1999,
100	1	13/4/1975	CR	1	1/1/1997			mult	24/5/1984	
106	1	29/9/1978	CR	2				Q	9/2/1981	10/5/1984,1/1/1985, 2/12/1987
127	1	21/6/1980	CR	2				Q '86-'96	7/7/1986	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
128	1	13/9/1975	CR	2				mult Q,HSQ'97	18/4/1984	
137	1	2/4/1974	CR	2				Q '83	10/11/1983	10/11/1983, 21/6/1990
142	1	12/10/1975	CR	1	14/5/1987			Q	21/6/1984	
154	1	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96 '98	29/9/1983	17/12/1995,13/3/1996, 5/10/2001
226	1	10/10/1980	CR	2				Q'84-'88	14/6/1984	18/7/1987,16/3/1988,
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
329	1	20/6/1971	CR	1	25/3/1987			Q	12/4/1984	
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
367	1	22/2/1981	CR	1	9/8/1995			mult Q	26/7/1984	
539	1	2/5/1972	CR	2				mult'95,'98	24/5/1984	1/5/1996,26/22/1991

Dataset 3.2: Study of natural history of Rett Syndrome

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	3.2	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
3	1	8/5/1980	CR	2				'93	25/8/1983	1/11/2000
33	1	15/7/1973	CR	2				mult'93,'95,'98	26/10/2083	
50	1	20/1/1976	CR	2				mult	5/5/1983	12/12/1987
87	1	12/8/1977	CR	2				mult '93, '94,'95	20/10/1983	8/4/1986, 5/12/1987, 11/6/1994, 1/6/1996, 28/7/1997
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/1999,
100	1	13/4/1975	CR	1	1/1/1997			mult	24/5/1984	
106	1	29/9/1978	CR	2				Q	9/2/1981	10/5/1984,1/1/1985, 2/12/1987
127	1	21/6/1980	CR	2				Q '86-'96	7/7/1988	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
128	1	13/9/1975	CR	2				mult Q,HSQ'97	18/4/1984	
137	1	2/4/1974	CR	2				Q '83	10/11/1983	10/11/1983, 21/6/1990
142	1	12/10/1975	CR	1	14/5/1987			Q	21/6/1984	
154	1	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96,'98	29/9/1983	17/12/1995,13/3/1996, 5/10/2001
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1986	28/7/97
226	1	10/10/1980	CR	2				Q'84-'88	14/6/1984	16/7/1987,16/3/1988,
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
308	1	30/5/1959	CR	1	4/7/1992			Q	1/5/1986	
329	1	20/6/1971	CR	1	25/3/1987			Q	12/4/1984	
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
367	1	22/2/1981	CR	1	9/8/1995			mult Q	26/7/1984	
370	1	12/11/1979	CR	2				Q	14/11/1985	6/6/1986
495	1	16/11/1983	not R	2		del15	del 15	Q	6/11/1984	5/1/1996
539	1	2/5/1972	CR	2				mult'95,'98	24/5/1984	1/5/1996,26/22/1991

Dataset 4.1: Hands and Mind in Rett Syndrome

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	4.1	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
3	1	8/5/1980	CR	2				'93	25/8/1983	1/11/2000
33	1	15/7/1973	CR	2				mult'93,'95,'98	26/10/2083	
50	1	20/1/1976	CR	2				mult	5/5/1983	12/12/1987
87	1	12/8/1977	CR	2				mult '93, '94,'95	20/10/1983	8/4/1988, 5/12/1987, 11/8/1994, 1/6/1996, 28/7/1997
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/1999,
100	1	13/4/1975	CR	1	1/1/1997			mult	24/5/1984	
127	1	21/6/1980	CR	2				Q '88-'96	7/7/1986	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
128	1	13/9/1975	CR	2				mult Q,HSQ'97	18/4/1984	
142	1	12/10/1975	CR	1	14/5/1987			Q	21/6/1984	
154	1	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96.'98	29/9/1983	17/12/1995,13/3/1996, 5/10/2001
193	1	6/10/1972	CR						1/10/1985	
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1986	28/7/97
227	1	17/3/1974	CR	1	20/8/1994			HSQ	28/7/1986	
234	1	24/8/1980	CR	2		1	c763C>T;R255X(AC	mult '91,'94,'98	1/10/1986	28/8/1988, 1/8/1989, 12/6/1991,
257	1	6/5/1980	CR	2		1	c473C>T; T158M &	mult'93,'95,'00	1/10/1986	21/7/1987,28/3/1990,19/2/1991,21/6/2000
259	1	24/7/1959	CR	2				Q '86	7/2/1986	30/3/2001,19/4/2002
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
335	1	25/5/1971	CR	2				Q'84	28/8/1984	1.9.1986,21/7/1987
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
367	1	22/2/1981	CR	1	9/8/1995			mult Q	26/7/1984	
370	1	12/11/1979	CR	2				Q	14/11/1985	6/6/1988
539	1	2/5/1972	CR	2				mult'95,'98	24/5/1984	1/5/1996,26/22/1991

Dataset 4.3: Nurse recognition of deviation

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	4.3	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
79	1	13/2/1987	CR	1	9/4/2001	1	T158M (Manchester)	mult. '93,'94,'96,'99	6/10/1990	1/10/1994,
234	1	24/8/1980	CR	2		1	c763C>T;R255X(AC	mult '91,'94,'98	1/10/1988	28/8/1988, 1/6/1989, 12/6/1991,
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,18/7/1987,30/11/1988,11/1/1993,28/7/1993
307	1	15/3/1964	CR	2		1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/1995, 1/10/1996,
312	1	9/2/1970	CR	2				Q'91 inv	1/10/1989	
468	1	2/6/1992	CR	2				HSQ.'96,1/10/2003	11/11/1995	
546	1	13/11/1991	CR	2		1	del exon 4	mult. '93,'94,'03	28/10/1993	28/10/1993, 1/6/1995, 1/11/1995,13/10/1996,
595	1	8/9/1964	CR	2		1	R255X	mult'94,'98		
690	1	13/11/1993	CR	2		1	R168X(MH)trunc	mult. '95, '97, '98	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002
826	1	21/8/1991	R nonC	2		1	C to G base 401	mult'97,'98,'01	18/6/1997	30/1/2002
870	1	12/8/1995	CR	2		1	c455c>G;P152R(MH	HSQ.'99	30/11/1998	1/10/1999,15/10/2001,, 12/10/2002
873	1	19/11/1996	CR	2		1	c473C>T; T158M	HSQ'98	14/10/1998	12/10/2002
908	1	27/4/1997	CR	2		1	c502c>t;R168X (AC)	HSQ.'00	19/1/2000	1/2/2000
926	1	3/7/1997	CR	2		1	Q244X(MH)	mult.'00,'02	19/1/2000	1/2/2000

Dataset 4.4: Abnormal general movements in Rett

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	4.4	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
8	1	27/3/1987	CR	2				mult '90,'94,'95	6/10/1990	23/1/1991,21/1/1992,
79	1	13/2/1987	CR	1	9/4/2001	1	T158M (Manchester)	mult. '93,'94,'96,'99	6/10/1990	1/10/1994,
169	1	31/3/1993	CR	2		1	Q244X (MB)(MH)	mult. '95, '96, '98	15/6/1995	16/6/1996, 1/10/1999,
209	1	26/1/1989	CR	2		1	T158M	mult.'91 ,'03	11/6/1991	17/1/1995
234	1	24/6/1980	CR	2		1	c783C>T;R255X(AC	mult '91,'94,'98	1/10/1986	28/8/1988, 1/8/1989, 12/8/1991,
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
307	1	15/3/1964	CR	2		1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/1995, 1/10/1996,
312	1	9/2/1970	CR	2				Q'91 Inv	1/10/1989	
348	1	2/10/1980	CR	2				Inv	20/1/1993	
431	1	28/10/1997	R nonC	2		2	not found (AC)	HSQ '01	6/6/2001	
468	1	2/6/1992	CR	2				HSQ.'95,1/10/2003	11/11/1995	
546	1	13/11/1991	CR	2		1	del exon 4	mult. '93,'94,'03	28/10/1993	28/10/1993, 1/6/1995, 1/11/1995,13/10/1996,
550	1	29/9/1990	CR	2		1	del exon3-4 (initially	mult. '93,'94,'96	15/10/1993	4/2/1995,4/2/1999
678	1	14/5/1991	R nonC	2		1	c502C>T;R168X	mult. '95,'96	21/6/1995	16/6/1996,1998
690	1	13/11/1993	CR	2		1	R168X(MH)trunc	mult. '95, '97, '98	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002
826	1	21/8/1991	R nonC	2		1	Cto G base 401	mult'97,'98,'01	16/6/1997	30/1/2002
870	1	12/8/1995	CR	2		1	c455c>G;P152R(MH	HSQ '99	30/11/1998	1/10/1999,15/10/2001,, 12/10/2002
873	1	19/11/1996	CR	2		1	c473C>T; T158M	HSQ'98	14/10/1998	12/10/2002
883	1	23/8/1995	CR	2		2	none(AC)	HSQ		
908	1	27/4/1997	CR	2		1	c502c>t;R168X (AC)	HSQ.'00	19/1/2000	1/2/2000
926	1	3/7/1997	CR	2		1	Q244X(MH)	mult.'00,'02	19/1/2000	1/2/2000
964	1	20/5/1998	CR	2		1	1118-1201del 86	HSQ'00	1/11/2001	1/11/2001, 20/4/2001,6/1/04
972	1	15/10/1997	R nonC	2		2	not found (AC)	mult '01,'03	31/1/2001	
978	1	14/9/1995	CR	2			uncertain result	HSQ '01	30/1/2001	30/1/2001

Dataset 5.2 & 3: Hyperventilation in awake state & Correlation of events

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	5.2	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
2	1	24/3/1981	CR	2				Q '86	24/5/1986	24/7/1987,11/6/1991
3	1	8/6/1980	CR	2				'93	25/8/1983	1/11/2000
6	1	9/8/1976	CR	2				Q	20/7/1987	12/1/1994
20	1	22/8/1977	CR	2		1	917G>A(AC)R306H(	mult.'91,'94,'96,'98,'	24/5/1988	21/8/2000,24/10/2001,15/10/2001, 12/10/2002,
29	1	21/5/1970	CR	2		1	P152R (MB)	HSQ. '96	14/7/1987	28/1/1988,16/5/1992, 1/6/1996, 19.9.2004
33	1	15/7/1973	CR	2				mult'93,'96,'98	26/10/2083	
50	1	20/1/1978	CR	2				mult	5/5/1983	12/12/1987
88	1	14/10/1985	CR	2		2	not found (MB)(AC)	HSQ. '95	1/4/1989	26/6/1993
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/1999,
106	1	29/9/1978	CR	2				Q	9/2/1981	10/5/1984,1/1/1985, 2/12/1987
123	1	10/11/1986	CR	2		1	T158M (MB)	Q . '97	7/7/1993	27/6/97, 3/10/1997, 1/11/1997,
127	1	21/6/1980	CR	2				Q '86-'96	7/7/1986	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
137	1	2/4/1974	CR	2				Q '83	10/11/1983	10/11/1983, 21/6/1990
154	1	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96.'98	29/9/1983	17/12/1995,13/3/1996, 5/10/2001
162	1	14/9/1986	CR	2		1	R133C (MB)	mult. '90, '98,	1/9/1991	29/4/1992, 17/7/1998, 1/6/2000, 1/11/2000
181	1	18/3/1988	inc CR	1				Q'90	1/10/1990	
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1988	28/7/97
226	1	10/10/1980	CR	2				Q'84-'88	14/6/1984	18/7/1987,16/3/1988,
257	1	6/5/1980	CR	2		1	c473C>T; T158M &	mult'93,'95,'00	1/10/1986	21/7/1987,28/3/1990,19/2/1991,21/6/2000
258	1	7/1/1987	CR	2				mult'98	1/6/1983	
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
282	1	3/7/1981	CR	2		1	107in frame	mult.'92'93,'95,'98	24/7/1987	1/1/1989,1/1/1992,
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
335	1	25/5/1971	CR	2				Q'84	28/6/1984	1.9.1988,21/7/1987
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
366	1	23/10/1981	R nonC	2		1	c916C.T;R306C (AC)	mult.'92,'98	4/2/1992	14/6/1994,1/10/1996
367	1	22/2/1981	CR	1	9/8/1995			mult Q	26/7/1984	
380	1	6/2/1985	CR	2		1	P302L	mult. '94,'95,'96,'98	7/8/1991	26/7/1996,5/10/2001
402	1	12/10/1988	CR	2				mult'93,'95,'96,'99	15/1/1992	25/6/1998,24/10/2001,
487	1	8/9/1974	R nonC	2		1	44bpdel.1163-(Wes	Q.'88.Inv	6/6/1988	10/10/1990, 1/5/1992,
540	1	1/3/1989	CR	2				mult.'93,'95,'98	25/10/1993	1/10/1996,17/6/1998

Dataset 5.4: Functional evidence of brain stem immaturity

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	5.4	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
347	1	30/1/1982	R nonC	2		2	not found (Wessex	mult.	1/10/1992	18/1/1995,16/8/1996
380	1	6/2/1985	CR	2		1	P302L	mult. '94,'95,'96,'98	7/8/1991	26/7/1996,5/10/2001
402	1	12/10/1988	CR	2				mult'93,'95,'96,'99	15/1/1992	25/5/1998,24/10/2001,
510	1	28/7/1989	CR	2				mult.	5/8/1992	1/1/94,1/1/96,1/1/2000
738	1	14/4/1992	CR	2		1	R255X	inv	1/8/1996	30/7/1996
783	1	14/4/1994	CR	2				HSQ'96	17/12/1996	17/12/96

Dataset 5.5: Characterisation of breathing

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

In this study four more cases were included from Sweden for which data is not in the BIS

BIS	5.5	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
9	1	2/2/1978	CR	2				mult '95,'98	28/8/1987	6/6/1997
33	1	15/7/1973	CR	2				mult'93,'95,'98	26/10/2083	
75	1	28/2/1985	CR	2				HSQ '97	1/10/1989	1/10/1989
83	1	27/7/1977	R nonC	2				inv	23/7/1991	20/8/1999
87	1	12/8/1977	CR	2				mult '93, '94,'95	20/10/1983	8/4/1986, 5/12/1987, 11/6/1994, 1/6/1996, 28/7/1997
123	1	10/11/1986	CR	2		1	T158M (MB)	Q . '97	7/7/1993	27/6/97, 3/10/1997, 1/11/1997,
148	1	25/4/1981	R nonC	2		1	c397C>TR133C(AC	Q.'92	30/8/1988	1/1/1989,5/6/1992,13/6/1995,30/11/1997,12/10/2002
149	1	10/4/1985	R nonC	2		1	c397C>TR133C(AC	Q.'91	6/6/1991	30/11/1997, 12/10/2002,1/10/2003
162	1	14/9/1986	CR	2		1	R133C (MB)	mult. '90, '98,	1/9/1991	29/4/1992, 17/7/1998, 1/8/2000, 1/11/2000
182	1	26/8/1988	CR	1	13/8/2005			mult.'94,'95,'97,'98,'	1/10/1991	30/1/1992,10/11/1997,15/10/2001
194	1	7/7/1985	CR	2		1	916C>T(AC)R306C(	mult '93,'94, '97,	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995, 30/5/1997,
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1988	28/7/97
258	1	7/1/1967	CR	2				mult'96	1/6/1983	
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
347	1	30/1/1982	R nonC	2		2	not found (Wessex	mult.	1/10/1992	18/1/1995,16/8/1996
359	1	11/8/1988	R nonC	2				mult '93	26/10/1987	1/6/1996,29/11/1997,1/6/1998,1/11/1999,1/6/2003
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
380	1	6/2/1985	CR	2		1	P302L	mult. '94,'95,'96,'98	7/6/1991	26/7/1996,5/10/2001
381	1	10/11/1987	CR	1	1/4/2003			mult.'91,	4/9/1991	16/5/1992,1/1/1997,13/11/1998,4/9/2000
397	1	20/12/1989	inc CR	2				Q	19/10/1991	5/2/1992
402	1	12/10/1988	CR	2				mult'93,'95,'96,'99	15/1/1992	25/5/1998,24/10/2001,
409	1	4/9/1989	CR	2		1	158(d'E)	Q	1/10/1992	1/10/1996
427	1	26/5/1973	CR	2				HSQ	25/2/1992	19/2/1998
502	1	6/5/1989	CR	2		1	1152del144bp(AC)	mult.'93,'94,'96,'97,'	4/6/1992	1/11/1997,1/10/2001
508	1	14/2/1976	CR	2				mult '94,'98	4/6/1992	14/9/1993,11/6/1994,14/8/1998,1/12/1998,13/11/1999,
510	1	28/7/1989	CR	2				mult.	5/8/1992	1/1/94,1/1/96,1/1/2000
568	1	16/8/1987	CR	2		1	R168X(MB)	HSQ.'98	15/6/1994	26/3/1999
631	1	21/6/1990	CR	2		2	none(MB)	HSQ.'94	5/6/1995	18/6/1996,1/11/1997
635	1	27/11/1991	CR	2		1	792-804del13, I	mult. '95, '96,	2/12/1994	
650	1	24/12/1992	CR	2		1	R270X(AC)	mult. '95, '97	24/12/1992	2/2/1995, 1/10/1996, 1/11/1997, 7/10/1999,
653	1	1/3/1993	CR	2		1	R270X (MB)	mult	18/1/1995	19/6/01, 15/1/01,23/10/01, 12/10/02,1/10/04
690	1	13/11/1993	CR	2		1	R168X(MH)trunc	mult. '95, '97, '98	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002
712	1	10/5/1984	R nonC	2		2	not found (Wessex)	mult'95,'96,'98	10/1/1996	6/6/1997,18/6/1998,9/2/2000,1/10/2003
728	1	20/10/1993	CR	2				mult '96,'97	20/10/1993	
738	1	14/4/1992	CR	2		1	R255X	inv	1/6/1996	30/7/1996
783	1	14/4/1994	CR	2				HSQ'96	17/12/1996	17/12/96
797	1	26/4/1991	CR	2		1	1164-1207del44(A	mult. '96, '97, '98,	15/1/1997	26/9/1997,21/6/2000,
803	1	14/6/1980	CR	2				mult '97,'98,'04	10/10/1997	12/10/2002
806	1	17/6/1994	CR	2		1	R306C (Edin)(MB)	HSQ. '97	17/6/1994	14/3/1997, 1/11/2000
809	1	22/11/1994	inc CR	2				HSQ.'97	1/11/1997	
820	1	17/5/1994	R nonC	2		1	c753delC(AC)	HSQ '97	17/6/1997	1/10/2001, 12/1/2003
829	1	26/8/1989	R nonC	2				HSQ '98	1/3/1998	3/7/98
833	1	13/1/1995	CR	2		1	c126-127insG (AC)	inv	1/11/1997	16/6/1998
854	1	4/7/1991	CR	2		1	c1157-1200del144	mult'98, '99,	3/7/1998	4/2/1999,22/6/1999,20/6/2000,31/1/2001, 30/1/2002
858	1	26/9/1988	CR	2		2	not found (AC)	HSQ. '98	19/6/1998	7/8/1998,11/7/1998,11/6/2002
901	1	1/8/1963	CR	2						
902	1	26/1/1979	CR	2						
903	1	17/11/1987	CR	2					26/4/1998	
904	1	24/4/1982	CR	2						
905	1	25/1/1991	CR	2						
906	1	17/4/1991	CR	2						
907	1	12/11/1987	CR	2						

Dataset 5.6: Critical examination of e.e.g....

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

Longitudinal data is shown for the presence of epilepsy in the
final column. Each digit represents a five year period, except the first which
represents the period before regression if regression occurred,
1=epilepsy present, 2=no epilepsy present

BIS	5.6	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
2	1	24/3/1981	CR	2				Q '86	24/5/1986	24/7/1987,11/6/1991
3	1	8/5/1980	CR	2				'93	25/8/1983	1/11/2000
6	1	9/8/1976	CR	2				Q	20/7/1987	12/1/1994
16	1	27/2/1983	CR	2		2	none(MB)	HSQ. '98	24/8/1986	23/1/1991
25	1	29/7/1980	CR	2				Q'91	23/1/1991	29/1/1993
29	1	21/5/1970	CR	2		1	P152R (MB)	HSQ. '96	14/7/1987	28/1/1988,16/5/1992, 1/6/1996, 19.9.2004
37	1	13/6/1986	CR	1	5/1/2005	1	P302L(AC)	mult.'93. '94'03	28/10/1989	23/1/1991, 8/6/1994,
40	1	12/5/1978	CR	2				Q	1/10/1987	28/10/1989
41	1	16/5/1978	CR	2				HSQ '98	1/10/1987	
44	1	23/8/1982	CR	2		1	c880c>t;R294X (AC)	HSQ'98	22/1/1991	22/1/1991; 29/1/2001
50	1	20/1/1976	CR	2				mult	5/5/1983	12/12/1987
62	1	21/2/1975	CR	1	23/11/1998			HSQ '90,'98	19/10/1991	
63	1	3/2/1980	CR	2				mult '90,'96		
78	1	14/8/1979	CR	2				inv	20/6/1991	
81	1	10/8/1980	CR	2		1	c502C>T;R168X	Q '91	21/1/1992	
87	1	12/8/1977	CR	2				mult '93, '94,'95	20/10/1983	8/4/1988, 5/12/1987, 11/6/1994, 1/6/1996, 28/7/1997
88	1	14/10/1985	CR	2		2	not found (MB)(AC)	HSQ. '95	1/4/1989	26/6/1993
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1988,22/7/1987,20/12/1988,21/7/1993,1/11/1999,
100	1	13/4/1975	CR	1	1/1/1997			mult	24/5/1984	
106	1	29/9/1978	CR	2				Q	9/2/1981	10/5/1984,1/1/1985, 2/12/1987
113	1	5/5/1977	CR	2		1	c763c>t;R255Xd'E)	HSQ, '94	20/6/1991	11/1/1994
116	1	24/11/1967	CR	2				Q.'91	20/7/1994	13/11/1991, 14/6/1994
123	1	10/11/1988	CR	2		1	T158M (MB)	Q . '97	7/7/1993	27/6/97, 3/10/1997, 1/11/1997,
127	1	21/6/1980	CR	2				Q '88-'96	7/7/1986	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
128	1	13/9/1975	CR	2				mult Q,HSQ'97	18/4/1984	
131	1	16/7/1983	CR	2		1	1157del144bp (CS)	mult.'90,'93'95'98'9	1/10/1989	11/1/1994,21/6/2000,4/4/2001
137	1	2/4/1974	CR	2				Q '83	10/11/1983	10/11/1983, 21/6/1990
142	1	12/10/1975	CR	1	14/5/1987			Q	21/6/1984	
146	1	2/8/1984	R nonC	2		1	1157-1197del.41bp(	mult'95,'96,'03	28/5/1993	
154	1	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96,'98	29/9/1983	17/12/1995,13/3/1996, 5/10/2001
157	1	6/12/1985	CR	2		1	G252fsX287(MB)	Q.inv	18/1/1995	
162	1	14/9/1986	CR	2		1	R133C (MB)	mult. '90, '98,	1/9/1991	29/4/1992, 17/7/1998, 1/6/2000, 1/11/2000
165	1	29/10/1990	CR	2				inv	7/11/1995	
181	1	18/3/1988	Inc CR	1				Q'90	1/10/1990	
196	1	12/10/1984	CR	2				Q '92,	24/6/1987	18/6/1997,21/6/2000
197	1	18/5/1964	R nonC	2		1	c763CC>T;R255X(A	HSQ'04	22/2/1991	
198	1	18/6/1964	CR	1	14/5/2003	1	c763C>T;R255X(AC)	Q	20/2/1991	
207	1	14/8/1980	CR	2		1	T158M (TW)	mult '94 '95,'96,'98	23/7/1991	
209	1	26/1/1989	CR	2		1	T158M	mult.'91 ,'03	11/6/1991	17/1/1995
222	1	8/5/1978	CR	1	27/12/1999			Q	12/11/1987	1/6/1998
225	1	4/2/1980	CR	2				Q '90	1/6/1989	1/10/1992
226	1	10/10/1980	CR	2				Q'84-'88	14/6/1984	18/7/1987,16/3/1988,
250	1	7/10/1983	CR	2				inv	3/6/1989	11/6/1991
254	1	5/5/1988	CR	2		1	Y141X(Aberdeen)	mult.'90,'94,'95,'96,'	25/6/1990	
257	1	6/5/1980	CR	2		1	c473C>T; T158M &	mult'93,'95,'00	1/10/1988	21/7/1987,28/3/1990,19/2/1991,21/6/2000
258	1	7/1/1967	CR	2				mult'96	1/6/1983	
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
269	1	16/10/1968	R nonC	2				Q '91	12/6/1991	
282	1	3/7/1981	CR	2		1	107in frame	mult.'92'93,'95,'98	24/7/1987	1/1/1989,1/1/1992,
300	1	19/6/1985	CR	2		1	R270X (MB)	mult. '93, '96,	23/1/1991	22/1/1993
301	1	8/11/1974	CR	1	6/12/1998			HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/1993
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
306	1	13/8/1976	CR	2		1	R270X(MB)	HSQ.'95	13/9/1976	1/4/1991
307	1	15/3/1964	CR	2		1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/1995, 1/10/1996,
329	1	20/6/1971	CR	1	25/3/1987			Q	12/4/1984	
330	1	7/3/1973	CR	2				Q		
335	1	25/5/1971	CR	2				Q'84	28/6/1984	1.9.1988,21/7/1987
340	1	12/7/1987	CR	2				Q.'91	23/1/1991	3/2/1992
356	1	3/9/1980	CR	2		1	R255X (TW,AC,MH),	Q'90,'88	1/10/1987	1/6/1988,1/4/1989,15/10/2001,1/10/2003
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
367	1	22/2/1981	CR	1	9/8/1995			mult Q	26/7/1984	
378	1	30/10/1973	CR	1	23/11/1993			Q'90	1/4/1989	1/6/1990
380	1	6/2/1985	CR	2		1	P302L	mult. '94,'95,'96,'98	7/8/1991	26/7/1996,5/10/2001
391	1	28/3/1975	CR	2				HSQ '99		
402	1	12/10/1988	CR	2				mult'93,'95,'96,'99	15/1/1992	25/5/1998,24/10/2001,
405	1	24/11/1987	CR	2		1	R306C (Wessex)	mult '96.'02	22/1/1992	
479	1	10/12/1980	CR	2		1	R133C	Q.'90.	1/6/1990	1/11/1999,
539	1	2/5/1972	CR	2				mult'95,'98	24/5/1984	1/5/1996,28/22/1991
540	1	1/3/1989	CR	2				mult.'93,'95,'98	25/10/1993	1/10/1996,17/6/1998
544	1	16/5/1990	CR	2				mult.'93,'96,'99,'01	2/11/1993	19/6/2001
546	1	13/11/1991	CR	2		1	del exon 4	mult. '93,'94,'03	28/10/1993	28/10/1993, 1/6/1995, 1/11/1995,13/10/1996,
550	1	29/9/1990	CR	2		1	del exon3-4 (initially	mult. '93,'94,'96	15/10/1993	4/2/1995,4/2/1999
553	1	8/5/1991	CR	2		1	R168X (MB)	mult.'93,'00	24/1/1994	4/4/2001, 12/10/2002
573	1	7/1/1992	CR	2		2	neg(AC)	mult '94,'96	14/3/1994	1/1/2001
577	1	28/7/1990	CR	2		1	502C>T(AC)R168X	HSQ.'95	18/1/1995	19/6/1996,
636	1	26/1/1989	R nonC	2				inv	1/10/1994	
690	1	13/11/1993	CR	2		1	R168X(MH)trunc	mult. '95, '97, '98	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002
694	1	19/11/1993	CR	2		1	R255X (MH)	mult. '95,'98,	11/11/1995	5/2/1996,23/10/2001,12/10/2002

Dataset 6.1:Neurophysiological observations on the corticospinal projections to upper limb

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

BIS	6.1	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
68	1	10/3/1962	CR	2		1	1157del141bp (d'E	mult.'94,'95,'98	29/10/1988	
101	1	29/5/1981	CR	2		2	none (AC)	HSQ '98	1/1/1988	
148	1	25/4/1981	R nonC	2		1	c397C>TR133C(AC	Q.'92	30/8/1988	1/1/1989,5/6/1992,13/6/1995,30/11/1997,12/10/2002
149	1	10/4/1985	R nonC	2		1	c397C>TR133C(AC	Q.'91	6/6/1991	30/11/1997, 12/10/2002,1/10/2003
234	1	24/6/1980	CR	2		1	c763C>T;R255X(A	mult '91,'94,'98	1/10/1986	28/8/1988, 1/6/1989, 12/6/1991,
239	1	7/7/1979	CR	1	1/12/1995	2	(AC) not found	Q '89	1/9/1988	10/6/1992,8/4/1999
257	1	6/5/1980	CR	2		1	c473C>T; T158M &	mult'93,'95,'00	1/10/1986	21/7/1987,28/3/1990,19/2/1991,21/6/2000
263	1	14/10/1971	CR	2		1	158(d'E)	HSQ'01	24/5/1988	1/1/1987,2/9/1988,19/6/2001
356	1	3/9/1980	CR	2		1	R255X	Q'90,'88	1/10/1987	1/8/1988,1/4/1989,15/10/2001,1/10/2003

Dataset 6.2: Short 4th ray in Rett Syndrome

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

In this dataset, the final column records any other suggested cause for the brain disorder.
The dataset contains additional cases with short 4th ray recorded after the project.

BIS	8.2	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
6	1	9/8/1976	CR	2				Q	20/7/1987	12/1/1994
7	1	13/8/1964	CR	2				Q'86	28/4/1986	
9	1	2/2/1976	CR	2				mult '95,'98	28/8/1987	6/6/1997
20	1	22/8/1977	CR	2		1	917G>A(AC)R306H	mult.'91,'94,'96,'98,	24/5/1986	21/6/2000,24/10/2001,15/10/2001, 12/10/2002,
21	1	14/6/1978	CR	2		1	R106W(AC)106(d'E	mult '93,'95,'98	14/6/1978	30/3/1992
37	1	13/6/1986	CR	1	5/1/2005	1	P302L(AC)	mult.'93. '94'03	28/10/1989	23/1/1991, 6/6/1994,
52	1	7/6/1976	CR	1	6/10/1997			HSQ	1/10/1989	1/10/1991
93	1	29/7/1984	CR					Q'90	8/6/1993	
103	1	20/4/1973	CR	2		1	missense T158M	HSQ. '95,	17/1/1995	14/1/1998
110	1	22/5/1981	Inc CR					inv	23/1/1991	
113	1	5/5/1977	CR	2		1	c763c>t;R255X(d'E)	HSQ. '94	20/6/1991	11/1/1994
127	1	21/6/1980	CR	2				Q '86-'96	7/7/1986	22/8/1987,25/11/1988,12/5/1992,1/6/1996,
133	1	8/1/1982	CR					Q '91,	1/10/1991	17/6/1997
135	1	16/1/1982	CR	1	31/1/1998			Q inv	1/5/1986	1/1/1987
155	1	8/9/1969	CR	2		2	(AC)(d'E)not found	mult.'94,'96,'98,'99	1/10/1992	
170	1	27/6/1970	CR	2				mult '94,'95,'98	11/1/1994	
174	1	5/7/1979	CR	1	12/10/1995			HSQ. '95	3/6/1989	17/6/1995
176	1	1/9/1981	CR					HSQ '95	1/10/1989	1/1/1993
192	1	2/4/1972	CR					mult '94.'98	1/11/1985	
194	1	7/7/1985	CR	2		1	916C>T(AC)R306C(	mult '93,'94, '97,	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995, 30/5/1997,
212	1	13/7/1983	CR	2		1	101d'E)	HSQ'95	1/10/1990	21/1/1993,1/10/1994,
218	1	19/9/1980	CR	2		1	R306H (MB)	HSQ '92.'03		
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1986	28/7/97
228	1	4/3/1963	CR	1	1/1/1995			HSQ'93	3/8/1989	15/10/1993
234	1	24/6/1980	CR	2		1	c763C>T;R255X(A	mult '91,'94,'98	1/10/1986	28/8/1988, 1/6/1989, 12/6/1991,
239	1	7/7/1979	CR	1	1/12/1995	2	(AC) not found	Q '89	1/9/1988	10/5/1992,8/4/1999
243	1	14/5/1956	CR	2				mult'97,'98,'04	27/11/1990	
245	1	8/2/1984	CR					Q'90	1/1/1987	1/4/1989, 4/6/1992
252	1	23/3/1977	CR	2		1	c.695delG(AC)	mult.'95,'98,'00	23/1/1991	11/6/2002
259	1	24/7/1959	CR	2				Q '86	7/2/1986	30/3/2001,19/4/2002
261	1	16/6/1982	CR	2				inv	14/5/1992	
277	1	1/8/1969	CR	2				mult.'95,'98,'00	23/1/1991	10/1/1996,15/2/2000
278	1	7/8/1977	CR	2				mult.'96,'99	14/1/1998	
297	1	8/6/1976	CR	2		1	P152R(MB)	mult '95, '98	1/6/1993	
302	1	28/9/1979	CR	2		1	c502C>T; R168X	Q'91	25/5/1992	
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
306	1	13/8/1976	CR	2		1	R270X(MB)	HSQ.'95	13/9/1976	1/4/1991
342	1	13/3/1968	CR	2				Q	1/10/1992	
359	1	11/8/1968	R nonC	2				mult '93	26/10/1987	1/6/1996,29/11/1997,1/6/1998,1/11/1999,1/6/2003
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
373	1	12/11/1971	CR	1	1/4/2001			mult.'93,'96,'98	1/6/1993	
382	1	3/6/1974	CR	2				HSQ'96	8/1/1996	
388	1	25/12/1979	CR					Q	14/6/1993	
392	1	28/11/1985	R nonC	2				mult '91,'94	25/5/1992	
396	1	18/10/1984	CR	2		1	T158M missense	mult '94 '95 '97,	15/6/1994	
423	1	16/5/1971	CR					HSQ'97	18/7/1997	
427	1	28/5/1973	CR	2				HSQ	25/2/1992	19/2/1998
483	1	10/5/1976	CR	1	5/1/2004	1	R270X(MB)	HSQ.'98,'02	22/1/1991	25/1/1993
487	1	8/9/1974	R nonC	2		1	44bpdel.1163-(Wes	Q.'86.inv	6/6/1986	10/10/1990, 1/5/1992,
491	1	20/9/1970	R nonC	2		2	neg(AC)	HSQ.'97,'03	29/7/1997	
500	1	15/10/1971	Inc CR	1	17/1/2005			HSQ'94	10/6/1992	20/1/1994
511	1	18/6/1979	not R	2				HSQ '95	5/8/1992	
532	1	17/12/1961	CR	2		1	R133C(MB)	mult'93,'95,'98	19/1/1994	
549	1	18/1/1977	CR					HSQ '03	13/6/1994	1/10/2001
554	1	30/9/1969	CR	2				HSQ'95	15/10/1993	
561	1	11/5/1961	R nonC	2				HSQ.'96	2/2/1994	
562	1	20/7/1981	not R	2		2	(AC) none found	inv	21/1/1994	
564	1	14/9/1983	R nonC	2		1	c397C>T; R133C	mult. '94,'98	12/1/1994	15/10/2001,
568	1	18/8/1987	CR	2		1	R168X(MB)	HSQ.'98	15/6/1994	26/3/1999
579	1	27/2/1935	not R	2				mult'94,'96	1/6/1998	
587	1	20/9/1950	CR	2				HSQ	18/3/1991	
588	1	12/3/1961	Inc CR	2				inv		
592	1	2/9/1965	R nonC	2				inv	1/4/1994	
595	1	8/9/1964	CR	2		1	R255X	mult'94,'98		
600	1	30/12/1970	CR	2				mult.'94,'95	14/6/1994	16/6/1998
603	1	13/7/1983	not R	2				mult '94,'97,'98	14/6/1994	
605	1	23/10/1977	CR	2		2	negative(MB?) 7MH	mult.'94,'98	14/6/1994	12/10/2002
634	1	24/6/1970	CR	1	2/1/2000			mult.'95,'96,'97,'989	1/10/1994	
635	1	27/11/1991	CR	2		1	792-804del13, I	mult. '95, '96,	2/12/1994	
665	1	20/6/1971	CR	2		1	208(d'E)(MH)	mult.'95'98	19/1/1993	
683	1	2/6/1970	CR	2				HSQ '95	25/7/1995	
701	1	17/10/1968	Inc CR					Inv	14/6/1994	
718	1	21/9/1961	R nonC	2				HSQ. '95	9/1/1996	
719	1	4/5/1973	CR	1	1/9/2003			HSQ.'95,	9/1/1996	
736	1	23/9/1961	R nonC	2				HSQ.'96	24/6/1996	31/5/1996
750	1	1/12/1978	Inc CR	2				inv	17/6/1996	
774	1	14/11/1957	Inc CR	2		1	exons 1-2	mult'96,'98,'02	14/1/1998	12/10/2002,1/10/2003
783	1	14/4/1994	CR	2				HSQ'96	17/12/1996	17/12/96
835	1	23/11/1980	not R	2				inv		
838	1	1/7/1985	not R					Inv	5/4/1999	
847	1	6/5/1964	R nonC	2		2	not found(AC)	mult '98,'99	23/1/1991	26/3/1999,14/6/1999,1/10/1999
848	1	13/2/1966	R nonC	2				HSQ '96	24/1/1998	
858	1	26/9/1968	CR	2		2	not found (AC)	HSQ. '98	19/6/1998	7/8/1998,11/7/1998,11/6/2002
920	1	20/1/1998	CR	2		1	c473c>tT158M	HSQ'00	19/1/2000	1/2/2000
935	1	13/9/1980	not R					Inv		
967	1	10/6/1975	CR	2		1	R270X (WGH) neg	HSQ. '02	23/2/2001	
976	1	10/10/1962	CR	2				HSQ '01	30/1/2001	30/1/2001
1009	1	21/6/1965	CR	2		1	530del448(MH)	HSQ '01	29/1/2002	
1021	1	8/10/1974	CR					HSQ	29/1/2002	
1088	1	16/5/1987	R nonC	2		2	negative(DR)	HSQ.'02	11/6/2002	
1190	1	17/12/1987	not R			2	neg(AC)	HSQ	1/7/2004	

Dataset 6.3: Visual function in Rett Syndrome

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

The final column in this dataset shows the severity score for cases. The severity score calculation is shown in figure 2.2.1, Appendix 1 The score is out of 10 points, higher number indicating greater severity. In this dataset maximum severity is shown as 100%

BIS	6.3	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
33	1	15/7/1973	CR	2				mult'93,'95,'98	26/10/2083	
89	1	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/19
154	1	29/6/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96,'98	29/9/1983	17/12/1996,13/3/1996, 5/10/2001
221	1	28/8/1972	CR	2				mult'93,'01	1/4/1986	28/7/97
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
301	1	8/11/1974	CR	1	6/12/1998			HSQ	6/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/
303	1	30/9/1970	CR	2				mult '86,'96	9/11/1983	16/5/1992
360	1	23/4/1969	CR	2				HSQ	26/7/1984	27/6/1997
395	1	21/6/1976	CR	2				HSQ'94	29/4/1992	
402	1	12/10/1988	CR	2				mult'93,'95,'96,'99	15/1/1992	25/5/1998,24/10/2001,
508	1	14/2/1976	CR	2				mult '94,'98	4/6/1992	14/9/1993,11/6/1994,14/8/1998,1/12/1998,13/11/1

Dataset: 6.4: Urinary pterins in Rett Syndrome

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

European cases were included in this project which were not registered in BIS

BIS	6.4	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
22	1	12/7/1980	CR	2		1	c401C>G,S134C(A	mult.'80'94,'95,	22/1/1992	
30	1	3/9/1977	CR	2		1	R255X and	HSQ '96	1/5/1986	1/1/1987,1/10/1992,1/10/1994,
119	1	4/6/1990	CR	2				HSQ	10/6/1993	11/1/2004
194	1	7/7/1985	CR	2		1	916C>T(AC)R306C(	mult '93,'94, '97,	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995, 30/5/1997,
220	1	31/10/1986	CR	2				mult. '93, '95,	22/1/1991	1/10/1992, 21/1/1993
274	1	31/5/1980	CR	2		1	c.880C>T.R294X(D	mult.'94,'02	1/1/1987	1/10/1989,14/6/1994,1/10/1996,11/6/2002
346	1	12/1/1991	CR	2				mult '93,'95	9/6/1993	18/11/2004
368	1	8/8/1982	CR	2				Q.'92,	1/10/1991	1/2/1992,1/10/1996,7/10/1999,24/10/2001,
397	1	20/12/1989	inc CR	2				Q	19/10/1991	5/2/1992
399	1	12/4/1991	not R	2		2	(AC)(dE) none	mult	3/2/1992	
447	1	12/7/1990	CR	2				mult. '94, '97	25/5/1992	11/1/1994,17/6/1997
473	1	16/10/1963	CR	2				HSQ.'95	9/1/1996	
498	1	6/7/1964	CR	2		1	473C>T	mult. '97, '00,	1/5/1986	11/6/1991, 31/1/1995,11/6/1001, 1/10/2001,
502	1	6/5/1989	CR	2		1	1152del144bp(AC)	mult.'93,'94,'96,'97,'	4/6/1992	1/11/1997,1/10/2001
516	1	17/7/1989	CR	2				mult'94,'95,'96,'98	20/1/1993	
525	1	10/8/1990	CR	2		1	T158M (MB)	HSQ. '96	21/1/1993	1/10/1996
537	1	29/3/1990	not R	2				HSQ '93	5/1/1995	
543	1	16/2/1991	CR	2		1	C252X(MH)	mult	11/1/1994	1/10/1996,4/9/2000,15/10/2001,12/10/2002
546	1	13/11/1991	CR	2		1	del exon 4	mult. '93,'94,'03	28/10/1993	28/10/1993, 1/6/1995, 1/11/1995,13/10/1996,
550	1	29/9/1990	CR	2		1	del exon3-4	mult. '93,'94,'96	15/10/1993	4/2/1995,4/2/1999
551	1	13/12/1990	CR	2		1	c455	HSQ '94	11/1/1994	1/11/1995
553	1	8/5/1991	CR	2		1	R168X (MB)	mult.'93,'00	24/1/1994	4/4/2001, 12/10/2002
567	1	18/6/1990	CR					Inv	12/1/1994	
573	1	7/1/1992	CR	2		2	neg(AC)	mult '94,'96	14/3/1994	1/1/2001
598	1	2/10/1991	R nonC	2				mult.'94,'95	14/6/1994	
653	1	1/3/1993	CR	2		1	R270X (MB)	mult	18/1/1995	19/6/01, 15/1/01,23/10/01, 12/10/02,1/10/04
706	1	12/12/1951	CR	2				mult.'96,'98	11/11/1995	9/1/1996,10/10/1998,12/10/2002
791	1	19/4/1994	CR	2		2	negative MH?	mult '96,'98,'03	15/1/1997	1/10/1999,12/10/2002

Dataset: 7.1: Long read sequence analysis

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

This dataset contains further cases investigated after project 7.1

BIS	A...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
792	1	23/9/1992	not R	1	4/7/2003	2	none (AC)	mult.'97,'98,'03	13/1/1998	
797	1	26/4/1991	CR	2		1	1164-1207del44(A	mult. '96, '97, '98,	15/1/1997	26/9/1997,21/6/2000,
800	1	21/4/1994	R nonC	2		2	none(AC)	mult.'97,'98,'00,'03	15/1/1997	10/2/2000
812	1	29/1/1991	not R	2		2	none(AC)	HSQ.'97	18/6/1997	
817	1	14/12/1989	R nonC	2		2	none (AC)	HSQ'97	17/6/1997	
818	1	10/9/1992	not R	2		2	none(AC)	mult.'98,'02	13/1/1998	
822	1	27/8/1979	not R	2		2	none (AC)	mult.'97,'98,'02	18/6/1997	
828	1	15/5/1989	CR	2		2	none(AC)	'02	1/11/2000	
831	1	19/10/1990	CR	1	1/1/2003	1	c730C>T;Q244X			
833	1	13/1/1995	CR	2		1	c126-127insG (AC)	inv	1/11/1997	16/6/1998
844	1	10/10/1990	CR	2		2	(d'E, AC)none	mult'98,'01	14/1/1998	20/6/2001
847	1	6/5/1984	R nonC	2		2	not found(AC)	mult '98,'99	23/1/1991	26/3/1999,14/6/1999,1/10/1999
849	1	7/8/1993	CR	2		1	position to come	HSQ.'98	17/6/1998	
850	1	6/5/1995	R nonC	2		2	none (AC,MB)	HSQ.'98	6/11/1998	
853	1	27/9/1993	CR	2		1	c916C>T; R306C	mult'98,'00	23/6/1998	
854	1	4/7/1991	CR	2		1	c1157-1200del144	mult'98, '99,	3/7/1998	4/2/1999,22/6/1999,20/6/2000,31/1/2001,
858	1	26/9/1988	CR	2		2	not found (AC)	HSQ. '98	19/6/1998	7/8/1998,11/7/1998,11/6/2002
859	1	26/9/1995	R nonC	2		2	negative (AC)	HSQ.'98	16/6/1998	12/10/2002
864	1	24/7/1990	R nonC	2		2	none(AC)none (DR)	HSQ'98	26/6/1998	
866	1	26/3/1995	R nonC	2		1	c502 C>T; R168X	inv	30/1/2000	
867	1	11/5/1986	CR	2		2	none(AC)	HSQ. '98		
869	1	7/3/1995	CR	2		1	R168X(AC)	HSQ'99	1/3/1999	
871	1	13/10/1995	not R				none (AC) but del	HSQ '03		
873	1	19/11/1996	CR	2		1	c473C>T; T158M	HSQ'98	14/10/1998	12/10/2002
876	1	26/2/1997	CR	2		2	not found(AC) still	inv	20/6/2000	20/6/2000
878	1	7/4/1996	CR	2		1	c473C>T; T158M	inv	7/2/2003	
880	1	16/12/1995	CR	2		1	c302C>T; P101L	HSQ'99,'03	1/11/1999	
885	1	25/9/1990	CR	2		1	c502C>T;R168X	HSQ '01,'03	20/6/2001	
895	1	13/1/1988	R nonC	2		2	none (AC)	inv	16/6/1999	
897	1?	15/7/1974	R nonC	2		1	c502C>T;	HSQ'00	20/6/2000	
908	1	27/4/1997	CR	2		1	c502c>t;R168X	HSQ.'00	19/1/2000	1/2/2000
913	1	22/5/1990	unknow	2		2	none(AC)			
914	1	8/10/1989	unknow	2		2	none(AC)			
915	1	16/11/1998	R nonC	2		2	negative(AC)?MH	HSQ'00	30/1/2001	
916	1	16/2/1992	R nonC	2		2	none (AC)	HSQ.'00	20/6/2000	
918	1	17/4/1991	R nonC	2		1	c808C>T;R270X	HSQ '02	18/6/2002	
920	1	20/1/1998	CR	2		1	c473c>t;T158M	HSQ'00	19/1/2000	1/2/2000
922	1	9/3/1994	CR	2		2	none, testing for	inv	14/11/2000	
931	1	20/3/1996	Inc CR	2		1	T158M (AC)	HSQ'01	19/6/2001	
936	1	11/12/1997	unknow	2		2	none(AC)			
938	1	24/11/1997	CR	2		1	c808C>T;R270X(A	inv	1/9/2000	1/9/2000
939	1	3/7/1994	CR	2		1	c397C>T1207del44	HSQ '00	1/6/2001	
942	1	14/11/1995	CR	2		1	c916C.T;R306C	HSQ. '02	19/4/2002	
943	1	4/3/1995	CR	2		1	808delC(AC)	HSQ.'01,'02,'04	20/6/2000	
944	1	17/6/1997	R nonC	2		2	none(AC) but del	HSQ '01	29/1/2001	
946	1	20/7/1979	R nonC	2		2	?silentT299T (AC)	HSQ '00	20/6/2000	
947	1	11/8/1996	CR	2		1	1164-1207del44(M	HSQ'00	20/6/2000	
955	1	24/8/1997	R nonC	2		2	none (AC)	HSQ.'00.'03	30/1/2001	
957	1	28/1/1998	CR	2		1	1.R294X(AC)	HSQ'01	30/1/2001	
959	1	1/8/1994	CR	2		1	?? none(MB)	HSQ. '02,	1/11/2000	
964	1	20/5/1996	CR	2		1	1116-1201del 86	HSQ'00	1/11/2001	1/11/2001, 20/4/2001,6/1/04
965	1	9/2/1998	CR	2		1	1157-1197del41(A	mult '00,'02,'03	1/11/2000	5/10/200119/9/204
967	1	10/6/1975	CR	2		1	R270X (WGH) neg	HSQ. '02	23/2/2001	
969	1	21/10/1998	R nonC	2		1	del.exon4-3prime	mult.'00,'01	30/1/2001	12/10/2002, 12/1/2003,1/10/2003
970	1	29/9/1981	R nonC	2		2	none(AC) still	HSQ '01	31/1/2001	
972	1	15/10/1997	R nonC	2		2	not found (AC)	mult '01,'03	31/1/2001	
973	1	11/3/1993	unknow			2	none (AC)	inv		
974	1	21/10/1998	CR	2		1	1150-1153delAGA	inv	30/1/2001	
978	1	14/9/1995	CR	2			uncertain result	HSQ '01	30/1/2001	30/1/2001
979	1	18/1/1999	R nonC	2		2	none(AC)	HSQ '01	30/1/2001	
980	1	29/8/1996	R nonC	2		1	c502c>t;	HSQ.'01	31/1/2001	
983	1	22/10/1967	R nonC	2		1	c880c>t; R294X	HSQ'01		

BIS	A...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
1	1	1/10/1979	R nonC	2		2	none (AC)	HSQ.'94	3/6/1991	21/1/1994
11	1	24/1/1980	unknow	2		1	c808C>T;	inv		
20	1	22/8/1977	CR	2		1	917G>A(AC)R306H	mult.'91,'94,'96,'98,	24/5/1986	21/6/2000,24/10/2001,15/10/2001, 12/10/2002,
21	1	14/6/1978	CR	2		1	R106W(AC)106(d'E	mult '93,'95,'98	14/6/1978	30/3/1992
22	1	12/7/1980	CR	2		1	c401C>G,S134C(A	mult.'80'94,'95,	22/1/1992	
26	1	13/2/1976	CR	2		1	R168X(AC)(d'E166)	HSQ.'96	16/10/1989	12/10/2002
28	1	22/7/1980	CR	2		1	c808 C>T;R270X	mult. '96, '98,	18/1/1993	1/10/1999, 12/10/2002
37	1	13/6/1986	CR	1	5/1/2005	1	P302L(AC)	mult.'93. '94'03	28/10/1989	23/1/1991, 8/6/1994,
39	1	18/12/1981	CR	2		1	c473C>T; T158M	HSQ.'96	5/2/1992	17/1/1995, 10/1/1996, 15/1/1997
44	1	23/8/1982	CR	2		1	c880c>t;R294X	HSQ'96	22/1/1991	22/1/1991; 29/1/2001
46	1	2/2/1982	CR	2		1	c316C>T;R106W	HSQ.'99	1/10/1990	
59	1	4/7/1982	CR	2		2	AC none	HSQ. '00	21/6/2000	
71	1	21/6/1983	CR	2		2	AC not found	Q.'90		
73	1	13/9/1974	CR	1	13/2/1992	1	c654-657delGAAG	Q'91		
81	1	10/8/1980	CR	2		1	c502C>T;R168X	Q.'91	21/1/1992	
97	1	22/1/1987	inc CR	2		1	c502C>T; R168X	inv	3/6/1989	
98	1	20/12/1984	CR	2		1	c916C>T;	Q.'91	1/10/1991	
113	1	5/5/1977	CR	2		1	c763c>t;R255X(d'E)	HSQ. '94	20/6/1991	11/1/1994
118	1	17/3/1985	CR	2		1	c808C>T;R270X(A	HSQ.'93	8/6/1993	
120	1	10/5/1978	inc CR	2		1	c502C			
121	1	8/12/1984	CR	2		1	c502C>T;	HSQ. '99	1/4/1989	10/6/1992,17/6/1995,16/6/1999,
136	1	9/2/1972	CR	2		1	c763 C>T; R255X	mult.'95'98'00'02	1/11/1987	11/2/2000,29/1/2002,
141	1	9/3/1987	CR	2		1	R168X(AC)(168d'E)	Q.'92	25/5/1992	
145	1	22/2/1987	inc CR	2		1	c473c>t; T158M	Q.'91	1/10/1990	
146	1	2/8/1984	R nonC	2		1	1157-1197del.41bp	mult'95,'96,'03	26/5/1993	
147	1	26/2/1994	unknow	2		2	AC none found			
148	1	25/4/1981	R nonC	2		1	c397C>TR133C(AC	Q.'92	30/8/1988	1/1/1989,5/6/1992,13/6/1995,30/11/1997,12/10/20
149	1	10/4/1985	R nonC	2		1	c397C>TR133C(AC	Q.'91	6/6/1991	30/11/1997, 12/10/2002,1/10/2003
150	1	6/11/1978	CR	1	20/9/2000	1	c316C>T; R106W	mult. '91,'99	22/8/1987	1/10/1989
155	1	8/9/1969	CR	2		2	(AC)(d'E)not found	mult.'94,'96,'98,'99	1/10/1992	
156	1	18/2/1970	CR	2		2	none(AV)	mult.'93,'95,'96,'98,'	1/1/1989	11/6/1991
161	1	10/9/1982	CR	2		1	none(MB)168(d'E)(	mult.'92,'95,'98		
173	1	3/3/1987	R nonC			2	none (AC)	HSQ'04		
191	1	16/7/1974	CR	2		1	c808C>T;R270X,	inv	1/4/1989	23/4/1999
194	1	7/7/1965	CR	2		1	916C>T(AC)R306C(	mult '93,'94, '97,	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995, 30/5/1997,
197	1	18/5/1964	R nonC	2		1	c763CC>T;R255X(	HSQ'04	22/2/1991	
198	1	18/5/1964	CR	1	14/5/2003	1	c763C>T;R255X(A	Q	20/2/1991	
199	1	1/7/1983	CR	2		1	c316 C>T; R106W	HSQ '94	19/1/1993	
209	1	26/1/1989	CR	2		1	T158M	mult.'91 ,'03	11/6/1991	17/1/1995
234	1	24/6/1980	CR	2		1	c763C>T;R255X(A	mult '91,'94,'98	1/10/1986	28/8/1988, 1/6/1989, 12/6/1991,
239	1	7/7/1979	CR	1	1/12/1995	2	(AC) not found	Q.'89	1/9/1988	10/6/1992,8/4/1999
249	1	31/10/1983	CR	2		2	none(d'E. MB,AC)	mult. '93, '94, '95,	20/1/1993	1/10/1994, 19/6/1995
256	1	20/3/1985	CR	2		1	473C>T(AC)	HSQ '02	1/10/1992	16/1/1995,31/1/2001, 1/10/2001,1/10/2003
262	1	4/4/1985	CR	2		1	R168X(AC)(WGH)	mult	1/10/1987	19/9/2004
273	1	21/11/1969	R nonC	2		2	(AC) none found	HSQ	1/4/1989	4/9/1989
276	1	9/12/1987	CR	2		2	not found (MB)	mult. '94,'95, '98	22/6/1991	
282	1	3/7/1981	CR	2		1	107in frame	mult.'92'93,'95,'98	24/7/1987	1/1/1989,1/1/1992,
284	1	14/3/1983	CR	2		1	c302C>A;P101H(A	Q'90,	22/6/1991	11/1/1994
287	1	1/4/1978	R nonC	2		2	none(AC)	inv		
289	1	15/9/1976	unknow	1	6/12/1998	2	AC) none found	inv		
291	1	4/7/1990	CR	2		1	c877delG,I293fsx7	mult. '94, '95, '97,	2/2/1995	
299	1	14/12/1978	R nonC	2		1	IVS3-3C>G(mosaic	inv	8/6/1993	7/7/1993, 11/1/2004
302	1	28/9/1979	CR	2		1	c502C>T; R168X	Q'91	25/5/1992	
307	1	15/3/1984	CR	2		1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/1995,
319	1	18/6/1987	CR	2		2	neg(AC)	mult.'94.'97,'98	21/1/1994	
322	1	4/3/1983	CR	2		1	880C>T;R294X(AC)	mult.,'94	21/1/1992	
356	1	3/6/1980	CR	2		1	R255X	Q'90,'88	1/10/1987	1/6/1988,1/4/1989,15/10/2001,1/10/2003
388	1	23/10/1981	R nonC	2		1	c918C.T;R306C	mult.'92,'98	4/2/1992	14/6/1994,1/10/1996
399	1	12/4/1991	not R	2		2	(AC)(d'E) none	mult	3/2/1992	
416	1	30/9/1993	CR	2		1	c502C>T;	HSQ.'99	8/3/1999	
422	1	16/9/1982	CR	2		1	c808C>T;	HSQ'95		
431	1	26/10/1997	R nonC	2		2	not found (AC)	HSQ '01	6/6/2001	
432	1	24/9/1999	R nonC	1	19/1/2001	1	c473G>T; T158M	HSQ,'01		
440	1	5/4/1977	not R	2		2	(AC) none found	Q	18/11/1992	
441	1	26/7/1994	R nonC	2		1	R133C(Wessex)(C	HSQ. '01,'04	23/10/2001	30/1/2002
445	1	17/3/1973	not R	2		2	(AC none found	Q'92	18/11/1992	
455	1	25/10/1994	not R	2		2	none (AC)	HSQ	3/11/2000	
457	1	30/4/1986	R nonC	2		2	none(AC)	HSQ,'99	4/1/1999	
464	1	22/9/1978	CR	2		2	none(AC)(CS)	mult,'94,'95,'97,'98	12/1/1994	
466	1	6/12/1994	CR	2		1	c880C>T;R294X	inv	30/1/2001	
491	1	20/9/1970	R nonC	2		2	neg(AC)	HSQ.'97,'03	29/7/1997	
497	1	16/11/1986	CR	2		1	c763C>T;	Q'92		
498	1	6/7/1964	CR	2		1	473C>T	mult. '97, '00,	1/5/1966	11/6/1991, 31/1/1995,11/6/1001, 1/10/2001,
502	1	6/5/1989	CR	2		1	1152del144bp(AC)	mult.'93,'94,'96,'97,'	4/6/1992	1/11/1997,1/10/2001
517	1	13/6/1990	CR	2		1	c763C>T;R255X	mult. '94,'96,'00	1/10/1996	1/10/2001, 12/10/2002
536	1	29/10/1984	R nonC	2		1	316C>T	Q '93		
538	1	27/11/1984	R nonC	1	10/2/2004	2	none(AC)	HSQ.'96		
551	1	13/12/1990	CR	2		1	c455	HSQ '94	11/1/1994	1/11/1995
559	1	21/2/1990	not R	2		2	noneAC)	inv	12/1/1994	
560	1	21/2/1990	not R	2		2	none(AC)	inv	12/1/1994	
562	1	20/7/1981	not R	2		2	(AC) none found	inv	21/1/1994	
564	1	14/9/1983	R nonC	2		1	c397C>T; R133C	mult. '94,'98	12/1/1994	15/10/2001,
565	1	11/10/1980	R nonC	2		2	none(AC)	mult.'94,'95,'97,'00	11/1/1994	16/6/1997
577	1	26/7/1990	CR	2		1	502C>T(AC)R168X	HSQ.'95	18/1/1995	19/6/1996,
580	1	30/11/1988	R nonC	2		1	c301C>A;	HSQ'98		
597	1	8/1/1991	CR	2		1	c502C>T; R168X	inv	14/6/1994	15/6/1995
619	1	7/5/1992	CR	2		1	1157-1200del44bp	HSQ.'02	3/6/1994	1/10/1996,11/6/2002, 12/10/2002,2/7/2003
630	1	10/12/1990	R nonC			2	none AC)	inv	16/1/1995	
649	1	12/9/1992	inc CR	2		1	c1130C.TA444T	inv	18/1/1995	
650	1	24/12/1992	CR	2		1	R270X(AC)	mult. '95, '97	24/12/1992	2/2/1995, 1/10/1996, 1/11/1997, 7/10/1999,
678	1	14/5/1991	R nonC	2		1	c502C>T;R168X	mult. '95,'96	21/8/1995	18/6/1996,1998

BIS	A...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
1061	1	8/7/1991	unknow			1	c401C>G;S134C			
1062	1	4/11/1996	CR			1	c473C>T;T158M		1/11/2004	
1063	1	30/9/2000	unknow			1	multiple defects			
1064	1	15/8/1999	CR	2		2	none found (AC)	HSQ.'02	18/6/2002	
1065	1	15/10/1990	unknow			1	c1164-1207del44			
1066	1	22/10/1993	unknow			1	c316C.G;R106G(A			
1067	1	8/9/1988	CR	1	16/8/2002	1	c502C>T;R168X	inv		
1069	1	19/3/1995	unknow			1	c1164-1207del44			
1070	1	29/4/1996	Inc CR			1	c916C.T;R306C(AC	inv	1/10/2003	
1071	1	4/12/1996	unknow	2		1	3'UTR-TGA+68-9S			
1086	1	25/3/1989	CR	2		2	none (AC)	HSQ.'02		
1087	1	2/12/1999	CR	2		1	502C>T (AC)	HSQ. '02	11/6/2002	
1088	1	16/5/1987	R nonC	2		2	negative(DR)	HSQ.'02	11/6/2002	
1095	1	29/5/1994	not R	2		2	none (AC)	HSQ'02	12/1/2003	
1107	1	2/5/2000	CR	2		1	c916C>T;R306C	inv	17/12/2003	
1184	1	3/11/1996	R nonC			2	none (AC)	HSQ'04		
1228	1	3/7/1971	R nonC	2		1	R168X (AC)	inv		
679	1	30/11/1991	CR	2		1	IVS2-9A>G-8nt	inv	7/6/1995	
680	1	16/2/1991	R nonC	2		2	none (AC)	mult.'95,'98	6/6/1995	
684	1	11/10/1991	CR	2		1	R106W (MB)	HSQ. '96,	9/1/1996	
691	1	13/11/1991	R nonC	2		2	none(AC)	inv	27/11/1995	
692	1	13/11/1991	R nonC	2		2	none(AC)	inv	27/11/1995	
698	1	26/9/1988	R nonC	2		2	neg (AC)	HSQ'95	19/12/1995	19/12/95
708	1	4/5/1983	CR	2		2	(AC)none	inv	16/12/2003	
722	1	20/12/1993	CR	2		1	del exon 3-4.1 (DR)	mult. '98,'97	17/6/1997	
725	1	4/3/1970	CR	2		1	del exon 4 c	mult.'96,'02	8/1/1996	12/2/2002
730	1	8/1/1997	CR	2		1	c397C>T;R133C	HSQ.'02	18/6/2002	
734	1	25/4/1991	CR	2		1	c808C.T;R270X	inv	18/6/1996	
748	1	22/5/1973	R nonC	2		2	neg(AC)	inv	17/6/1996	9/10/1998
762	1	18/8/1961	R nonC	2		2	neg (MB)	HSQ.'96	19/6/1996	
764	1	7/1/1995	CR	2		1	R270X(AC)	mult.'76,'97,'98,'02,	13/10/1998	13/1/1998,15/10/2001,1/10/2003
765	1	28/4/1989	R nonC	2		1	c397C>T;R133C	HSQ.'96	14/10/1996	
774	1	14/11/1957	Inc CR	2		1	exons 1-2	mult'96,'98,'02	14/1/1998	12/10/2002,1/10/2003
779	1	27/10/1993	R nonC	2		2	none(AC)	mult.'96,'98	15/1/1997	
780	1	17/2/1992	R nonC	2		2	none(AC)	mult. '96, '98	15/1/1997	
782	1	26/1/1974	not R	2		2	none (AC)	mult '02.	1/1/1982	29/9/1996, 28/10/1996
985	1	16/5/1996	R nonC	2		2	none)(AC)	inv		
990	1	21/8/1986	CR	2		1	397C>T.R133C(AC)	HSQ '01,'03	20/7/2001	
991	1	3/11/1987	CR	2		2	not found (?where)	HSQ'01	20/6/2001	
997	1	7/3/1995	CR	2		1	c473C>T;T158M(A	HSQ'01	19/6/2001	
1001	1	1/1/1998	Inc CR	2		1	del exons 3-4(AC)	inv	15/10/2001	
1006	1	24/9/1996	Inc CR	2		2	none(AC)	inv	29/1/2002	29/1/2002
1010	1	26/5/1998	CR	2		1	c880 R294X (AC)	HSQ'01	14/10/2001	14/10/2001, 29/1/2002, 12/10/2002,1/10/2003
1013	1	27/8/1998	CR	2		1	c.502C>T;R168X	HSQ.'02	29/1/2002	
1014	1	24/9/1996	R nonC	2		2	none (AC)	HSQ. '02	29/1/2002	
1015	1	2/6/1994	CR	2		1	c808C>T;R270X	HSQ'01	1/10/2002	12/10/2002
1016	1	20/5/1995	CR	2		1	44 base pair del	HSQ.'02	30/1/2002	6/3/2002
1019	1	23/2/1989	R nonC	2		2	none(AC)	HSQ'02	30/1/2002	
1022	1	4/12/1988	R nonC	2		1	c.502C>T.R168X	HSQ'02	29/1/2002	1/10/2003
1024	1	20/8/1997	unknow			1	del exon 3(DR) and			
1025	1	26/2/1998	unknow			2	c1215C>T;P405P(			
1026	1	9/9/1987	unknow			1	c473C>t;T158M(AC			
1027	1	26/7/1978	unknow			1	c763C>T;R255X			
1028	1	2/8/1994	CR			1	c397C>T;R133C	HSQ'04		
1029	1	19/3/1999	unknow			1	c763C>T;R255X(A	inv		
1030	1	2/2/1998	unknow			1	c808C>T;R270X(A			
1031	1	2/2/1998	unknow			1	c.808C>T;R270X(A	inv	12/10/2002	1/10/2003
1033	1	21/12/1996	unknow			1	poly IVS3+22C>G			
1034	1	19/3/1995	unknow			1	c1372C>T;R485C(			
1035	1	26/4/1997	unknow			1	c1097-1203			
1036	1	13/8/1990	unknow			1	c473C>T;T158M(A			
1037	1	24/6/1999	CR			1	no mutation?, poly	Q		
1038	1	4/5/1998	unknow			1	c1126C>T;P376S(			
1039	1	21/9/1993	unknow			1	c897C>T;T299T(AC			
1040	1	30/11/1989	unknow			1	c311-323del13bp	HSQ		
1041	1	23/8/1998	unknow			1	1168-1173del			
1042	1	12/12/1998	CR	2		1	c91delG (AC)	HSQ'02	12/10/2002	1/10/2003
1043	1	6/9/1988	unknow			1	c964C>G;P322(AC)			
1044	1	21/11/1995	unknow							
1045	1	21/12/1997	unknow			1	c311G>A;W104X(A			
1046	1	14/2/1999	R nonC			1	c473C>T;T158M(A	HSQ'03	11/6/2002	
1047	1	19/11/1997	unknow			1	c763C>T;R255X(A			
1048	1	28/6/1964	Inc CR			1	del (exon 4.3DR)	inv		
1049	1	12/4/1994	unknow			1	c1152del44de			
1050	1	6/6/1998	unknow			1	3'UTR-TGA+98-9S			
1051	1	27/4/1998	unknow			1	c763C>T;R255X&c		1/10/2003	
1052	1	3/8/1971	unknow			1	c1164-1208del457			
1054	1	15/5/1996	CR			1	c880;C>TR294X(A	HSQ'03		
1055	1	16/10/1997	R nonC			1	c455C.G;P152R			
1056	1	24/11/1997	unknow			1	C1081C>G;P361A			
1057	1	6/9/2001	CR			1	R255X (AC)	HSQ'03	18/9/2003	1/10/2003
1058	1	15/4/1993	unknow			1	c502C>T;R168X			
1059	1	19/7/1989	R nonC			1	c397C>T;R133C			
1060	1	14/10/1996	unknow			1	c917G>T;R306L(A			

Dataset: 7.2: Mutation analysis in British & Italian population

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R nonC=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

The column 'd'E' gives the cases study numbers in this project

BIS	d'E	d of birth	d of death	status	mut	test	Kerr Q	AK saw	AK dates
20	1	22/6/1977		CR	1	917G>A(AC)R306H(AC)	mult.'91,'94,'96,'98,'00	24/5/1966	21/6/2000,24/10/2001,15/10
21	1.M16	14/6/1978		CR	1	R106W(AC)106(d'E)	mult '93,'95,'98	14/6/1978	30/3/1992
22	1.N35	12/7/1980		CR	1	c401C>G,S134C(AC)(d'E134)E3	mult.'80'94,'95,	22/1/1992	
26	1.N14	13/2/1976		CR	1	R168X(AC)(d'E168)	HSQ '96	16/10/1989	12/10/2002
68	1.S18	10/3/1962		CR	1	1157del141bp (d'E	mult.'94,'95,'96	29/10/1986	
76	1.N17	19/1/1983	29/12/1994	CR	1	168d'E)	mult '93,'95	1/5/1987	
104	1. N19	26/2/1981		CR	1	R133C(d'E)(MB)	mult.'93,'94,'95,'98,'00	11/1/1994	
109	1.N4	9/10/1983		R nonC	1	A133C(d'E,MH)	HSQ '00	1/10/1990	11/6/1991,1/6/1994
113	1.L20	5/5/1977		CR	1	c763c>t;R255X(d'E)	HSQ, '94	20/6/1991	11/1/1994
131	1. S22	16/7/1983		CR	1	1157del144bp (CS)	mult.'90,'93'95'98'99'00	1/10/1989	11/1/1994,21/6/2000,4/4/20
141	1.N6	9/3/1987		CR	1	R168X(AC)(168d'E)	Q '92	25/5/1992	
152	1.5	19/10/1970		CR	2	d'E not found,neg(AC)	mult. '93,'95,'98	1/6/1989	12/6/1991
155	1.7	8/9/1969		CR	2	(AC)(d'E)not found	mult.'94,'96,'98,'99	1/10/1992	
161	1.N8	10/9/1982		CR	1	none(MB)168(d'E)(TW)none(AC)	mult.'92,'95,'98		
209	1.Y26N	26/1/1989		CR	1	T158M (AC)(158d'E)473C>T	mult.'91 ,'03	11/6/1991	17/1/1995
212	1.M23	13/7/1983		CR	1	101d'E)	HSQ'95	1/10/1990	21/1/1993,1/10/1994,
234	1.Y33L	24/6/1980		CR	1	c763C>T;R255X(AC)(d'E)(TW)	mult '91,'94,'98	1/10/1986	28/8/1988, 1/6/1989,
241	1.N24	8/5/1973		CR	1	1133d'E)	mult'94,'04	15/6/1994	
249	1.Y34	31/10/1983		CR	2	none(d'E. MB.AC)	mult. '93, '94, '95, '01,	20/1/1993	1/10/1994, 19/6/1995
263	1.N10	14/10/1971		CR	1	158(d'E)	HSQ'01	24/5/1986	1/1/1987,2/9/1988,19/6/200
268	1.P9	8/7/1978		CR	1	(306d'E)	HSQ,'93	1/11/1995	
282	1.S11	3/7/1981		CR	1	107in frame	mult.'92'93,'95,'98	24/7/1987	1/1/1989,1/1/1992,
307	1.L25	15/3/1984		CR	1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/19
322	1.P26	4/3/1983		CR	1	880C>T;R294X(AC)(d'E)	mult.,'94	21/1/1992	
409	1.Y20N	4/9/1989		CR	1	158(d'E)	Q	1/10/1992	1/10/1996
417	1.Y14N	26/11/1986		CR	1	(158d'E)	HSQ '93	1/10/1992	
502	1.Y32N	6/5/1989		CR	1	1152del144bp(AC)158(d'E)1152	mult.'93,'94,'96,'97,'98,'	4/6/1992	1/11/1997,1/10/2001
665	1. L21	20/6/1971		CR	1	208(d'E)(MH)	mult.'95'96	19/1/1993	
669	1.Y35			unknow	2	(d'E) none found			
843	1.37	30/5/1978		R nonC	2	(d'E)none,mutSTK	mult '98,'01	14/1/1998	
844	1.38	10/10/1990		CR	2	(d'E, AC)none	mult'98,'01	14/1/1998	20/6/2001

Dataset: 7.4: Dimensional phenotypic analysis...

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R non C=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B
The column R gives code numbers for the study.
The column S Score gives severity score (max 100%, see fig 2.2.1)

BIS	R...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
1	33	1/10/1979	R nonC	2		2	none (AC)	HSQ.'94	3/6/1991	21/1/1994
8	31	27/3/1987	CR	2				mult '90, '94, '95	6/10/1990	23/1/1991,21/1/1992,
10	252	15/5/1979	Inc CR	2				Q.'90		
14	253	16/5/1989	R nonC	2				inv		
15	32	14/5/1978	CR	2				mult. '91, '95	9/1/1996	
16	27	27/2/1983	CR	2		2	none(MB)	HSQ. '96	24/6/1986	23/1/1991
18	26	28/11/1979	CR	2				mult. '92, '94,	4/6/1992	18/1/1995
20	46	22/6/1977	CR	2		1	917G>A(AC)R306H	mult.'91,'94,'96,'98,	24/5/1986	21/6/2000,24/10/2001,15/10/2001, 12/10/2002,
21	50	14/6/1978	CR	2		1	R106W(AC)106(dE	mult '93,'95,'98	14/6/1978	30/3/1992
27	42	23/11/1974	CR	1	24/3/2001			mult.'95,'98	16/10/1989	
28	38	22/7/1980	CR	2		1	c808 C>T;R270X	mult. '96, '98,	18/1/1993	1/10/1999, 12/10/2002
29	1	21/5/1970	CR	2		1	P152R (MB)	HSQ. '96	14/7/1987	28/1/1988,16/5/1992, 1/6/1996, 19.9.2004
32	254	2/10/1985	R nonC	2				Q '91		
35	255	27/8/1952	R nonC	2		2	none (AC)	mult '93,'98		
37	36	13/6/1986	CR	1	5/1/2005	1	P302L(AC)	mult.'93. '94'03	28/10/1989	23/1/1991, 8/6/1994,
39	51	18/12/1981	CR	2		1	c473C>T; T158M	HSQ.'96	5/2/1992	17/1/1995, 10/1/1996, 15/1/1997
42	47	16/8/1976	CR	2		1	K352fsX366	mult. '97,'98,'02	1/10/1992	16/6/1997,
46	44	2/2/1982	CR	2		1	c316C>T;R106W	HSQ.'99	1/10/1990	
47	37	22/5/1984	CR	2				mult '96,'00	1/1/1987	1/10/1991,1/10/1994,1/11/1995,1/2/2000,12/10/20
53	52	6/6/1971	unknow	2				inv		
59	65	4/7/1982	CR	2		2	AC none	HSQ. '00	21/6/2000	
60	60	28/10/1960	CR	2				inv	13/6/1994	
70	68	4/2/1963	CR	2			(MB) awaited	mult'95,'96,'98,'00	1/1/1990	22/1/1991,
71	67	21/6/1983	CR	2		2	AC not found	Q.'90		
75	256	28/2/1985	CR	2				HSQ.'97	1/10/1989	1/10/1989
77	74	18/7/1982	CR	2				Q.'90		
78	59	14/6/1979	CR	2				inv	20/6/1991	
79	66	13/2/1987	CR	1	9/4/2001	1	T158M	mult. '93,'94,'96,'99	6/10/1990	1/10/1994,
80	63	16/9/1980	CR	2				mult '95, '96,'97, '00	11/6/1991	17/6/1995,
82	58	13/7/1973	R nonC	2			MH?	mult'94,'98,'00	1/5/1986	22/1/1991,1/10/1991,15/10/1993,23/1/1992,31/1/1
83	257	27/7/1977	R nonC	2				inv	23/7/1991	20/8/1999
84	76	19/12/1987	CR	2				Q.'90	22/1/1991	1/10/1991,1/10/1996,
86	258	1/11/1978	Inc CR	2				Q '91		
88	5	14/10/1985	CR	2		2	not found (MB)(AC)	HSQ. '95	1/4/1989	25/6/1993
89	427	11/9/1980	CR	2		2	none (MB) checking	mult.'85, '93, '03	7/7/1983	6/6/1986,22/7/1987,20/12/1988,21/7/1993,1/11/19
95	383	23/4/1985	CR	2				mult '95,'97	19/1/1993	
97	345	22/1/1987	Inc CR	2		1	c502C>T; R168X	inv	3/6/1989	
99	112	7/7/1982	CR	2		2	none(Wallis,	mult.'95,'98	14/1/1997	
103	8	20/4/1973	CR	2		1	missense T158M	HSQ. '95,	17/1/1995	14/1/1998
104	83	26/2/1981	CR	2		1	R133C(dE)(MB)	mult.'93,'94,'95,'98,	11/1/1994	
105	80	21/11/1982	CR	2		1	R168X (AC)(MB)	HSQ.'98	1/5/1986	
107	79	5/6/1977	CR	2		1	L386fsX389(MB)	mult.'94,'95	1/5/1986	1/4/1989
116	87	24/11/1967	CR	2				Q.'91	20/7/1994	13/11/1991, 14/6/1994
121	346	8/12/1984	CR	2		1	c502C>T;	HSQ. '99	1/4/1989	10/6/1992,17/6/1995,16/6/1999,
122	90	8/10/1975	CR	2				mult.'90,'96,'98,'03	19/1/1993	
123	10	10/11/1986	CR	2		1	T158M (MB)	Q. '97	7/7/1993	27/6/97, 3/10/1997, 1/11/1997,
126	259	5/5/1979	R nonC	2				mult.'94,'98	23/1/1991	5/2/1992
131	96	16/7/1983	CR	2		1	1157del144bp (CS)	mult.'90,'93'95'98'9	1/10/1989	11/1/1994,21/6/2000,4/4/2001
136	100	9/2/1972	CR	2		1	c763 C>T; R255X	mult.'95'98'00'02	1/11/1987	11/2/2000,29/1/2002,
137	260	2/4/1974	CR	2				Q.'83	10/11/1983	10/11/1983, 21/6/1990
145	348	22/2/1967	Inc CR	2		1	c473c>t; T158M	Q.'91	1/10/1990	
146	349	2/8/1984	R nonC	2		1	1157-1197del.41bp	mult'95,'96,'03	26/5/1993	
148	104	25/4/1981	R nonC	2		1	c397C>TR133C(AC	Q.'92	30/6/1988	1/1/1989,5/6/1992,13/6/1995,30/11/1997,12/10/20
149	105	10/4/1985	R nonC	2		1	c397C>TR133C(AC	Q.'91	6/6/1991	30/11/1997, 12/10/2002,1/10/2003
150	110	6/11/1978	CR	1	20/9/2000	1	c316C>T; R106W	mult. '91,'99	22/6/1987	1/10/1989
152	108	19/10/1970	CR	2		2	dE not	mult. '93,'95,'98	1/5/1989	12/6/1991
153	261	15/1/1983	CR	2				Q '90,	22/1/1991	18/10/1991
154	125	29/8/1974	CR	2		1	P152R (Glasgow)	mult.'94,'96,'98	29/6/1983	17/12/1995,13/3/1996, 5/10/2001
155	116	8/9/1969	CR	2		2	(AC)(dE)not found	mult.'94,'96,'98,'99	1/10/1992	
156	134	18/2/1970	CR	2		2	none(AV)	mult.'93,'95,'96,'98,	1/1/1989	11/6/1991
157	205	6/12/1985	CR	2		1	G252fsX287(MB)	Q.inv	18/1/1995	

BIS	R...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
331	221	6/2/1971	unknow	2				inv		
337	225	17/9/1979	CR	2				mult.'91,'98	12/6/1991	
340	232	12/7/1987	CR	2				Q.'91	23/1/1991	3/2/1992
345	245	14/10/1979	CR	2				mult '95,'96,'98	11/1/1992	21/1/1992
347	271	30/1/1982	R nanC	2		2	not found (Wessex	mult.	1/10/1992	18/1/1995,16/6/1996
349	272	18/11/1960	CR	2				mult.'91,'95	23/1/1991	
354	273	17/7/1986	CR	2				Q.'91		
356	243	3/9/1980	CR	2		1	R255X	Q'90,'88	1/10/1987	1/8/1988,1/4/1989,15/10/2001,1/10/2003
358	24	29/8/1985	CR	2		1	473C>T,T158M (	mult. '94, '95, '97,	1/4/1989	1/10/1990
366	247	23/10/1981	R nanC	2		1	c916C.T;R306C	mult.'92,'96	4/2/1992	14/6/1994,1/10/1996
368	240	6/6/1982	CR	2				Q.'92,	1/10/1991	1/2/1992,1/10/1996,7/10/1999,24/10/2001,
375	241	8/9/1971	CR	2				HSQ'03		
376	242	3/1/1973	R nanC	2				mult.'98,'00	3/6/1992	
380	352	6/2/1985	CR	2		1	P302L	mult. '94,'95,'96,'98	7/8/1991	26/7/1996,5/10/2001
381	274	10/11/1987	CR	1	1/4/2003			mult.'91,	4/9/1991	16/5/1992,1/1/1997,13/11/1998,4/9/2000
383	229	5/12/1974	unknow	2				inv		
386	275	30/9/1986	CR	2				HSQ '94		
387	276	27/12/1988	R nanC	2				mult. '91,'96		
392	277	28/11/1985	R nanC	2				mult '91,'94	25/5/1992	
396	4	18/10/1984	CR	2		1	T158M missense	mult '94 '95 '97,	15/6/1994	
398	45	21/3/1971	CR	1?		1	del exon 3-4 MH	mult.'93,'96	19/10/1991	1/11/1995, 21/1/1992
400	155	13/12/1987	Inc CR	1	12/11/2002			inv	1/10/1991	1/10/1992,1/10/1994,
405	354	24/11/1987	CR	2		1	R306C (Wessex)	mult '95,'02	22/1/1992	
406	355	7/5/1988	R nanC	2		2	none (AC)	HSQ. '01	22/1/1992	
409	356	4/9/1989	CR	2		1	158(d'E)	Q	1/10/1992	1/10/1996
416	124	30/8/1993	CR	2		1	c502C>T;	HSQ.'99	8/3/1999	
417	357	26/11/1986	CR	2		1	(158d'E)	HSQ '93	1/10/1992	
419	30	12/3/1988	CR	2				mult.'97, '98,	1/10/1992	11/1/1994
429	169	11/7/1987	CR	2				HSQ.'00	1/10/1992	8/2/1993,1/10/1994,1/10/1996,8/2/2000,24/10/200
431	356	28/10/1997	R nanC	2		2	not found (AC)	HSQ '01	6/6/2001	
433	70	6/9/1988	CR	2				mult'94,'96,'98	1/10/1992	8/2/1993,18/6/1996,
437	278	14/4/1963	CR	2				mult.'95,'98		
441	359	26/7/1994	R nanC	2		1	R133C(Wessex)(C	HSQ. '01,'04	23/10/2001	30/1/2002
447	220	12/7/1990	CR	2				mult. '94, '97	25/5/1992	11/1/1994,17/6/1997
449	71	22/11/1989	CR	2		1	R306C(MB)	HSQ.'94	8/6/1994	13/1/1998
451	251	18/11/1989	CR	2		1	R270X (MB)	HSQ'03,Q '02	1/10/1992	30/1/1995
452	57	23/11/1971	unknow	2				inv		
454	384	19/7/1986	CR	2				HSQ '93	8/7/1993	
457	279	30/4/1986	R nanC	2		2	none(AC)	HSQ,'99	4/1/1999	
462	17	29/12/1985	CR	2		1	R306C(MB)	mult. '94, '97.	25/5/1992	17/6/1997
464	97	22/9/1978	CR	2		2	none(AC)(CS)	mult.'94,'95,'97,'98	12/1/1994	
467	123	9/6/1964	CR	2			awaited	HSQ.'93	17/1/1995	1/11/1999
468	143	2/6/1992	CR	2				HSQ.'95,1/10/2003	11/11/1995	
469	360	7/8/1985	CR	2		1	P302R	mult'95,'00	1/10/1994	30/1/2001
473	145	16/10/1963	CR	2				HSQ.'95	9/1/1996	
483	91	10/5/1976	CR	1	5/1/2004	1	R270X(MB)	HSQ.'98,'02	22/1/1991	25/1/1993
487	249	8/9/1974	R nanC	2		1	44bpdel.1163-(Wes	Q.'86.Inv	6/6/1986	10/10/1990, 1/5/1992,
491	260	20/9/1970	R nanC	2		2	neg(AC)	HSQ.'97,'03	29/7/1997	
492	281	7/4/1983	unknow	2				inv		
498	84	6/7/1964	CR	2		1	473C>T	mult. '97, '00,	1/5/1986	11/6/1991, 31/1/1996,11/6/1001, 1/10/2001,
502	165	6/5/1989	CR	2		1	1152del144bp(AC)	mult.'93,'94,'96,'97,	4/6/1992	1/11/1997,1/10/2001
512	282	30/5/1989	R nanC	2				mult. '96,'96	9/5/1995	
514	283	4/7/1962	R nanC	2				inv	1/1/1993	
517	126	13/6/1990	CR	2		1	c763C>T;R255X	mult. '94,'96,'00	1/10/1996	1/10/2001, 12/10/2002
522	103	28/8/1962	CR	2				HSQ.'97	19/1/1993	
523	248	9/2/1960	CR	1	26/10/2003	2	neg (AC)	mult.'95,'98,'00	19/1/1993	
525	3	10/8/1990	CR	2		1	T158M (MB)	HSQ. '96	21/1/1993	1/10/1996
526	5	31/12/1988	CR	2		1	R306C(MB)&T197M	HSQ. '94	20/1/1993	
529	248	6/6/1986	CR	2				HSQ . '95	1/10/1992	23/6/1995
530	284	13/1/1988	R nanC	2				HSQ.'94	1/10/1992	
532	196	17/12/1961	CR	2		1	R133C(MB)	mult'93,'95,'96	19/1/1994	
533	285	2/6/1952	CR	2				HSQ. '96	26/1/1993	
534	77	9/7/1981	R nanC	2		2	15Q duplication not	mult.'93,'95,'98	21/1/1993	14/1/1997
536	286	29/10/1984	R nanC	2		1	316C>T	Q '93		
538	287	27/11/1984	R nanC	1	10/2/2004	2	none(AC)	HSQ.'98		
540	176	1/3/1989	CR	2				mult.'93,'95,'98	25/10/1993	1/10/1996,17/6/1998
542	288	8/12/1955	Inc CR	2				inv	19/10/1989	
543	109	16/2/1991	CR	2		1	Q262X(MH)	mult	11/1/1994	1/10/1996,4/9/2000,15/10/2001,12/10/2002
544	289	16/5/1990	CR	2				mult.'93,'96,'99,'01	2/11/1993	19/5/2001
546	119	13/11/1991	CR	2		1	del exon 4	mult. '93,'94,'03	28/10/1993	28/10/1993, 1/6/1995, 1/11/1995,13/10/1996,
550	161	29/9/1990	CR	2		1	del exon3-4	mult. '93,'94,'96	15/10/1993	4/2/1995,4/2/1999
551	361	13/12/1990	CR	2		1	c455	HSQ '94	11/1/1994	1/11/1995
553	131	8/5/1991	CR	2		1	R168X (MB)	mult.'93,'00	24/1/1994	4/4/2001, 12/10/2002
555	202	8/2/1970	CR	2		1	T158M (MB)	mult.'93,'95,'98	15/10/1993	
556	117	15/1/1991	CR	2				HSQ.'98	15/1/1991	15/10/1993
557	55	25/7/1992	Inc CR	2				mult'93,'94,'96,'97,'	15/10/1993	
558	93	12/1/1990	CR	2				mult.'93,'96		
561	290	11/5/1961	R nanC	2				HSQ.'96	2/2/1994	
562	291	20/7/1981	not R	2		2	(AC) none found	Inv	21/1/1994	
563	9	24/6/1962	CR	2		1	R294X(MB)	mult. '94, '95, '98,	11/1/1994	
564	86	14/9/1983	R nanC	2		1	c397C>T; R133C	mult. '94,'98	12/1/1994	15/10/2001,
565	292	11/10/1960	R nanC	2		2	none(AC)	mult.'94,'95,'97,'00	11/1/1994	18/6/1997
566	89	19/5/1989	CR	2				HSQ.'94	11/1/1993	
568	216	16/8/1967	CR	2		1	R168X(MB)	HSQ.'98	15/6/1994	25/3/1999
570	362	29/10/1990	not R	2		2	none (Addenbr)	HSQ.'94	10/1/1994	
573	160	7/1/1992	CR	2		2	neg(AC)	mult '94,'96	14/3/1994	1/1/2001
575	293	16/7/1991	R nanC	2			del exon 3-4.1(AC)	inv	17/6/1995	10/10/1999,1/10/2003
577	115	26/7/1990	CR	2		1	502C>T(AC)R168X	HSQ.'95	18/1/1995	19/6/1996,
582	217	19/2/1991	unknow							
583	174	19/3/1991	CR	2		1	1157del44(MH)	mult '98 '02	1/11/1997	1/6/1998,22/10/2001
591	294	1/9/1948	R nanC	2				inv	31/3/1993	
592	295	2/9/1965	R nanC	2				Inv	1/4/1994	

BIS	R...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
631	244	21/6/1990	CR	2		2	none(MB)	HSQ,'94	5/6/1995	18/6/1996,1/11/1997
632	163	18/10/1991	CR	2				mult,'94,'98	16/1/1995	
634	82	24/8/1970	CR	1	2/1/2000			mult.'95,'96,'97,'989	1/10/1994	
635	62	27/11/1991	CR	2		1	792-804del13, I	mult. '95, '96,	2/12/1994	
636	301	26/1/1989	R nanC	2				inv	1/10/1994	
640	102	31/10/1967	R nanC	2				inv	1/10/1994	17/1/1995
642	129	2/12/1992	CR	2				mult.'95,'98	24/1/1995	14/1/1998,
644	40	31/10/1990	R nanC	2				inv	16/1/1995	
648	231	22/5/1984	CR	2		1	R306C (MB)	HSQ '95,'02	17/1/1995	17/6/1998
650	35	24/12/1992	CR	2		1	R270X(AC)	mult. '95, '97	24/12/1992	2/2/1995, 1/10/1996, 1/11/1997, 7/10/1999,
653	43	1/3/1993	CR	2		1	R270X (MB)	mult	18/1/1995	19/6/01, 15/10/01,23/10/01, 12/10/02,1/10/04
654	302	11/4/1990	R nanC	2		1	yes, no details	mult.'95,'96,'98	6/6/1995	
657	303	13/8/1989	R nanC	2				inv	17/1/1995	9/1/1996
658	106	21/8/1992	R nanC	2		2	none '02 (Dennis)	HSQ,'95	12/1/2003	
660	304	23/9/1981	R nanC	2		1	R133C (Ed)	HSQ,'96	2/5/1995	5/10/2001
661	305	4/6/1991	R nanC	2				HSQ,'95	15/6/1995	
665	96	20/6/1971	CR	2		1	208(d'E)(MH)	mult.'95'98	19/1/1993	
675	92	12/8/1987	CR	2		1	P378fsX400(MB)	mult,'95'98	17/6/1995	19/6/2001
676	306	21/6/1967	CR	2		1	R306C	inv	5/6/1995	
677	18	10/7/1993	CR	2		2	R270X(MB)	HSQ. '95	6/6/1995	10/1/1996
678	365	14/5/1991	R nanC	2		1	c502C>T;R168X	mult. '95,'96	21/6/1995	18/6/1996,1998
680	307	16/2/1991	R nanC	2		2	none (AC)	mult.'95,'98	6/6/1995	
681	308	12/2/1993	R nanC	2				mult	7/6/1995	23/6/1995, 15/1/1997, 10/2/2000
682	212	6/9/1990	CR	2				HSQ. '97,	17/6/1997	
684	26	11/10/1991	CR	2		1	R106W (MB)	HSQ. '96,	9/1/1996	
685	111	21/3/1982	CR	2				HSQ,'98	17/6/1998	
687	162	7/2/1987	R nanC	2				HSQ,'95	1/11/1995	9/1/1996
690	12	13/11/1993	CR	2		1	R168X(MH)trunc	mult. '95, '97, '98	25/10/1995	9/10/1998, 1/10/2001, 12/10/2002
691	309	13/11/1991	R nanC	2		2	none(AC)	inv	27/11/1995	
692	310	13/11/1991	R nanC	2		2	none(AC)	inv	27/11/1995	
694	189	19/11/1993	CR	2		1	R255X (MH)	mult. '96,'98,	11/11/1995	5/2/1996,23/10/2001,12/10/2002
696	130	29/12/1981	CR	2		1	c397c>t; R133C	mult'95,'97	9/1/1998	13/1/1998, 14/10/2001,28/1/2002
697	235	29/5/1988	R nanC	2		1?	no mut(Salis) yes	inv	8/1/1998	
698	188	26/9/1988	R nanC	2		2	neg (AC)	HSQ '96	19/12/1995	19/12/95
702	183	4/7/1992	CR	2		1	exon4.3	inv	11/11/1995	12/10/2002
703	53	26/7/1967	R nanC	2		2	no mut (Salis)	mult'95,'98,'02	11/11/1995	30/1/2002,
706	234	12/12/1951	CR	2				mult.'96,'98	11/11/1995	9/1/1996,10/10/1998,12/10/2002
709	208	9/11/1984	Inc CR	2				mult '95,'98	1/11/1995	
711	81	2/8/1993	CR	2		1	R255X(MB)	HSQ '03	10/1/1996	
712	146	10/5/1984	R nanC	2		2	not found (Wessex)	mult'95,'96,'98	10/1/1996	6/6/1997,16/6/1998,9/2/2000,1/10/2003
713	236	10/1/1968	R nanC	2		1	R306C(MB)	mult'95,'98,'99	18/6/1996	1/10/2001
714	215	17/10/1993	CR	2				mult. '96,'98	9/1/1996	14/1/1998,1/10/1999,12/10/2002,1/10/2003
718	147	21/9/1981	R nanC	2				HSQ. '95	9/1/1996	
719	34	4/5/1973	CR	1	1/9/2003			HSQ.'95,	9/1/1996	
722	141	20/12/1993	CR	2		1	del exon 3-4.1 (DR)	mult. '96,'97	17/6/1997	
724	209	25/1/1977	R nanC	2		2	none(MB)	mult.\96,'98,'02,'03	8/1/1996	
725	185	4/3/1970	CR	2		1	del exon 4 c	mult.'96,'02	8/1/1996	12/2/2002
726	366	30/11/1991	CR	2		1	T158M	HSQ.'96	1/6/1996	27/3/97
727	29	19/8/1993	CR	2				HSQ. '96,	1/10/1994	1/10/1994,18/6/1996, 13/10/1996, 1/10/2001
733	385	15/9/1986	R nanC	2		1	yes (AC)	mult '96,'98	20/3/1996	
734	367	25/4/1991	CR	2		1	c808C.T;R270X	inv	18/6/1996	
735	226	1/2/1969	CR	2				mult.'96,'98	17/6/1996	
736	311	23/9/1981	R nanC	2				HSQ.'96	24/6/1996	31/5/1996
740	218	24/4/1984	CR	2		2	none(MB)	mult '96,'01	18/6/1996	29/6/2001
742	75	6/5/1984	CR	2				mult'96,'98	18/6/1996	
748	312	22/5/1973	R nanC	2		2	neg(AC)	inv	17/6/1996	9/10/1998
749	313	1/7/1969	R nanC	2		2	neg(AC)	inv	17/6/1996	
750	314	1/12/1978	Inc CR	2				inv	17/6/1996	
751	315	6/2/1965	CR	2				HSQ.'96	18/6/1996	
755	316	20/12/1986	CR	2				inv	18/6/1996	
756	224	12/3/1994	CR	2		1	753insC (MH)	mult.'96, '98	18/6/1996	1/10/1999,1/10/2003
757	69	14/1/1992	CR	2				inv	18/6/1996	
759	133	4/9/1994	CR	2		1	G252fsX287(MB)	mult. '96,'97	17/6/1997	
762	237	18/6/1961	R nanC	2		2	neg (MB)	HSQ.'96	19/6/1996	
763	107	5/10/1994	CR	2		1	R168X (MH)	mult.'97, '98,	17/6/1996	13/10/1996,1/9/1998,1/10/2001,
764	152	7/1/1995	CR	2		1	R270X(AC)	mult.'76,'97,'98,'02,	13/10/1996	13/1/1998,15/10/2001,1/10/2003
765	317	28/4/1989	R nanC	2		1	c397C>T;R133C	HSQ.'96	14/10/1996	
766	186	17/12/1989	CR	2				HSQ.'96	15/1/1997	
773	140	18/9/1990	CR	2		1	pos(MB)	HSQ '02	1/10/1996	
779	176	27/10/1993	R nanC	2		2	none(AC)	mult.'96,'98	15/1/1997	
780	177	17/2/1992	R nanC	2		2	none(AC)	mult. '96, '98	15/1/1997	
781	138	18/8/1988	Inc CR	2		1	R294X(TW)	HSQ. '96		
792	368	23/9/1992	not R	1	4/7/2003	2	none (AC)	mult.'97,'98,'03	13/1/1998	
794	318	5/3/1970	R nanC	2				HSQ'96	14/1/1997	
795	154	2/10/1983	CR	2				mult. '96, '98,'03	14/1/1997	23/10/2001
797	78	28/4/1991	CR	2		1	1164-1207del44(A	mult. '96, '97, '98,	15/1/1997	26/9/1997,21/6/2000,
800	213	21/4/1994	R nanC	2		2	none(AC)	mult.'97,'98,'00.'03	15/1/1997	10/2/2000
801	369	23/6/1995	R nanC	2		2		inv	15/1/1997	
804	159	2/1/1988	CR	2						
806	7	17/6/1994	CR	2		1	R306C (Edin)(MB)	HSQ. '97	17/6/1994	14/3/1997, 1/11/2000
807	164	9/7/1994	R nanC	2		2	none MECP2,	mult.'98,'02,	13/1/1998	14/1/1999
808	319	22/4/1987	R nanC	2				HSQ.'97	20/6/2000	
809	39	22/11/1994	Inc CR	2				HSQ.'97	1/11/1997	
811	199	15/10/1992	CR	2		1	1157del44bp	HSQ.'97,'04	17/6/1997	
817	370	14/12/1989	R nanC	2		2	none (AC)	HSQ'97	17/6/1997	
819	132	26/5/1991	R nanC	2			? awaited	HSQ.'97	18/6/1997	
820	233	17/5/1994	R nanC	2		1	c753delC(AC)	HSQ '97	17/6/1997	1/10/2001, 12/1/2003
821	320	12/5/1994	not R	2				HSQ '97	17/6/1997	
822	222	27/8/1979	not R	2		2	none (AC)	mult.'97,'98,'02	18/6/1997	
823	190	28/4/1995	CR	2		1	R255X(MH)	mult '95,'97	17/6/1997	
826	95	21/8/1991	R nanC	2		1	Cto G base 401	mult'97,'98,'01	18/6/1997	30/1/2002
828	197	15/5/1989	CR	2		2	none(AC)	'02	1/11/2000	

BIS	R...	d of birth	status	died	d of death	mut	test	Kerr Q	AK saw	AK dates
863	198	22/4/1991	CR	2		1	1157-1197del 41	mut'98,'03	19/1/1999	23/6/1998, 1/10/98
864	373	24/7/1990	R nanC	2		2	none(AC)none (DR)	HSQ '96	26/6/1998	
865	73	30/12/1992	CR	2		1	1157del44	HSQ.'99	1/11/1999	
866	374	26/3/1995	R nanC	2		1	c502 C>T; R168X	inv	30/1/2000	
867	325	11/5/1986	CR	2		2	none(AC)	HSQ. '96		
868	375	31/1/1992	R nanC	2		1	7bp del (WGH)	inv	26/6/1998	
869	376	7/3/1995	CR	2		1	R168X(AC)	HSQ'99	1/3/1999	
870	41	12/6/1995	CR	2		1	c455c>G;P152R(M	HSQ '99	30/11/1998	1/10/1999,15/10/2001,, 12/10/2002
871	377	13/10/1995	not R				none (AC) but del	HSQ '03		
876	378	26/2/1997	CR	2		2	not found(AC) still	inv	20/6/2000	20/6/2000
880	379	16/12/1995	CR	2		1	c302C>T; P101L	HSQ'99,'03	1/11/1999	
885	380	25/9/1990	CR	2		1	c502C>T;R168X	HSQ '01,'03	20/6/2001	
886	326	30/9/1988	R nanC	2		2	no mutation(MB)	mult.'99,'00	20/6/2000	
895	381	13/1/1988	R nanC	2		2	none (AC)	inv	16/6/1999	
908	327	27/4/1997	CR	2		1	c502c>t;R168X	HSQ.'00	19/1/2000	1/2/2000
911	61	31/10/1995	CR	2				mult '99.'00	19/1/2000	1/2/2000,31/1/2001,15/10/2001, 12/10/2002
912	328	1/1/1998	CR	2		1	pos (AC)	inv	14/10/2001	12/10/2002
915	382	16/11/1998	R nanC	2		2	negative(AC)?MH	HSQ'00	30/1/2001	
916	329	16/2/1992	R nanC	2		2	none (AC)	HSQ.'00	20/6/2000	
918	386	17/4/1991	R nanC	2		1	c808C>T;R270X	HSQ '02	18/6/2002	
919	330	25/7/1997	CR	2				HSQ.'00	19/1/2000	1/1/00,
920	387	20/1/1998	CR	2		1	c473c>t;T158M	HSQ'00	19/1/2000	1/2/2000
922	388	9/3/1994	CR	2		2	none, testing for	inv	14/11/2000	
925	158	2/9/1995	CR	2		1	1157del44(MH)	HSQ. '01	9/10/1998	15/10/2001,22/10/2001
926	331	3/7/1997	CR	2		1	Q244X(MH)	mult.'00,'02	19/1/2000	1/2/2000
929	332	15/11/1993	CR	2			polymorphism ?	HSQ.'00	20/6/2000	
931	389	20/3/1998	inc CR	2		1	T158M (AC)	HSQ'01	19/6/2001	
938	390	24/11/1997	CR	2		1	c808C>T;R270X(A	inv	1/9/2000	1/9/2000
939	333	3/7/1994	CR	2		1	c397C>T1207del44	HSQ '00	1/6/2001	
944	391	17/6/1997	R nanC	2		2	none(AC) but del	HSQ '01	29/1/2001	
945	191	4/6/1989	CR	2		1	A466TaX464(Mitcalf	HSQ.'00	20/6/2000	
953	334	30/3/1992	R nanC	2		1	mosaic	HSQ.'01	31/1/2001	12/10/2002
955	335	24/6/1997	R nanC	2		2	none (AC)	HSQ.'00,'03	30/1/2001	
956	336		unknow			2	no mut			
957	392	28/1/1998	CR	2		1	1.R294X(AC)	HSQ'01	30/1/2001	
959	16	1/6/1994	CR	2		1	?? none(MB)	HSQ. '02,	1/11/2000	
963	393	18/6/1998	CR	2		2	none (WGH)none	inv	15/10/2001	
964	394	20/5/1996	CR	2		1	1116-1201del 86	HSQ'00	1/11/2001	1/11/2001, 20/4/2001,6/1/04
965	395	9/2/1996	CR	2		1	1157-1197del41(A	mult '00,'02,'03	1/11/2000	5/10/200119/9/204
966	396	6/1/1999	CR	2		2	none(Wessex)	HSQ'01	19/6/2001	
969	337	21/10/1998	R nanC	2		1	del,exon4-3prime	mult.'00,'01	30/1/2001	12/10/2002, 12/1/2003,1/10/2003
972	397	15/10/1997	R nanC	2		2	not found (AC)	mult '01,'03	31/1/2001	
973	122	11/3/1993	unknow			2	none (AC)	inv		
976	48	10/10/1962	CR	2				HSQ.'01	30/1/2001	30/1/2001
979	338	18/1/1999	R nanC	2		2	none(AC)	HSQ.'01	30/1/2001	
980	339	29/6/1998	R nanC	2		1	c502c>t;	HSQ.'01	31/1/2001	
981	398	4/7/1997	R nanC	2		2	polymorphism	HSQ'01	6/4/2001	
982	399	29/5/1998	R nanC	2		2	negative	mult '01,'02,'03	19/6/2001	12/10/2002,1/10/2003
985	400	16/5/1996	R nanC	2		2	none)(AC)	inv		
986	401	10/4/1991	CR	2		1	291 C>A; D97E	inv	10/6/2001	
987	340	20/11/1985	unknow	2			awaited	inv		
988	402	12/5/1999	CR	2		1	R106W(Wessex)	HSQ '01,'03	19/6/2001	12/10/2002,1/10/2003
989	403	19/10/1998	CR	2		1	c512C.T;R168X	HSQ'01	19/6/2001	
990	404	21/6/1986	CR	2		1	397C>T.R133C(AC)	HSQ '01,'03	20/7/2001	
991	405	3/11/1987	CR	2		2	not found (?where)	HSQ'01	20/6/2001	
993	341	7/3/1986	R nanC	2		2	none	HSQ.'01	11/12/2001	91/9/2004
998	342	12/1/1999	CR	2		1	R270X	HSQ. '02	1/10/2003	
1006	406	24/8/1998	inc CR	2		2	none(AC)	inv	29/1/2002	29/1/2002
1007	407	1/1/1998	R nanC	2		1	positive R270X ??,	inv	5/10/2001	
1008	408	20/4/1999	inc CR	2		1	positive (Hollandi)	mult '01, '03	1/10/2004	
1010	409	26/5/1998	CR	2		1	c880 R294X (AC)	HSQ'01	14/10/2001	14/10/2001, 29/1/2002, 12/10/2002,1/10/2003
1012	410	15/10/1998	CR			1	41 base del	inv	11/10/2002	12/10/2002
1013	411	27/8/1998	CR	2		1	c.502C>T;R168X	HSQ '02	29/1/2002	
1014	343	24/9/1996	R nanC	2		2	none (AC)	HSQ. '02	29/1/2002	
1015	412	2/6/1994	CR	2		1	c808C>T;R270X	HSQ '01	1/10/2002	12/10/2002
1016	101	20/5/1995	CR	2		1	44 base pair del	HSQ.'02	30/1/2002	8/3/2002
1017	413	2/3/1999	CR	2		1	C617delG (?Notts)	HSQ'01	29/1/2002	12/10/2002,1/10/2003
1018	414	12/8/1997	CR	2		1	\mutation 910\(?)	HSQ'02	29/1/2002	
1019	415	23/2/1989	R nanC	2		2	none(AC)	HSQ'02	30/1/2002	
1020	416	17/5/1996	not R			2	none (Manchester)	HSQ '02	29/1/2002	29/1/2002
1022	417	4/12/1968	R nanC	2		1	c.502C>T.R168X	HSQ'02	29/1/2002	1/10/2003
1031	418	2/2/1998	unknow			1	c.808C>T;R270X(A	inv	12/10/2002	1/10/2003
1032	214	9/1/1992	unknow							
1042	419	12/12/1998	CR	2		1	c91delG (AC)	HSQ'02	12/10/2002	1/10/2003
1084	420	15/8/1999	CR	2		2	none found (AC)	HSQ.'02	18/6/2002	
1067	421	8/9/1968	CR	1	16/6/2002	1	c502C>T;R168X	inv		
1068	2	7/8/1996	unknow			2	no mut (MB)	inv		
1072	344	22/2/1999	R nanC			1	R168X & 7bpdel	HSQ'03		
1075	25	28/4/1995	unknow							
1076	84	27/1/1989	unknow	2						
1077	99	31/7/1978	unknow	2						
1078	114	5/7/1983	unknow	2						
1079	139	13/4/1991	unknow	2				inv		
1080	142	5/1/1993	unknow	2						
1081	422	6/1/1999	CR	2		1	44bp del	HSQ '02	11/6/2002	1/10/2003
1082	193	19/9/1992	CR	2		1	P152R (MB)	HSQ. '02		
1083	204	31/8/1980	unknow	2						
1084	211	19/1/1990	unknow	2				inv		
1085	230	9/9/1961	CR	2		1	R168X	HSQ '03		
1086	239	25/3/1989	CR	2		2	none (AC)	HSQ '02		
1087	423	2/12/1999	CR	2		1	502C>T (AC)	HSQ. '02	11/6/2002	
1088	424	16/5/1967	R nanC	2		2	negative(DR)	HSQ.'02	11/6/2002	
1090	425	23/2/1991	R nanC	2				inv	12/6/2002	
1113	426	3/9/2000	CR	2		1	positive (Aug '02)	HSQ '02	12/1/2003	

593	156	28/9/1988	CR	2		2	none (where?)	HSQ,'01	14/6/1994	26/6/1996	
594	137	12/11/1979	CR					mult,'94,'96			
596	296	8/12/1990	R nonC	2				HSQ,'94			
597	363	6/1/1991	CR	2		1	c502C>T; R168X	inv	14/6/1994	15/6/1995	
598	297	2/10/1991	R nonC	2				mult,'94,'95	14/6/1994		
600	250	30/12/1970	CR	2				mult,'94,'95	14/6/1994	16/6/1996	
601	298	31/3/1972	R nonC	2				mult. '94,'95,'96	13/6/1994		
602	11	6/2/1973	CR	1	21/10/2001	2	neg (AC)	mult. '94, '96,	14/6/1994		
605	195	23/10/1977	CR	2		2	negative(MB?) ?MH	mult,'94,'98	14/6/1994	12/10/2002	
609	364	11/6/1987	CR	2				mult'94,'02	15/6/1994	16/6/002	
611	228	29/5/1992	CR	2				mult,'94,'97	29/5/1992	1/10/1996,15/1/1997	
618	299	3/2/1987	R nonC	2		2	none(AC)	mult.'94,'95,'96,'98	14/6/1994		
619	184	7/5/1992	CR	2		1	1157-1200del44bp	HSQ.'02	3/6/1994	1/10/1996,11/6/2002, 12/10/2002,2/7/2003	
622	223	6/5/1991	CR	2		1	Q47X(MH)	mult '94,'96,'98	16/1/1995	9/1/1996,1/10/1996,15/10/2001,	
623	88	12/11/1992	CR	2		1	R270X (MH)	mult.'94,'95,'96.'00	16/1/1995	10/1/1996,13/1/1998,10/2/2000	
626	175	19/9/1990	CR	2				HSQ'94			
627	300	26/4/1985	not R	2			balanced inversion	mult '94,'98			
629	54	6/12/1991	CR	2				mult. '94, '96,	1/10/1994	18/1/1995, 14/10/2001, 12/10/2002	
630	179	10/11/1994	CR	2				mult. '97,'98	20/10/1997	14/1/1998,	
633	161	13/1/1995	CR	2		1	c126-127insG (AC)	inv	1/11/1997	16/6/1998	
635	321	23/11/1980	not R	2				inv			
637	94	11/5/1995	CR	2				inv	13/1/1995		
639	166	18/3/1991	not R	2			awaited	HSQ.'98	13/1/1998		
640	162	29/4/1970	R nonC	2		1	c1164-1207del44b(	mult'98, '02,'04	14/1/1998		
644	372	10/10/1990	CR	2		2	(d'E, AC)none	mult'98,'01	14/1/1998	20/6/2001	
647	227	6/5/1984	R nonC	2		2	not found(AC)	mult '98,'99	23/1/1991	26/3/1999,14/6/1999,1/10/1999	
649	135	7/6/1993	CR	2		1	position to come	HSQ.'98	17/6/1998		
650	322	6/5/1995	R nonC	2		2	none (AC,MB)	HSQ.'98	6/11/1998		
653	208	27/9/1993	CR	2		1	c916C>T; R306C	mult'98,'00	23/6/1998		
654	201	4/7/1991	CR	2		1	c1157-1200del144	mult'98, '99,	3/7/1998	4/2/1999,22/6/1999,20/6/2000,31/1/2001,	
656	323	13/6/1987	R nonC	2		2	none (Belgium) MB	HSQ.;98,'02			
657	85	26/4/1986	R nonC	2		2	none (AC)	HSQ. '98	16/6/1998		
658	49	26/9/1988	CR	2		2	not found (AC)	HSQ. '98	19/6/1998	7/8/1998,11/7/1998,11/6/2002	
659	324	28/9/1995	R nonC	2		2	negative (AC)	HSQ.'98	16/6/1998	12/10/2002	
661	192	10/9/1995	CR	2				inv	16/6/1998		
662	56	26/7/1993	inc CR	2		2	polymorphismc386	HSQ. '00	17/6/1998	19/1/2000	
158	128	13/4/1973	CR	2	15/6/2004	1	R255X(MB)	mult.'86,'95,'98	1/5/1986	17/6/1995, 20/6/2000	
161	118	10/9/1982	CR	2		1	none(MB)168(d'E)(	mult.'92,'95,'98			
162	13	14/9/1986	CR	2		1	R133C (MB)	mult. '90, '98,	1/9/1991	29/4/1992, 17/7/1996, 1/6/2000, 1/11/2000	
164	127	5/4/1974	unknow	1				inv			
167	238	20/3/1986	CR	2				HSQ.'93	20/6/1999		
168	121	8/11/1972	CR	2		1	T158M (Glasgow)	mult.'94,'96	14/6/1994	25/6/1996	
171	120	19/6/1974	CR	2				mult.'95,'96,'98			
169	23	31/3/1993	CR	2		1	Q244X (MB)(MH)	mult. '95, '96, '98	15/6/1995	18/6/1996, 1/10/1999,	
182	138	26/6/1988	CR	1	13/8/2005			mult.'94,'95,'97,'98,'	1/10/1991	30/1/1992,10/11/1997,15/10/2001	
185	15	3/3/1980	CR	2		1	1152-93.del.41(MB)	HSQ.'98	11/6/1991	14/6/1994	
188	350	3/6/1985	CR	2		1	c473C>T; T158M &	HSQ'00	1/10/1992		
194	14	7/7/1985	CR	2		1	916C>T(AC)R306C(	mult '93,'94, '97,	3/1/1991	1/0/1994, 18/1/1995, 1/11/1995, 30/5/1997,	
201	262	6/7/1976	inc CR	2				Q '90	31/1/1995	18.1.1995	
206	144	14/10/1982	CR	2		1	T158M(MB)	mult. '95,'96,'98,'02	1/10/1986		
208	263	7/8/1983	not R	2		2	del 1p	mut.'94,'95,'98	13/6/1991		
209	153	26/1/1989	CR	2		1	T158M	mult.'91 ,'03	11/6/1991	17/1/1995	
210	157	21/10/1976	CR	1	17/3/2002			mult.'94,'98,'02	1/10/1987	21/1/1992	
212	151	13/7/1983	CR	2		1	101d'E)	HSQ'95	1/10/1990	21/1/1993,1/10/1994,	
217	150	10/7/1986	CR	2				mult. 93,'98,	1/10/1991	10/6/1992	
218	149	19/9/1980	CR	2		1	R306H (MB)	HSQ '92,'03			
220	148	31/10/1986	CR	2				mult. '93, '95,	22/1/1991	1/10/1992, 21/1/1993	
225	170	4/2/1980	CR	2				Q '90	1/6/1989	1/10/1992	
232	172	3/3/1981	CR	2				inv	1/1/1987	1/1/1989,	
234	171	24/6/1980	CR	2		1	c763C>T;R255X(A	mult '91,'94,'98	1/10/1986	28/8/1988, 1/6/1989, 12/6/1991,	
242	264	1/2/1969	unknow	2				inv			
249	173	31/10/1983	CR	2		2	none(d'E. MB.AC)	mult. '93, '94, '95,	20/1/1993	1/10/1994, 19/6/1995	
251	265	2/9/1980	CR	2		2	neg(AC)	Q '86.inv	7/6/1995	30/3/2001,21/6/1995	
254	167	5/5/1988	CR	2		1	Y141X(Aberdeen)	mult.'90,'94,'95,'96,'	25/6/1990		
256	168	20/3/1985	CR	2		1	473C>T(AC)	HSQ'02	1/10/1992	16/1/1995,31/1/2001, 1/10/2001,1/10/2003	
259	266	24/7/1959	CR	2				Q '86	7/2/1986	30/3/2001,19/4/2002	
269	160	16/10/1968	R nonC	2				Q '91	12/6/1991		
270	267	19/12/1974	CR	2				mult. '95,'98			
276	20	8/12/1987	CR	2		2	not found (MB)	mult. '94,'95, '98	22/6/1991		
277	187	1/8/1969	CR	2				mult.'95,'98,'00	23/1/1991	10/1/1996,15/2/2000	
279	21	10/9/1982	CR	2		1	495-1164del669.	mult'95, 96, '98	15/10/1994	1/11/1995, 1/10/1996,1/10/2001,	
282	194	3/7/1981	CR	2		1	107in frame	mut.'92'93,'95,'98	24/7/1987	1/1/1989,1/1/1992,	
284	210	14/3/1983	CR	2		1	c302C>A;P101H(A	Q'90,	22/6/1991	11/1/1994	
289	207	15/8/1976	unknow	1	6/12/1998	2	AC) none found	inv			
291	113	4/7/1990	CR	2		1	c877delG,I293fsx7	mult. '94, '95, '97,	2/2/1995		
294	72	15/6/1969	CR	1	17/5/2001			inv	8/6/1993		
297	19	8/6/1976	CR	2		1	P152R(MB)	mult '95, '98	1/6/1993		
299	268	14/12/1979	R nonC	2		1	IVS3-3C>G(mosaic	inv	8/6/1993	7/7/1993, 11/1/2004	
300	22	19/6/1985	CR	2		1	R270X (MB)	mult. '93, '98,	23/1/1991	22/1/1993	
306	200	13/6/1976	CR	2		1	R270X(MB)	HSQ.'95	13/9/1976	1/4/1991	
307	203	15/3/1964	CR	2		1	806delG(AC)	mult.'93,'95,'97	1/10/1987	1/1/1989,1/10/1992,1/10/1994,17/1/1995,	
312	269	9/2/1970	CR	2				Q'91 inv	1/10/1989		
322	219	4/3/1983	CR	2		1	880C>T;R294X(AC)	mult.,'94	21/1/1992		
325	351	21/1/1985	CR	2		1	del exon 3	HSQ'00	21/6/2000		
328	270	9/6/1977	CR	2				mult.'90,'95,'98			

Dataset:8.2 Results of Surgery for Scoliosis

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R non C=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

S Sc ore gives severity score (see figure 2.2.1 , appendix A)
EpL =epilepsy longitudinal (1=resent, 2=not present)
hand skill L=hand skill longitudinal (1=spoon/mug, 2 fingers, 3 none)
scol L=scoliosis longitudinal (1=none, 2=slight,3=marked,4=severe,
5=operated.

Longitudinal fields record one digit for every five years
throughout life except the first which refers to pre-regression
if the individual regressed

BIS	d of birth	status	S score	mut	test	epL	loco skillL	hand skillL	scolL
26	13/2/1976	CR	40%	1	R168X(AC)(d'E168)	22.22.	21.11.	13.33	11.25
30	3/9/1977	CR	90%	1	R255X and	21.11	22.22	22.22	12.34
46	2/2/1982	CR	100%	1	c316C>T;R106W	99.11	92.22	33.33	92.45
52	7/6/1976	CR	90%			21.11	12.22	13.33	12.45
101	29/5/1981	CR	90%	2	none (AC)	21.11	22.22	23.33	12.45
103	20/4/1973	CR	100%	1	missense T158M	21.12.1	22.22.2	22.22.1	12.45.5
108	6/8/1975	CR	80%			21.11.11	22.22.22	13.33.33	19.45.55
113	5/5/1977	CR	90%	1	c763c>t;R255X(d'E)	22.11.	22.22.	13.33.	11.45
138	7/1/1969	CR	80%			21.11.11.	22.22.22	22.22.22.	11.25.55.
185	3/3/1980	CR	80%	1	1152-93.del.41(MB)	21.11	11.22	12.22	14.55
212	13/7/1983	CR	90%	1	101d'E)	21.11	22.22	12.22	13.55
218	19/9/1980	CR	60%	1	R306H (MB)	11.11.1	11.11.1	12.22.2	93.55.5
231	23/6/1982	CR	50%			22.22	12.22	93.33	11.45
263	14/10/1971	CR	100%	1	158(d'E)	21.11.11	22.22.22	13.33.33	11.55.55
275	8/6/1976	CR	90%			21.12.2	22.22.2	23.33.3	99.55.5
280	17/6/1977	CR	100%			22.11	22.22	23.33	12.45
306	13/8/1976	CR	90%	1	R270X(MB)	22.12	11.22	33.33	99.45
314	31/7/1982	CR	90%	1	R255X(TW)	21.11	22.22	33.33	15.55
363	13/7/1976	CR	50%			22.22.22	11.12.22	19.33.33	19.55.55
413	7/1/1990	CR	70%			22.2	22.2	33.3	12.5
423	16/5/1971	CR	90%			22.11.11	22.22.22	93.33.33	11.25.55
451	18/11/1989	CR	80%	1	R270X (MB)	22.2	22.2	23.3	15.5
473	16/10/1963	CR	40%.			21.11.22.9	12.11.11.9	12.22.22.2	11.12.45.5
483	10/5/1976	CR	80%	1	R270X(MB)	22.11.1	22.22.2	13.33.3	12.45.5
500	15/10/1971	inc CR	70%			21.11	22.12	11.11	94.55
548	3/9/1977	CR	90%			21.1	22.2	23.3	95.5
842	21/4/1971	CR	80%			21.11	22.22	23.33	11.12
858	28/9/1988	CR	90%	2	not found (AC)	21.1	22.2	22.2	14.4
900	4/8/1971	CR	70%			21.11.1	21.99.2	23.33.3	99.45.5
1021	8/10/1974	CR	90%			21.11.11	22.22.22	23.33.33	11.29.33
8	27/3/1987	CR	50%			22.22	22.1	13.33	13.55
21	14/6/1978	CR	80%	1	R106W(AC)106(d'E	21.11	21.12	12.2	12.45
27	23/11/1974	CR	90%			21.11.12	22.22.22	19.33.33	12.45.55
45	20/5/1980	CR	90%			21.11	22.22	93.33	12.34
76	19/1/1983	CR	100%	1	168d'E)	21.1	22.2	23.3	14.5
87	12/8/1977	CR	40%			22.22.2	11.11.1	11.11.1	11.24.5
89	11/9/1980	CR	100%	2	none (MB) checking	21.12.1	22.22.2	23.33.3	12.45.5
122	8/10/1975	CR	60%			21.11.11	11.11.11	12.22.21	11.34.55
130	22/4/1985	CR	90%			22.1	11.22	12.22	12.55
131	16/7/1983	CR	80%	1	1157del144bp (CS)	21.11	12.22	13.33	13.45
136	9/2/1972	CR	80%	1	c763 C>T; R255X	21.11.11	11.11.11	13.33.33	11.55.55
150	6/11/1978	CR	90%	1	c316C>T; R106W	21.11.	22.22	12.22	23.45
171	19/6/1974	CR	60%			22.2	22.22	13.33	99.45.
186	25/9/1976	inc CR	70%			92.11.1	99.92.1	99.11.1	99.95.5
194	7/7/1985	CR	70%	1	916C>T(AC)R306C(	21.19	11.11	22.22	12.25
207	14/8/1980	CR	80%	1	T158M (TW)	21.11.	11.22.	23.33.	11.45.
209	26/1/1989	CR	80%	1	T158M	21.1	22.2	12.3	13.5
210	21/10/1978	CR	100%			22.11	22.22	23.33.	94.55.
233	28/1/1981	CR	50%			22.21.11	21.11.19	11.11.39	12.35.59
234	24/6/1980	CR	70%	1	c763C>T;R255X(A	22.22	22.22	13.33	16.55
279	10/9/1982	CR	70%	1	495-1164del669.	22.29	22.22	23.3	12.55
282	3/7/1961	CR	100%	1	107in frame	21.11	22.22	23.33	14.55
297	8/6/1976	CR	40%	1	P152R(MB)	22.11.1	11.12.1	99.11.1	13.45.5
367	22/2/1981	CR	100%			21.1	22.2	12.2	14.5
373	12/11/1971	CR	70%			22.22.2	22.22.2	23.33.3	13.45.5
405	24/11/1987	CR	60%	1	R306C (Wessex)	22.2	22.2	13.3	13.3
469	7/8/1985	CR	30%	1	P302R	22.2	11.1	12.2	12.2
550	29/9/1990	CR	100%	1	del exon3-4	21.1	22.2	23.3	12.4
555	8/2/1970	CR	80%	1	T158M (MB)	21.11	22.22	19.33	11.45.
602	6/2/1973	CR	40%.	2	neg (AC)	22.22.22	11.11.11	11.11.11	15.55.55
609	11/6/1987	CR	90%			21.1	22.2	13.3	12.3
653	1/3/1993	CR	80%	1	R270X (MB)	22.	22.2	12.	14.
911	31/10/1995	CR	90%			21.	22.	23.	13.

Dataset: 9.1 & 2: Analysis of deaths in BIS

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R non C=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

This dataset lists all deaths reported to BIS in people with CR
It includes cases referred to in studies 9.1 and 9.4.
PM indicates autopsy but not necessarily tissue donation
The column D indicates donations of tissue to co-author DA
S Score gives severity score (see figure 2.2.1 Appendix A)
The column headed 'Death T' indicates the type of death, F=frail
U=unexpected, S=epilepsy associated, G=general causes

BIS	d of birth	status	died	deathT	d of death	mut	test	Kerr Q	AK saw	AK dates
24	29/3/1987	CR	1	G	17/11/1994			inv	12/6/1991	
27	23/11/1974	CR	1	9	24/3/2001			mult.'95,'98	16/10/1989	
34	10/12/1975	CR	1	S	13/11/1995			Q	1/6/1989	
37	13/6/1986	CR	1		5/1/2005	1	P302L(AC)	mult.'93. '94'03	28/10/1989	23/1/1991, 8/6/1994,
38	27/4/1973	Inc CR	1	F	7/2/1991			inv		
45	20/5/1980	CR	1	F	1/10/1998			mult'93,95,'97	1/10/1991	
51	21/10/1976	CR	1	F	1/4/1995				1/4/1989	
52	7/6/1976	CR	1	F	6/10/1997			HSQ	1/10/1989	1/10/1991
62	21/2/1975	CR	1	U	23/11/1998			HSQ '90,'98	19/10/1991	
67	14/2/1971	Inc CR	1	F	1/1/1992					
69	14/5/1973	CR	1	F	2/10/1990			Q'92		
73	13/9/1974	CR	1	F	13/2/1992	1	c654-657delGAAG.	Q'91		
76	19/1/1983	CR	1	U	29/12/1994	1	168dTE)	mult '93,'95	1/5/1987	
79	13/2/1987	CR	1	F	9/4/2001	1	T158M	mult. '93,'94,'96,'99	6/10/1990	1/10/1994,
90	17/1/1983	R nonC	1	F	9/8/1995			mult '94,'96	21/1/1992	
91	16/12/1985	CR	1	9	27/10/1998			inv	7/6/1993	
100	13/4/1975	CR	1	F	1/1/1997			mult	24/5/1984	
112	12/3/1985	CR	1	U	14/1/1989					
124	3/3/1949	CR	1	F	17/1/1993			HSQ	3/6/1987	
129	18/6/1987	CR	1	F	11/1/1997			inv	17/3/1994	
134	14/5/1971	CR	1	F	6/4/1997			HSQ	19/1/1993	
135	16/1/1982	CR	1	F	31/1/1998			Q inv	1/5/1986	1/1/1987
142	12/10/1975	CR	1	U	14/5/1987			Q	21/6/1984	
144	29/11/1977	R nonC	1	S	23/12/1985					
150	6/11/1978	CR	1	F	20/9/2000	1	c316C>T; R106W	mult. '91,'99	22/6/1987	1/10/1989
159	23/3/1973	CR	1	F	20/6/2002			inv	22/1/1991	
160	17/5/1986	CR	1	9	1/1/1994			inv	12/6/1991	
164	5/4/1974	unknow	1	U				inv		
174	5/7/1979	CR	1	U	12/10/1995			HSQ. '95	3/6/1989	17/6/1995
181	18/3/1988	Inc CR	1					Q'90	1/10/1990	
182	26/8/1988	CR	1		13/8/2005			mult.'94,'95,'97,'98,	1/10/1991	30/1/1992,10/11/1997,15/10/2001
195	25/9/1973	unknow	1	9	12/12/2002			inv		
198	18/5/1964	CR	1	F	14/5/2003	1	c763C>T; R255X(A	Q	20/2/1991	
202	9/5/1975	Inc CR	1	9	15/3/1993			Q'90		
205	9/11/1977	CR	1	S	4/12/1995			HSQ.'95		
210	21/10/1976	CR	1	U	17/3/2002			mult.'94,'98,'02	1/10/1987	21/1/1992
222	8/5/1978	CR	1	F	27/12/1999			Q	12/11/1987	1/6/1998
227	17/3/1974	CR	1	G	20/8/1994			HSQ	28/7/1986	
228	4/3/1963	CR	1	G	1/1/1995			HSQ'93	3/6/1989	15/10/1993
229	27/6/1974	CR	1	F	7/10/1994			Q		
237	9/1/1972	CR	1	U	2/9/1994				15/6/1994	
239	7/7/1979	CR	1	F	1/12/1995	2	(AC) not found	Q '89	1/9/1988	10/6/1992,8/4/1999
253	7/10/1980	CR	1	F	1/1/1999			Q	6/6/1986	
255	22/11/1984	CR	1	U	11/4/1990			Q		
280	17/6/1977	CR	1	F	2/1/1996			HSQ.'96,'02	1/10/1991	10
286	9/2/1971	CR	1	F	18/1/2003			mult '95,'96,'00		
289	15/9/1976	unknow	1	F	6/12/1996	2	AC) none found	inv		
293	9/5/1964	not R	1	9	15/10/1992					
294	15/6/1989	CR	1	F	17/5/2001			inv	8/6/1993	
295	17/6/1982	CR	1	F	17/6/1996			HSQ '93		

298	14/12/1979	not R	1	F	5/5/1994				Q '93	8/6/1993	
301	8/11/1974	CR	1	F	8/12/1998				HSQ	8/9/1983	29/10/1985,16/7/1987,30/11/1988,11/1/1993,28/7/
308	30/5/1959	CR	1	U	4/7/1992				Q	1/5/1986	
309	4/12/1984	CR	1		13/12/1999				inv	12/6/1991	1/10/1992
313	6/6/1973	CR	1	F	3/3/1990					1/10/1989	
318	16/3/1960	unknow	1	U	8/9/2002						
329	20/6/1971	CR	1	F	25/3/1987				Q	12/4/1984	
357	29/9/1984	CR	1	F	1/10/1995				QHSQ '95		
361	18/8/1975	CR	1	F	25/5/1991				Q '86,'95	1/5/1986	
364	1/7/1980	CR	1	F	12/3/1999				mult. '90 '95		
365	17/12/1980	CR	1	F	12/5/1992				Q '91		
367	22/2/1981	CR	1	F	9/8/1995				mult Q	26/7/1984	
369	2/9/1966	CR	1	F	4/4/1996				HSQ,'94	3/6/1992	4/4/1996
372	10/1/1984	CR	1	F	31/1/1997				Q'91	1/10/1987	1/1/1969,22/6/1991, 15/6/1995
373	12/11/1971	CR	1	U	1/4/2001				mult.'93,'96,'98	1/6/1993	
378	30/10/1973	CR	1	F	23/11/1993				Q'90	1/4/1989	1/6/1990
381	10/11/1987	CR	1	U	1/4/2003				mult.'91,	4/9/1991	16/5/1992,1/1/1997,13/11/1998,4/9/2000
389	24/4/1973	Inc CR	1	S	1/1/1991						
398	21/3/1971	CR	17			1	del exon 3-4 MH		mult.'93,'98	19/10/1991	1/11/1995, 21/1/1992
400	13/12/1987	Inc CR	1	U	12/11/2002				Inv	1/10/1991	1/10/1992,1/10/1994,
408	14/5/1970	CR	1	S	1/1/2001				mult '95,'98	21/1/1992	
410	15/3/1962	CR	1	G	20/10/1993					21/1/1992	
432	24/9/1999	R nonC	1	9	19/1/2001	1	c473G>T; T158M		HSQ,'01		
438	12/4/1980	R nonC	1		6/7/2003				HSQ'98	17/8/1998	
459	5/6/1985	R nonC	1	9	17/2/2002				HSQ	26/5/1992	10/6/1992, 15/6/1995
483	10/5/1976	CR	1		5/1/2004	1	R270X(MB)		HSQ,'98,'02	22/1/1991	25/1/1993
496	11/7/1974	Inc CR	1	F	1/2/1997						
500	15/10/1971	Inc CR	1	F	17/1/2005				HSQ'94	10/6/1992	20/1/1994
503	7/10/1972	unknow	1	F	23/3/1998						
504	2/3/1985	not R	1	F	16/11/1996					10/3/1987	
515	15/4/1967	Inc CR	1	U	13/10/1992						
523	9/2/1960	CR	1	U	26/10/2003	2	neg (AC)		mult.'95,'98,'00	19/1/1993	
538	27/11/1984	R nonC	1		10/2/2004	2	none(AC)		HSQ,'98		
547	2/2/1947	CR	1	F	14/5/2001				mult '93,'98	8/6/1994	
578	11/7/1961	Inc CR	1	9	1/1/2003				HSQ'98	15/1/1994	
602	6/2/1973	CR	1	G	21/10/2001	2	neg (AC)		mult. '94, '96,	14/6/1994	
610	4/2/1988	CR	1	G	17/5/1997				HSQ	1/5/1994	
633	2/4/1982	not R	1	9	4/4/1996				Q	26/2/1986	
634	24/8/1970	CR	1	F	2/1/2000				mult.'95,'96,'97,'98	1/10/1994	
638	24/6/1988	unknow	1	9	26/7/2002						
695	14/5/1991	R nonC	1	F	9/7/1997	2	none(AC)		Inv	17/6/1996	
707	12/12/1936	Inc CR	1	F	1/7/1996				Inv	11/11/1995	
719	4/5/1973	CR	1	S	1/9/2003				HSQ,'95,	9/1/1996	
747	27/12/1979	unknow	1	G	1/1/1981						
768	12/10/1948	not R	1	9	2/7/1962						
789	20/1/1962	CR	1	G	15/1/1987						
792	23/9/1992	not R	1	S	4/7/2003	2	none (AC)		mult.'97,'98,'03	13/1/1998	
831	19/10/1990	CR	1	G	1/1/2003	1	c730C>T;Q244X				
933	11/6/1968	unknow	1	U	13/2/2000						
984	17/1/1975	CR	1	U	2/4/2001						
1067	8/9/1988	CR	1	S?	16/8/2002	1	c502C>T;R168X		Inv		
1074	6/4/1977	unknow	1	U	22/3/2002						
1112	26/7/2001	R nonC	1	9	12/5/2003	1	132 bp del		HSQ'03		
1114	13/3/1971	R nonC	1	9	1/5/2003	2	none (Yorkhill)		HSQ '02	30/9/1993	
1191	15/7/1994	R nonC	1	F	3/4/2004	1	R270X (J C-S)		HSQ'04		

Dataset: 9.4: People with mutation positive Rett syndrome who converse

Explanation of Symbols:
BIS=Survey code number, 1=yes,2=no, 3=presumed present,
9 or nk or no entry=not known, AK saw=first examination,
AK dates=subsequent examinations, infant V=infant video,
Kerr Q=health questionnaire, (HSQ=single, mult=multiple)
age upd=age at update, CR=classic Rett, incCR=incomplete data,
probably CR, R non C=Rett not classic, not R=not Rett,
mut=mutation tested(no entry=not tested), test=result

further data for all cases in the Survey is shown in Appendix B

The column sp st indicates study 9.4
S Sc ore gives severity score (see figure 2.2.1 , appendix A)
EpL =epilepsy longitudinal (1=resent, 2=not present)
hand skill L=hand skill longitudinal (1=spoon/mug, 2 fingers, 3 none)
scol L=scoliosis longitudinal (1=none, 2=slight,3=marked,4=severe,
5=operated.

Longitudinal fields record one digit for every five years
throughout life except the first which refers to pre-regression
if the individual regressed

BIS	d of birth	status	S score	mut	test	epL	loco skillL	hand skillL	scolL	sp ...
104	26/2/1981	CR	40%	1	R133C(dE)(MB)	21.11	11.11	11.11	11.22	1
441	26/7/1994	RnonC	10%	1	R133C(Wessex)(C	22.	11.	11.	11.	1
487	8/9/1974	RnonC	50%	1	44bpdel.1163-(Wes	22.11	11.11	11.12	11.22	1
725	4/3/1970	CR	10%	1	del exon 4 c	22.22.2	11.11.1	11.11.1	11.11.1	1
765	26/4/1989	RnonC	10%	1	c397C>T;R133C	22.	11.	11.	11.	1
787	26/4/1991	CR	60%	1	1164-1207del44(A	21.2	11.2	11.2	13.4	1
840	29/4/1970	RnonC	20%	1	c1164-1207del44b(	22.22.22.2	11.11.11.1	11.11.12.2	11.22.22.2	1
1022	4/12/1988	RnonC	20%	1	c.502C>T,R168X	22.2	11.1	11.1	12.3	1
1116	19/3/1967	RnonC	0%	1	803delG inTRD	22.22.22	11.11.11	11.11.11	11.11.11	1
1176	15/6/1987	RnonC	30%	1	1162-1172 del 11bp	22.22	11.11	11.11	11.55	1
1218	31/3/1978	RnonC	30%	1	R133C (AC)	22.22.22	11.11.11	11.11.11	12.55.55	1
1220	1/10/1986	RnonC	0%	1	R133C (AC)	99.11	11.11	11.11	99.92	1
1228	3/7/1971	RnonC	0%	1	R168X (AC)	22.22.22	11.11.11	11.11.11	11.92.22	1

APPENDIX D: SURVEY QUESTIONNAIRE AND DATA COMPUTER HELD

Health Data stored in the British Survey BIS (BIRS)

Completed health questionnaires (HSQs) a copy of which is attached, are retained for each individual with Rett syndrome or suspected Rett syndrome. Parents/carers who completed the HSQs are provided with a copy. Data from clinical examinations, reports and completed HSQs, is entered on a free standing computer with fully informed parental consent. This list indicates the items stored.

Items marked (L) are entered once in every five year period throughout life. One digit represents one five year period with the exception of the first in children who regressed, in whom the first digit refers to the period before onset of regression: e.g. comL. 11.11.11.11.11. indicates that words were used until 50 years; handsL 12.22.33. indicates that the person used spoon or mug before regression (or before age 5 if there was no regression), used only finger after that until 20 years and thereafter did not use the hands for self feeding.

Unique BIS code
Personal identification
Dates of birth and death
sex
Grandparents' dates of birth / death
Parents' dates of birth
Siblings of parents
siblings, miscarriages, dates
Any mental or brain or genetic disorders
Parents' age completing full time education
Regular medical advisers
Health questionnaires (HSQ) invited, completed
dates seen by AK
Video recorded
Infant video donated

Health during gestation
Adverse birth circumstances
Gestation weeks
Birth weight
Age to sit unsupported
Age of full crawling
Age of solo walking - for how long
List of words spoken (before regression or 5y)
Ability to self feed, fingers, spoon, mug, none (before regression)
Age when disability suspected
First skill lost- if any, at what age

Rett status
Date of Rett diagnosis if made, by whom
Presence of some early development
Occurrence and if any, age at onset of regression
Dyspraxia

Hand stereotypy
Birth OFC
All other OFC measure to present

Other positive medical investigations, reports & dates
Any diagnosis made other than Rett
All genetic reports - including *MECP2*
Weights & heights with ages
Feeding difficulty items & score (see figure 2.2.1)
also L see explanation above)

Abdominal distension, aerophagy
Epilepsy diagnosed
E.e.g and reports of e.e.g (entered for 5 year periods)
Deep breathing/ hyperventilation noticed
Breath holding noticed
non-epileptic vacant spells thought to occur
cold blue feet, how constantly
predominant respiratory rhythm (if monitored)

understanding of speech yes/ no (L see explanation above)
use of speech, single words, sentences in context
(L see explanation above)
reception or expression by other means
walking unsupported (yes / no) (L see explanation above)

Contractures / joints displaced hips, knees, ankles, feet
Scoliosis or kyphosis (L see explanation above)
Distress due to scoliosis (walking, sitting, standing etc ....)
Is a brace worn with dates and duration of wear
Distress/ discomfort due to brace (walking, sitting etc...)
Scoliosis surgery with date, place, surgeon
Change after surgery for better or worse (walking, sitting etc...)
Problems during scoliosis surgery
problems after scoliosis surgery
Change in the scoliosis since surgery

unexplained excitement or sadness
Injury to self or others
sleep disturbance at night or day

General health good, fair or poor (last 12 months)
All episodes of illness in last 12 months
All current medications including alternative therapies
Presence of squint (strabismus) ever / now
Any defect in hearing diagnosed - reports
Puberty onset signs, menarche, regularity

Date of death
place of death
reported cause of death
PM report if any
state of health before final illness

(1)

BRITISH ISLES RETT SURVEY:HEALTH QUESTIONNAIRE.

Please return completed as far as possible, to:- Dr Alison Kerr, Monitoring Unit, Academic Centre Dept Psychological Medicine, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH

Please answer yes(1), no(2), don't know(3) if box provided. Otherwise circle or write in answers. Put a line through a question if not relevant but please don't leave blanks. Do use extra pages. Write in black.

PERSONAL DATA :- date of completion by family:- **Survey code**

Name of person date of birth

Usual address tel no.

postal code.....

How many people normally live in this dwelling?

School or day centre address (say if none).

Respite care : available used frequency and type
(short term care)

Person completing the questionnaire (name) relationship
Address if different from above;

Mother's ethnic group father's ethnic group

Age at completion of full time education: father mother

General Practitioner's Name
Address

Other regular medical advisers (with hospitals or centres)

All types of therapy attended (e g physio,music,etc. in or out of school), with frequency for each

Other kinds of organised activity (e g. riding, swimming, dancing) with frequencies

(2)

FEATURES OF RETT SYNDROME:use boxes (1=yes, 2=no, 3=don't know)
Please discuss these points with your doctor. If an answer is "no" please give brief details

a) Was she/he **free from other neurological disorders or injuries during development which might have caused her mental handicaps? (apart from Rett Syndrome problems)?** ☐

b) Was the **development within the normal range for the first few months of life?** ☐

c) **Following** the **initial progress was there deterioration in speech, hand use and personal contact without obvious serious illness?** ☐

d) **Is there now severe stable mental handicap with minimal use of the hands and speech?** ☐

e) **Is there repetitive hand movement (clapping, squeezing or patting)?** ☐

f) **Is there any difficulty in maintaining an upright posture ?** ☐

g) Was the **head size considered normal in the first 4 months? (give it if you can)** ☐

What was the **birth weight?** Was s/he premature (give weeks)?

When first, if ever, did s/he walk unsupported? until what age?

Did s/he ever crawl with hands and knees / feet, tummy off the ground? From what age?

Did s/he ever sit steadily on the floor without any support? From what age?

Did s/he **have words?** **which words (& how many)?**

Could s/he self-feed unaided **with fingers?** with spoon? **with mug?**

At what age was a problem in development first suspected? by whom **(first)?**

What behaviour led to this suspicion?

Which skill did s/he lose first? At what age?

Who first diagnosed Rett Syndrome? give date

Medical investigations:
Did medical investigation reveal abnormalities which might explain the mental handicap?
Please give tests, dates and results

Have her chromosomes been examined if so when? where? and what was reported?

Has the new test for MECP2 mutations been done? Where?
(give the result if you can)

(3)

GROWTH.
Please give present weight (kg) Standing height (cm)

Please measure and write in the lengths from the midline at the base of the neck, along each arm straight to the finger tips (centimeters preferred)

Head
right arm----------O----------left arm
.....cm .....cm

NUTRITION
The following factors may contribute to difficulty in feeding. Please select the degree of difficulty due to each factor which is encountered in feeding this person.

Shape or posture: no problem	some problem	severe problem
Mouth closure: no problem	some problem	very poor closure
Chews well	chews poorly	does not chew
Swallows well	some problem	severe problem
No obstructing tongue, jaw or throat movements	some	severe
No vomiting or regurgitation	some	severe problem
No problem with secretions	some problem	severe problem
No problem of poor apetite	some problem	severe problem
No problem drinking	some problem	severe problem
Feeds self	constant supervision	totally dependent

How long does a full meal take? Is food liquidised? Chopped fine? Chopped roughly?

Has **tube feeding** been used in the last 12 months? Starting date Continuing now?

Is the tube in nose? mouth? direct to stomach? Tube feeding continuous ? intermittent?

Do certain foods regularly upset this person? Which foods?

How is s/he affected?

Constipation and Diarrhoea:
Usual stools ..hard/ soft / fluid Average number of stools per week

With/ without pain ? requiring laxatives? requiring manual assistance?

Does she indicate toilet needs? perform when placed on toilet?

Does the **abdomen become distended with air?** how often?

if so do you feel that this gives her pain?

have you found a way to bring relief

④

SEIZURES (EPILEPTIC FITS)

Have there ever been true seizures? age at first seizure?
Please describe seizures

Do you think they are triggered in some way? by what?

Frequency over the last year (number in a typical day, week or month)?

Has electro encephalography (e.e.g.) been carried out?
Where? By whom? When? Report?

BREATHING ABNORMALITY & VACANT SPELLS

Has this person ever hyperventilated (deep, fast breathing)?

If so, at what age did it start?

Does it still happen? (if not say when it stopped)

Did s/he ever hold her breath for long periods?

At what age did this start?

Does it still happen? (if not say when it stopped)

Have there ever been "funny turns" (vacant spells) which do not appear to be epileptic fits?

When was the most recent of these?

Please describe them and give frequency

Do these seem related to the breathing irregularity?

How do you deal with them?

Are the feet cold and blue? Constantly? Occasionally?

(5)

PRESENT SKILLS: **use boxes (1=yes, 2=no, 3=don't know) & comment**

Understanding communication: Does his girl or woman **understand**:--

Situations?(for example anticipating bath time)

Gestures?(please specify which)

Does s/he understand your words? (if you do not also make gestures)

Communicating: Can she **use** :-

Facial expression?

Meaningful sounds?

Eye pointing?

Precise gestures?

Mechanical aids?

Does she use real words? (understandable by anyone) please say which and how many. Are they used in context?

Hand use: Can this person :-

Eat with a spoon or mug unaided ? with help?

Eat using fingers unaided? with help?

Help him/herself by using the hands in any way?

Which hand is most useful? Right Left both the same

Getting about: Can s/he :-

Sit without support?

stand unaided? with support?

walk unaided? with support?

Move about the floor in another way? Describe

(6)

JOINTS AND POSTURE

Scoliosis:

If there has been any curviture of the spine (scoliosis) when **first** was it noticed?

If anyone has ever given you measurements of the **scoliosis angle.** If so, please give them all with **dates or ages.**

Please try to draw the **PRESENT** shape of the spine:
(It will help if you can draw the curve you see from behind when this person is sitting, or take a photo for me after marking the central bony points of the spine with washable ink).

Example drawing of back

please make your drawing here

Please state whether you consider the curve NOW to be:-

slight moderate severe

In your opinion does the **present scoliosis** cause her distress or difficulty with the following (not counting difficulties due to a brace):-

Walking? Standing?

Sitting? Lying down?

Eating? Digesting food ?

Passing stools? Breathing?

Other comments?

Back support Has a back brace or support been worn **now or ever?** (please describe it giving dates and/ or durations of use)

(7)

If a brace is worn **now**, does the **brace itself** cause distress or difficulty during:-

Walking? Standing?

Sitting? Lying down?

Eating? Digesting food ?

Passing stools? Breathing?

Other comments?

Operations:

Has scoliosis (back) surgery been carried out?

When? where? Surgeon's name? Hospital?

If an operation has been carried out to correct scoliosis:-

Did operation alter general well-being for the better? or for the worse? or not at all?

State the effects of surgery on the following stating:- **better' or 'worse' or 'no change':-**

Weight changes (figures and dates if possible) Changes in lung complaints

Changes in walking Changes in standing

Changes in sitting Changes in lying down

Changes in eating Changes in digestion of food.

Changes in passing stools Effects on the family

(8)

\Did the **scoliosis operation** cause other problems (describe problems & give durations):-
During the operation?

Directly after the operation?

Since then?

Has the curve got worse since the operation?

Other joints
Is there displacement of either hip joint:-- right ? left?

Can you straighten the hip joints completely: -- right? left?

Can you straighten the knees fully:--- right? left?

Can you place the feet at right angles to the legs - right? left?

Has there been any surgery to these joints?
Which joints? When? Where? Surgeon? Hospital? Did it help?

(9)

BEHAVIOUR & MOODS use boxes (1=yes, 2=no, 3=don't know) & comment..

Does this person , **have unexplained periods of excitement or agitation** ☐

Please describe them

How often do they occur?

How long do they continue

Does anything bring them on?

Does anything make them worse?

Does anything help?

Does this person **have unexplained attacks of sadness** ☐

Please describe them

How often do they occur?

How long do they continue

Does anything bring them on?

Does anything make them worse?

Does anything help?

Does injury result from her activities: ☐

Injury to self (please describe)

What makes this worse?

What reduces it?

Injury to others? (please describe)

Is the sleep regularly disturbed ? ☐

At what time (times) of night? For how long is she awake?

What does s/he do when she wakens during the night?

What do you do when s/he wakens you at night?

When do you usually put her to bed in the evening?

When does s/he usually waken in the morning?

Do you usually waken him/her ? or does she usually waken spontaneously?

Does s/he usually sleep in daytime? at what time(s) of day

for how long? do you waken her or let her waken herself?

(10)

GENERAL HEALTH:-

Has this person's **general health** in the last 12 months been:- good ? fair? bad?

Please list all admissions to hospital in the last 12 months

Reason for admission	date admitted	date discharged

Please list other episodes of acute illness or longstanding health disorders and which have given trouble in the last year with dates and durations of episodes:-

Problem	date of onset of this episode	duration of episode

Please list all medications in the last 12 months **(conventional and unconventional).**

Condition treated	Medication	Dose	Date started	finished

Vision: Has a squint ever been noticed? at what age(s)

Is this still present?

Has any other visual defect been detected? Are spectacles worn?

Hearing: Does this person have defective hearing?

Please state abnormal tests, if carried out

(In female) **Puberty**: Has breast fullness appeared? at what age ?

Has pubic hair appeared? at what age?

Are breast and body hairs fully adult? from what age?

Has menstruation started? from what age ?

If started, is it regular? Troublesome? if finished when did it stop?

Family details:-

Please complete, or bring up to date, the family tree on the last page. There is no need to repeat information already given but please give any new family developments, pregnancies. Births, deaths or illnesses.

State any major change in circumstances in the care arrangements for this person in the last 12 months

The section below refers to the inclusion of the health information you have provided in the British Isles survey for Rett Syndrome. For more details please read the accompanying information sheet

May I have your permission to ask your doctors and surgeons for further information? Yes/ No

May I share the information with doctors collaborating closely with me in Rett research? Yes / No

My I include this information in scientific publications (separated from names)? Yes/ No

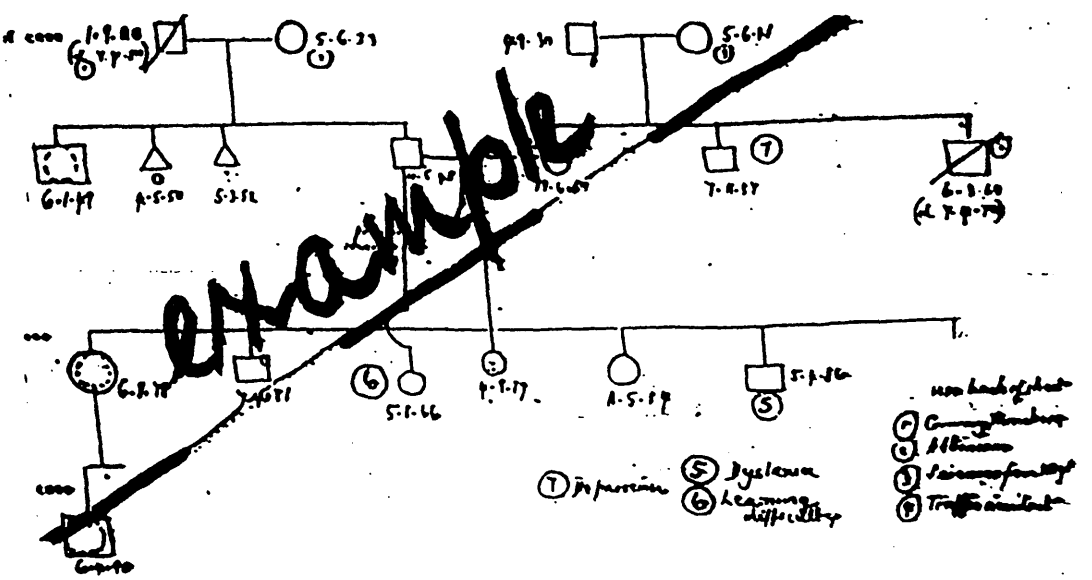
Are you willing for me to keep the health data you have given me on my computer? Yes/ No
My computer has no automatic link to any other and none is planned.

Date signed your relationship to the person

I have/ have not already made a copy of the questionnaire for myself (please do this if you can)

The health information which I hold with the permission of families provides a valuable foundation for research into the causes and treatment of Rett Syndrome because it represents the experience of a large number of girls and women, raises questions which direct much of the research and provides answers to many practical questions regarding the difficulties which girls and families have to deal with, making it possible for me to produce advice for families and professionals.

PLEASE DON'T FORGET TO COMPLETE THE FAMILY TREE ON THE BACK OF THIS SHEET OR BRING IT UP TO DATE IF YOU HAVE SENT ONE PREVIOUSLY. Here is an example to demonstrate how to complete it.

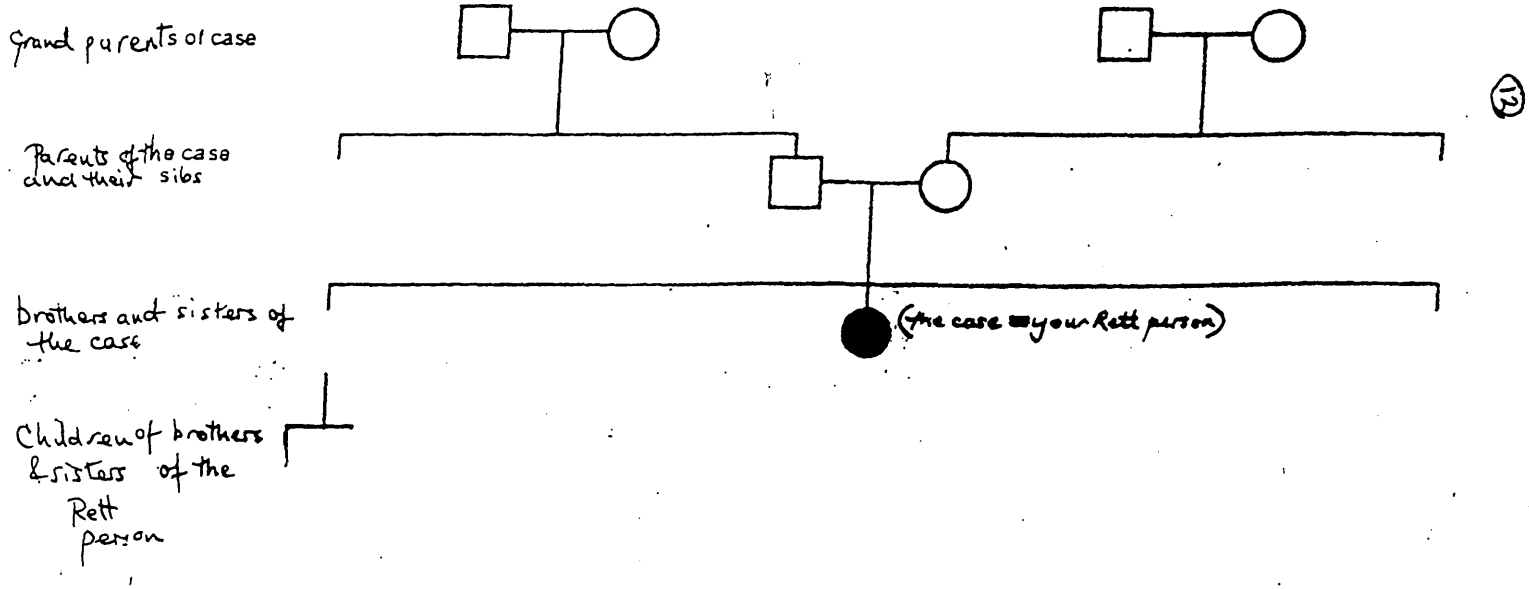


Name:-
Date completed

FAMILY TREE: one to be completed for each case (see example)
Please complete a family tree for each case, giving the following information for every pregnancy indicated on the form, including the children of siblings of the case:
date of birth (and death) and sex. Include still births and miscarriages.
Any serious illness or disability — including any learning difficulties and any mood problems eg depression

SYMBOLS FOR USE ON THE FAMILY TREE:

male □ female ○
marriage to a blood relative ○—□
miscarriage or abortion △
still born or died ☒ ⌀
affected with Rett Syndrome ■ ●
identical twins ○—○ not identical ○○
live born; sex unknown ◇



(12)

APPENDIX E: SUBJECT INFORMATION SHEETS AND CONSENT FORMS

Typical material for recent projects:

Format has varied according to situations and projects

Dr Alison M Kerr FRCP FRCP&CH
Senior lecturer, honorary consultant
in paediatrics and learning disability
tel/ans 0141 211 0281, fax 357 4899,
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UNIVERSITY
of
GLASGOW

CONSENT FORM for .....date of birth.....

Title: **The British Isles Survey for Rett Syndrome**
A descriptive study of Rett disorder throughout life

Please initial the boxes as appropriate and sign below

1. I confirm that I have read and understand the information sheet dated 6.5 2003 for the above study and have had the opportunity to ask questions ☐

2. I understand that participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason, without the medical care or legal rights of this person being affected ☐

3. I understand that sections of the medical notes of this person may be looked at by responsible individuals working with Dr Alison Kerr where it is relevant to this research. I give my permission for such individuals to have access to these records ☐

4 . I agree to inclusion of the person named above in this study

....
name of the person giving consent date signature

.....
relationship to the individual (parent, or welfare guardian)

Dr Alison Kerr..... .....
researcher signature

DEPARTMENT OF PSYCHOLOGICAL MEDICINE
Academic Centre, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH
Professor Sir Michael Bond *Head of Department* Dr R N Herrington

[1] while this is typical material for recent projects the format has varied according to the project and situations

The British Isles Survey for Rett Syndrome: Information sheet: 6.May 2003

What is the British Survey for Rett Syndrome? The survey for Rett syndrome is the national register of people who have been diagnosed with the Rett Syndrome. For each individual, concise data is stored on a free standing project computer to indicate the health of the individual and the severity of the condition. Any video donated by families expressly for research is also stored in a secure room at Glasgow University.

What is the purpose of the survey? It was formed because it was realised that far too little was known about the condition for effective treatment to be developed. Also the diagnosis was being made in many cases long after the severity of the condition was appreciated, causing great distress among families and uncertainty among professionals. The survey aims to gather concise information for each person on the problems encountered, diagnostic tests, and indications of the health of each person. This accumulated information will give a clearer picture of the life time problems of Rett syndrome and will lead to the formation of further key questions which can find their answers through new research studies. For example we are concerned to chart the early difficulties of babies born with Rett so that the condition can be recognised earlier and can be more effectively supported. We need to know the long term outcome of surgical correction for scoliosis so that informed decisions can be taken when and how to operate.

About taking part. The family or carer of every person known to have the disorder is invited to contribute information because it will require large numbers in order to understand the special problems of people of different ages with different levels of severity. For example some people require specialised treatment for scoliosis, feeding difficulties, breathing or heart irregularity. It is only if many people contribute information that the usual outcomes of such intervention will become clear so that families and doctors can be offered informed advice on management. Taking part involves completing the enclosed questionnaire with consent for that information to be included with the survey data. If you choose to consult me for clinical advice on Rett syndrome I will request your permission to include any new clinical data with that data. No one is obliged to take part and everyone is free to withdraw from the study at any time. Withdrawal does not in any way restrict your opportunities to seek my advice.

What will happen to the results of the survey? The information gathered will be shared with my closely collaborating professional colleagues and will be presented in a series of scientific publications in which identities will be masked. If a situation is so rare that the identity of the individual might be evident then that family will be offered the choice to refuse participation. Articles based on the survey information will be provided to the Rett Associations

Who is organising and funding the survey? I developed the survey and have conducted it since 1988. The survey itself is not funded and my work on it is voluntary, however the two British Rett Assocations have facilitated my work by providing helpful contact with families and funding my service to them. I receive advice from Professor Angus Clark, geneticist, at Cardiff Institute of Medical Genetics, Dr Bronwen Burford, psychologist, at Glasgow University and Professor Robin Prescott, statistician, at Edinburgh University.
Thank you for reading this summary about the project. Please feel free to ask me if you have further questions.

the material has varied according to projects and situations

Dr Alison M Kerr OBE FRCP FRCP&CH
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questionnaire speech in Rett 04

January 2004

Dear

Re: Speech in Rett

We are reviewing the progress of girls with Rett syndrome who have useful speech because there is so much to be learned from these people and their families which will help in the development of more effective ways to support learning in everyone with Rett.

From your earlier reports we realise that your daughter has been able to use speech meaningfully and we will be very grateful if along with this fresh Rett survey health questionnaire you are willing to answer to some new questions about speech and learning in your daughter. If she can answer simple questions in words or signs it will be helpful if you can explain the questions to her and write down and explain her answers for us – great if she is able to write any answers herself!! Please feel free to add any information you consider relevant – such observations are really welcome. If there are questions which do not apply just put a line through them or comment.
Please return completed the questionnaires to Dr Kerr at the address above.
What we find will be published in a scientific paper with the identity of individuals masked.

We do hope to hear from you but will quite understand if you cannot help.

Yours sincerely,

Alison Kerr Hayley Archer

.....

Speech in Rett disorder:
If you can help in the project please complete this permission slip:-

I .....full name.....signature.....date
do give my permission for scientific publications to include the information I am providing on speech and learning in people with Rett. I understand that identities will be masked.
Please state your relationship to the person with Rett.....
.....

while this is typical material for recent projects the format has varied according to the project and situations

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Dear

Re:.....

As you may know, since 1982 I have been engaged in research into Rett Syndrome and other disorders with strong clinical similarities. This work relies on my own observations and those of families and professional colleagues and is directed to understand what happens over a life time with the disorder in people with different levels of severity, how the health of the individual is affected by the care provided and the bases for the similarities to other conditions. During the next few years I hope to complete the publication of this collected information. Publications will carry no individual identification.

Although the number of the people reported to have Rett syndrome in the British Survey is now large (over 1000), the number in each subgroup is still quite small, for example those at just one age, those who have had a particular form of medical or surgical treatment or those with any one of the many known mutations on the *MECP2* gene. This is why I am continuing to offer the questionnaire. I do appreciate that some families or carers will be unable to agree to assist me.

I will be much obliged if you consider it appropriate to complete the enclosed questionnaire or to pass it on to the family or a colleague who is more directly involved. If you have any questions about the study or about Rett Syndrome I will be glad to try to answer them

With kind regards,

Alison Kerr

while this is typical material for recent projects the format has varied according to the project and situations

Autonomic Assessment for people with Rett Syndrome.

Alison Kerr: Academic Centre, University of Glasgow Department of Psychological Medicine, Royal Gartnavel Hospital, Great Western Road, Glasgow G12 OXH

This is a non-invasive outpatient procedure lasting about two hours. It is directed to measure respiratory rhythm and brain stem regulation of pulse rate and blood pressure. The patient is seated and sensors are placed in contact with the skin. Nothing pierces the skin. All the recordings are viewed continuously on monitors and stored with a time trace for analysis. Families and the referring physician are invited to be present. Patients usually seem to enjoy the event and sometimes fall asleep. The assessment is conducted by Dr Peter Julu, neuro-physiologist, Dr Stig Hansen, senior physicist and an e.e.g. technician.

The e.e.g. is monitored using a light rubber cap with a contact gel injected though holes in the cap. This records the spontaneous electrical activity on the surface of the brain, which is usually abnormal and often epileptogenic in Rett. Breathing movements are measured through a stretch sensitive band round the lower chest and upper abdomen. Thirteen different respiratory rhythms have been described in Rett. Most people with Rett display several of these and there are characteristic changes with age. Blood pressure and pulse are monitored through a finger sensor and heart action is recorded by electrocardiogram. Blood levels of oxygen and carbon dioxide are measured though skin sensors on the chest. Activity is recorded on time-locked video.

The central autonomic (brain stem) control of cardioinhibitory activity is monitored by the NeuroScope which calculates cardiac vagal tone from the e.c.g. R-R intervals, beat by beat. The cardiac vagal tone is expressed in arbitrary units on a linear vagal scale. Taken altogether these measurements allow recognition of the characteristic abnormality of brain stem control in the Rett disorder and provide insight into the effects of that disturbance on the individual being assessed. All measures are displayed on monitors throughout a one hour recording period and stored for later analysis. In Rett, vagal tone is characteristically low, often at neonatal levels and central autonomic regulation of cardio-respiratory function is weak. Several types of non-epileptic vacant spells may occur due to interruption or abnormal activation of brain stem control mechanisms.

On the basis of what is found the family and physician are advised on management. The assessment assists planning of intervention and provides an objective measure of its efficacy. It helps to differentiate epilepsy (also present in about 50% of people with Rett) from non-epileptic vacant spells which are even more common and readily mistaken for minor or partial epilepsy.

Developed in Glasgow, this neuro-physiological assessment is now offered by Dr Peter Julu at Central Middlesex Hospital, London for people with Rett Syndrome and other conditions involving disordered central cardio-respiratory regulation on referral by the physician. It is also established in the Rett Centre, Sweden, and recently in Sydney, Australia.

while this is typical material for recent projects the format has varied according to the project and situations

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I am sending you a copy of the health questionnaire for Rett syndrome and will be very pleased if you can find time and are willing to complete it as far as you can for this person and return it to me at the above address.

As you may know, since 1982 I have been working with the Rett Associations to see and advise people with Rett syndrome and their families and professionals and to carry out research. The research is directed to understand what happens over a life time with the disorder in people with different levels of severity in order to develop more effective support. I am also concerned to find out how the health of the individual is affected by the care already being provided. Although the number of the people in the British Survey is now large (over 1000), the number in each subgroup with special problems or skills is still quite small, for example those at just one age, those with special problems of epilepsy, breathing irregularity or scoliosis, those with speech and those who have had a particular form of medical or surgical treatment. In order to develop more effective support for each person we need to know more about each group of people and this is why I am inviting you to complete the questionnaire.

I do appreciate that some families or carers will be unable to agree to this. Whether you can agree or not please feel free to discuss my request and the questionnaire with your medical advisers and to ask me further questions if you wish.

The results of the survey study will be published in scientific journals and also in the newsletters of the Rett Associations, care being taken to ensure that individual identities are not disclosed.

With kind regards,

Alison Kerr

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