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A comparative investigation of longevity and morbidity in Angelman syndrome and Prader-Willi syndrome

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A comparative investigation of longevity and morbidity in Angelman syndrome and Prader-Willi syndrome

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Abstract

The present study examined the life histories of individuals in Western Australia with a dingnosis of Angelman or Prader-Willi syndrome. Angelman and Prader-Willi syndromes are phenotypically diverse disorders both of which result from the failure of imprinting at the chr15qll-q13 locus. In most cases, loss of the maternal imprint from the region leads to Angelman syndrome, while lack of a paternal pattern results in Prader-Willi syndrome. Between 4-14% of Angelman cases have a mutation in a single gene, *UBE3A*.

Subjects for the study were identified from the Disability Services Commission of Western Australia. Data on these individuals were obtained from the client files held by the Commission, and supplementary data were added by linkage to a number of datasets via the Western Australian Data Linkage Unit. The information was then compiled into a database to provide information to physicians, families, and carers on the life histories and ageing patterns of people with either disorder.

Fifty-six of the 90 subjects identified had a diagnosis of Prader-Willi syndrome. Ten of the individuals clinically diagnosed with Prader-Willi syndrome were analysed separately (Prader-Willi-like), as they had returned a normal methylation test and therefore were unlikely to have the disorder. This left a group of 46 individuals in the Prader-Willi cohort, and 34 persons with Angelman syndrome. Nine individuals were deceased by the time of data collection.

Both disorders are now diagnosed at an earlier age than was common ten years ago, although there was still some degree of delay in diagnosing Angelman syndrome when compared to Prader-Willi syndrome. In addition, the majority of recent diagnoses were confirmed by genetic testing, as opposed to the lack of genetic verification for earlier cases.

The clinical presentation of both syndromes was generally similar to the expected profiles. Throughout their lives, individuals with Angelman syndrome exhibited most of the major clinical features; however epilepsy usually did not appear until after the age of three years. Conversely, the Prader-Willi cases tended to present different characteristics at various ages. During infancy, feeding

difficulties and hypotonia were almost universal, but these symptoms became less common in later life. By age three to four years most of the Prader-Willi children had an insatiable appetite, leading to obesity unless the diet was strictly controlled. Some features, such as hypogonadism, were present from birth, but in females it was not always obvious until puberty. There were some diagnostic clinical criteria which were unreported for many cases, e.g., microcephaly or prognathia in Angelman syndrome, and hyperphagia or the characteristic facies in Prader-Willi syndrome.

For many subjects either no genetic test had been requested, or karyotype or banding tests only were undertaken, many of which were uninformative. The incidence of uniparental disomy in Prader-Willi syndrome was around half that expected, although the rate for Angelman syndrome was within the expected range.

On average, individuals with Angelman syndrome had been admitted to a hospital on nine occasions, and those with Prader-Willi syndrome on seven occasions. Dental work and respiratory disorders were the main reasons for hospital admission for both groups of patients. However, significantly more Angelman syndrome patients were admitted with epilepsy than Prader-Willi cases, and treatment for undescended testes was needed only by those with Prader-Willi syndrome.

Intellectual function ranged from normal to profoundly disabled, with 88% of the Angelman group within the moderate-severe categories, and 72% of Prader-Willi cases with a mild-moderate disability. There were many fewer than expected Prader-Willi patients with an IQ>70 (9% vs 40%). But since Disability Services Commission does not accept individuals with an IQ>70, case ascertainment was effectively biased to exclude such people. This may explain the low rate of uniparental disomy in the Prader-Willi group, since such cases have a less severe phenotype than those with any other disruption of chr15q11-q13.

In many cases the Disability Services Commission files contained only limited information on the clinical and behavioural presentation of these individuals. Often this was due to a lack of contact with the Commission, for any of a number of possible reasons, e.g., distance from services, reduced need for

services, or migration into or out of Western Australia. The clinical criteria for both syndromes have only been published within the last 10-12 years, which meant that reporting of some characteristics was lacking as the relevance of these features was unknown prior to those publications.

Previous reports on ageing in people with intellectual disability have indicated that many of their ageing issues mirror those in the general population, e.g., visual or hearing impairment, loss of mobility, and mental health disorders. Since the oldest member of the study group was aged 48 years, it was not possible to produce a comprehensive picture of the age-associated morbidity typical of either disorder. However, the study does provide a valuable comparative baseline for ongoing investigations into both syndromes.

Declaration

I certify that this thesis does not, to the best of my knowledge and belief:

(i) incorporate without acknowledgement any material previously submitted for a degree or diploma in any institution of higher education;

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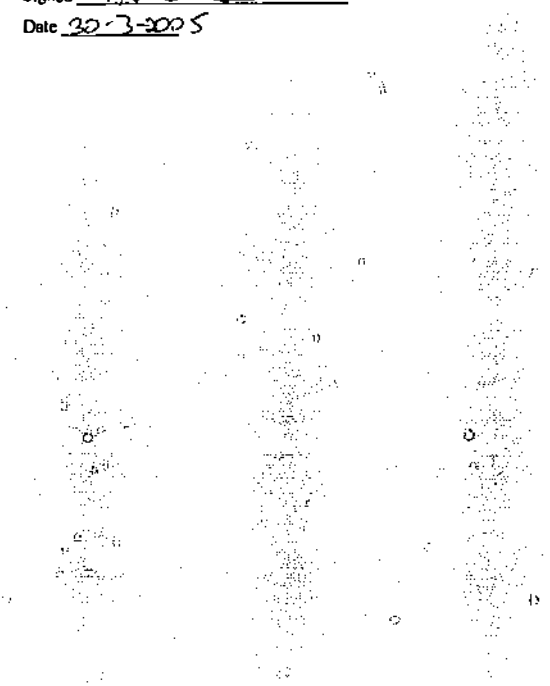

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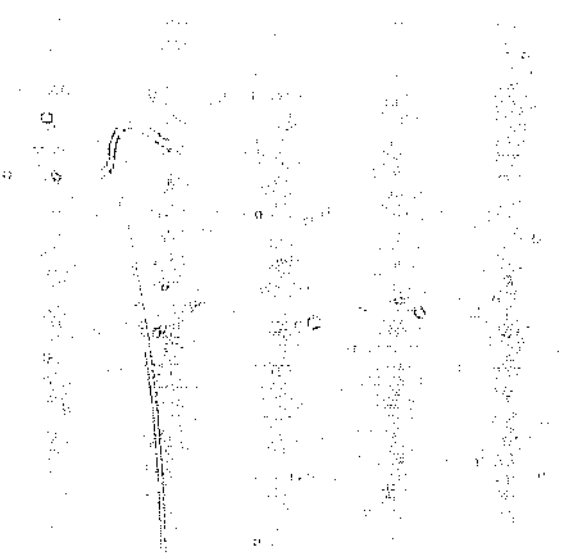


LIST OF ABBREVIATIONS

ART:	Assisted reproductive technology
AS:	Angelman syndrome
AS-IC:	Angelman syndrome imprinting centre
AS-SRO:	Angelman syndrome smallest region of overlap
ATR-X:	α-thalassemia retardation syndrome
BP:	Break point
BWS:	Beckwith-Wiedeman syndrome
DSC:	Disability Services Commission of Western Australia
EEG:	Electroencephalogram
FISH:	Fluorescence in-situ hybridisation
FRPQ:	Food-Related Problems Questionnaire
GH:	Growth hormone
GSWA:	Genetic Services of Western Australia
HGP:	Human Genome Project
HMDS:	Hospital Morbidity Data System
IC:	Imprinting centre
ICSI:	Intracytoplasmic spermatozoa injection
ID:	Intellectual disability
IVF:	In-vitro fertilization
MBS:	Medicare Benefits Schedule
MHIS:	Mental Health Information System
OCA2:	Oculocutaneous albinism type 2
PBS:	Pharmaceutical Benefits Schedule
PWS:	Prader-Willi syndrome
PWS-IC:	Prader-Willi syndrome imprinting centre
PWS-SRO	Prader-Willi syndrome smallest region of overlap
SMC:	Supernumerary marker chromosome
SMR:	Standardised mortality rate
snoRNA:	Small nucleolar RNA
SNP:	Single nucleotide polymorphism
SRS:	Silver-Russell syndrome
TND:	Transient neonatal diabetes
UPD:	Uniparental disomy
WA:	Western Australia
WeeFIM:	Functional Independence Measure for children

1. INTRODUCTION

1.1 The significance of this project

The World Health Organization has called for research into practices that successfully promote longevity and healthy ageing in persons with intellectual disability (ID) (Hogg *et al.*, 2001). In terms of life expectancy, the population profiles of both developed and developing countries differ greatly from those of one hundred years ago. For example, the median age in Australia in 1901 was 22.6 years, but by 1999 it had risen to 34.9 years (Australian Bureau of Statistics, 2000), because of the increasing ratio of older people to those middle-aged and younger. People with intellectual disabilities are also living significantly longer than in the past (Eyman *et al.*, 1987; Janicki *et al.*, 1999; Bittles *et al.*, 2002). Those with mild ID have approximately the same mean life expectancy as the general population, although severe ID decreases life expectancy by as much as 20% (Patja *et al.*, 2000; Patja *et al.*, 2001; Bittles *et al.*, 2002; Sutherland *et al.*, 2002).

The *International Plan of Action on Ageing* (United Nations, 1998) suggested that data relating to older people were critical for the successful development of processes and policies aimed at improving the longevity and quality of life of an ageing population. There are a number of identified predictors of chronic disease that lead to a limitation of functional abilities in the older population, including poverty, being female, having a lower education level, and reduced access to health services (Walsh, 2002). These predictors apply equally to those with ID, especially as members of the ID population often fall into two or more of those categories (Holland, 2000). However, one of the main difficulties in the provision of healthcare for people with ID is the communication barrier that often exists between the patient and the doctor, and the difficulty experienced by an individual with ID in recognising worrying symptoms or conveying relevant information to the physician (Evenhuis, 1997; Lunsky & Reiss, 1998; Janicki *et al.*, 1999; Hogg, 2001). On average, individuals with ID have less access to preventative health care programs, have more sedentary lifestyles, and are less likely to complain of ill-health, although those with

mild/moderate ID can and do make independent healthcare decisions (Allan, 1997).

1.2 The nature of Angelman syndrome and Prader-Willi syndrome

Angelman syndrome (AS: MIM 105830) and Prader-Willi syndrome (PWS; MIM 176270) are specific chromosomal disorders located in the q11-q13 region of chromosome 15. They both involve abnormalities of genomic imprinting, i.e., the process by which genetic material is differentially expressed according to its parental origin. Angelman syndrome occurs when the maternal imprint is absent from the region, while Prader-Willi syndrome results from absence of the paternal imprint. Imprinting is one of the mechanisms involved in epigenetics, i.e., changes in gene activity that occur without variation of the underlying DNA sequence (Riddihough & Pennisi, 2001; Wu & Morris, 2001). It is thought that epigenetic processes, such as DNA methylation and RNA-mediated silencing, evolved in part as defence mechanisms against parasitic DNA, transposon damage or virus invasion (Falls *et al.*, 1999; Matzke *et al.*, 2001; Bestor, 2003). Currently there are 47 human genes listed in the Imprinted Gene Catalogue, with a relatively even distribution between maternal and paternal expression (Morison *et al.*, 2001; Morison, 2004). However, as the roles and actions of the estimated 25,000-27,000 genes in the human genome are further clarified, the number of imprinted genes may be expected to rise accordingly (NHGRI, 2004). To date, most of the known imprinted genes are involved in either pre- or post-natal growth and development (Maher *et al.*, 2003a).

Although the two syndromes are similar in terms of their basic genetic mechanisms, they differ significantly in clinical presentation. Angelman syndrome occurs in 1 per 10,000-20,000 births (Hou *et al.*, 1998; Stromme, 2000). The disease phenotype is characterised by severe ID, limited speech, an unstable jerky gait, and seizures. While AS was first clinically described by Angelman in 1965, the underlying genetic defect was not recognised until the late 1980s, with a consensus opinion on the clinical criteria for diagnosis of the syndrome published in 1995 (Williams *et al.*, 1995).

Prader-Willi syndrome has a similar prevalence rate to AS of between 1 per 10,000-25,000 births (Stromme, 2000; Whinington *et al.*, 2001; Smith *et al.*,

2003). The phenotypic characteristics include mild to severe ID, short stature, hypogonadism, an insatiable appetite and resultant obesity. It was originally described in 1956, and clinical diagnostic criteria were developed in 1993 (Prader *et al.*, 1956; Holm *et al.*, 1993). As with Angelman syndrome, the genetic basis was only elucidated in the late 1980s.

There is considerable phenotypic heterogeneity among people with each syndrome, possibly related to the nature of the underlying defect. The relatively recent description and diagnosis of the syndromes means that information on their clinical progression is still very limited, and there may be many older, institutionalised individuals who have remained undiagnosed throughout their adult life. In addition, little information is available on the relationship between the disease phenotype and the specific genetic anomaly, or on the medical and health obstacles faced by people with either syndrome in adulthood. This knowledge is of primary importance in improving our understanding of the nature and progression of the disorders. It is also needed for appropriate family counselling and health care services, and to increase basic knowledge of the influence of imprinting in the chr15q11-q13 region on the overall function of the human genome.

1.3 The purpose of the study

The present project aimed to establish a dedicated database of people in Western Australia (WA) diagnosed with AS or PWS. The purpose was to allow estimates of the population prevalence of each disorder to be made, and comparisons drawn between individuals within each group. The database also can be used as a resource for further research into the syndromes and the ageing of the study cohort.

Descriptions of the survival and mortality patterns of people with AS and PWS are recorded, together with hospital morbidity histories, so that information on the life-course and survival of people with AS and PWS can be provided to families, clinicians and genetic counsellors. Information of this nature will aid individuals and their families in predicting future health needs and in planning appropriate interventions. As the life expectancy of people with ID has increased, the age of their parental carers has similarly extended. This results in families

facing a range of problems, including diminishing health of the ageing carer, the possibility of a sudden end to the caring relationship due to incapacity or death of the carer, and fewer options for employment and/or social activity for the middle-aged or older ID individual (Holland, 2000; Bigby *et al.*, 2002). More frequently, arrangements for guardianship for adults with ID may be necessary when parents are no longer available to fulfil this role, in a manner similar to the increase in guardianships for adults with dementia that has occurred in Japan since 1980 (Mizuno & Nanba, 2003).

Detailed information on the life-courses of people with AS and PWS has been collated and analysed. This project is one of the first in Australia to investigate health and ageing issues pertaining to AS and PWS in a defined population, and the data can be expanded by the continued future collection of information on these individuals.

1.4 Research questions

1. What are the prevalence rates of AS and PWS in Western Australia?
2. What life-time morbidities are common and/or specific to each syndrome?
3. What ageing issues are relevant to people diagnosed with each syndrome?

2. REVIEW OF LITERATURE

2.1 The human genome

2.1.1 Overview

The information collected as part of the Human Genome Project (HGP) has had a major impact on previously held views of the genetic code. It was formerly believed that each gene encoded a specific protein, and therefore the human genome would contain more than 70,000 genes (the smallest estimated number of human proteins). However, to date the HGP has identified only some 25,000-27,000 genes, indicating much greater complexity in terms of gene interactions and variations of expression than were previously believed (National Human Genome Research Institute, 2004). On average, each human gene can produce three different proteins, simply by changes in the initiating sites for transcription and to the splicing points (Pennisi, 2001). Almost 50% of the human haploid genome, approximately 3 billion base pairs, is composed of repeat sequences. It is not yet known if these areas perform a particular function, perhaps as regulators of gene expression. According to the director of National Human Genome Research Institute (Collins *et al.*, 2003), the aims of the HGP now include:

1. Identification of all structural and functional components (genes or regulators) encoded in the genome;
2. Investigation of the structure of the protein pathways and genetic interactions within the genome, and establishment of the role of each component in the phenotype;
3. Identification of the range of heritable variation found within the human genome, especially the more common variants, e.g., single nucleotide polymorphisms (SNPs), small deletions, and insertions.

The role of individual genes in the production of a specific phenotype is complicated by the very large number of SNPs, which may add many small effects to a single phenotype. Alternate mutations or mutations at different sites on the same gene can result in different disorders. For instance, a disruption of the dystrophin gene at one point leads to Duchenne muscular dystrophy while a

similar mutation at a different point results in the clinically less severe Becker muscular dystrophy (Gilchrist *et al.*, 2000). In addition, the expression patterns of variant alleles can be affected by a wide range of factors, e.g., environmental interactions, stochastic events, and intergenetic interactions (Hartman *et al.*, 2001).

In some cases, a number of different genes can produce a phenotypically identical disorder, such as autosomal dominant polycystic kidney disease (Gilchrist *et al.*, 2000), and different forms of imprinting failure within chr15q11-q13 can result in PWS or AS. Continued progress on the delineation of these interactions by the HGP and similar organisations will increase knowledge in these areas, and provide explanations for the variations in phenotype between individuals with the same syndrome, but different genotypes. It is also envisaged that detailed knowledge of the differences between genotypes will allow precision matching of medications to act optimally for that individual, e.g., a specific epilepsy drug which will be effective for treating individuals with Angelman syndrome caused by a deletion (Prows & Prows, 2004).

2.1.2 Genomic imprinting

2.1.2.1 Normal effects of imprinting

The process of imprinting is thought to involve the differential methylation of CpG islands (cytosine/guanine-rich regions of DNA) in genes located close to the imprinting centre. Gene-rich segments of the genome tend to have higher concentrations of CpG islands than areas with a lower gene density (Pennisi, 2001). If methylation occurs within a promoter region of a gene where transcription is initiated, then transcription of the particular gene is blocked. This form of silencing is evident in imprinted genes, during X-chromosome inactivation, and when parasitic or transposable gene elements are silenced (Falls *et al.*, 1999; Jones & Takai, 2001; Park & Kuroda, 2001; Bestor, 2003).

It has been hypothesised that genomic imprinting is a solution to the conflict of interest that is presumed to exist between the paternal and maternal genomes, in which the paternal role is to increase the fitness of progeny, irrespective of maternal cost. In contrast, the maternal objective is to limit offspring fitness by an amount sufficient to prevent overuse of maternal resources

while continuing to maintain fetal health (Haig & Wharton, 2003). The mixture of paternally and maternally imprinted genes found throughout the genome is thus likely to represent a compromise between the two positions, especially as most known imprinted genes affect pre- or postnatal growth (Falls *et al.*, 1999; Haig & Wharton, 2003; Maher *et al.*, 2003a).

Methylation has been shown to alter the interactions between proteins and DNA. These interactions can lead to changes in chromatin structure and to an increase or decrease in the rate of transcription, which is sometimes linked to cancerous growth patterns (Belinsky *et al.*, 1998; Morison *et al.*, 2001; Martinez-Delgado *et al.*, 2002). For example, a tumour suppressor gene (*p16*) is inactivated by hypermethylation of the promoter region in a number of tumour types, including lung cancers and squamous cell carcinomas. The degree of methylation within the region increases as the level of abnormality of the cells increases, indicative of a possible link between methylation of the promoter, loss of expression, and development of the carcinoma (Belinsky *et al.*, 1998).

Hypermethylation of histones, especially histone3 on Lys9 (H3L9), has been linked to the formation of stably-silenced chromatin regions on the maternal chromosome 15 at the Prader-Willi syndrome imprinting centre (PWS-IC). Conversely, the methylation of histone3 Lys4 (H3L4) has been associated with the paternal chromosome 15 in the same area (Xin *et al.*, 2001; Lau *et al.*, 2004). The chromatin modifications which result from this selective histone methylation are proposed epigenetic markers, as the changes persist throughout development and are parent-specific (Xin *et al.*, 2001; Rougeulle *et al.*, 2003; Lau *et al.*, 2004). In addition, acetylated histones have been identified on the unmethylated and active paternal CpG island of the *SNURF-SNRPN* (*SNRPN* upstream reading frame-small nucleolar ribonucleoprotein N) region, whereas the inactive maternal copy is not associated with acetylation (Saitoh & Wada, 2000). The silenced genes have been experimentally reactivated by treatment with a DNA methyltransferase inhibitor which induces hypomethylation of the *SNURF-SNRPN* CpG island. However, it is not known if this technique could be used therapeutically to help alleviate the symptoms of those with imprinting disorders (Saitoh & Wada, 2000).

The epigenetic imprint markers that identify the parent of origin are erased during early gametogenesis, and then reset with the new parent-of-origin mark at or before meiosis II (Tada *et al.*, 1998; Kerjean *et al.*, 2000; Ferguson-Smith & Surani, 2001; Cox *et al.*, 2002; Kelly & Trasler, 2004). In male mice an imprinted gene, *H19*, which produces a fetal liver mRNA, has been shown to be fully methylated on the male strand by day 15.5 post-coitus, i.e., the paternal imprint is fully established by the early spermatocyte stage of gametogenesis, before the completion of meiosis I (Lucifero *et al.*, 2002). Similarly, in human males the *H19* imprint is acquired by the spermatogonia stage of gametogenesis (Kelly & Trasler, 2004).

Likewise, in the female mouse a range of imprinted genes have been shown to undergo methylation at a variety of times and speeds. Most of the loci investigated by Lucifero *et al.* (2004), i.e., *Snrpn*, insulin-like growth factor 2 receptor (*Igf2r*), paternally expressed gene 3 (*Peg3*), and mesoderm-specific transcript (*Mest*), are completely methylated by 25 days postpartum, although the process occurs at different stages of oogenesis for each gene (Lucifero *et al.*, 2002; Lucifero *et al.*, 2004). In humans, maternal methylation of the *SNURF-SNRPN* exon 1 normally is fully established during late ovulation or after fertilisation (El-Maarri *et al.*, 2001). The chromosomes in a female mouse also gain methylation asynchronously, i.e., the maternally-contributed strand of *Snrpn* acquires the imprint earlier in development than the paternal strand. This discrepancy between the timing of methylation indicates that some form of recognition process is available in primordial germ cells which forms a means of differentiating between the origins of each chromosome, even in the absence of hypermethylation (Davis *et al.*, 2000; Kerjean *et al.*, 2000; Kelly & Trasler, 2004). Selective acetylation of histones may be such a means of identification, although there may also be other epigenetic changes yet to be identified (Saitoh & Wada, 2000).

2.1.2.2 Failure of imprinting

Loss of effective imprinting can be due to:

1. Deletion of a portion of either the paternal or maternal chromosome which includes the relevant gene/s.

2. Uniparental disomy (UPD), i.e., the inheritance of two chromosomes from one parent and none from the other. This may be an isodisomy (two identical chromosomes), or a heterodisomy (two different chromosomes). The effect of UPD on gene expression can vary greatly, depending on the normal role of each allele at that locus. For genes that are not imprinted, UPD has usually no effect on expression, although there are cases where a recessive allele is 'unmasked' due to the presence of two copies from one parent, instead of one from each parent (Hitchins & Moore, 2002). Any imprinted gene which is hypermethylated on both alleles due to UPD will not be expressed (nullisomy), but it would be expected that imprinted genes which are non-methylated on both alleles will both be expressed, leading to a diploid overdose effect (Smith, 1996). In situations where there is phenotypic variation between UPD and deletion patients, it is possible that the difference results from a gene dosage effect.

3. Mutation by deletion or substitution within the imprinting centre (IC) that leads to disruption of the imprinting process and hence silencing of the imprinted gene/s on both chromosomes (Jiang *et al.*, 1999; Clayton-Smith, 2001).

Methylation usually acts to silence the relevant gene, thereby limiting its expression to the allele from the other parent. The importance of the contribution of both parents to normal development is shown by the production of modified mouse embryos. Androgenetic embryos, containing paternal genes only, suffer from reduced fetal growth and exhibit a very high growth rate for the extra-embryonic tissues (placenta and amnion). Parthenogenetic embryos, with only a maternal gene contribution, show normal fetal growth but greatly reduced extra-embryonic growth. Neither type of embryo is viable to term (Falls *et al.*, 1999).

The delay in resetting the epigenetic marker on specific chromosome strands, (Section 2.1.2.1), may help to explain the recently reported increase in the risk of imprinting disorders found in children conceived by intracytoplasmic spermatozoa injection (ICSI) or other assisted reproductive technologies (ART). It is possible that the oocyte may fail to complete its normal post-fertilisation maturation, which includes the resetting of the epigenetic mark, when undergoing the laboratory processes involved in ICSI or other types of ART (Ferguson-Smith

& Surani, 2001; Cox *et al.*, 2002; DeBaun *et al.*, 2003; Orstavik *et al.*, 2003). In addition, defective *H19* methylation has been shown to be associated with abnormal spermatogenesis and a consequent low sperm count (Marques *et al.*, 2004), which may also have implications for the long-term outcomes of assisted reproduction techniques.

A report on the safety of ICSI found no abnormal methylation effects in infants conceived by this method, although the sample size was quite small (n = 92), and subsequent analysis of sperm samples (n = 90) collected for ICSI showed no imprinting abnormalities (Manning *et al.*, 2000; Manning *et al.*, 2001). A Danish investigation into the outcomes of ART had concluded that the slight increase in perinatal mortality and congenital malformations was most likely due to the effects of multiple births (Westergaard *et al.*, 1999). More recently, however, infants conceived by ART in Western Australia have been shown to be twice as likely to suffer from a major birth defect as naturally conceived infants, and to have lower birth weights (Hansen *et al.*, 2002), and similarly conceived infants in Finland have higher rates of congenital heart malformation (Koivurova *et al.*, 2002). Both sets of results were significant even after controlling for the effects of multiple births, which are more common in ART conceptions, and there are specific morbidity problems associated with such births (Sutcliffe, 2002). A subsequent review of the literature on ICSI indicated an increased risk of congenital and genetic abnormalities, although the authors concluded that the increase could be related to the underlying cause of infertility in the parents (Retzloff & Hornstein, 2003).

Assisted reproductive technology may also affect the incidence of imprinted disorders. Both Angelman syndrome and Beckwith-Wiedemann syndrome (BWS; MIM 130650) have been reported to occur 2-6 times more often than expected in children conceived by in-vitro fertilisation (IVF) or ICSI (Hansen *et al.*, 2002; DeBaun *et al.*, 2003; Gicquel *et al.*, 2003; Gosden *et al.*, 2003; Orstavik *et al.*, 2003; Halliday *et al.*, 2004). BWS is an overgrowth syndrome characterised by macroglossia (pathological and congenital enlargement of the tongue), pre- or postnatal overgrowth, and abdominal wall defects (Paulsen & Ferguson-Smith, 2001). Almost half of all BWS cases have been associated with abnormal imprinting of the *KCNQ1OT* gene at chr11p15. This leads to

demethylation of the *KvDMR1* region of the gene and subsequent biallelic expression of insulin-like growth factor II (*IGF2*), which appears to contribute to abnormal development of the hypothalamic-pituitary-adrenal axis and subsequent growth acceleration (Cole, 1998; Gicquel *et al.*, 2003; Maher *et al.*, 2003b). Despite an exhaustive search of online databases, there appear to be no published reports of PWS in artificially-conceived children, which may be due to the fully functional paternal imprint by the time fertilisation takes place, in contrast to the sub-functional maternal imprint (Geuns *et al.*, 2003).

In addition to Angelman, Beckwith-Wiedemann and Prader-Willi syndromes, transient neonatal diabetes (TND; MIM 601410) and Silver-Russell syndrome (SRS; MIM 180860) have been identified as imprinting disorders. Paternal uniparental disomy of chromosome 6 (UPD6) has been linked with the development of TND, and two imprinted genes are known to be located in the chr6q24 region. These are inferred to have some effect on the disease phenotype (Arima *et al.*, 2001). Similarly, maternal UPD7 is implicated in 7-10% of SRS cases. In Silver-Russell syndrome both pre- and postnatal growth retardation are present, seemingly caused by either under-expression of paternal growth-promoting genes, or over-expression of maternal growth-inhibitors. There are also a range of dysmorphic features associated with the syndrome (Hitchins & Moore, 2002).

2.1.2.3 The role of imprinting failure in the development of PWS and AS

Angelman and Prader-Willi syndromes differ phenotypically, although they both result from failure of imprinting or gene mutation within the same region of chr15q11-q13. In general, if the affected chromosome is maternally derived then Angelman syndrome occurs, whereas Prader-Willi syndrome results if the paternal chromosome is altered. Usually there is no obvious gender bias in either syndrome, although more boys than girls are identified with PWS before adolescence, possibly due to the more subtle phenotypic changes in prepubescent girls (Smith *et al.*, 2003).

Genetic testing for PWS or AS commonly begins with methylation analysis. There are a number of sites within the chr15q11-q13 region that are hypermethylated on the maternal chromosome, e.g., *SNRPN*, *NDN*, *ZNF127*,

and PW71, and some which are preferentially methylated on the paternal strand, e.g., u1D, YL48E and *SNURF/SNRPN* intron 7. Of these loci, *5'SNRPN* has been recommended as the most accurate and reliable site for the assessment of hypermethylation and it has been adopted for prenatal diagnosis (Kubota *et al.*, 1996; Glenn *et al.*, 2000; Geuns *et al.*, 2003). *SNRPN* is expressed from only one allele by the 4-cell, i.e., pre-implantation, stage of embryonic development (Huntriss *et al.*, 1998). The other hypermethylation sites (*NDN*, *ZNF127*, PW71, u1D, YL48E and *SNURF/SNRPN* intron 7) have been found to be less informative than *5'SNRPN*, and to give higher rates of incorrect diagnoses (Geuns *et al.*, 2003). Comprehensive methylation analysis of both PWS and AS cases with an imprinting defect showed that a variety of loci were affected, with methylation abnormal on both chromosome strands (Runte *et al.*, 2001a).

The presence of a single band on methylation testing indicates uniparental methylation, and the size of the band identifies which parental pattern is present, i.e., 4.2kb for the maternal band and 0.9kb for the paternal at *5'SNRPN* (Kubota *et al.*, 1996). The changes in methylation may be due to deletion, UPD or an IC defect, therefore further testing is necessary to determine which of these specific mechanisms is present (Williams *et al.*, 1998). The discovery of two bands (biparental methylation) is sufficient to exclude the diagnosis of PWS in most cases, but not to exclude AS (Buchholz *et al.*, 1998; Friidman *et al.*, 2000b; Glenn *et al.*, 2000). Biparental methylation in AS can be an indication of a single gene (E6-AP ubiquitin-protein ligase; *UBE3A*) mutation (Matsuura *et al.*, 1997; Moncla *et al.*, 1999a), but there also is a proportion of clinically-diagnosed AS patients with no currently identifiable genetic defect.

2.2 Angelman syndrome

2.2.1 History and background

Angelman syndrome was first described in 1965. The phenotype was characterised as a combination of severe learning disability, seizures with a specific electroencephalogram (EEG) pattern, absent speech, jerky ataxic movements, and a happy sociable disposition (Angelman, 1965). Consensus diagnostic criteria, listed in Table 2.1 (p.13), were subsequently published in 1995 (Williams *et al.*, 1995).

Table2.1 Diagnostic criteria for Angelman syndrome

Consistent (100%)
Functionally severe developmental delay
Speech impairment, no or minimal use of words
Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
Behavioural uniqueness: any combination of frequent laughter/smiling; apparent happy demeanour; easily excitable personality, often with hand-flapping movements; hypermotoric behaviour; short attention span
Frequent (>80%)
Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2 years
Seizures, onset usually <3 years of age
Abnormal EEG, characteristic pattern with large amplitude slow-spike waves (usually 2-3/s), facilitated by eye closure
Associated (20-80%)
Flat occiput; occipital groove
Protruding tongue
Tongue thrusting; suck/swallowing disorders
Feeding problems during infancy
Prognathia; wide mouth, wide-spaced teeth
Frequent drooling; excessive chewing/mouthing behaviours
Strabismus
Hypopigmented skin, light hair and eye colour (compared to family), seen only in deletion cases
Hyperactive lower limb deep tendon reflexes
Uplifted, flexed arm position especially during ambulation
Increased sensitivity to heat
Sleep disturbance
Attraction to/fascination with water

Adapted from Williamset al. (1995)

The diagnosis of AS is usually based on clinical findings, and it is now confirmed in 80-85% of cases by cytogenetic or DNA testing (Laan *et al.*, 1999a). The first diagnostic tests for AS were introduced in 1987 (Clayton-Smith & Laan, 2003). Since that time, efforts have focused on further elucidating the genetic mechanism underlying AS, and many descriptions of the variant phenotype and life-course of the syndrome have been produced.

2.2.2 *The Angelman syndrome phenotype*

2.2.2.1 *Developmental characteristics*

Angelman syndrome patients have been reported to be phenotypically normal during the prenatal and perinatal periods, with no diagnostic characteristics in the newborn infant (Cassidy & Schwartz, 1998). However, 63% of the deletion patients seen by Smith (1996) showed hypotonia at birth, and even more (77%) had experienced feeding difficulties during infancy. Developmental delay is generally manifest by 6-12 months of age, when a delay in independent sitting becomes evident (Williams *et al.*, 1995; Cassidy & Schwartz, 1998; Laan *et al.*, 1999a). Sitting is normally accomplished at around one year of age, and walking may be delayed until the eighth year (Smith *et al.*, 1996; Laan *et al.*, 1999a). Males tend to achieve motor milestones at an earlier age than females (Leitner & Smith, 1996), although the two non-ambulant individuals from a group of 11 patients seen by Sandanam *et al.* (1997) were both male. Walking often becomes more difficult with increasing age, with as many as 42% of patients becoming wheelchair-bound in adulthood due to a range of problems including obesity, an unwillingness to exercise, and scoliosis (Clayton-Smith, 2001).

Delayed or absent speech is one of the cardinal features of AS. Few patients ever learn to speak and any who do generally acquire only a very limited vocabulary, although comprehension of language is usually reasonable (Andersen *et al.*, 2001). Small amounts of gestural or signed language may be learned (Williams *et al.*, 1995; Cassidy & Schwartz, 1998; Laan *et al.*, 1999a). A vocabulary of 4-10 words was used by half of the *UBE3A* mutation patients ($n = 14$) studied by Moncla and co-workers (1999). These patients showed a higher level of comprehension and non-verbal communication than is normal for people with AS. Clayton-Smith (2001) also reported improved non-verbal communication skills in a group of older patients ($n = 28$; ages 16-40 years), due to the improved concentration span frequently found in older AS individuals.

ID is present in all people with AS and is usually within the severe to profound range, i.e., with measured IQ levels and an adaptive behaviour assessment of less than 40 points (Smith *et al.*, 1996; Clayton-Smith & Laan, 2003; Beckung *et al.*, 2004). On average, patients with an imprinting centre

disorder have been found to have less severe ID than those with AS caused by other genetic mechanisms (Gillessen-Kaesbach *et al.*, 1999).

2.2.2.2 Physical characteristics

The jerky, ataxic movements associated with AS are apparent at an early age and continue into later life. When walking, the arms are commonly raised and held at a distance from the body, with flexed wrists and elbows. Hand-flapping is also often involved, and the legs are generally kept stiff (Smith *et al.*, 1996; Laan *et al.*, 1999a; Beckung *et al.*, 2004). Scoliosis develops in an estimated 40-70% of affected individuals (Laan *et al.*, 1996; Sandanam *et al.*, 1997; Clayton-Smith, 2001), and can contribute to a loss of mobility as the patients age (Clayton-Smith & Laan, 2003). Surgery for scoliosis has been performed on some patients, often with good results, and the operation is quite well tolerated by most individuals (Lossie *et al.*, 2001). Hypertonicity (high muscle tone) of the limbs, generally found in conjunction with truncal hypotonia (low muscle tone), can lead to joint contractures and a stooping posture as patients become older, and it may have a detrimental effect on mobility (Cassidy & Schwartz, 1998; Clayton-Smith, 2001; Clayton-Smith & Laan, 2003).

During the first few years of life AS patients often develop a distinctively shaped head, commonly either brachycephaly (a disproportionately wide head) or microcephaly (small head size) (Smith *et al.*, 1996; Sandanam *et al.*, 1997; Laan *et al.*, 1999a). Facial features that may occur include a long mouth with widely-spaced teeth, flat occiput, mandibular prognathia with a pointed chin, and a protruding tongue. These characteristics tend to become more pronounced with advancing age (Laan *et al.*, 1999a; Clayton-Smith & Laan, 2003).

Between 15-32% of adult AS patients become obese, although true hyperphagia, as found in PWS, is rare (Smith *et al.*, 1996; Clayton-Smith & Laan, 2003). Obesity can lead to oesophageal reflux, and also contribute to loss of mobility. It is common for AS individuals to show hypopigmentation, i.e., with a lighter skin, eye and hair colour than their unaffected siblings (Laan *et al.*, 1999a; Lossie *et al.*, 2001). However the hair may darken with age, as is common in the general population (Sandanam *et al.*, 1997). Older AS patients are often found to suffer from strabismus (37-57%), and keratoconus (7%) (Laan *et al.*, 1996;

Sandanam *et al.*, 1997). There is no evidence of abnormal genital development in AS cases, unlike the hypoplasia found in PWS, and puberty occurs at the expected age and proceeds in a normal fashion (Williams *et al.*, 1998; Clayton-Smith & Laan,2003). Females with severe ID may, however, have difficulty dealing with menstruation and many are prescribed contraceptives to control menstrual bleeding.

2.2.2.3 Behavioural aspects

Angelman syndrome was once termed the 'happy puppet syndrome', because of the characteristic gait (Section 2.2.2.2) and behavioural traits of patients (Laan *et al.*, 1999a). Inappropriate smiling or laughter, a happy sociable disposition, short attention span, and an easily excitable personality are present in most individuals with AS (Williams *et al.*, 1995; Smith *et al.*, 1996; Laan *et al.*, 1999a). Even babies have been noticed laughing during the first few weeks of life and this form of laughter generally continues throughout life, albeit at reduced frequencies (Sandanam *et al.*, 1997; Clayton-Smith & Laan, 2003). Hyperactivity and excitability are less common in older individuals with AS, who have a better concentration span than younger patients (Laan *et al.*, 1996; Clayton-Smith, 2001). A significant proportion of AS cases suffer from sleep disturbances, with either a reduced need for sleep or abnormal sleep/wake cycles. These abnormal sleeping habits often improve with age (Smith *et al.*, 1996; Sandanam *et al.*, 1997; Williams *et al.*, 1998; Ohta *et al.*, 1999a; Clayton-Smith, 2001; Clayton-Smith & Laan,2003).

Many AS patients are reported to have a fascination for water, reflective surfaces, and balloons (Williams *et al.*, 1995; Clayton-Smith & Laan, 2003), although the significance of this behaviour is unknown.

2.2.2.4 Neurological findings

Seizures are present in approximately 80% of AS cases during childhood, with onset normally within the first few years of life. The seizures are often difficult to control, especially in patients where the causative abnormality involves the deletion of genetic material (Leitner & Smith, 1996; Smith *et al.*, 1996; Minassian *et al.*, 1998; Clayton-Smith & Laan, 2003). Some studies have reported a decrease in seizure frequency during adolescence, but with many

individuals experiencing a return of the seizures in adulthood (Laan *et al.*, 1996; Sandanam *et al.*, 1997; Clayton-Smith, 2001). By comparison, other researchers have described a sustained decrease in seizure frequency into adulthood (Buntinx *et al.*, 1995).

Almost all AS patients have an abnormal EEG profile, even in the absence of seizure activity (Sandanam *et al.*, 1997; Smith *et al.*, 1997; Minassian *et al.*, 1998; Gillessen-Kaesbach *et al.*, 1999; Clayton-Smith & Laan, 2003; Valente *et al.*, 2003). A number of specific patterns have been identified which may be present at different times in the same individual. Many AS children show persistent high amplitude 4-6Hz slow-wave brain activity which is not associated with drowsiness (the delta pattern), although this will often disappear in later life (Matsumoto *et al.*, 1992; Minassian *et al.*, 1998; Laan *et al.*, 1999a; Laan *et al.*, 1999b; Valente *et al.*, 2003). In older AS patients, prolonged runs of triphasic 2-3Hz rhythm, primarily over the frontal region, have been found to be more common (Laan *et al.*, 1996), and spikes associated with 3-4Hz waves across the posterior area have also been identified (Clayton-Smith & Laan, 2003; Valente *et al.*, 2003).

2.2.3 *Genetic basis of Angelman syndrome*

Table 2.2 Categories of Angelman and Prader-Willi syndrome by genotype

Type of mechanism	Persons affected (%)		Methylation	Recurrence
	AS	PWS		
Deletion	65-75	70-74	Abnormal	Very low
Uniparental disomy (UPD)	2-7	24-28	Abnormal	Very low
Imprinting centre (IC) defects	6-10	1-3	Abnormal	Significant
UBE3A gene	4-6	n/a	Normal	Significant
Unknown	10-20	<1	Normal	Rare

Adapted from Jiang et al. (1999)

As shown in Table 2.2 (p. 17), the genetic basis of AS has been subdivided into four main mechanisms, described below. However, there is also a significant proportion of cases in which no specific aetiology has been defined, and some of these may be confused with a range of mimicking conditions, such as Rett syndrome or Lennox-Gastaut syndrome.

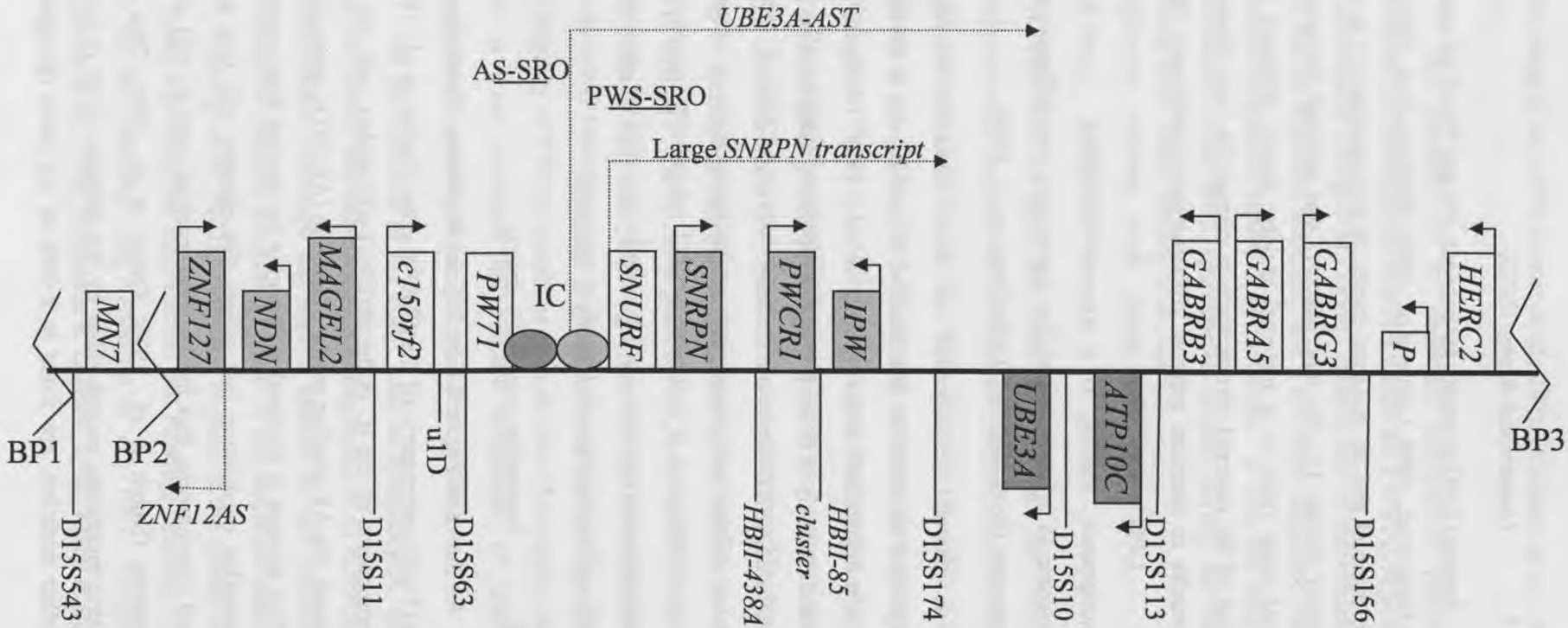
2.2.3.1 *Deletion*

Table 2.2 (p. 17) indicates that the most common cause of AS is a ~4Mb deletion in the chr15q11-q13 region of the maternally-derived chromosome, found in 65-75% of AS cases (Jiang *et al.*, 1999). In addition to this large-scale deletion, there is a small group of individuals with unbalanced translocations and smaller deletions in chr15q11-q13. The deletions are detected either by high resolution banding, or by fluorescence in-situ hybridisation (*FISH*) after a uniparental methylation pattern hasbeen identified (Williams *et al.*, 1998).

The region of chromosome 15 commonly deleted in AS isshown in Figure 2.1 (p 20). It involves two centromeric break-points (BP1 & BP2), and one telomeric break point (BP3), with approximately 500kb between BP1 and BP2 (Butler *et al.*, 2004). The deletions are thought to result from unequal crossing-over between either complete or truncated copies of the *HERC2* gene, which form one set of low-copy repeats at the telomeric end of the region, and another set at the centromeric end (Carrozzo *et al.*, 1997; Ji *et al.*, 1999; Mann & Bartolomei, 1999). The *Herc2* gene in the mouse has no repeats, but mutations in this gene lead to a range of defects, i.e., neuromuscular, secretory vesicle and sperm acrosome defects, and juvenile lethality (Ji *et al.*, 1999).

A recent study found that a heterozygous inversion between BP2 and BP3 was relatively common (67%) in the mothers of AS patients with a BP2-BP3 deletion, but a similar inversion was not present in the mothers of individuals with BP1-BP3 deletions or with UPD (Gimelli *et al.*, 2003). It is suggested that the BP2-BP3 inversion, which is present in around 9% of the general population, could predispose to breakage at these specific points. However, as the risk of recurrence for AS deletions is less than 1% (Jiang *et al.*, 1999), the penetrance of the increased risk of chromosome breakage is likely to be very low at 0.1-0.2% (Gimelli *et al.*, 2003).

Figure 2.1 The AS/PWS region of chr15q11-q13



The common telomeric breakpoint and two centromeric breakpoints are depicted as vertical jagged lines and are separated by 4Mb (distances not to scale). The imprinting centre (IC) is bipartite, with the *cis* element required for maternal-to-paternal switching shown as a blue oval overlapping the *SNRPN* promoter (deletions in this region cause PWS). The more upstream element of the IC required for switching from paternal-to-maternal is shown as a pink oval (deletions in this region cause AS). Genes or transcripts known to be paternally expressed are blue, and maternally expressed transcripts or genes are shown as pink. Transcripts that are not imprinted, or those for which the imprinting status is unknown are not given any colour. Transcription direction, if known, is indicated by arrows.

Adapted from Jiang *et al.* (1999) and Meguro *et al.* (2001)

2.2.3.2 *Uniparental disomy (UPD)*

Paternal UPD accounts for between 2% and 7% of AS cases (Glenn *et al.*, 1997; Jiang *et al.*, 1999; Lossie *et al.*, 2001; Williams *et al.*, 2001). The presence of two paternal and no maternal copies of chromosome 15 is often a result of monosomy rescue, i.e., the inheritance of one paternal chromosome 15 and no maternal copy (due to a maternal meiotic error), followed by post-zygotic doubling of the paternal chromosome to correct the total chromosome number. This results in identical paternal chromosomes (isodisomy) (Robinson *et al.*, 2000). UPD may also result from meiotic non-disjunction during spermatogenesis, leading to a trisomic conceptus. Loss of the maternal chromosome 15 (trisomy rescue) then leaves only two different paternally-derived chromosomes (heterodisomy) (Gyftodimou *et al.*, 1999).

A parental translocation or other structural rearrangement within chr15q11-q13 increases the likelihood of recurrence, due to the higher probability of a non-disjunction event (Smith *et al.*, 1997; Robinson *et al.*, 2000). Microsatellite analysis of the proband and parents, using markers from outside the PWS/AS area, will differentiate between UPD and a deletion. That is, if markers from both parents are present, the patient has a deletion, if not, then UPD is indicated (Williams *et al.*, 1998; Jiang *et al.*, 1999). The type of disomy can also be distinguished in this manner, e.g., if only one type of allele from the father is found at each marker, then isodisomy is indicated.

2.2.3.3 *Imprinting centre (IC) defects*

As shown in Figure 2.1 (p. 20), the imprinting centre spans the section of chr15q11-q13 centromeric of the *SNRPN* gene (Farber *et al.*, 1999). There are two components of the IC in the chr15q11-q13 region, with the more upstream component, the AS smallest region of overlap (AS-SRO), approximately 900bp in size. This element is involved in changing the imprint from paternal to maternal. Any mutation or deletion that affects this element will lead to a maternally-inherited chromosome that has paternal marking, and so will act as a paternal chromosome (Saitoh *et al.*, 1996; Farber *et al.*, 1999; Ohta *et al.*, 1999a). Imprinting mutations, caused either by the deletion of all or part of the IC, or some other mutation, are found in 2-10% of AS cases (Rougeulle & Lalande,

1998; Jiang *et al.*, 1999; Lossie *et al.*, 2001; Williams *et al.*, 2001; Buiting *et al.*, 2003).

The presence of an abnormal methylation pattern and biparental inheritance of microsatellite markers within the PWS/AS region is indicative of an IC abnormality (Jiang *et al.*, 1999). Almost half of individuals with an IC defect have had no mutation identified, and it has been suggested that these defects are abnormal epigenetic states, or epimutations. It also has been hypothesised that epimutations arise from spontaneous events during the fertilisation process (Buiting *et al.*, 2000; Buiting *et al.*, 2003).

2.2.3.4 UBE3A gene

The *UBE3A* gene has been described as the 'AS gene', and point mutations within the gene on the maternal chromosome have been found in 4-14% of AS patients (Kishino *et al.*, 1997; Jiang *et al.*, 1999; Lossie *et al.*, 2001; Williams *et al.*, 2001). The *UBE3A* gene is located downstream of the IC and the *SNRPN* gene (Figure 2.1, p.20), and the gene product is a ubiquitin-protein ligase (E6-AP), which is involved in the degradation of a range of proteins (Jiang *et al.*, 1999). In *UBE3A* patients the methylation pattern within the PWS/AS region is normal, i.e., biparental, and the analysis of microsatellites also shows biparental inheritance. Testing for *UBE3A* mutations is indicated whenever there is an AS phenotype, including an abnormal EEG, with normal methylation and biparental chromosomal inheritance as evidenced by genetic testing (Laan *et al.*, 1999b). The majority of *UBE3A* mutations arise *de novo* (Matsuura *et al.*, 1997), although there is some evidence for somatic mosaicism of *UBE3A* mutations in phenotypically normal carriers (Moncla et al., 1999a).

In various cells of the body, such as lymphocytes, fibroblasts and cells from the kidney and heart, *UBE3A* is expressed from both the maternal and the paternal alleles, although the imprint marker is still present and the paternal expression is reduced compared to that of the maternal allele (Vu & Hoffman, 1997; Herzing *et al.*, 2002). However, in parts of the central nervous system and the brain, especially the hippocampal and Purkinje neurons, *UBE3A* is expressed only by the maternal copy (Albrecht *et al.*, 1997; Rougeulle *et al.*, 1997; Rougeulle *et al.*, 1998; Rougeulle & Lalande, 1998; Mann & Bartolomei, 1999).

Two alternative *UBE3A* RNA transcripts have been identified. One, the *UBE3A* sense transcript, was expressed biallelically in glial cells in the embryonic brain, but from only the maternal chromosome in neurons. The other antisense transcript (*UBE3A-ATS*) was only expressed from the paternal chromosome, and only in neurons (Yamasaki *et al.*, 2003). As shown in Figure 2.1 (p. 20), the *UBE3A-ATS* extends downstream from the imprinting centre, through the *SNURF-SNRPN* and *IPW* loci, and overlaps *UBE3A* (Runte *et al.*, 2001b; Rougeulle & Heard, 2002). There are two alternate splice configurations of the *UBE3A-ATS*, both of which appear to function as suppressors of the expression of *UBE3A* from the paternal chromosome (Chamberlain & Brannan, 2001; Landers *et al.*, 2004). As yet the role played by *UBE3A* and *UBE3A-ATS* in the development of the AS phenotype has not been determined. It is, however, anticipated that as more gene products and the interactions between them are identified, the information made available will improve understanding of the role of *UBE3A* in the aetiology of AS.

2.2.3.5 Unknown

In approximately 10-20% of clinically diagnosed AS patients (Table 2.2), none of the above genetic abnormalities have been identified using current laboratory techniques. For this reason, cases with biparental methylation and no identifiable *UBE3A* mutation are classed as 'Unknown'. It has been suggested by Williams and co-workers (2001) that some of these cases may actually be different disorders that mimic the AS phenotype. Possible candidate disorders in this category are Rett syndrome, α-thalassaemia retardation syndrome (ATR-X), autism spectrum disorders, any one of a variety of chromosomal defects, Lennox-Gastaut syndrome, Gurrieri syndrome, and general developmental delay (Williams *et al.*, 2001; Clayton-Smith & Laan, 2003).

There is also the possibility that mutations in other, as yet unidentified, genes which form part of the ubiquitin pathway could lead to either the non-expression of *UBE3A* or blockage of the pathway at some other point, and thus result in the AS phenotype (Lossie *et al.*, 2001; Clayton-Smith & Laan, 2003). In addition, there may be genes within chr15q11-q13, unconnected to the ubiquitin pathway, that affect the AS phenotype. One such candidate gene is *ATP10C*,

mapped to 230kb distal of *UBE3A* (Figure 2.1, p 20), which produces an aminophospholipid-transporting ATPase, and is preferentially expressed from the maternal chromosome in the brain (Herzing *et al.*, 2001; Meguro *et al.*, 2001). *ATP10C* may be implicated in chromosome 15-associated autism, and it may also influence the development of AS, as the gene product is postulated to be involved in cell signalling (Herzing *et al.*, 2001). However, in humans no evidence of mutation within this gene has yet been produced (Clayton-Smith & Laan, 2003).

Mosaicism has been identified in some AS patients. On investigation with *FISH*, a case of clinically typical AS with biparental methylation was found to have somatic mosaicism for a deletion of chr15q11-q13 (Tekin *et al.*, 2000). It is possible that further cases of mosaicism may remain unidentified because of a lack of *FISH* testing after the discovery of a biparental methylation pattern.

2.2.4 *Genotype/phenotype correlations*

The phenotype of AS may vary according to the underlying genetic mechanism. In general, patients with UPD or an IC defect have the least deleterious phenotypes, while deletion cases are the most severely affected (Lossie *et al.*, 2001).

Angelman syndrome individuals with chr15q11-q13 deletions have been shown to have lower body mass indices, earlier onset of seizures, and more severe epilepsy than those with *UBE3A* mutations, followed by those with UPD and IC defects (Smith *et al.*, 1997; Minassian *et al.*, 1998; Gillessen-Kaesbach *et al.*, 1999; Moncla *et al.*, 1999b; Ohta *et al.*, 1999a). It has been hypothesised that the more severe seizure activity found in deletion cases may be due to the loss of the *GABRB3* gene which is situated downstream to *UBE3A* (Figure 2.1, p. 20). Deletion cases are also more likely to walk at a later age than individuals with UPD, 2-8 years for deletion vs <3 years for UPD, although the number of UPD patients sampled has been small (Smith *et al.*, 1996; Smith *et al.*, 1997).

Microcephaly is less common in UPD and *UBE3A* patients than in deletion cases (Smith *et al.*, 1996; Smith *et al.*, 1997; Moncla *et al.*, 1999a; Moncla *et al.*, 1999b). UPD or IC patients are more likely to achieve a larger vocabulary than those with deletions, *UBE3A* abnormalities, or with AS of unknown etiology (Moncla *et al.*, 1999a; Moncla *et al.*, 1999b; Fridman *et al.*,

2000a; Lossie *et al.*, 2001). IC patients are more liable to be hypotonic and/or obese, and to have a mild/moderate intellectual disability. They are less ataxic, less prone to epilepsy, and have a normal head circumference (Gillessen-Kaesbach *et al.*, 1999).

The age at diagnosis does not seem to be greatly affected by the underlying genetic mechanism of AS. Deletion patients have been reported with a mean age at diagnosis of 8.8 years, and UPD cases at 6.6 years, a non-significant difference (Smith *et al.*, 1996; Smith *et al.*, 1997). Other studies confirm that there is no substantial discrepancy in the ages at diagnosis between deletion and non-deletion patients (Moncla *et al.*, 1999b).

It is thought that loss of the maternal allele of the *P* gene from the telomeric end of chr15q11-q13 (Figure 2.1), coupled with the presence of a mutation in the remaining paternal allele, is responsible for the lack of hair, eye and skin colouration found mainly in deletion cases. Mutation in the *P* gene has been shown to lead to oculocutaneous albinism type 2 (OCA2), an autosomal recessive disorder in which melanin production in the skin, hair and eyes is defective (Jiang *et al.*, 1999; Snitoh *et al.*, 2000). UPD patients with hypopigmentation may have had a paternal recessive allele 'unmasked' when it is present in both isochromosomes.

In deletion cases it has been suggested that haplo-insufficiency, i.e., deficient gene expression by the lone allele, of any non-imprinted genes in the PWS/AS region could magnify the effects of the loss of expression of *UBE3A*. In turn, this would lead to the more severe clinical manifestation observed in these cases. Similarly, the extra dosage of paternally expressed genes found in UPD and IC cases may ameliorate the effects of the loss of *UBE3A* expression on the disease phenotype (Lossie *et al.*, 2001). However, there is no obvious reason why IC patients, who have two paternal-type chromosomes, have PWS-like features (obesity and hypotonia) when these traits occur in PWS patients who have no paternally marked chromosome 15 (Gillessen-Knesbach *et al.*, 1999).

An even milder phenotype than that generally described for AS patients has been reported in a single AS case with UPD, and an additional small supernumerary marker (SMC) chromosome 15. This patient showed less ataxia than more typical cases, better communication skills, milder seizure activity

(confined to infancy), and normal pigmentation (Thompson & Bolton, 2003). The SMC may have contained genes that were not present in an active form on the chromosomes, thus supplying the products absent in those with the classical AS phenotype.

2.3 Prader-Willi syndrome

2.3.1 History and background

This disorder was first described by Prader, Labhart and Willi in 1956. Symptoms common to all patients were learning disability and behaviour problems, hyperphagia and obesity, and delayed sexual development (State & Dykens,2000). The genetic basis of PWS was clarified in the late 1980s, with consensus diagnostic criteria published by Holm and others in 1993.

A model for PWS has been proposed which represents PWS as a starvation syndrome, rather than one of over-eating as is commonly accepted (Holland *et al.*, 2003). The theory supposes that the body falsely perceives a state of starvation when the hypothalamic pathways that signal satiety are disrupted. This leads to a similar drop in metabolic rate and gonadotropin release to that apparent in people suffering from anorexia nervosa. At the same time, a high rate of ghrelin secretion causes desensitisation of the growth hormone secretory response, suppressing growth hormone production.

It is likely that mutations in any genes within the PWS region that disrupt the function of the hypothalamus could account for the main features of PWS, i.e., overeating, growth deficiency, and hypogonadism (Holland *et al.*, 2003). In fact, a number of genes affecting the development of the paraventricular nucleus in the hypothalamus have been identified. These include *NDN* on chromosome 15 and *SIM1* on chromosome 6, which are both imprinted genes (Nicholls, 2000; Michaud, 2001; Michaud *et al.*, 2001). As yet there has been no positive link between any specific gene/s and the development of the PWS phenotype.

2.3.2 The Prader-Willi syndrome phenotype

Table 2.3 (p. 28) lists the PWS diagnostic criteria, which are divided into eight major and 11 minor elements. Most of the major clinical signs are present to varying degrees at all ages, whereas many of the minor criteria are found only in

older patients (Holm *et al.*, 1993). Late identification of the disorder was common in the past, with 36% of the cases studied by Greenswag (1987) diagnosed after 16 years of age. However, these late diagnoses were generally made prior to the publication of clinical criteria and the development of diagnostic laboratory tests for the syndrome, so that in general the age at diagnosis is now decreasing. A number of studies have recruited only children with genetically confirmed PWS, indicative of diagnosis prior to adolescence (Lindgren *et al.*, 1998; Haulfa *et al.*, 2000; Wigren & Heimann, 2001; Trifiro *et al.*, 2003).

2.3.2.1 Developmental characteristics

Young PWS patients usually exhibit poor suckling abilities, feeding difficulties, and developmental delay. Webb *et al.* (2002) reported 100% occurrence of these three criteria in their PWS subjects. Developmental motor delay is evidenced by the later average age of sitting unsupported (12 months) and of walking (24-29 months), although not all cases are similarly delayed in their development (Gillessen-Kaesbach *et al.*, 1995; Cassidy & Schwartz, 1998). Speech acquisition is also somewhat belated, often into the third year of life (Gillessen-Kaesbach *et al.*, 1995; Clayton-Smith, 2001; Williams *et al.*, 2001), and speech articulation defects, found in 79-90% of patients, are common throughout life (Gillessen-Kaesbach *et al.*, 1995; Webb *et al.*, 2002; Whittington *et al.*, 2002).

Mild to moderate ID occurs in the majority of cases, with associated learning difficulties (Holm *et al.*, 1993; Eiafeld *et al.*, 1999; Fridman *et al.*, 2000b). Approximately 27-40% of PWS cases function at low average or borderline intelligence levels, and 7-19% of patients are severely intellectually disabled (Cassidy & Schwartz, 1998; Einfeld *et al.*, 1999; State & Dykens, 2000; Clayton-Smith, 2001; Clarke *et al.*, 2002). Across all IQ groups, PWS patients are found to perform academically below the expected levels for their intelligence rating (Descheemaeker *et al.*, 2002).

Table 2.3 **Diagnostic criteria for Prader-Willi syndrome (score of 5 points needed)**

Major criteria (1 pt each)
Neonatal and infantile hypotonia, with poor suckling, improving with age
Feeding problems in infancy
Excessive or rapid weight gain between 1 and 6 years of age: central obesity in the absence of intervention
Characteristic facial features with narrow face, almond-shaped eyes, small mouth with thin upper lip, down-turned corners of the mouth, micrognathia (3 or more features required to score)
Hypogonadism: hypogonadism, or delayed or incomplete gonadal maturation
Global developmental delay <6 years; mild–moderate ID in older persons
Hyperphagia/food obsession
Deletion at 15q11-q13, maternal disomy or imprinting centre anomaly
Minor criteria (1/2 pt each)
Decreased fetal movement, infantile lethargy or weak cry
Characteristic behaviour problems – temper tantrums, violent outbursts; obsessive behaviour; tendency to be argumentative, oppositional, rigid, manipulative, possessive and stubborn; perseveration (stereotypical actions); lying and stealing (5 or more features needed to score)
Sleep disturbance or sleep apnoea
Short stature for genetic background, in the absence of growth hormone therapy
Hypopigmentation – fair hair and skin compared to family
Small hands or feet for height age
Narrow hands with straight ulnar border
Eye abnormalities
Thick viscous saliva
Speech articulation defects
Skin picking
Supportive food logs (not scored)
High pain threshold
Decreased vomiting
Temperature instability in infancy, or altered temperature sensitivity in older children and adults
Scoliosis and/or kyphosis
Early adrenarche
Osteoporosis
Unusual skill with jigsaw puzzles
Normal neuromuscular studies

Adapted from Holm et al. (1993)

2.3.2.2 *Physical characteristics*

The poor suckling and feeding difficulties found in most PWS infants (Section 2.3.2.1) are a result of the muscular hypotonia generally associated with this syndrome (Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Webb *et al.*, 2002; Triffiro *et al.*, 2003). Hypotonia in PWS is normally observed in infancy, but some adults continue to suffer from low muscle tone throughout their lives. Eating ability improves with age and pronounced weight gain between the ages of 12 months and 6 years is a common characteristic of people with PWS. Without intervention, excessive weight gain is one of the major diagnostic criteria (Holm *et al.*, 1993).

Many PWS patients, children and adults alike, have an unusually low resting metabolic rate which appears to be related to the abnormal fat mass to lean mass ratio found in the disorder (Carrel *et al.*, 2002). Young underweight PWS patients have a greater proportion of body fat than healthy children at any particular body mass index (BMI), and this is also apparent in older, obese PWS children (Brambilla *et al.*, 1997; Eiholzer *et al.*, 1999). In fact, the ratio of lean body mass to fat mass is lower in PWS cases of all ages than in both obese controls and normal weight controls.

The unusual body composition in patients with PWS can be improved with growth hormone therapy, which decreases the percentage of body fat and increases that of lean body mass, thus resulting in an increased resting metabolic rate (Davies *et al.*, 1998; Lindgren *et al.*, 1998; Lindgren & Ritzen, 1999; Myers *et al.*, 1999; Carrel *et al.*, 2002; Hoybye *et al.*, 2003; Paterson & Donaldson, 2003). The combination of hypotonia, low metabolic rate and lack of activity, all of which are associated with PWS, may help to explain the apparent low caloric requirement of patients. Extremely restrictive diets have been found necessary to control weight gain in many PWS patients (Hoffman *et al.*, 1992; Cassidy & Schwartz, 1998; Goldstone *et al.*, 2002).

The obesity that generally results from uncontrolled eating can significantly increase morbidity and mortality rates in PWS patients (State & Dykens, 2000; Clayton-Smith, 2001). However, with effective weight control, patients with PWS can survive into their 8th decade (Greenswag, 1987; Carpenter, 1994). Among the morbidities associated with excess weight are limited mobility,

cardio-pulmonary disease, leg ulcers, and diabetes mellitus, any or all of which can lead to increased hospitalisation and earlier death (Greenswag, 1987; Goldberg *et al.*, 2002; Hoybye *et al.*, 2002). Diabetes was formerly thought to be present as a major health risk for PWS cases, however, there have been more recent reports which suggest that the prevalence of diabetes in PWS may not be as high as previously believed (Greenswag, 1987; Goldberg *et al.*, 2002; Hoybye *et al.*, 2002).

Most PWS patients are reduced in stature when compared to relatives. This is thought to be primarily due to the absence of a naturally-occurring pubertal growth spurt, although birth weights and lengths have been reported to be lower in PWS cases than in healthy infants (Gillessen-Kaesbach *et al.*, 1995; Cassidy *et al.*, 2000; State & Dykens, 2000). Growth hormone (GH) treatment has been used to increase the growth velocities of PWS children, with partial success (Davies *et al.*, 1998; Lindgren *et al.*, 1998; Lindgren & Ritzen, 1999; Myers *et al.*, 1999; Carrel *et al.*, 2002). This therapy can also minimise the development of the characteristic facies, improve respiratory and muscle function, and reduce depressive symptoms, especially in individuals over 11 years of age (Lindgren *et al.*, 1999; Myers *et al.*, 1999; Whitman *et al.*, 2002). In addition, children younger than 11 years tend to show less deterioration of behaviour after treatment than is expected of PWS patients (Whitman *et al.*, 2002).

Specific facial features are often present in individuals with PWS. These features include dolichocephaly (a relatively long head), almond-shaped eyes, small bifrontal diameter, a thin upper lip in a small mouth, and/or down-turned corners of the mouth (Laurnce *et al.*, 1981; Holm *et al.*, 1993). However, one study found that only 49% of PWS cases had the characteristic facies, making this one of the least sensitive major criteria for the disorder (Gunay-Aygun *et al.*, 2001). In Italy, 57% of PWS neonates had three or more of the craniofacial features, with a further 28% of cases showing two features (Trifiro *et al.*, 2003).

Genital hypoplasia and/or delayed or incomplete gonadal maturation are commonly found in PWS patients. Male cases frequently exhibit undescended testes and/or a small penis (Greenswag, 1987; Webb *et al.*, 2002; Trifiro *et al.*, 2003). The presence of these highly visible signs of hypogonadism in males facilitates diagnosis in childhood, unlike females who often lack visible signs of

genital hypoplasia (Smith *et al.*, 2003; Trifiro *et al.*, 2003). Primary amenorrhoea is the most common sign of hypogonadism in females, with 60% of women never reaching menarche. Individuals of both gender generally undergo delayed and incomplete secondary sexual development (Crino *et al.*, 2003).

In women with some history of menses, the majority report delayed or irregular periods (Greenswag, 1987). There have been several papers reporting fertility in female PWS cases, although only two of the five mothers had an unequivocal genetic diagnosis (Hockey *et al.*, 1987; Akefeldt *et al.*, 1999; Schulze *et al.*, 2001). Of these two women, one had a maternal UPD and her child showed no abnormality, due to the transmission of a normal maternally-imprinted chromosome from the mother (Akefeldt *et al.*, 1999). The other individual was a deletion case who gave birth to an infant with Angelman syndrome, because the deletion was inherited on the maternal chromosome (Schulze *et al.*, 2001).

Strabismus occurs in 58-75% of PWS cases (Gillessen-Kaesbach *et al.*, 1995; Cassidy & Schwartz, 1998; Cassidy *et al.*, 2000; Whittington *et al.*, 2002). Hypopigmentation also is found in many PWS patients, especially those with the common deletion in chr15q11-q13 (Gillessen-Kaesbach *et al.*, 1995; Cassidy & Schwartz, 1998; Cassidy *et al.*, 2000). In similar fashion to the AS deletion, the PWS deletion also includes the *P* gene (Figure 2.1, p. 20), associated with the pigmentation of hair, skin and eyes. A single missense mutation in the *P* gene on the maternal chromosome in a PWS patient thus affects the functionality of the gene product and results in OCA2 (Lee *et al.*, 1994).

Scoliosis has been found in 34-75% of PWS cases entering adulthood, and its progress appears to be unresponsive to GH therapy (Laurance *et al.*, 1981; Cassidy *et al.*, 2000; Carrel *et al.*, 2002). In addition, osteopoenia or osteoporosis occurs in 75% of adults with PWS, possibly as a result of hypogonadism which is a known risk factor for osteoporosis (Hoyhye *et al.*, 2002). It has been established that bone mineral density (BMD) tends to be lower in PWS patients than in age- and BMI-matched obese individuals (Brambilla *et al.*, 1997). Although initial studies reported no change in BMD after one year of GH therapy, an improvement has been achieved in PWS children after a 4-year course of GH treatment (Lindgren *et al.*, 1998; Carrel *et al.*, 2002). The widespread incidence of scoliosis

and/or osteoporosis in PWS contributes to the reduced mobility found in many adults with the syndrome.

A number of the characteristic features of PWS are thought to result from the interruption of correct hypothalamic function. Growth hormone production is regulated from the hypothalamus, as is the satiety signal which appears to be dysfunctional in PWS patients with hyperphagia. It has been hypothesised that the comparative lack of lean body tissue, which itself relates to GH deficiency, is associated with the development of many of the features of PWS, i.e., the presence of hypotonia, low resting metabolic rate, poor feeding in infancy, and the low caloric requirement that appears to be typical of PWS patients (Brambilla *et al.*, 1997; Martin *et al.*, 1998). Further research into the effects of GH therapy should aid understanding of the role played by the hypothalamus in the production of the PWS phenotype.

2.3.2.3 Behavioural aspects

Although hypotonia, low metabolic rate and inactivity all contribute to obesity in PWS, ultimately the weight gain is caused by hyperphagia, i.e., compulsive eating and food obsession, which is present in most PWS patients (Einfeld *et al.*, 1999; Fridman *et al.*, 2000b; Gunay-Aygun *et al.*, 2001; Russell & Oliver, 2003). Food and other less palatable materials, such as dog food or food scraps, often need to be locked out of reach in an effort to control patients' eating urges (Laurance *et al.*, 1981).

Tests of the eating behaviour of PWS patients compared to those of obese and normal weight subjects have revealed that PWS individuals tend to eat for a longer time than either of the other two groups and with no diminution of eating rate, probably due to a lack of satiety response. The rate of food consumption exhibited by the PWS individuals was less varied, with no difference between the rate of eating at the beginning of the session and the rate at the end of the session. It therefore appears that PWS individuals do not experience the same intensity of hunger signals as control subjects (Lindgren *et al.*, 2000). Similarly, PWS subjects are likely to choose a larger quantity of food, regardless of their preference rating for that food, even when the larger quantity comes only after a time-delay (Joseph *et al.*, 2002). These results support the theory that PWS

patients suffer from lack of satiation rather than hunger *per se* (Holland *et al.*, 2003).

A Food-Related Problems Questionnaire (FRPQ) has been developed in the U.K. which can help to characterise each individual's responses to food (Russell & Oliver, 2003). The three main areas covered are preoccupation with food, impairment of satiety, and composite negative behaviours (i.e., taking and/or storing food, the eating of inedible items, and inappropriate response when food is not accessible). When the FRPQ is used there is significant variability in the resulting scores between individuals with PWS, which may help therapists to provide appropriate programs to alleviate the specific behaviour patterns of each person (Russell & Oliver, 2003).

The range of minor criteria often seen in PWS subjects is listed in Table 2.3 (p. 28), and includes both biological and behavioural traits (Greenswag, 1987; Holm *et al.*, 1993; Einfeld *et al.*, 1999; Fridman *et al.*, 2000b; Webb *et al.*, 2002; Whittington *et al.*, 2002). Daytime sleepiness is reported in many PWS cases, and this is generally unaffected by weight loss. However, both sleep apnoea and obstructed breathing are often relieved when body weight is reduced (Gillessen-Kaesbach *et al.*, 1995; Harris & Allen, 1996). Skin picking is common in individuals with PWS, often commencing before the age of 7 years. The behaviour may be episodic, i.e., occurring once or twice a year, or it may be more frequent. In either case the behaviour usually persists throughout life. Complications such as cutaneous infections may occur, and similar behaviours, e.g., hair or clothes picking, are often found in conjunction with skin picking (Wigren & Heimann, 2001).

PWS patients, especially those with UPD and/or with moderate to severe ID, are prone to the development of psychoses and other mental disturbances in adulthood (Clarke *et al.*, 1998; Verhoeven *et al.*, 1998; Boer *et al.*, 2002; Descheemacker *et al.*, 2002; Verhoeven *et al.*, 2003b, 2003a). Psychotic episodes tend to be preceded by a specific event, e.g., loss or the threat of loss, a change in life situation, or the introduction of a strict diet regime (Vogels *et al.*, 2004). It has been suggested that there may be a maternally expressed gene within chr15q11-q13 that results in a gene dosage effect when present in two active copies, as is found in UPD. There is, however, no identified gene in the region

which can be predicted to affect the brain chemistry sufficiently to induce psychosis (Smith, 1996).

2.3.2.4 *PWS-like phenotype*

In the U.K., PWS-like patients with no genetic confirmation of the syndrome were assessed and compared to those with a genetic diagnosis of PWS (Webb *et al.*, 2002). The results showed that most of the minor criteria of PWS and some of the major criteria were present in similar proportions in both groups. Hypotonia at birth, feeding difficulties in infancy, and genital hypoplasia were all more frequent in true PWS than in those with a PWS-like phenotype. This would suggest that these criteria are of greatest application in differentiating PWS from other disorders associated with developmental delay, hyperphagia, and obesity (Webb *et al.*, 2002).

2.3.2.5 *Mortality in Prader-Willi syndrome*

The main causes of mortality in a series of PWS cases varied with age at death (Schrander-Stumpel *et al.*, 2004). In the younger age group (<5 years, n = 13), six children died from acute respiratory infections, three from hypoventilation, two from gastrointestinal problems associated with fever, one from a parapharyngeal abscess, and one from accidental causes. None of these disorders are normally associated with obesity, as would be expected at the younger ages where typically there is no huge increase in weight. Among the group of 14 subjects aged nine years or older, the causes of death for four individuals were respiratory complaints, four had cardiac diseases, three had gastrointestinal disorders, and one each were due to carcinoma, a stroke and spinal myelitis. There is a credible link between obesity and some of these causes of death, notably cardiac complaints and stroke, as PWS cases in this age group are very likely to be overweight (Paterson & Donaldson, 2003; Schrander-Stumpel *et al.*, 2004).

2.3.3 *Genetic basis for Prader-Willi syndrome*

2.3.3.1 *Deletion*

The vast majority of PWS cases show an abnormal methylation pattern when tested (Fridman *et al.*, 2000b; Glenn *et al.*, 2000; Hanel & Wevrick, 2001b).

As is the case with AS, the major mutation associated with PWS is a deletion in chr15q11-13, although in PWS the affected chromosome is inherited from the father (Table 2.2, p. 17). Between 70-74% of PWS subjects have the ~ 4 Mb deletion which shares the common break points (Figure 2.1, p. 20) with the deletion that causes AS (Gillessen-Kaesbach *et al.*, 1995; Glenn *et al.*, 1997; Cassidy *et al.*, 2000). At least seven cases of somatic mosaicism for PWS deletion have been recorded in the literature (Malzac *et al.*, 1998), and there may be difficulty in identifying these cases, as the methylation pattern often appears to be biparental. *FISH* testing is most effective at identifying somatic mosaicism, as well as more common deletions.

2.3.3.2 *Uniparental disomy*

Maternal UPD15 accounts for 24-28% of PWS cases compared to 2-7% of AS subjects (Table 2.2, p. 17), reflecting the greater likelihood of nondisjunction during oogenesis than spermatogenesis (Gleon *et al.*, 1997; Cassidy & Schwartz, 1998; Cassidy *et al.*, 2000). The increased parental age associated with maternal UPD could be related to the fact that older women are more prone to defects of oogenesis than younger females (Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b). Almost a quarter of the maternal UPD cases investigated by Robinson *et al.* (2000) were shown to result from post-zygotic rescue of a trisomic conceptus, resulting in heterodisomy.

A similar case with maternal heterodisomic UPD15 was also found to have a SMC 15. The phenotype was typical of PWS, with the addition of early-onset Type 1 diabetes (Borelina *et al.*, 2004). Mosaic trisomy 15, in conjunction with maternal UPD15, has been reported to produce a severe version of PWS with an increased risk of congenital heart disease. Incomplete trisomic rescue is the mechanism that has been proposed in explanation of this phenomenon (Olander *et al.*, 2000).

2.3.3.3 *Imprinting centre defects*

IC abnormalities are present in 1-5% of PWS, including most of the families within which there have been two or more affected individuals. Deletions in the IC, which occur in 14% of PWS cases with IC defects, have a recurrence risk of 50%, making correct identification of the genotype an important

genetic counselling tool (Saitoh *et al.*, 1997; Cassidy & Schwartz, 1998; Rougeulle & Lalande, 1998; Buiting *et al.*, 2000; Buiting *et al.*, 2003). The PWS section of the IC is located just upstream of *SNRPN* (Figure 2.1, p. 20), and any disruption of the IC eliminates resetting of the imprint from maternal to paternal in the male germ-line (Saitoh *et al.*, 1997; Buiting *et al.*, 2000). The PWS–SRO has been narrowed to a 4.3kb section of chromosome which contains both *SNURF* and the promoter region for the *SNRPN* gene (Saitoh *et al.*, 1996; Ohta *et al.*, 1999b).

2.3.3.4 Single gene defects

As shown in Figure 2.1 (p. 20), there are several genes in the chr15q11-q13 region that are solely expressed from the paternal gene in some tissues, and *SNRPN*, *IPW*, *MAGEL2* (*NDNL1*), *NDN* and *ZNF127* (also known as *MKRN3*) have all been considered as candidate genes for PWS (Saitoh *et al.*, 1997; Cassidy & Schwartz, 1998; Cassidy *et al.*, 2000; Lee *et al.*, 2000; Hanel & Wevrick, 2001b).

There is some evidence that complete transcription of *SNRPN* will prevent development of the PWS phenotype (Kuslich *et al.*, 1999). Experimental treatment of *SNRPN* with 5-aza-deoxycytidine, an inhibitor of methylation, has resulted in reactivation of expression from the previously silent allele (Fulmer-Smentek & Francke, 2001). However, the demethylation was not accompanied by acetylation of the H3 and H4 histones in the region, contrary to the findings of other workers who have successfully reactivated the allele (Saitoh & Wada, 2000). As yet, reactivation of *SNRPN* has not been tested *in vivo* for suitability as a therapeutic measure to alleviate the PWS phenotype.

The *SNURF-SNRPN* locus is complex, and at least four functions are encoded within this area, including part of the PWS imprinting centre which is overlapped by *SNURF*. Exons 4-10 of *SNRPN* encode a core spliceosomal protein (SmN) that has an active function in brain tissue involving mRNA splicing (Gray *et al.*, 1999). In addition, there are a number of alternative splice sites within *SNURF-SNRPN*, including many within the noncoding exons 10a-20 (Wirth *et al.*, 2001). The alternate 3' transcripts produced from these sites may be the source of other proteins, such as that produced by the *HBII-85* snoRNA (small

nucleolar RNA) gene cluster, the *HBII-438A* snoRNA gene, and the *IPW* gene (de los Santos *et al.*, 2000; Gallagher *et al.*, 2002). Further elucidation of the roles of these different transcripts will be of potential interest to researchers of PWS.

The 2.2kb single-exon gene *NDN* encodes a protein, NECDIN, from the MAGE family (Figure 2.1, p. 20). This protein is involved in the regulation of cell proliferation, and it can bind to a number of different transcription factors. It is imprinted in humans and mice, with the maternal allele relatively hypermethylated in all tissues, and highly methylated in the brain (Lau *et al.*, 2004). The result is that *NDN* is preferentially expressed from the paternal allele, with high levels of activity in the developing hypothalamus, which is associated with a number of phenotypic features of PWS, e.g., hyperphagia and lack of growth hormone (Sutcliffe *et al.*, 1997; Lee & Wevrick, 2000; Nicholls & Knepper, 2001). Disruption of *necdin* production in mice leads to the development of reduced numbers of oxytocin-producing cells in the paraventricular nucleus of the hypothalamus, a region that contains a critical regulator of appetite (Michaud, 2001).

In a similar fashion, *MAGEL2* is monoallelically expressed from the paternal chromosome in tissues of the central nervous system (Boccaccio *et al.*, 1999). During development, high levels of expression are found in sites that include the hypothalamus, the first branchial arch and tongue, the genital tubercule, the limb buds, and the otic vesicle. Characteristics of PWS that are connected to these areas of expression include, hyperphagia and short stature (hypothalamus), articulation defects and thick saliva (tongue), hypogonadism (genital tubercule), small hands and feet (limb buds), and eye abnormalities (otic vesicle) (Lee *et al.*, 2000).

ZNF127 encodes a zinc-finger protein which may have a function as a ribonucleoprotein, and is expressed only from the paternal allele. Figure 2.1 shows that *ZNF127* overlaps a second gene (*ZNF12AS*) which is transcribed from the antisense strand, producing a different protein albeit of unknown function (Jong *et al.*, 1999).

None of the mouse models that possess only a single, paternally-inherited *Snrpn*, *Ipw* or *Zfp127* gene have shown an identifiable PWS phenotype. However, *Ndn*-deficient strains have given variable results; one showing no

abnormal phenotype, the other exhibiting a failure to thrive and a lethal respiratory defect (Hanel & Wevrick, 2001a; Michaud, 2001). Since no specific gene has been positively identified as the cause of PWS, it is inferred that PWS is a contiguous gene disorder, i.e., there is more than one gene affecting the syndrome phenotype (Nicholls & Knepper, 2001).

2.3.3.5 Unknown

A small minority of patients with the PWS phenotype lack any of these three major forms of chr15q11-q13 defect. In infancy, PWS shares some features with Down syndrome, trisomy 18, and hypothyroidism. Similarly, a number of different syndromes, e.g., Sotos, Wilson-Turner, Cohen, and Bardet-Biedel, as well as hyperinsulinism and growth hormone deficiency, all have similar phenotypes to PWS as it manifests in older children (Nolan, 2003; Delrue & Michaud, 2004). Many of the PWS diagnostic criteria, i.e., neonatal hypotonia, infantile feeding difficulties, obesity after 2 years old, and facial dysmorphism, are also present in persons with a deletion of the paternal allele of the *SIM1* gene at chr6q16.2 (Falvro *et al.*, 2002). The *SIM1* gene has been linked to the development of the paraventricular nucleus of the hypothalamus, and mouse studies indicate that haploinsufficiency of the gene leads to the PWS-like phenotype (Michaud *et al.*, 2001; Delrue & Michaud, 2004). In addition, certain X-chromosome abnormalities, e.g., Klinefelter's syndrome, Fragile-X, and supernumerary X-marker chromosomes, also show some of the characteristics of PWS (Monaghan *et al.*, 1998; Stratakis, 1998; Delrue & Michaud, 2004). Individuals with a PWS-like phenotype and normal methylation patterns should therefore be examined carefully for any of these mimicking conditions.

The presence of a maternal interstitial duplication of chr15q11-q13 has been linked to a separate phenotype which shares some features with both PWS and AS. Individuals with these duplications have developmental delay, intellectual handicap, speech delay, and some autism-like characteristics. Many are prone to seizures, display unprovoked laughter, make involuntary hand movements, and are hypotonic. Growth retardation and hypogonadism are, however, not features of this phenotype (Repetto *et al.*, 1998; Thomas *et al.*, 1999). These characteristics are similar to those exhibited by individuals with SMC15 (Webb *etal.*, 1998).

2.3.4 *Genotype/phenotype correlations*

It was believed that there were no phenotypic differences between PWS patients with chr15q11-q13 deletions and those with UPD and IC defects (Greenswag, 1987). However, the mean birth weights and birth lengths of infants with a deletion may be larger than of those with UPD (Gunay-Aygun *et al.*, 1997), even though previous research had indicated larger birth weights for non-deletion cases and similar birth lengths (Gillessen-Kaesbach *et al.*, 1995). As the latter study included both UPD and IC patients, the conclusions drawn from the two sets of results were not necessarily contradictory. In fact, no significant differences have been identified between the standard deviations of measurements of height, weight or body mass index in PWS patients diagnosed with the three different types of PWS defect, deletions, UPD and IC (Hauffa *et al.*, 2000).

Compared to patients with a deletion, especially females, the mean age at diagnosis is significantly higher for individuals with UPD. This probably reflects the milder phenotype often reported for UPD patients compounded by the difficulty of recognising female genital hypoplasia prior to puberty (Cassidy *et al.*, 1997; Gunay-Aygun *et al.*, 1997; Cassidy & Schwartz, 1998). Speech articulation defects are also more common in PWS cases resulting from a deletion (Cassidy *et al.*, 1997; Webb *et al.*, 2002).

Two of the physical features of PWS that are more common in deletion patients are an increased frequency of the 'typical' facial features, and of hypopigmentation (Gillessen-Kaesbach *et al.*, 1995; Cassidy & Schwartz, 1998). Individuals with a deletion are more likely to present with hyperphagia at an early age and excessive skin picking. They also exhibit a higher pain threshold than non-deletion cases (Cassidy *et al.*, 1997; Cassidy & Schwartz, 1998; Fridman *et al.*, 2000b; Webb *et al.*, 2002). Many PWS individuals with a deletion are purported to show superior spatial skills, e.g., in solving jigsaw puzzles, however these reports have been largely confined to adults (Cassidy *et al.*, 1997; Cassidy & Schwartz, 1998; Webb *et al.*, 2002).

Patients with a deletion between BP1 and BP3 have been described as having greater difficulty in controlling their compulsions, whether regarding food intake, daily routines, or obsessive tendencies, than those with a BP2-BP3 deletion. This observation has been interpreted as suggesting the presence of a

gene in the region between BP1 and BP2 which exerts some effect on compulsive behaviours (Butler *et al.*, 2004), although no such gene has been identified.

Maternal UPD increases the probability of psychotic episodes in adulthood, with heterodisomy elevating the risk to a greater degree than isodisomy (Clarke *et al.*, 1998; Verhoeven *et al.*, 1998; Boer *et al.*, 2002; Descheemacker *et al.*, 2002; Verhoeven *et al.*, 2003b, 2003a). The reason for this finding is unclear, although the hypothalamic dysfunction associated with the PWS phenotype has been linked to the development of behavioural and psychopathological abnormalities (Verhoeven *et al.*, 1998; Verhoeven *et al.*, 2003a). If this proves to be the case, there may be a gene (or genes) that adversely affect the development of the hypothalamus, or a pathway that affects mental health. However, expression would only be observed when there were two different functional alleles, instead of the single functional gene found in non-affected people, or in the case of the total lack of functionality found in PWS cases with a deletion or an IC defect, i.e., a gene dosage effect.

2.5 Summary

The disease phenotypes of AS and PWS vary considerably, both between and within the two disorders. The variety of physical and behavioural characteristics commonly found in individuals with AS or PWS may be attributed to the differences between the specific underlying genotypes. There has been only limited information available as to the effects of ageing on either disease phenotype or on the common morbidities faced by people with AS or PWS. There will, however, be some health issues that are universal to many ageing people, encompassing the wider ID populace and those with PWS or AS, including visual or hearing impairment, restricted mobility, and co-morbidities associated with obesity. In addition, there are some conditions, commonly found in people with ID, that are likely to be frequent among those with AS and PWS, e.g., high rates of respiratory diseases, seizure activity, psychiatric disorders and dementia. The existence of morbidities specific to either PWS or AS has, however, been a matter for conjecture.

3. METHODOLOGY

3.1. The data sources

The Disability Services Commission (DSC) has been responsible for providing services to Western Australians with ID since 1953. Any individual referred to DSC during the last 50 years has an electronic record stored in the client database, which until June 2003 contained diagnostic and demographic information on over 15,000 persons. Clients are referred to DSC for initial assessment from a variety of sources around the state, including hospitals, specialist physicians and general practitioners. Referrals also may be made by family members on behalf of people with intellectual handicap.

Historically, clients have been offered regular appointments with DSC physicians who provide an assessment of need and offer advice about disability-related services. In addition to the DSC client database, paper records are kept on each client, including information on medical, allied health care, accommodation, and psychological assessments, and general correspondence relating to each client's health care needs.

Demographic data recorded electronically at DSC include sex, date of birth, contact details, type of residence (e.g., complete residential care, group home or family home), marital status, employmentstatus and ethnicity (Appendix I). Diagnostic variables that are coded include the clinical diagnosis, level of severity of ID, and additional co-morbidities such as congenital malformations, sensory disabilities, and any associated physical disability. Information is also included if a genetic aetiology is suspected, and whether any psychiatric condition exists (Appendix II). This last field tends to be limited in its interpretation and only indicates whether a person has a behavioural, neurotic or psychotic component to their presentation.

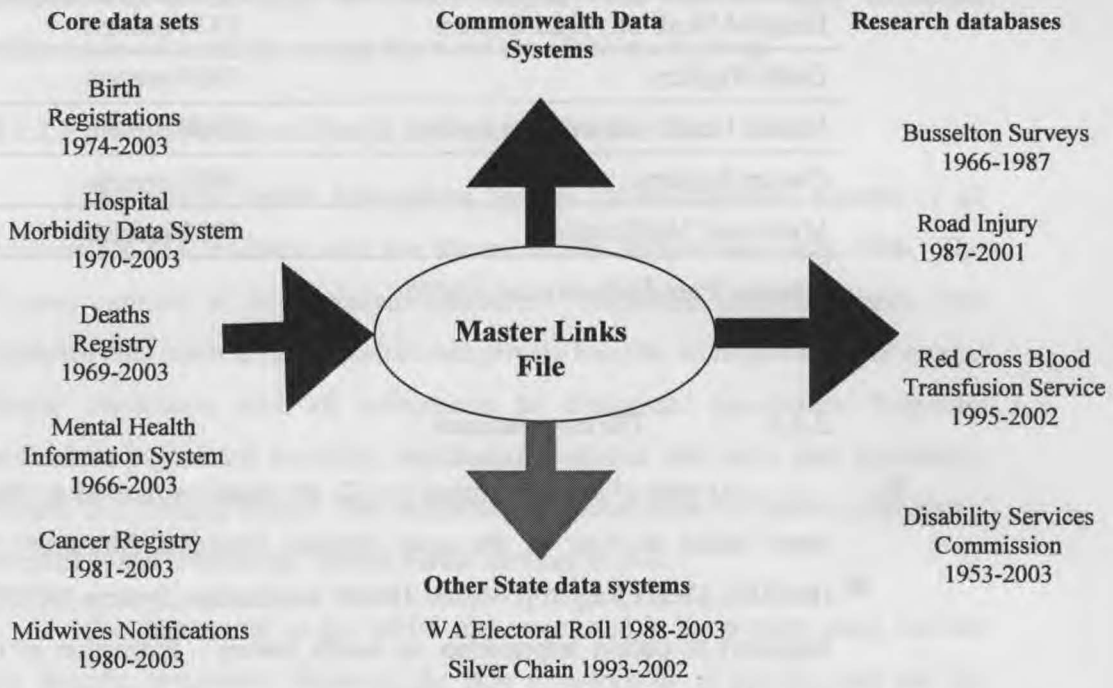
The electronic and paper records for individuals are sometimes incomplete due to varied contact of the client with DSC-based health care workers and the age of the client. The quality of data collection has also been affected by changes in information collection practices since the inception of the database (Megahey, 1996).

3.2 Record linkage

3.2.1 Overview of the Data Linkage Unit

In addition to analysis of the DSC electronic and paper records, health information for each AS and PWS case was obtained by record linkage to the core datasets held in the Western Australian (WA) Data Linkage Unit. The Data Linkage Unit was established in 1995 and is supported by the Health Information Centre in the Department of Health, the Centre for Health Services Research at the University of Western Australia, the Telethon Institute for Child Health Research, and the Centre for Health Informatics at Curtin University of Technology (Figure 3.1).

Figure 3.1 Truncated structure of the data-linkage system in Western Australia



WA Data Linkage System structure as of May, 2003

The method employed for record linkage involves the probabilistic matching and clerical reviews of health records from the six core datasets listed in Table 3.1, using vital information such as names, addresses and dates of birth (Holman *et al.*, 1999). There are three basic steps to the process of linkage. Records that have a potential relationship are first collected into a block, and in the second stage they are matched to determine if they are likely to be related. In the third stage, the matched records are linked for analysis of the information pertaining to each individual (Holman *et al.*, 1999). During the past ten years, the Data Linkage Unit has refined the system of linking the various health databases in WA, and the process is estimated to be at least 99% accurate.

Table3.1 Time-span of records from the six core datasets of the Data Linkage Unit

Core dataset	Time-span
Birth Registrations	1974-present
Hospital Morbidity Data System	1970-present
Death Registry	1969-present
Mental Health Information System	1966-present
Cancer Registry	1981-present
Midwives' Notifications	1980-present

Adapted from Holman et al. (1999)

3.2.2 The core datasets

As part of a wider project on ID, all clients registered at DSC since 1953 were linked to four of the core datasets (Hospital Morbidity Data System (HMDS), Death Registry, Mental Health Information System (MHIS) and Cancer Registry) to obtain information on health history. Extraction of the data from these datasets was completed in 2002.

3.2.2.1 The Hospital Morbidity Data System

The Hospital Morbidity Data System (HMDS) has been active in WA since 1970 to monitor and record more than 12 million episodes of acute care in

public and private hospitals, and free-standing day hospitals throughout the State. Information on the principal reason for admission and a variety of co-morbidities is stored in the HMDS. The HMDS contains up to 21 diagnostic and 11 procedure codes for each admission, and it is this information that was used to identify physical morbidity among the AS and PWS clients. Diagnoses are stored according to the coding systems of the International Classification of Disease manuals, termed ICD-8, ICD-9 and ICD-10 codes (World Health Organization, 1967; World Health Organisation, 1977-1978; World Health Organization, 1992-c1994). To facilitate analysis, records were updated from the earlier systems to their equivalent in the ICD-10 coding system.

3.2.2.2 The Deaths Registry

The Deaths Registry provides information on the date, place and cause of death of individuals whose death was registered in WA since 1969. The data for the Deaths Registry were obtained directly from the Office of the Registrar General, and in the study the Deaths Registry was used to supply additional information on mortality among the members of the study group.

3.2.2.3 The Mental Health Information System

The Mental Health Information System (MHIS) contains records of all contacts for WA residents with the Mental Health Service since July 1966. The System consists of two separate databases – inpatients and outpatients. The inpatient data cover all acute public and private hospital admissions due to mental health conditions, and all admissions to designated psychiatric hospitals, authorised psychiatric hospitals, residential programs and units, and psychiatric hostels and nursing homes. The outpatient data encompass all public psychiatric outpatient and community mental health services in WA.

The data stored on the MHIS that were used in the present study include the specific psychiatric diagnosis, the type of admission or service used and the length of stay (inpatients) or length of use of services (outpatients). As with the HMDS, the data are stored in a mixture of ICD coding systems editions, which were updated to the ICD-10 format prior to analysis.

3.2.2.4 *The Cancer Notifications Registry*

The Cancer Notifications Registry has been in existence since 1981 and holds a list of all cases of carcinoma diagnosed in WA from that time. Owing to the relatively recent establishment of this dataset there were some members of the study group whose results were not recorded by the Cancer Registry.

3.2.3 *Supplementary dataset*

For the current project the database at the Genetic Services of Western Australia (GSWA) was also sourced during 2003-2004. GSWA provides genetic health services to individuals with genetic disorders or those at risk of carrying genetic disorders, and their families. A referral from a Medical Practitioner is needed to book a consultation at GSWA, although the initial impetus for investigation may come from an individual or couple if they have reason to be concerned about hereditary disorders.

A range of diagnostic, counselling, and predictive services are available through GSWA for those affected by, or at risk of, genetic and congenital disorders. Details of the specific molecular and/or cytogenetic tests conducted, and the results of those tests, are maintained on the GSWA database.

3.3 Data collection protocol

The cases were initially identified by the selection from the DSC database of all individuals with a clinical diagnosis of Angelman syndrome (Heber code: 6759) or Prader-Willi syndrome (Heber code: 6715) (Heber, 1959). The paper files were ordered from the Records Department of DSC, with a maximum of ten files ordered at any given time. The files were reviewed and details of the clinical presentation of the cases were confirmed. All of the data extraction procedures were conducted within the DSC premises in West Perth.

The proforma used to record the information extracted from the paper files is reproduced in Appendix III. It included provision for recording the presence or absence of clinical signs, especially those included in the diagnostic criteria for each syndrome, as well as demographic data, details of any genetic tests conducted, family history, and data on illness or medical conditions.

The types of data included in the DSC files varied from case to case, but on the whole there was a great deal of consistency. Every file contained basic data as outlined previously (Section 3.1). In addition, most parents had provided information on family background, ante- and postnatal history, and the developmental history of their offspring (Appendix IV), and the referrals were accompanied by a Client Referral form and a Clinical Information form (Appendices V & VI). It is usual for DSC physicians to conduct an initial physical examination, followed by periodic updates where possible. The results of these examinations were recorded in the patient's file (Appendix VII). The results and details of DSC specialist services, such as speech therapy, physiotherapy, hearing tests or optical testing were also included in the client files. As the individual continued to use DSC services, more data were added, including reports from non-DSC service providers as available.

A database of extracted information pertaining to each individual was created in the Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows. The list of variables included in the database is contained in Appendix VIII. Many of these variables were taken directly from the proforma, with others being added as further data were collected. Any clinical data which were not specifically mentioned in the files were recorded either as unknown or 'no data' within the dataset.

Supplementary information was merged from the four other core State sources as described above: Hospital Morbidity Data System, Deaths Registry, Mental Health Information System, and Cancer Registry, as well as the Genetic Services WA database. As can be seen from Table 3.1 (p. 43), some of the data sets have been in existence for a shorter time than the DSC records, which meant that in certain cases limited amounts of information were available in the other databases. The Hospital Morbidity database, for instance, only commenced in 1970 and so 18 of the study group had no recorded hospital admissions between their year of birth and the establishment of the database.

3.4 Data analysis

The study was population-based, using comparisons between the two groups of patients. The data were analysed in a quantitative manner, using the

Statistical Package for the Social Sciences (SPSS) version 11.5 for Windows. Given the relatively low prevalence of AS and PWS, quite limited numbers of subjects were available for study. This was particularly the case for deceased subjects (AS, n = 2; PWS, n = 6; PWS-like, n = 1) and for this reason mortality and survival rates were not calculated.

The project was primarily descriptive in its outputs, analogous to international studies addressing similar research questions, and hence most of the findings are presented in the form of summary statistics.

3.5 The study population

The American Association of Mental Retardation (AAMR) criteria for intellectual disability shown in Table 3.2 are used by DSC to determine client eligibility for registration and services (Grossman, 1983).

Table3.2 Level of intellectual function as indicated by IQ range

Term	IQ range	AAMR Code
Low average/borderline disability	71-84	
Mild intellectual disability	55-70	317.0
Moderate intellectual disability	40-54	318.0
Severe intellectual disability	25-39	318.1
Profound intellectual disability	<25	318.2
Unspecified		318.3

Adapted from Grossman (1983)

The specific criteria of acceptance for DSC registration include sub-average intellectual functioning (i.e., IQ<70) that has an onset before 18 years of age, and evidence of significant impairment (i.e., 2SD below the mean) as measured by an Adaptive Behaviour Assessment. Adaptive skills are assessments of learning, personal independence, and socialisation skills, as appropriate to an individual's age and cultural background (Grossman, 1983). In practice, persons with an IQ>70 but with significantly limited adaptive behaviour skills are

sometimes included in the DSC registration process, due to their demonstrated level of overall disability.

As outlined in Section 3.3, all individuals with a Heber diagnosis of either Angelman syndrome (n = 35) or Prader-Willi syndrome (n = 59) from the Disability Services Commission were selected for the study (total, n = 94). After reviewing the patient files, it was apparent that two of these cases had been incorrectly labelled as PWS (Heber 6715). In another two cases the diagnosis had been changed; one from AS to Lennox-Gastaut spectrum, a type of epileptic disorder, the other from PWS to Stein-Leventhal syndrome, defined as polycystic ovaries, obesity, hirsutism and amenorrhoea (MIM 184700). These four cases were therefore excluded from the analysis, reducing the total study sample to 90 subjects.

An additional three people were identified from the GSWA database as having AS or PWS, although they had never been registered as clients of DSC. Since no further information was available on these individuals, none was included in the cohort. A person identified from GSWA records with abnormal methylation of chr15q11-q13 had a male child registered at DSC, with a genetic diagnosis of PWS. This child was already included in the study group.

Within the PWS group, a set of ten individuals who had normal methylation patterns were analysed separately (referred to as the 'PWS-like' group), since biparental methylation has been considered as sufficient reason to exclude PWS as a diagnosis in >98% of cases (Buchholz *et al.*, 1998; Fridman *et al.*, 2000b; Glenn *et al.*, 2000). Hence there was a strong possibility that most of these people had some other as yet unidentified genetic abnormality. The exclusion of these ten individuals left a central group of 80 cases for whom a specific genetic anomaly had been identified, or who had a robust clinical diagnosis of AS or PWS.

3.6 Ethical Issues and approval

Ethical approval for the project was given by the Edith Cowan University Ethics Committee. The Disability Services Commission of Western Australia (DSC) Ethics Committee also gave permission for use of the DSC client database to conduct the research, and specifically granted permission for the project to be

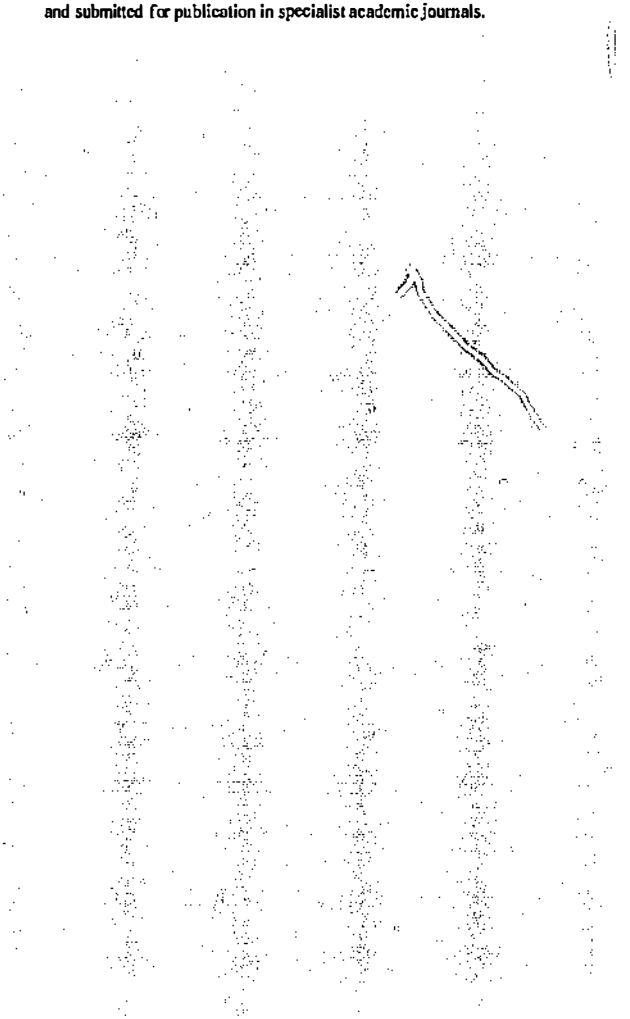
undertaken on DSC premises. The study was epidemiological in nature and analyses were conducted on a group level. Individuals were not identified in any documents or reports. Subjects and their families were not contacted for the research, and as previously noted, no client files were removed from DSC premises.

Ethical approval for the linkage of clients to the four Data Linkage Unit core databases was received from both DSC and the WA Confidentiality of Health Information Committee at the Department of Health, which is responsible for the maintenance and linkages of these external databases. All DSC cases (n = 15,000) were linked to obtain this additional information, since it was expected that not all AS and PWS diagnoses would be specifically entered into the DSC database, or conversely that they had been retrospectively diagnosed during their contact with DSC. As stipulated under the terms imposed by the Confidentiality of Health Information Committee, the data linkage was undertaken by the personnel responsible for record linkage within the WA Data Linkage Unit. The datasets contained within the Data Record Linkage Project are available for research purposes. They are a highly effective, proven tool for health information retrieval and analysis, and are almost unique worldwide in the breadth and depth of coverage offered.

The general and medical files for each DSC client were kept in secure storage on DSC premises when not in use, and were accessed only by the candidate and her supervisors. After data linkage and extraction, subjects contained in the database were identified by an unique number, which was used for all recording of information relevant to the client, including medical details extracted from the DSC files. Electronic information was protected by passwords and unique numbers, and any hard copies were kept in secure storage at the Centre for Human Genetics, Edith Cowan University.

The completed database will be held on a password-protected computer at the Centre for Human Genetics, and it is envisaged that, subject to ethics approval, the information will be made available to Medical Practitioners, carers and service providers for individuals with either syndrome. Generally, the data will be available in the form of summaries, although reports will be prepared for

specific interested agencies, such as DSC. In addition, articles will be prepared and submitted for publication in specialist academic journals.



4. RESULTS OF THE STUDY

4.1 Profiles of the study cohort

As shown in Table 4.1, 34 of the 90 individuals selected for study (19 females and 15 males) had a diagnosis of AS, 46 (23 females and 23 males) had a diagnosis of PWS, and there were seven males and three females in the PWS-like group totalling 10 cases. One of the PWS cases was of Indigenous Australian descent, but none of the AS or PWS-like cases. The ages at the censor date (30.06.2003) or age at death ranged from 10 months to 48 years 4 months. All members of the AS group were aged six years or older, but nine individuals with PWS were less than six years of age. The birth years for the patients in both the AS and PWS-like groups ranged between 1967 and 1998, whereas the PWS group were born between 1954 and 2002 (Figure 4.1, p. 52). Nine of the 90 subjects (2 AS, 6 PWS, 1 PWS-like) were deceased by the censor date.

Table 4.1 Characteristics of the study cohort (n = 90)

		AS	PWS	PWS-like	Total
Diagnosis: (number of individuals)		34	46	10	90
Gender: number(%)	Male	15 (44)	23 (50)	7(70)	45 (50.0)
	Female	19 (56)	23 (50)	3 (30)	45 (50.0)
Ages (in years): mean (range)		21.6 (6.5-36.6)	21.0 (0.9-48.3)	24.7 (15.1-33.1)	
Deceased: (number of individuals)		2	6	1	9

4.1.1 Residence

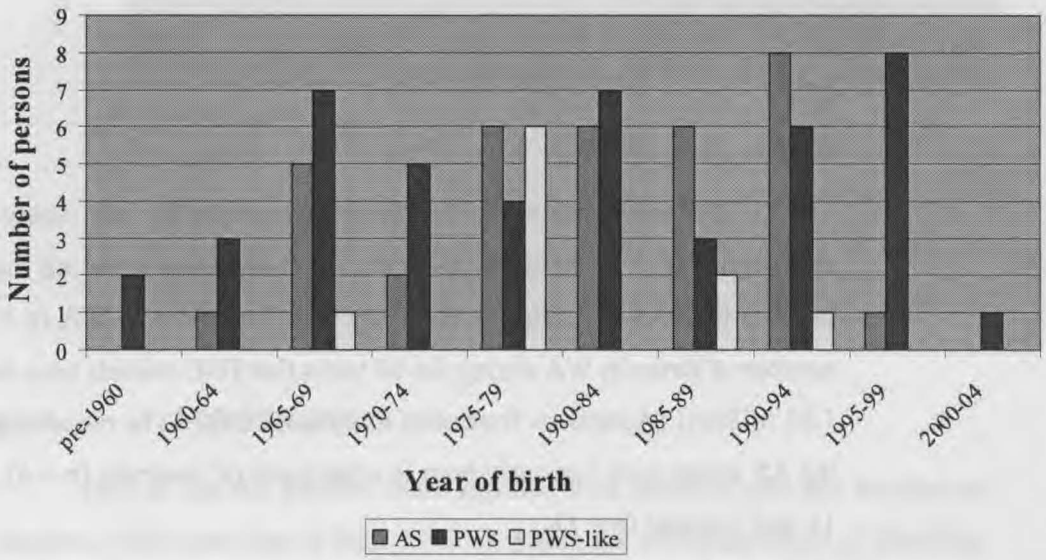
Of the 32 living AS cases, 20 resided at home, nine were resident in group homes or hostels, and one each in foster care, an independent home, and living with adoptive parents. The mean age of individuals living in private residences was significantly lower than those in sheltered accommodation (20.2 years vs 27.9

years: t = -2.255, p = 0.032). The majority of people were registered within the Perth metropolitan regions (90.6%), with the remaining 9.4% living in rural areas.

Members of the PWS group were also mainly resident at home (n = 28) or in group homes or hostels (n = 6). Once again, there was a significant difference between the mean ages of individuals living at home and those living in residential care (20.2 years vs 32.6 years: t = -2.584, p = 0.015). The place of residence for six individuals was not recorded, and the remaining six were deceased. The Perth metropolitan regions were home to 70.0% of living PWS individuals, with a further 17.5% living in rural and remote regional locations throughout Western Australia. Five individuals were not in receipt of DSC services at the time of sampling and therefore were not allocated to a region of residence.

The residences of the nine surviving PWS-like patients were recorded as home (n = 7) and group home or hostel (n = 2); three were from the Perth metropolitan regions, and the remaining six individuals lived in country districts. There was no significant difference between the mean ages of the cases residing in private homes compared with sheltered accommodation.

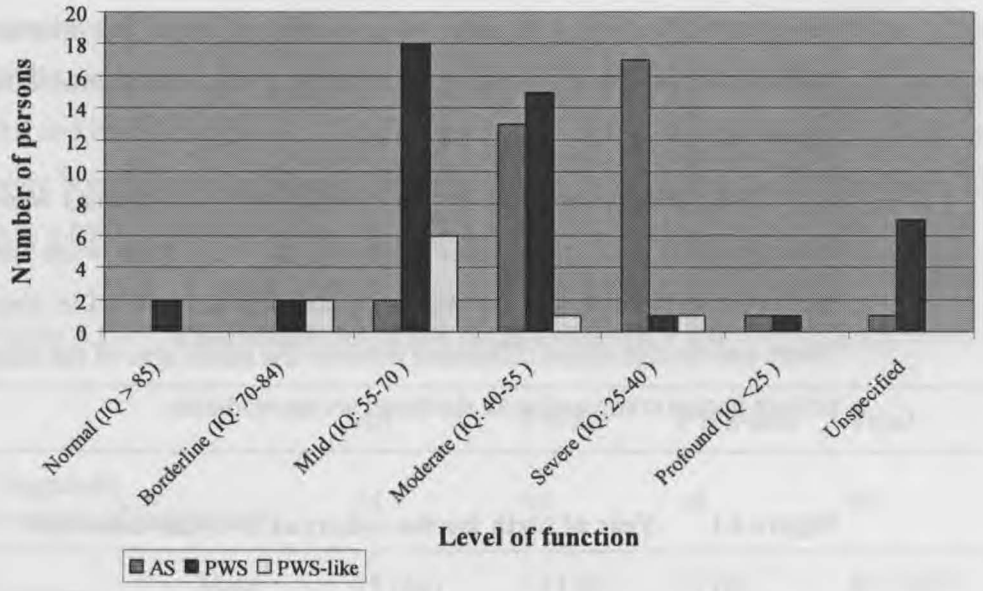
Figure 4.1 Year of birth for the cohort at five year intervals



4.1.2 Level of intellectual function

The level of intellectual function of the study group varied from 'low average' to profoundly handicapped, with 4.4% being unspecified, i.e., the subjects may not have been formally tested due to their youth or for other reasons. The range of IQ scores reported for the study group are shown in Figure 4.2.

Figure 4.2 Levels of intellectual function of the study group (n=90)



4.2 Angelman syndrome

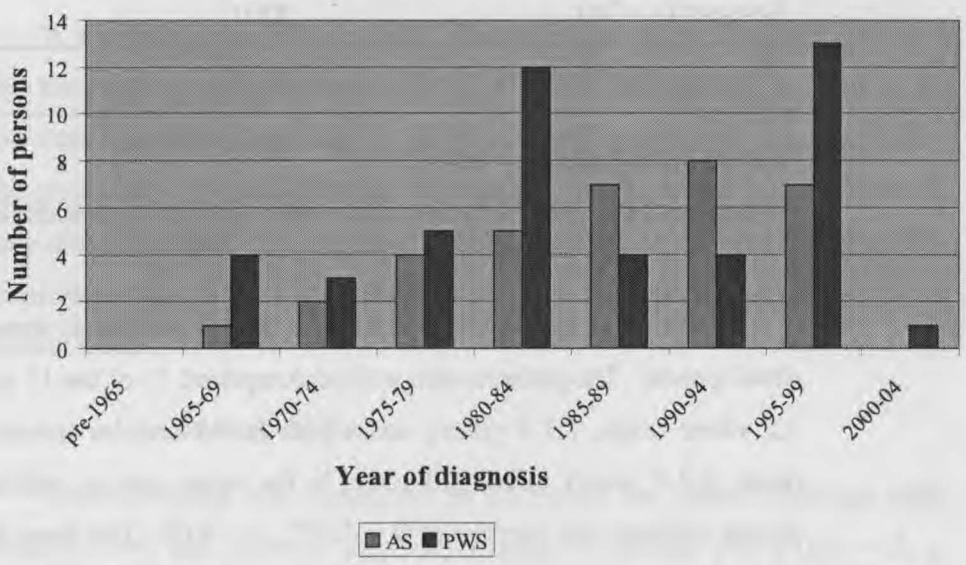
4.2.1 Prevalence

The prevalence of Angelman syndrome in the study group was approximately 1 in 40,000 live births. This figure is based on the numbers of patients with AS identified in the study who were born in WA (n = 26), and the number of births in WA during the 50 years that DSC records have been kept (n = 1.05 million) (Australian Bureau of Statistics, 2003). The remaining members of the AS group were variously born in other parts of Australia (n = 6), Canada (n = 1), and England (n = 1).

4.2.2 Age at diagnosis

The diagnosis of AS was made for members of the study group at a mean age of 5.8 years (range, 1-27 years). On average, the deletion cases were diagnosed at a later age than those with other forms of AS defect (6.9 years and 5.0 years respectively), and females were diagnosed earlier than males (5.2 years and 6.5 years respectively), although neither difference was statistically significant. There have been no AS cases registered in WA since 1999, even though prior to that date the numbers registered per five year period were gradually increasing, possibly in line with the increasing total population of the State (Figure 4.3). On the basis of the established clinical criteria, one individual was originally diagnosed in childhood with PWS, but subsequent methylation testing confirmed a diagnosis of AS.

Figure 4.3 Date of diagnosis for the study cohort at five-year intervals



4.2.3 Major AS clinical criteria

Half of the AS patients were assessed with severely affected intellectual function, with more than a third (38.2%) within the moderate range of disability (Figure 4.2, p. 53). Developmental motor delay was not universally evident in the

group as a whole, as shown by the lower boundary of the sitting/walking range which fell within the parameters for the general population (Table 4.2).

Table4.2 Frequencies of the major clinical sigos of Angelman syndrome withio the study sample

Clinical criteria	Positive (%)	Negative (%)
Motor development (age in years): mean (range) (n = 29, n = 33)	sit, 1.4y (0.5-4.9y) walk, 4.4y (1.1-9.0y)*	
No speech or minimal words (o=34)	82.4	Some delay 17.6
Ataxia (n = 34)	91.0	9.0
Inappropriate laughter or smiling (n=34)	76.5	23.5
Microcephaly(n = 20)	44.0	15.0
Seizures (n= 34)	88.0	12.0
Abnormal EEG (n = 30)	82.0	6.0

*Five subjects had never walked

o = number of subjects for whom data was available for each clinical symptom

The majority of AS patients (o = 29/34) walked at some stage of early development. The patients who walked comprised 13 of the 15 males (mean age, 3.5 years; range, 1.1-9 years), and 16 of the 19 females (mean age, 5.2 years; range, 2.2-9 years). This difference in the mean ages at walking of male and female children was significant (t = -2.052, p = 0.05) The three females who had never walked were aged 21 years, 6 years, and 6.5 years (deceased), while the two non-ambulant males were aged 11.8 years, and 12.8 years (deceased) respectively.

All of the subjects had delay and/or inadequacy of speech, with the majority acquiring few, if any, words. Ataxia and inappropriate laughter also were present in most cases. Microcephaly was diagnosed in 44% of subjects, although the number of cases for whom data were available (n = 20) was too few for statistical comparisons to be made. A large proportion of cases (88%) were

reported to have experienced seizures, with 26% suffering frequent episodes. In addition, the majority of individuals had at least one abnormal EEG reading (82%), with only three subjects never having been tested (Table 4.2, p. 55).

4.2.4 Minor AS clinical criteria

The presence or absence of the characteristic facial features such as flat occiput, mandibular prognathia, drooling, mouthing, and tongue thrusting was rarely noted in the patient files (Figure 4.4, p. 57). Strabismus was recorded in almost half (47%) of the cases, and hypopigmentation in 35%, although information on these characteristics was unavailable for significant numbers of patients. Few data were available on the presence of the raised, flexed arm position claimed to be characteristic of AS, or on sleep disturbances. A small number of subjects (n = 3) were recorded as having a fascination with water (Figure 4.4, p. 57).

4.2.5 Other clinical findings

A number of additional clinical characteristics were frequently reported within the study group. Most cases (79%) of AS were hypotonic, and half of the group were regarded as hyperactive. Over 38% were considered obese, and 50% of the group were of normal stature. Skin picking was reported in seven patients, mainly older individuals. Scoliosis was present in 33% of all patients and in 56% of those more than 16 years old. Three of the males had either undescended testes or a small penis.

4.2.6 Laboratory diagnosis

Genetic testing was conducted on 88.2% of the cohort, although eight patients (23.5%) had received only karyotyping or banding tests (Table 4.3, p. 58), of which half were positive. Two persons with a deletion, as indicated by chromosomal banding, had returned normal biparental methylation tests and were therefore included in the 'inconclusive' group. One test had been performed for *UBE3A* abnormalities (which was negative), but none at all for IC defects. Of the 19 methylation tests conducted, 11 were positive and eight were negative, and three of the four *FISH* tests were positive. Deletions accounted for 33.3% of the positive results, and UPD for a further 6.7% (Table 4.3, p.58).

Figure 4.4 Frequency of the minor clinical signs of Angelman syndrome within the study group (n = 34)

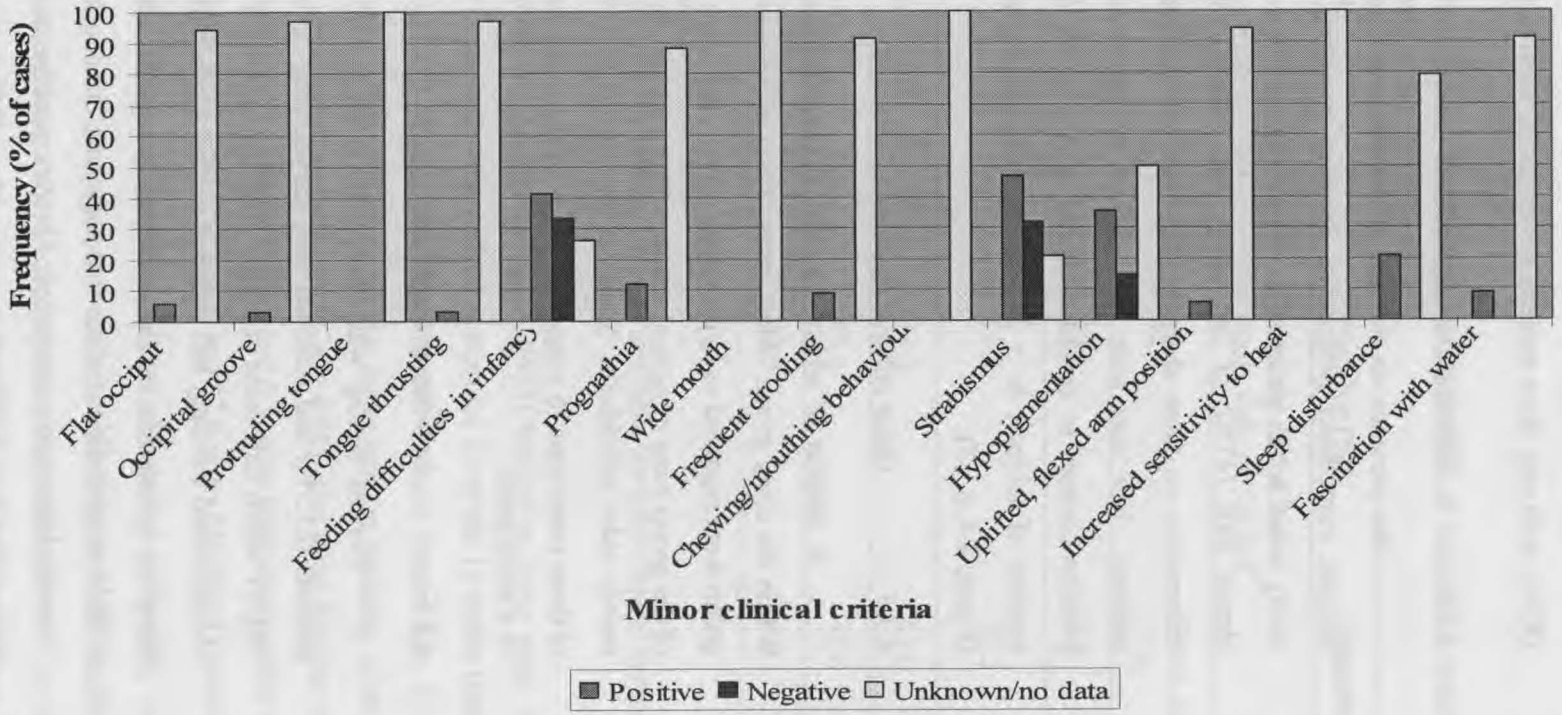


Table 4.3 Details of diagnostic tests used for Angelman syndrome cases (n=34)

Type of molecular tests (%)	Karyotype/banding	23.5
	FISH	11.8
	Methylation	55.9
	Unknown/no test	11.8
Molecular test results: number (% of those tested)	Deletion	n = 10 (33.3)
	Uniparental disomy	n = 2 (6.7)
	Positive (not specified)	n = 2 (6.7)
	No abnormality detected	n = 13 (43.3)
	Inconclusive	n = 3 (10.0)

4.2.7 Hospital admissions

Individuals with AS had been admitted to hospital on a total of 301 occasions, with an average of 8.8 (SD = 8.6) inpatient episodes. As shown in Table 4.4 (p. 59), epilepsy and/or seizures were the most common reasons for admission (14.3%), followed by gastrointestinal tract disorders (13.0%), holiday/respite care (11.3%), dental care (9.6%), and respiratory tract disorders (8.6%). The remaining admissions covered a wide variety of reasons, e.g., eye abnormalities, burns, congenital deformities. Four people had no recorded hospital admissions.

More than half of the individuals with AS were admitted one or more times for dental work (n = 18), and almost as many for epilepsy (n = 16). A further 12 individuals were hospitalised for failure to thrive or developmental delay (Table 4.4, p. 59). Admission for dental work was over-represented in patients with severe or profound intellectual disability (62% of dental admissions), even though this group comprised less than 53% of the AS population.

Three individuals were admitted to psychiatric units for up to three days duration. The reasons listed for their admission were developmental delay (all three persons), and epilepsy (two persons). Three other AS patients attended

psychiatric outpatient clinics on two, six and eighteen occasions respectively. The diagnoses reported for these persons were severe ID, microcephalus, and psychosocial circumstances (unemployment) respectively.

Table4.4 Hospital admissions for the Angelman syndrome group

Reason for admission	Total number of admissions (% of total admissions)	Number of individuals admitted
Epilepsy	43 (14.3)	16
Gastrointestinal disorders	39 (13.0)	10
Holiday care	34 (11.3)	1
Dental	29 (9.6)	18
Respiratory disorders	26 (8.6)	10
Ear problems	15 (5.0)	7
Skin disorders	15 (5.0)	4
Open wound, various sites	13 (4.3)	8
Failure to thrive/feeding difficulties	12 (4.0)	12
Foreign body inserted, various sites	9 (3.0)	5
Congenital anomaly	8 (2.7)	5
Urinary tract disorders	6 (2.0)	4
Fractured bone ± complications	5 (1.7)	4
Other causes (various)	47 (15.6)	19

4.2.8 Mortality

There had been two deaths within the group of 34 AS patients. One person died of *status epilepticus* at the age of 12 years 10 months, and the other patient was aged 6 years 6 months at death from pneumonia.

4.3. Prader-Willi syndrome

4.3.1 Prevalence

A birth prevalence of 1 in approximately 29,500 was calculated on the basis of the number of PWS cases identified for this study who were born in

Western Australia (n = 31) and the number of births were registered in WA over the last 50 years (n = 1.05 million) (Australian Bureau of Statistics, 2003). Ten other members of the PWS group had been born in other parts of Australia, and one each in Hong Kong, Scotland, South Africa and Spain. The remaining individual had no record of country of birth in the relevant DSC files.

4.3.2 Age at diagnosis

The average age at diagnosis of PWS was 5.3 years, with 34.8% of the entire PWS group diagnosed before the age of one year. Within the subset of 11 individuals who were added to the database after 1998, the mean age at diagnosis was 1.1 years (range, 0.1-6.0 years), while the 35 individuals who were included prior to 1998 had a mean age at diagnosis of 6.6 years (range, 0.2-17.0 years). This difference was highly significant ($t = -3.5$, $p = 0.001$). Deletion cases were diagnosed at a slightly earlier but statistically non-significant age than those without a deletion (mean, 4.5 years and 5.9 years respectively; $t = -0.90$, n/s), and males earlier than females (mean, 4.6 years and 6.0 years respectively; $t = -1.015$, n/s). The numbers of PWS cases diagnosed were appreciably higher in the five-year periods of 1980-84 (n = 12) and 1995-99 (n = 13) than during any other time period (Figure 4.3, p. 54).

4.3.3 Major PWS clinical criteria

As indicated in Table 4.5 (p. 61), the majority of PWS cases reported hypotonia (96%), infantile feeding problems (85%), and rapid weight gain at an early age, followed by obesity (87%). Hyperphagia was described less often (61%). Reporting of the characteristic facial features was poor, with over 90% of case files without mention of this feature. Hypogonadism and/or cryptorchidism were present in two-thirds (67%) of PWS patients, i.e., 91% of males of all ages, and 58% of females over 15 years. All of the adult female patients with a confirmed deletion had absent or delayed menses, but this feature was reported in only 30% of females of the same age in the group of patients without an identified deletion. Motor developmental delay was found in many cases (n = 20), but there were some patients (n = 18) who did not show any marked delay in reaching physical milestones by comparison with the general population (Table 4.5, p. 61).

Table 4.5 Frequencies of the major clinical signs of Prader-Willi syndrome within the study sample

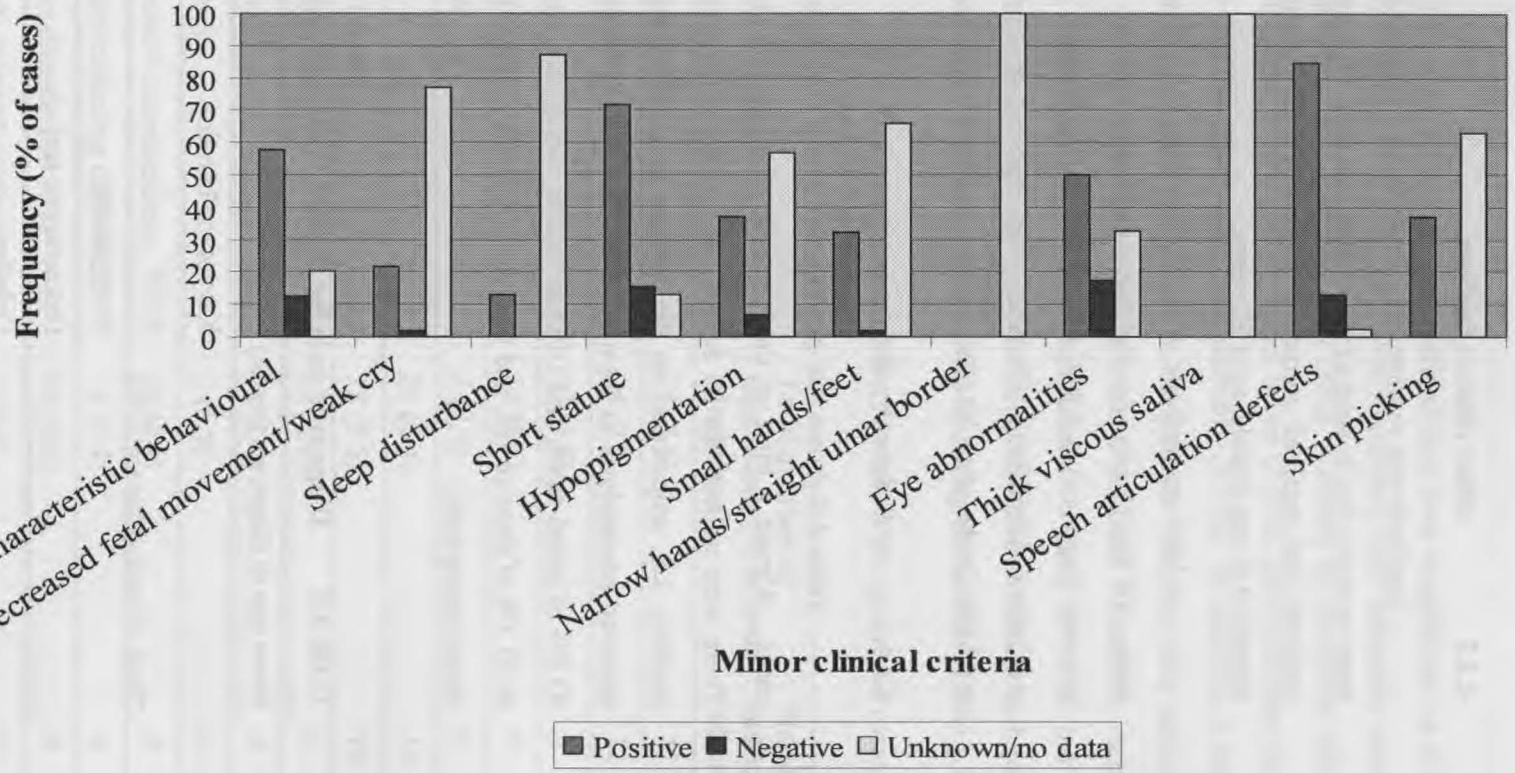
Clinical criteria	Positive (% of group)	Negative (% of group)
Hypotonia (n =46)	95.7	4.3
Feeding problems (n=43)	84.8	8.7
Excessive weight gain (n =46)	86.9	13.1
Characteristic facies (n = 2)	4.3	0
Hypogonadism (n=41)	67.4	21.7
Hyperphagia (n = 33)	60.9	10.9
Motor development (age in years): mean (range) (n =34, n = 39)	sit, 1.0y (0.5-2.5y) walk, 2.8y (1-10y)	1 subject unable to sit or walk at 0.9y

n = number of subjects for whom data was available for each clinical symptom

4.3.4 Minor PWS clinical criteria

Figure 4.5 (p. 62) shows that more than half of the study subjects (57%) had exhibited some of the characteristic behavioural patterns associated with PWS (temper tantrums and violent outbursts), and 72% were short in stature compared to family members. Individuals who had received growth hormone therapy (n = 4) were recorded as short, regardless of their current height. Ocular abnormalities were reported in half of cases, and a large percentage of PWS patients (85%) suffered from delayed speech development and/or articulation defects. Many of the remaining minor clinical signs were under-reported, with fewer than 40% of individuals having specific features recorded in their files; i.e., decreased fetal movement (23%), sleep disturbances (13%), size and shape of hands/feet (33%), presence of thick saliva (0%), and skin picking behaviours (37%).

Figure 4.5 Frequencies of the minor clinical signs of Prader-Willi syndrome within the study sample (n = 46)



4.3.5 Other clinical findings

Scoliosis was reported in 11 of the 30 subjects (37%) who were aged 15 years or more, but in none of those aged less than 15 years. Two individuals with scoliosis had received corrective surgery for the condition. Osteoporosis was identified in one female, aged 32 years.

At least one episode of epilepsy or convulsions was reported in 28.3% of cases. Of the 13 persons who had an epileptic episode, five showed a deletion, one was diagnosed as UPD, four had never been tested, and four had no genetic mechanism identified. Diabetes was reported in four adults, with no data available for the other 30 adult members of the PWS cohort.

4.3.6 Laboratory diagnosis

Table 4.6 shows that genetic testing was performed on 84.8% of the PWS cases. Almost a third of these people received only karyotyping or banding. There were no tests for IC defects. All of the *FISH* and methylation tests were positive, i.e., uniparental, as the patients with biparental methylation had been removed pre-analysis to form the PWS-like group. A deletion was identified in 43.6% of tested cases, and UPD in 10.2%. No genetic mechanism was identified in 23.1% of those tested, and the remainder had returned unspecified 'positive' or inconclusive tests.

Table 4.6 Diagnostic tests for Prader-Willi syndrome cases (n = 46)

Mean age at diagnosis (range)		5.3y (0.1-17y)
Type of molecular tests (%)	Karyotype/banding	30.5
	FISH	17.4
	Methylation	36.9
	Unknown/no test	15.2
Molecular test results; number (% of those tested)	Deletion	n = 17 (43.6)
	Uniparental disomy	n = 4 (10.2)
	Positive (not specified)	n = 6 (15.4)
	No abnormality detected	n = 9 (23.1)
	Inconclusive	n = 3 (7.7)

4.3.7 Hospital admissions

As shown in Table 4.7, PWS patients had been hospitalised on a total of 328 occasions (mean, 7.4; SD, 6.9), with respiratory tract infections accounting for the largest number of admissions (7.6%), followed by breathing difficulties (7.3%), dental care (6.4%), undescended testes (5.8%), gastrointestinal disorders (5.5%) and an unspecified congenital anomaly (5.5%). In addition, a large and varied number of reasons were listed in the patients' files for their admission to hospital. These included cellulitis, musculoskeletal disorders, congenital deformities, and ingestion of toxic substances. Nearly 37% of individuals suffered from at least one respiratory infection, and 14 individuals each had been admitted to hospital for dental work or with breathing difficulties (Table 4.7).

Table4.7 Hospital admissions for the Prader-Willi syndrome cases within the study group

Reason for admission	Total number of admissions (% of total admissions)	Number of individuals admitted
Respiratory infections	25 (7.6)	17
Breathing difficulties	24 (7.3)	14
Epilepsy	15 (4.6)	9
Gastrointestinal disorders	18 (5.5)	8
Holiday care	3 (0.9)	1
Dental	21 (6.4)	14
Congenital anomaly	18 (5.5)	10
Undescended testes	19 (5.8)	9
Ear problems	11 (3.4)	4
Skin disorders	5(1.5)	4
Fractured bone± complications	16(4.9)	8
Failure to thrive/feeding difficulties	11 (3.4)	6
Urinary tract disorders	11 (3.4)	9
Foreign body inserted, various sites	2(0.6)	2
Complications of pregnancy/childbirth	9(2.7)	1
Open wound, various sites	2(0.6)	1
Other causes (various)	118 (35.9)	

Six patients had been admitted to psychiatric units for an average of 24.5 days (range, 2-96 days), on the grounds of ID, developmental delay or, in one case, non-organic psychosis. One male PWS case, who recorded 1162 psychiatric outpatient visits, attended group therapy sessions for mixed disturbance of conduct and emotions over a period of nine years, at an average of 10 visits per month. Further outpatient visits to psychiatric units were made by three persons, with the total number of visits per person ranging from 3 to 12. ID, developmental delay and disturbance of conduct were the main reasons for attendance. Two individuals with PWS attended both as inpatients and outpatients (one person each with moderate ID and schizophrenia).

Three individuals had neoplasms reported in their files. One patient had been diagnosed with a benign tumour of an endocrine gland, another had a malignant melanoma removed at 16 years of age, and the third person had a thyroidectomy for malignancy at age 35 years. The only one of these three patients who was deceased had survived for 20 years after removal of the melanoma and then died of cardiac failure, aged 36 years. Only one of these cases was listed in the Cancer Registry, as the other two persons had been diagnosed before the Registry was commenced.

4.3.8 Mortality

Of the six deceased PWS cases, two had died from cardiac arrest/ myocardial infarction, one from pneumonia, and in the remaining three cases the cause of death was not recorded. The case notes for one individual had been referred to the Coroner, but no notification had been received by the Deaths Registry at the date of data linkage. The other two people were not listed in the Deaths Registry, and no data were included in their DSC files. Their ages at death ranged from 2.3 years to 36.5 years.

4.4 Methylation normal 'PWS-like' group

4.4.1 Clinical findings

As previously described (Section 3.5), this group comprised 10 people with a clinical diagnosis of PWS but who showed biparental methylation patterns (Table 4.1, p. 51). Their average age was 24.7 years (range, 15.1-33.1 years). As

can be seen from Figure 4.2 (p. 53), the level of ID reported was mild (n = 6), borderline (n = 2), moderate (n = 1) and severe (n = 1). Mean age at diagnosis was 10.6 years (range, 0.9-25 years). However, the age for two cases was unrecorded, and so the date of first contact with DSC was used as the upper limit of the age at diagnosis for those individuals.

Half of the subjects were reported to have hypotonia, and five individuals exhibited feeding problems in infancy. Eight were obese, one was of normal weight and stature, and one had no data on body habitus. Their average age of sitting was 0.8 years (range, 0.7-1.0 years), and it was 1.6 years (range, 1.1-2.7 years) for walking. Of the seven males, five were hypogonadal, whereas only one of the three females had no menses. Hyperphagia was reported as present in seven of the subjects, and speech delay or defects in nine cases (Table 4.8). Half of the group were either of normal stature or were tall. Skin picking behaviour was evident in two individuals. None of the other features regarded as characteristic of PWS (Table 2.3, p. 28) were recorded with sufficient frequency to enable a valid assessment. Four of the group had reported at least one epileptic episode.

Table 4.8 Frequencies of various clinical characteristics in the PWS-like subgroup (n = 10)

Clinical criteria	Positive (number)	Negative (number)
Hypotonia (n = 8)	4	4
Feeding problems (n = 8)	5	3
Excessive weight gain (n = 9)	8	1
Hypogonadism (n = 10)	6	4
Motor development (age in years): mean (range) (n = 7, n = 8)	sit, 0.8 (0.7-1.0) walk, 1.6 (1.1-2.7)	1 subject never walked
Hyperphagia (n = 10)	7	3
Stature compared to relatives (n = 9)	short = 4 tall = 1	normal = 4
Speech delay/defects (n = 10)	9	1
Skin picking (n = 10)	2	8

n = number of subjects for whom data was available for each clinical symptom

4.4.2 *Hospital admissions*

Members of the PWS-like group were admitted to hospital on a total of 70 occasions (mean, 7.0; SD, 10.3), but with a large proportion of these visits (32.9%) for epilepsy and convulsions in a single individual. Respiratory tract infections and gastrointestinal tract disorders accounted for ten (14.3%) and eight (11.4%) admissions respectively. Individuals (n = 4) were more commonly hospitalised for gastrointestinal disorders than for any other reason within this group of patients (Table 4.9).

As with the AS and PWS cases, there were various other reasons recorded for hospital admission, including syncope and collapse, disorders of the ligament/muscle, and viral/Chlamydial infection. Four people from the PWS-like group accounted for one day of inpatient and six visits to outpatient psychiatric services. ID, stress/anxiety disorders and infantile cerebral palsy were recorded as the main reasons for these attendances. One woman died at age 17.9 years, but no information on her cause of death was available from the Deaths Registry.

Table 4.9 Hospital admissions for the PWS-like cases within in the study group

Reason for admission	Total number of admissions (% of total admissions)	Number of Individuals admitted
Respiratory disorders	10 (14.3)	3
Epilepsy	27 (38.6)	3
Gastrointestinal disorders	8 (11.4)	4
Dental	1 (1.4)	1
Congenital anomaly	1 (1.4)	1
Ear problems	1 (1.4)	1
Skin disorders	1 (1.4)	1
Fractured bone ± complications	2 (2.9)	1
Failure to thrive/feeding difficulties	1 (1.4)	1
Urinary tract disorders	3 (4.3)	3
Other causes (various)	15 (21.5)	

5. DISCUSSION

A number of diverse demographic, clinical, genetic and technical factors need to be considered when assessing the overall findings of the study.

5.1 Potential limitations of the study

5.1.1 Case ascertainment

One disadvantage of using the DSC database for case ascertainment is the Commission's requirement that a specific level of ID is identified before a client is accepted for registration. This has particular relevance for individuals with PWS, because an estimated 27-40% are thought to have at least low-average intelligence (Cassidy *et al.*, 2000; Cimke *et al.*, 2002). Therefore PWS individuals who have normal or borderline intelligence are unlikely to be registered at DSC. In addition, a recent study of ID in WA found that a significant number of children with ID were identified either through the Department of Education, Catholic Education or the Association of Independent Schools, rather than via DSC (Leonard *et al.*, 2003). Globally, the majority of persons with ID fall within the mild/moderate ranges of functional limitation (Christianson *et al.*, 2002; Leonard *et al.*, 2003). Hence it is possible that additional people with AS or PWS are living undiagnosed in the community and could perhaps be identified if these educational agencies were used as sources of ascertainment.

The organisation known as Irrabeena, which later became the Disability Services Commission, was a centre originally established by the Slow Learning Children's Group (now the Activ Foundation) in 1954. The centre, which was used for the testing and diagnosis of ID, became the responsibility of the Mental Health Department of WA in 1964. Over those years of foundation and change there were a number of different physicians involved in record-keeping, and major changes in public attitudes to ID occurred (Gillgren, 1996).

The initial descriptions of PWS in 1956 and AS in 1965 were published during this period of development in the provision of services for the ID population in Western Australia. By the time the consensus diagnostic criteria were published (Holm *et al.*, 1993; Williams *et al.*, 1995), a majority of the individuals in the present study cohort had been diagnosed by the staff of DSC or

by another Medical Practitioner. The earliest recorded diagnosis of AS at DSC was in 1966, and that of PWS was in 1968. In some cases the Heber code was added retrospectively to the patient's file, and there was no way of ascertaining at what precise date the coding had been performed. There also was no guarantee that all cases of PWS or AS had been identified from the registered client population and had the requisite Heber code appended to their file.

Linkage of the GSWA records to all registered DSC clients ensured that all persons with ID who had undergone cytogenetic testing of chromosome 15 in Western Australian public laboratories were considered for inclusion in the study, thus ensuring the creation of a database comprising most of the known cases in WA. By definition, those cases identified at GSWA but who were not registered with DSC could not be included in the study, as no clinical data were available on these individuals. However, only three individuals who were identified through GSWA as having PWS or AS were not included in the DSC files, so it is unlikely that a significant number of cases were missed because of this limitation. It is known that at an early stage of the development of GSWA some individuals had samples for testing sent to laboratories in other States of Australia. Unfortunately, it was not possible to access the records of these laboratories to get confirmation of test results.

It was difficult to estimate the number of people with PWS or AS in the WA resident population who were not registered on the DSC database. Given that some 1.05 million people were born in WA between 1950 and 2003 (Australian Bureau of Statistics, 2003), and previous prevalence rates for both AS and PWS have been estimated at 1 in 10,000-25,000 births, it initially was expected that between 84 and 210 people would be identified as having one or other syndrome. As demonstrated in Section 3.5, 80 persons born before 2003 were identified from the DSC database. However, only 57 of these people (26 with AS, and 31 with PWS) were born in WA. This leads to the possibility that at least 27 and perhaps as many as 153 individuals born in WA with either syndrome may not have been diagnosed. If correct, several potential contributory circumstances can be identified:

1. The birth incidences for both syndromes are lower in WA than would seem probable from estimates derived for other populations.

2. A sizeable proportion of people with PWS or AS had migrated from WA before they were diagnosed.

3. A significant number of PWS or AS cases remain undiagnosed in the general population.

4. Individuals with one or other of the syndromes died before a diagnosis and/or contact with DSC was made.

Of these four possible outcomes, numbers 3 and 4 would seem to be the most feasible. Worldwide there appears to be comparatively little variation in the reported incidence rates for AS and PWS, therefore it is difficult to suppose credible grounds for their apparent low prevalence in this State (Hou *et al.*, 1998; Stromme, 2000; Whittington *et al.*, 2001; Smith *et al*, 2003). In addition, the population of WA is considered to be demographically quite stable, with very limited permanent migration from the State (Holman *et al.*, 1999; Trewin, 2003), so it is unlikely that many people have moved out of WA before being diagnosed with either syndrome. As 23 subjects were born outside WA, there appears to have been a steady rate of net inward migration over the last 50 years (Trewin, 2003). It is acknowledged that the diagnostic services offered by GSWA are both comprehensive and of high quality, but, as was noted above, there have been periods when genetic tests were conducted in the laboratories of other Australian States, and the results were not always available in the client files.

There remains the possibility that a substantial number of individuals with ID are registered at DSC but have not had a diagnosis of AS or PWS recorded. Over the last 15 years there has been a greater emphasis on community care for people with ID, so that more often patients are seen by a General Practitioner rather than by the specialist physicians at DSC (Stella, 1996). In these cases there probably is little chance that the individuals would have returned to DSC to have a retrospective diagnosis recorded in their files, especially if their level of ID was borderline or mild.

AS patients are difficult to diagnose in the first few years of life, before the characteristic patterns of developmental delay and epilepsy have become manifest, and some cases of PWS are not diagnosed until childhood or even later. It is therefore entirely possible that some individuals in WA with either syndrome

have not yet been identified. Due to the relatively recent development (post-1995) of specific diagnostic laboratory tests for both syndromes, it seems likely that a number of older people with AS or PWS have not been recognised as having either syndrome. In the Netherlands, for example, two middle-aged patients with PWS or AS were identified during a retrospective study of the residents of a single long-stay institution (van Buggenhout *et al.*, 2001). Similarly, four adult AS cases were diagnosed after screening a sub-section of the population of a large Developmental Centre in the U.S.A. (Jacobsen *et al.*, 1998). The large-scale deinstitutionalisation of the intellectually disabled population in WA since the 1970s makes it unlikely that many of these putative PWS or AS cases will ever be specifically diagnosed (Stella, 1996).

5.1.2 Data availability

Specific restrictions were effectively imposed on the study by the data collection method employed. As there was no direct or indirect patient or carer contact, the data collected were wholly dependent on the quality and quantity of information recorded in the various databases and in the client hard copy files. These records have been compiled and maintained by a relatively small number of Medical Practitioners, with the consequent expectation that they would be internally consistent. However, under-reporting of many of the recommended diagnostic signs for both disorders was apparent in a substantial number of the early patient files, possibly due to the relatively recent specification of the diagnostic clinical criteria for the two syndromes, allied to the retrospective nature of some of the diagnoses.

The volume of data contained in each file also depended on the degree of utilisation of DSC assistance and resources by individual clients. Some people were rarely in contact with DSC, especially those with a milder phenotype or whose parents/carers may have had more resources available to them. In the earlier years of what was to become the Disability Services Commission there was considerable distrust of the 'professionals' expressed by some parents, and it was also difficult for clients who lived in more remote regions of the State to access DSC services (Gillgren, 1996). The overall result was that the records of certain individuals contained relatively little information. In these cases, the

supplementary data accessed from the other Western Australian databases were of particular value in establishing the morbidity patterns of the patients.

The development and use of record sheets specifically for AS or PWS has greatly aided the collection of data pertaining to the major clinical signs of both disorders (Appendices IX & X). However, in the absence of professional help, the record sheets can only be completed with a level of accuracy dependent on the memory and opinions of the parents or carers of the patients. Terms such as 'feeding difficulties' are often subjective and vague, and they may elicit a wide variation in response, dependent on the perception of the meaning of the phrase on the part of the respondent. In addition, some of the characteristics, i.e., hypotonia and weak cry in PWS, and feeding difficulties in either syndrome, are generally confined to infancy and may not be recalled at a later date. Conversely, short stature and hyperphagia in PWS are normally features of the older child and adult, rather than the infant.

5.2 Prevalence estimates

5.2.1 Intellectual disability and ethnic origins

A study from Western Australia covering the period 1983 to 1992 estimated that 14.3 persons per 1000 births in WA had an ID, with the majority (10.6/1000) showing mild/moderate ID (Leonard *et al.*, 2003). The male to female ratio was 1.6:1, and there was a disproportionately high number of Indigenous Australian clients, with 2.3 Indigenous cases to each non-Indigenous patient (Leonard *et al.*, 2003), even though Indigenous people only comprise 3% of the State population (Australian Bureau of Statistics, 2002). The gender ratio was similar to that recently calculated for a rural South African population, but the overall prevalence in South Africa was much higher at 35.6 persons per 1000 births, of whom 29.1 per 1000 were mildly disabled (Christianson *et al.*, 2002).

The presence of high rates of specific morbidities in mothers, e.g., diabetes, hypertension and chronic renal disease, or in the child, e.g., fetal alcohol syndrome, postnatal lead poisoning, malnutrition and infantile anaemia, may be implicated in the increased occurrence of ID among both Indigenous Australians and Indigenous South Africans, as these disorders are indicative of the lower

socio-economic standing of many individuals in these two populations (Grossman, 1983; Christianson *et al.*, 2002; Leonard *et al.*, 2003).

As mentioned previously (Section 5.1.1), in WA more children with mild ID were identified through the Department of Education, Catholic Education and the Association of Independent Schools than from DSC (Leonard *et al.*, 2003). The prevalence of severe to profound ID varies widely across studies and populations, ranging from 0.64 per 1000 to 14.4 per 1000, although some of these figures refer to birth incidence while others signify prevalence in a surviving cohort, so that no overall comparative conclusions can be readily drawn (Durkin *et al.*, 2000; Christianson *et al.*, 2002; Arvio & Sillanpaa, 2003; Leonard *et al.*, 2003).

5.2.2 *Angelman syndrome*

The relatively low prevalence rate for Angelman syndrome suggested by the data from the present study group could reflect the problems in ensuring an accurate clinical diagnosis of AS, especially in infancy, although it is difficult to understand why this would be more relevant in WA than in other regions of Australia or internationally. The comparatively steady rate of migration into the State would indicate that there can be little ground for supposing a founder effect is operative, especially in the light of the ever-increasing ethnic diversity found in the migrant population. The apparent reduced incidence of the disorder is reflected in the absence of individuals diagnosed with AS within the last five years, even though the various cytogenetic and DNA-based diagnostic laboratory tests have been available throughout this time-period (Williams *et al.*, 1995; Saitoh *et al.*, 1996; Glenn *et al.*, 1997).

It would seem that there has been a lack of diagnostic testing in Western Australian cytogenetic and molecular genetic laboratories for IC or *UBE3A* defects, which were identified as significant causative mechanisms of AS in 1996 and 1997, respectively. Additionally, the tests that were used proved to be uninformative for many patients, suggesting that a number of AS cases remain undiagnosed in WA. For example, after a negative banding test or karyotype, in the past individuals may have been listed either as not having AS or been allocated some other diagnostic code (e.g., 'other unknown prenatal influence';

Heber 6900). If so, they would not have been selected for the study from the DSC database. Nevertheless, there were four people who had a negative karyotype/banding test but who were still considered to have Angelman syndrome based on clinical assessment, and were recorded as such.

To date, there has been no reported variation in prevalence of either PWS or AS which could be attributed to membership of any specific ethnic group. Therefore, the absence of Indigenous Australians from the AS cohort could be indicative of a lack of opportunity for identification due to remoteness from services, or of community-specific beliefs and attitudes (Morgan *et al.*, 1997). Aboriginal people often prefer to care for individuals with a disability within the community, rather than seeking outside help (Brown, 2001). This means that, despite over-representation of the Indigenous community (7.4% of cases) in the records of DSC (Glasson *et al.*, In Press), there still may be a significant number of individuals who have not been given a causative diagnosis for their intellectual disability. At the same time, as Indigenous Australians comprise just 3.5% of the total Western Australian population, small number effects may also provide a part-explanation (Australian Bureau of Statistics, 2002).

5.2.3 Prader-Willi syndrome

In a similar manner to the AS group, it was very difficult to estimate the birth incidence of PWS in WA from the data collected as part of the current study. Exclusion from the DSC records of persons with no or minimal ID would have meant that some PWS individuals with borderline ID were almost certainly missing from the study. The possibility of over-diagnosis was also a consideration since, as previously discussed in Section 2.3.3.5, there is a range of conditions that superficially resemble PWS if clinical criteria are used as the only basis for assessment. This was one of the reasons for removing methylation-normal individuals from the main study cohort (Section 3.5), as there is a high probability that few of these people have PWS, despite their clinical presentation being consistent with the symptoms of the syndrome.

Most previous studies have reported no gender bias among people with PWS, although females are often under-represented in the groups investigated (Greenswag, 1987; Akefeldt & Gillberg, 1999; Couper & Couper, 2000; Fridman

et al., 2000b). It has been suggested that the probability of mis-diagnosing PWS in females is increased by the difficulty of identifying female genital hypoplasia (Akefeldt & Gillberg, 1999; Crino *et al.*, 2003). In this study, there were equal numbers of males and females with either a strong clinical or a confirmed genetic diagnosis of PWS, and the mean age at diagnosis did not differ significantly between males and females.

5.3 Developmental characteristics

5.3.1 Angelman syndrome

Although severe or profound ID was common (52.9%) in the AS study group, the frequency was not as high as has been suggested in other reports (Laan *et al.*, 1996; Leitner & Smith, 1996). It would be expected that most people with severe ID in the State would be included in the records of DSC, as one of the primary functions of the Commission is to provide support for individuals with intellectual difficulties. Thus there is no obvious explanation for the relative paucity of people with severe ID in the study. Both of the AS patients identified with UPD had moderate ID, which may be indicative of the less severe phenotype previously described in this sub-class of AS patient (Moncla *et al.*, 1999b; Lossie *et al.*, 2001).

Table 5.1 (p. 76) provides a comparison between the frequencies of a number of diagnostic features found in the present study and those reported by other authors. A majority of the observed rates of clinical features did not vary greatly from those previously quoted, although some minor discrepancies were noted. Leitner and Smith (1996) found that males were more likely to become independently ambulant, and at an earlier age, than females. This was supported in the present study, where the mean age of independent walking was significantly greater for females (5.2 years) than for males (3.5 years) (Section 4.2.3). The average age of walking for the whole group (4.4 years) was in close agreement with figures reported by other authors (Laan *et al.*, 1999a; Moncla *et al.*, 1999b).

Characteristic	AS	Literature	References
Developmental delay: (n=29; n=28)	sit=17mth walk=53mth	sit = 12-20mth walk=33-72mth	(Buntinx *et al.*, 1995; Smith *et al.*, 1996; Laan *et al.*, 1999; Moncla*et al.*, 1999a; Moncla*et al.*, 1999b)
Absent/minimal speech (%) (n=34)	82	90-100	(Buntinx *et al.*, 1995; Moncla*et al.*, 1999a)
Ataxia (%) (n = 34)	91	79-96	(Buntinx *et al.*, 1995; Smith *et al.*, 1996; Laan *et al.*, 1999; Beckung *et al.*, 2004)
Behaviour (%) (n = 34)	76	77-100	(Buntinx *et al.*, 1995; Smith *et al.*, 1996; Laan *et al.*, 1999; Moncla*et al.*, 1999a)
Microcephaly (%) (n = 20)	44	62-93	(Buntinx *et al.*, 1995; Moncla *et al.*, 1999a; Moncla*et al.*, 1999b)
Epilepsy (%) (n = 34)	88	79-85	(Buntinx *et al.*, 1995; Leitner & Smith, 1996; Minassian, *et al.*, 1998; Moncla*et al.*, 1999a; Clayton-Smith & Laan, 2003)
Abnormal EEG (%) (n = 27)	82	90-100	(Buntinx *et al.*, 1995; Leitner & Smith, 1996; Moncla *et al.*, 1999a)
Feeding difficulties (%) (n = 25)	41	21-77	(Smith, *et al.*, 1996; Moncla*et al.*, 1999a)
Strabismus (%) (n = 27)	47	21-57	(Buntinx *et al.*, 1995; Laan *et al.*, 1996; Sandanam, *et al.* 1997; Moncla*et al.*, 1999a)
Hypopigmentation (%) (n= 17)	35	0-64	(Buntinx *et al.*, 1995; Moncla *et al.*, 1999a; Moncla*et al.*, 1999b)
Hypotonia (%) (n = 34)	79	48-63	(Buntinx *et al.*, 1995; Smith *et al.*, 1996)
Scoliosis (%) (> 15y: n = 23)	44	25-70	(Buntinx *et al.*, 1995; Laan *et al.*, 1996; Sandanam *et al.*, 1997; Moncla*et al.*, 1999b; Clayton-Smith, 2001)
Obesity (%) (n = 34)	38	15-50	(Smith *et al.*, 1996; Moncla *et al.*, 1999a; Moncla *et al.*, 1999b; Clayton-Smith & Laan, 2003)

The majority of individuals with AS never acquire more than a few words of speech (Buntinx *et al.*, 1995; Monela *et al.*, 1999b; Andersen *et al.*, 2001), and most of the AS cases studied had either no ability to speak, or had only a very few words in their vocabulary. Many individuals from the AS cohort were reported to be able to understand some verbal communication from others. Commonly, AS cases are reported to have a higher degree of speech comprehension than of expression (Buntinx *et al.*, 1995; Monela *et al.*, 1999b). In a Norwegian study (Andersen *et al.*, 2001), the median cognitive age for AS patients between the ages of two and 14 years was estimated to be 10 months (range, 7-23 months). This cognitive age corresponds to Stage 4 of the sensorimotor period of development as described by Piaget (Campbell, 1976), and one of the characteristics of this stage of development, defined as 'pre-language', is that there is a recognised ability to understand verbal communication and show intelligent behaviours (Campbell, 1976).

5.3.2 Prader-Willi syndrome

The PWS study group contained a much smaller percentage of normal or borderline intellectually disabled individuals than would be expected, i.e., <9% by comparison with the 30-40% reported by other researchers (Cassidy & Schwartz, 1998; Webb *et al.*, 2002). As previously indicated (Section 5.1.1), the case ascertainment method used in the present study was effectively biased to exclude those with a borderline level of ID. Unfortunately, the study design and ethical considerations precluded the use of the educational sources described in Section 5.1.1. as a means of identifying additional cases. The number of PWS cases falling into the severe or profound ID categories (4.4%) did not differ significantly from that given in most other reports (State & Dykens, 2000; Clayton-Smith, 2001), although one study did indicate that 18.8% of their group functioned at IQ <50 (Clarke *et al.*, 2002). Therefore, it seems probable that most of the more severely affected PWS patients in WA have been identified.

Table 5.2 Comparison of the Prader-Willi group with the literature

Characteristic	PWS	Literature	References
Hypotonia (%) (n = 46)	96	83-100	(Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Webb *et al.*, 2002; Whittington *et al.*, 2002)
Feeding difficulties (%) (n = 43)	85	81-100	(Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Webb *et al.*, 2002)
Weight gain (%) (n = 46)	87	73-93	(Gillessen-Kaesbach *et al.*, 1995; Gunay-Aygun *et al.*, 2001; Whittington *et al.*, 2002)
Hypogonadism (%) (n = 15; n = 19)	male = 91 female = 58	male = 94-100 female = 60-100	(Gillessen-Kaesbach *et al.*, 1995; Webb *et al.*, 2002; Whittington *et al.*, 2002)
Developmental delay (n = 34; n = 39)	sit = 12mth walk = 31mth	sit = 12mth walk = 24-29mth	(Gillessen-Kaesbach *et al.*, 1995; Webb *et al.*, 2002)
Hyperphagia (%) (n=33)	85	66-90	(Fridman *et al.*, 2000b; Whittington *et al.*, 2002)
Short stature (%) (n = 39)	72	48-83	(Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Whittington *et al.*, 2002)
Hypopigmentation (%) (n = 20)	75	33-57	(Gillessen-Kaesbach *et al.*, 1995; Cassidy & Schwartz, 1998; Whittington *et al.*, 2002)
Eye abnormalities (%) (n = 35)	66	58-77	(Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Butler *et al.*, 2002; Whittington *et al.*, 2002)
Speech defects (%) (= 45)	87	79-90	(Gillessen-Kaesbach *et al.*, 1995; Whittington *et al.*, 2002)
Scoliosis (%) (n = 30)	33	32-75	(Laurance *et al.*, 1981; Butler *et al.*, 2002; Whittington *et al.*, 2002)
Epilepsy (%) (n = 46)	39	14-46	(Gillessen-Kaesbach *et al.*, 1995; Fridman *et al.*, 2000b; Butler *et al.*, 2002)

The frequencies of selected clinical features within the PWS group were compared with previously published papers, and the results summarised in Table 5.2 (p. 78). Speech articulation problems or delayed acquisition of speech are listed as minor clinical signs of PWS (Holm *et al.*, 1993), however, in the current study 85.7% of PWS cases suffered from speech defects. According to data from the U.S.A., speech articulation defects and some of the other minor features appear to be more sensitive as diagnostic tools than many of the major criteria such as characteristic facies (Gunay-Aygun *et al.*, 2001).

This more recent research has produced additional information on the wide range of phenotypic variation found in people diagnosed with PWS, and for this reason it has been suggested that the existing clinical criteria may need to be revised (Gunay-Aygun *et al.*, 2001). It has also been recommended that specific features of PWS should be differentially weighted as diagnostic tools at different stages of life. For example, during infancy, hypotonia and feeding difficulties are the most reliable indicators of the syndrome, and it is only after the first two or three years of life that hyperphagia, global developmental delay and obesity become prominent diagnostic traits (Gunay-Aygun *et al.*, 2001; Whittington *et al.*, 2002).

5.4 Physical characteristics

5.4.1 Angelman syndrome

The comparatively high proportion of AS cases with hypotonia in this study (Table 5.1, p. 76) may be a consequence of clinicians becoming increasingly aware of the value of reporting such clinical details. Truncal hypotonia and limb hypertonia have previously been described as widespread in AS (Laan *et al.*, 1996; Smith *et al.*, 1996; Cassidy & Schwartz, 1998). As this feature was not included in the diagnostic criteria, it seems improbable that all physicians would have recognised the benefit of including the specific location of any hypotonia and hypertonia in client files. At the present time, however, the DSC specialist disability clinicians routinely include this type of detailed information in their reports.

Earlier reports have suggested frequencies of obesity in AS patients of 15-50%, and individuals with *UBE3A* mutations are usually reported to be more

prone to becoming overweight than those with other AS disease genotypes (Laan *et al.*, 1996; Moncla*et al.*, 1999a; Moncla *et al.*, 1999b). More than one-third of the AS cohort in the present study were obese at some period prior to the time of sampling (Table 5.1, p. 76), which was within the expected range for AS populations. There was one individual with AS who was originally thought to have PWS due to obesity and hyperphagia, but who had no ataxia or inappropriate laughter. This was similar to a patient described by Dupont *et al.* (1999), who showed also features of both AS and PWS and had, in addition to paternal UPD, a SMC 15 which was located outside the PWS/AS critical region.

Up to 64% of adults and 26% of adolescents with ID are obese or overweight (Beange & Lennox, 1998; Fisher, 2004), and a study from the U.K. described 4.5-6.8% of adults with ID as severely obese (Cooper, 1998b). Obesity is estimated to lessen the life-span by 6-7 years at age 40. Hypertension, Type II diabetes, coronary heart disease, dyslipidaemia, and gall bladder disease are all more common in those who are obese, compared to people with a normal body mass index, regardless of their level of intellectual function (Cooper, 1998b; Labib, 2003; Marshall *et al.*, 2003; St-Onge & Heymsfield, 2003). This means that the obese and overweight members of the AS group would benefit from regular physical assessment with the aim of minimising the risk of these adverse health effects as they become older.

Strabismus (47%) was present in the study cohort at a similar rate to other AS patient groups (Buntinx *et al.*, 1995; Laan *et al.*, 1996; Sandanam *et al.*, 1997), and the frequency was much higher than the 11-13% noted for the general population of people with ID (Reid & Ballinger, 1995; Thompson & Reid, 2002).

An estimated 25-70% of AS patients have been described as presenting with scoliosis (Laan *et al.*, 1996; Sandanam *et al.*, 1997; Moncla *et al.*, 1999a; Clayton-Smith, 2001), and the percentage of scoliosis cases in this study (43.5% of those >15 years old) fell within this range (Table 5.1, p. 76). None of this cohort of patients had received surgery for scoliosis prior to the collection of data, and none were recorded as having severe scoliosis. Follow-up at a later date may indicate that the level of severity increases in some cases, leading to possible surgical intervention.

Rates of osteoporosis increase with age in both the ID population and the general population, and the condition often leads to increased frequencies of fractures in people with ID (Beange & Lennox, 1998; Center *et al.*, 1998). None of the AS cases were reported to have osteoporosis, even though individuals receiving anti-epileptic medication are at a higher risk of developing osteoporosis, due to abnormalities in bone metabolism (Murchison *et al.*, 1975; Prestwood, 1997). An investigation into the correlation between epilepsy and bone fractures among people with ID showed that 26% of the epileptic ID population suffered from one or more fracture, but only 15% of those without epilepsy (Jancar & Jancar, 1998). Among the AS patients in this study, 17% of those with a history of epilepsy had bone fractures, but there were no reports of fractures in the four individuals who had no seizures. The sample sizes were too small for any firm conclusions to be drawn, but the direction of the correlation was in keeping with previous reports.

5.4.2 Prader-Willi syndrome

There was strong similarity between the frequencies of physical characteristics found in the PWS group and the literature, with the exception of the relatively high number of patients (n = 15) with hypopigmentation (Table 5.2, p. 78) among the 20 cases in whom this feature was recorded. There is, however, considerable disparity in the prevalence of hypopigmentation reported by other authors as the trait is assessed in a subjective manner, and comparison with family members may be influenced by the commonly observed darkening of hair and skin which tends to occur as children age. In several studies it was noted that the hair colour of both AS and PWS children with hypopigmentation became darker as they aged (Buntinx *et al.*, 1995; Sandanam *et al.*, 1997).

The very high rate of obesity in the PWS patients was as expected (Table 5.2, p. 78). There was a distinct age difference between individuals who were overweight or obese and those who were not (23.5 years for overweight, compared with 4.3 years for non-obese cases: $t = -4.033$, $p = 0.001$), indicating that younger patients generally fell within the normal weight range. The administration of growth hormone therapy to four children with PWS may assist the retention of a normal weight range into adolescence in these individuals, as

has been reported elsewhere (Lindgren & Ritzen, 1999; Camel *et al.*, 2002; Hoybye *et al.*, 2003; Paterson & Donaldson, 2003).

In general, people with ID tend to be significantly less active, even when able-bodied, than people in the wider population, which may contribute to the weight problems exhibited by so many ID individuals (Robertson *et al.*, 2000; Fisher, 2004). Their increasing obesity levels in turn tend to increase the incidence of secondary conditions such as Type II diabetes and cardiovascular disease (Turner & Moss, 1996; van Schrojenstein Lantman-de Valk *et al.*, 1997).

Comparable health problems are likely to beset overweight PWS patients, especially as they become older. In the U.S.A., rates of obesity for the general population have been increasing over the last 50 years. The proportion of adults who were obese in 1960-62 was 13.4%, however by 1999-2000, it was 30.9% (St-Onge & Heymsfield, 2003). It is estimated that the direct cost of obesity in the United States is 3-8% of the total health expenditure and, worldwide, there is considerable loss of productivity due to sickness or early death among the obese population (Labib, 2003). Similarly, obese PWS patients are likely to require greater levels of health care for weight-related morbidities.

Scoliosis has been reported in 32-75% of PWS subjects aged 15 years or older (Laurance *et al.*, 1981; Butler *et al.*, 2002; Whittington *et al.*, 2002). Some 37% of the PWS subjects older than 15 years in this study showed signs of scoliosis, and two had been surgically treated for the problem. There were, however, 40% of the study group for whom no data on scoliosis were available, so that no firm estimate of its prevalence could be made for the study sample (Table 5.2, p. 78). It is possible that scoliosis will become less of a problem in those individuals who are treated with growth hormone, as the lean body to fat mass ratio and the degree of weight control move closer to the normal range, thus placing less strain on the developing spine.

Relatively high rates of osteoporosis (21%) and osteopoenia (58%), i.e., a bone mass density of between -1.0 and -2.5 SD, have been found in PWS patients (Hoybye *et al.*, 2002). However, only two of the 30 PWS cases over 15 years of age were reported to have osteoporosis. As noted in Section 5.4.1, osteoporosis may be associated with the relatively high numbers of fractures reported in the PWS and/or ID population, as a single standard deviation decrease in bone

mineral density is estimated to increase the risk of breaking a bone by a factor of two (Marshall *et al.*, 1996; Center *et al.*, 1998; Butler *et al.*, 2002). Not surprisingly, females are more likely to experience fractures at some time of life, as young women generally reach a lower peak bone mass than men (Prestwood, 1997). After menopause, changes to hormonal levels cause an increase in the rate of bone density loss, leading to higher rates of osteoporosis (Ahlborg *et al.*, 2003). The reduced level of physical exercise and limited mobility which are both more common in PWS patients tend to decrease bone density (Bennge & Lennox, 1998), thus placing persons of either gender with PWS at greater risk of osteoporosis and bone fracture.

Among the PWS population studied by Butler *et al.* (2002), approximately 30% had sustained one or more fractured bones, with a comparable figure of 21% among those less than 18 years of age. The number of PWS patients with fractures was significantly lower in this study group, i.e., 14% overall, and 4% among those persons less than 18 years old. However, the data on fractures were only derived from data linkage to the Hospital Morbidity system. Hence any fractures that did not require hospital admission were not recorded, and there may have been more instances that were treated at an outpatient department or by General Practitioners. Given the small number of patients with osteoporosis recorded in the study, the low incidence of broken bones may not be unusual.

As in previous studies, cryptorchism/genital hypoplasia was present in a majority of males (91%) from this cohort (Cassidy & Schwartz, 1998; Nicholls *et al.*, 1998; Cassidy *et al.*, 2000; Fridman *et al.*, 2000b; State & Dykens, 2000). However female genital hypoplasia, as evidenced by absent or delayed menses, was reported in only 58% of the 19 female subjects over 15 years old (Table 5.2, p. 78). This was significantly lower than figures from the U.K. which ranged between 76-100% (Laurance *et al.*, 1981; Webb *et al.*, 2002; Whittington *et al.*, 2002; Crinu *et al.*, 2003).

Within the sub-group of adult female cases from the present study with an identified deletion, all had absent or delayed menses. The remaining eight female subjects, none of whom had confirmed genital hypoplasia, were composed of four cases with normal menses (including one who had three children), three who exhibited precocious puberty with early menses, and one for whom no relevant

data had been recorded. None of the eight individuals had received a genetic confirmation of PWS, therefore statistics related to these cases should be interpreted with appropriate caution. However, both precocious puberty and fertility have been reported in individuals with genetically-confirmed PWS (Akefeldt *et al.*, 1999; Schulze *et al.*, 2001; Crino *et al.*, 2003), so that diagnosis of PWS cannot be excluded for any of the eight women discussed above.

5.5 Behavioural aspects

Up to 69% of intellectually disabled individuals aged over 65 years experience a comorbid psychiatric disorder (Cooper, 1998a; Bowley & Kerr, 2000). Of these cases, 40% have been described as suffering from severe emotional or behavioural disturbance (King *et al.*, 1997). It has been suggested that the challenging behaviours often shown by people with ID may be related to the abnormally high anxiety levels they experience in situations which would not be perceived as stressful by persons with normal intellectual function (Janssen *et al.*, 2002). The limited social networks and poor self-esteem frequently exhibited by people with intellectual disabilities can also have a negative impact on their behaviour and mental health (Walsh, 2002). In addition, the presence of epilepsy has been linked to a variety of psychiatric disorders, maladaptive behaviours, and sleep disturbances, although it is not clear if epilepsy causes these conditions or is a co-morbid feature (Bowley &Kerr, 2000).

5.5.1 Angelman syndrome

The majority of AS subjects were reported to have the characteristic happy disposition associated with the syndrome, although some individuals occasionally had temper tantrums or periods of withdrawal. It seems probable that these episodes may have been related to the frustration often experienced by persons who are unable to communicate their wants or needs effectively. The few individuals from the cohort who had attended psychiatric clinics were not recorded as having specific psychiatric disorders; rather their admissions were a consequence of the developmental delay and intellectual disability associated with the syndrome. There were only limited data on the presence of sleep disturbances among the AS group, which previously had been described as a minor consequence of the syndrome.

5.5.2 *Prader-Willi syndrome*

Although no member of the study cohort was over 50 years old, eight individuals (17.4%) had some level of contact with the State psychiatric services by the time of data collection. Seven of these people were over 15 years old, and one was 12 years six months at first contact with psychintric services. The adult patient who had attended more than one thousand outpatient sessions suffered from a combination of behavioural and emotional disorders (Section 4.3.7). The majority of the cases were being assessed and treated by the mental health specialists for ID or developmental delay, rather than for psychotic episodes.

The behavioural traits exhibited by the PWS study group proved to be particularly problematic in terms of the administration of routine care. Temper tantrums, violent outbursts and stealing, commonly of food or money to buy food, were reported for a number of the PWS individuals. However, the diagnostic criteria require that five or more of the characteristic behaviour symptoms are present before they are accepted as a significant diagnostic feature (Holm *et al.*, 1993). On this basis, there was insufficient information to state the real prevalence of the characteristic behavioural features in the study sample.

5.6 Neurological findings

5.6.1 *Angelman syndrome*

Seizures were reported at some stage of life for 88% of the AS cases in the study. This was comparable to the prevalence statistics given in other studies (Table 5.1, p. 76), and almost double the mean frequency of seizures present in the wider ID population (Reid & Bullinger, 1995; Leitner & Smith, 1996; Smith *et al.*, 1996; Clayton-Smith & Laan, 2003). Seizures and epilepsy are more frequent in people with intellectual disabilities compared to the general population, and the presence of seizure disorders tends to correlate positively with the degree of intellectual handicap, varying from 14% of individuals with mild ID to 44% of those with severe ID (McGrother *et al.*, 1996; Beange & Lennox, 1998; Bowley & Kerr, 2000; van Schrojenstein Lantman-De Valk *et al.*, 2000; Fisher, 2004).

Some previous reports have stated that epilepsy in AS decreases in frequency and severity with advancing age (Buntinx *et al.*, 1995). However, there was little evidence of any reduction in the occurrence of seizures within the AS

study group. A sample of 100 individuals with severe or profound ID were followed by researchers in the U.K. over a 26-year period, and similar proportions of the group were epileptic at all data collection times (28-32%), indicative of the persistence of seizure activity throughout the life-course of many individuals (Reid & Ballinger, 1995; Thompson & Reid, 2002). Conversely, the incidence of epilepsy has been reported to decline among older intellectually disabled people in The Netherlands and the U.K. when compared to younger adults. This finding is possibly a sign of the healthy survivor effect, since the presence of seizures significantly lowers life expectancy (van Schrojenstein Lantman-de Valk *et al.*, 1997; Chaney & Eyman, 2000; Patja *et al.*, 2000; Morgan *et al.*, 2001).

Around a quarter (26%) of the seizure activity among the AS study group was reported to be difficult to control and/or of frequent occurrence, making epilepsy one of the most significant health problems for individuals with AS and their families and carers (Bowley & Kerr, 2000). The extensive amount of hospital care needed for treatment of epilepsy attests to the severity of the condition within this group (Table 4.4, p. 59). In addition, one of the two deaths in the AS group was attributed to epilepsy.

The majority of AS patients have specific abnormal EEG patterns (Leitner & Smith, 1996; Smith *et al.*, 1996; Moncla *et al.*, 1999a; Clayton-Smith & Laan, 2003). Among the AS cohort, abnormalities were evident in 25 of the 27 individuals who had at least one EEG performed (Table 4.2, p. 55). Of the individuals tested, three had no recorded epileptic episodes, even though two of these three people demonstrated the characteristic EEG patterns of AS. It has been proposed that the presence of suggestive EEG patterns, even in the absence of seizure activity, could be used to assist in differentiating between AS and some mimicking conditions, and for the confirmation of AS in those individuals lacking an identifiable genetic mechanism (Valente *et al.*, 2003). The results of the present study provide clear support for the potential application of this proposal.

5.6.2 *Prader-Willi syndrome*

Epilepsy has been previously reported in a significant proportion (34-42%) of PWS cases (Butler *et al.*, 2002), which is a slightly higher rate than the 21% given for the overall intellectually disabled population (Reid & Ballinger, 1995;

Cooper, 1998b; Thompson & Reid, 2002). Approximately 28% of the present cohort had at least one episode of epilepsy or convulsions throughout life (Table 5.2, p. 78). In fact, at 4.3% of total admissions, epilepsy was one of the more common reasons for hospital admission within the PWS group (Table 4.7, p. 67). It is possible that haploinsufficiency, i.e., low dosage due to the loss of one allele of a gene or genes within the PWS/AS critical region, may cause the development of epilepsy in patients with PWS, although the seizures were generally in a milder form than those suffered by individuals with AS.

5.7 Laboratory diagnosis

There appeared to be some lack of effective testing to determine the specific genetic mechanism(s) involved in the aetiology of AS in a considerable number of cases. More than a third of the AS group had either a karyotype or banding test only, or no diagnostic test at all. In addition, there had been no tests undertaken for IC defects, and only one (which was negative) for an *UBE3A* mutation, even though eight of the 34 subjects showed biparental methylation (Table 4.2, p. 55). Many of the patients had been offered the most recent laboratory diagnostic tests as they became available, but the take-up rate was exceptionally low. Further qualitative research would be needed to investigate the rationale for this apparent reluctance to take advantage of the newest diagnostic techniques, although much of the lack of motivation may be similar to that related to the limited use of screening tests by ID persons in the U.K., and the lower rates of mammography scans conducted on women with ID compared to the general population in WA (Pearson *et al.*, 1998; Djuretic *et al.*, 1999; Whitmore, 1999; Sullivan *et al.*, 2003).

There seems to be a perception by some physicians and/or carers that such tests are unnecessary, or that the patients will be markedly upset by the procedure. This view is supported by the fact that severely ID individuals may become excessively agitated when undergoing phlebotomy or other medical procedures (Pearson *et al.*, 1998; Aspray *et al.*, 1999; Djuretic *et al.*, 1999; Whitmore, 1999). Monetary considerations may also play a role in the unwillingness of families and carers to agree to comprehensive genetic testing, and almost 20% of the cases in this study lived in more remote regions of the State where sampling is more difficult to arrange. In addition, information about the new tests may not be freely

available, or, in some cases, comprehensible to many lay-persons. These could well be additional factors affecting the poor uptake of laboratory tests.

It is apparent that the average age at diagnosis for AS is continuing to fall, following an increased understanding and appreciation of the phenotype and improved genetic testing (Leitner & Smith, 1996; Laan *et al.*, 1999a; Smith *et al.*, 2003). The absence of unambiguous clinical signs in young AS patients may be the major reason for the mean age of diagnosis for the study group remaining at 5 or 6 years, even though there has been a rise in the numbers of AS cases identified before the age of 2 years during the course of the last decade. As with most other reports, no gender bias was apparent in the group of AS patients (Leitner & Smith, 1996; Smith *et al.*, 1997). The numbers of AS cases diagnosed per five-year period rose steadily until 1995, but there had been no individuals diagnosed with AS and registered with DSC after that time.

Substantial numbers of PWS patients also had not undertaken comprehensive diagnostic testing. However, all but one of the 14 cases added to DSC files since 1993 had a positive genetic diagnosis. The single individual who had not undergone genetic testing was clinically diagnosed at 6 months of age and was only 11 months old at the time of data analysis. Therefore, it seems probable that the requisite genetic tests had yet to be conducted. Of the 32 clients added to the files prior to 1994, six had not been tested, five had a karyotype examination only, nine were tested by banding, and the remainder were positive on *FISH* or methylation testing.

As was the case with Angelman syndrome, the issue of diagnostic testing for established clients is interesting in that, although specific new tests have become available over the course of the last decade, there are still many individuals who have not participated in genetic analyses which could provide confirmation of their genetic abnormality. If parental or carer inertia is the main reason for the lack of diagnostic testing, then a campaign of letters and interviews may be effective in helping to procure consent for these procedures. This strategy would need to explain the importance to future generations of improving the understanding of the mechanisms involved in the development of the syndrome, and the recurrence risks within the families concerned.

The presence of two distinct peaks in the rate of diagnosis of PWS per five-year period is an interesting phenomenon (Figure 4.3, p. 54). The first peak, in 1980-1984, coincided with the movement of ID individuals from Swanbourne Hospital to either Pyrton Training Centre or to one of the new hostels for people with ID. During the movement process, each person was reassessed at Irrabeena, which may have resulted in the larger numbers of diagnoses during that time period (Stella, 1996). The second peak, which occurred over the years 1995-1999, could be associated with the prior publication of the clinical criteria in 1993, and the development of laboratory tests for genetic diagnosis. It is, however, difficult to understand why no comparable peaks were observed in the diagnosis of AS.

The definitive identification of PWS has become easier in the last decade since the development of a comprehensive range of laboratory tests and, as a result, the age at diagnosis has been falling consistently. Over the last four years, nine of the eleven PWS cases added to the DSC database were diagnosed before the age of one year. This was similar to the results of an Australasian survey that found 71% of new diagnoses were being made before the first birthday (Smith *et al.*, 2003). These figures are in sharp contrast to an earlier report in which 36% of PWS cases were not diagnosed until after 16 years of age (Greenswag, 1987). The oldest age at which a member of the present study group was diagnosed was 17 years (in 1982).

5.8 Morbidity

5.8.1 Angelman syndrome

Epilepsy, respiratory infections, *Helicobacter pylori* infections, and gastric reflux, all of which can lead to oesophageal disease and/or oesophageal carcinomas, occur at higher frequencies among people with intellectual disabilities than in the general population (Turner & Moss, 1996). In this study, respiratory system disorders comprised a significant proportion of the primary grounds for hospitalization (Table 4.4, p. 59). Oesophagitis was also found in a significant number of those admitted for gastrointestinal problems, similar to the results observed by Clayton-Smith (2001), who described oesophageal reflux as one of the main medical problems found in 28 individuals with AS (aged 16-40

years). Epilepsy was also one of the most common reasons for hospital admission among the present study group (Table 4.4, p. 59).

As summarised in Section 4.2.7, a disproportionate number of the total hospital admissions for dental work were for AS cases with severe/profound ID. Much of the dental work conducted on the AS patients involved tooth filling, cleaning and scaling, which are normally considered to be minor procedures within the general population. However, many persons with severe ID require a general anaesthetic to allow any intrusive medical procedure to be carried out, including venesection, injections, and dental work (Bujok & Knapik, 2004), which would explain the high rates of hospitalization for these procedures.

People with intellectual disabilities have a higher prevalence of particular health problems than the general population. These include thyroid diseases, visual and hearing abnormalities, deficiencies in oral health, and cardiovascular disease (Beange & Lennox, 1998; Kapell *et al.*, 1998; Bowley & Kerr, 2000; Fisher, 2004), all of which are especially prevalent in Down syndrome patients (Prasher, 1996; van Schrojenstein Lantman-de Valk *et al.*, 1997; Saxena, 2001). Almost half of the AS group had visual problems, mostly strabismus, but there was very little information available on the presence of thyroid disease, hearing difficulties, or cardiovascular disease.

5.8.2 Prader-Willi syndrome

Respiratory disorders were previously noted in 46% of PWS patients (Butler *et al.*, 2002), and in the present study a similar proportion of subjects had been diagnosed with at least one episode of asthma, pneumonia or respiratory disease over their lifetime (Table 4.7, p. 64). Many of these illnesses required hospitalization, making respiratory problems the most common primary reason for hospital admission within the patient group. Respiratory diseases are among the most frequent causes of death for people with any form of intellectual disability (Beange & Lennox, 1998; Janicki *et al.*, 1999; Patja *et al.*, 2001). Respiratory infections, hepatitis B, C and D, and tuberculosis are also found more often in institutionalised populations (Turner & Moss, 1996), and there were two PWS patients in this study who had contracted hepatitis at some stage of their life.

As with Angelman syndrome, many of the PWS patients attended hospital for dental procedures (n = 14), and a significant number of the males (n = 9) also required treatment for undescended testes (Table4.7, p. 64). The former problem was probably associated with their intellectual disability, while the latter disorder is more specific to Prader-Willi syndrome.

Three carcinomas were recorded for the PWS group. Two were malignant, but all were treated successfully. Although the reported rates of cancers are relatively low, carcinomas may present a unique threat to those with intellectual disability, as there have been reports from the U.K. and Australia of a poor uptake of the available screening programs by individuals with ID, chiefly women (Pearson *et al.*, 1998; Aspray *et al.*, 1999; Djuretic *et al.*, 1999; Whitmore, 1999; Patja *et al.*, 2001; Sullivan *et al.*, 2003). There appear to be a variety of rationales for this under-utilisation of the available programs. Some members of the target groups may be dismissed by their doctor as not needing the tests, due to a presumption that there are fewer environmental risk factors associated with the lifestyles of the ID population, or to the assumption that people with ID are not sexually active (in the case of cervical smears). Some individuals are difficult to test because of behavioural or cooperation problems, and yet others refuse consent, or have consent refused on their behalf by carers, for unidentified reasons (Pearson *et al.*, 1998; Djuretic *et al.*, 1999; Hall & Ward, 1999; Whitmore, 1999). Although two of the cases of carcinoma had been made before the inception of the Cancer Registry, the particulars of the diagnoses and treatment were available through the DSC paper files, which strengthened the likelihood that all the data pertaining to cancers within this group were accessible.

The positive health consequences of screening can be considerable, as was found in New Zealand where comprehensive health screening of most of the ID population in a single region resulted in almost three-quarters of the people tested requiring further actions, e.g., vaccinations, optical work, blood tests, dental work, and ear, nose and throat consultations. If these interventions had not taken place the quality of life of the individuals may have been greatly impaired (Webb & Rogers, 1999). Other researchers have also found relatively high rates of unsuspected but treatable disorders among those with ID (Sutherland *et al.*, 2002).

5.9 PWS-like disorder compared to true PWS

Comparison of the phenotypic features of the small group of PWS-like patients with the PWS group revealed some features that were common to or differed between the two groups (Table 4.5, p. 61; Table 4.8, p. 66). The incidence of obesity, hypogonadism, hyperphagia, and speech defects was not significantly different between the two groups. Neither was the level of developmental delay. However, feeding difficulties, short stature, and skin picking were all notably less prevalent in the PWS-like group than in the PWS group. Epilepsy was reported somewhat more frequently in this group (40%) than in those with PWS (28%), although the small sample size meant that the difference was not statistically significant. There was no discernable pattern to the years in which the diagnoses of PWS were made for the people in this group.

In general, the PWS-like group showed many of the characteristics reported in a U.K. study of individuals who had a supernumerary inverse duplication(15) marker chromosome (Webb *et al.*, 1998). In that study, all ten probands who exhibited a maternally-derived inverse duplicate SMC15 had some level of phenotypic abnormality. All showed developmental delay, hypotonia, and ID, and most had some history of seizure activity, autistic characteristics and/or behavioural abnormality (Webb *et al.*, 1998). There was no record that any of the present PWS-like study group had been tested for autism. Six of the ten patients in the U.K. SMC study had three or more copies of the *D15S11* locus on the marker chromosome, and all of them possessed four copies of the PWS/AS critical region (Figure 2.1, p. 20). If the *D15S11* site is present on a SMC, then an abnormal phenotype, not necessarily PWS or AS, generally results (Cotter *et al.*, 1999).

It could be helpful if cases with clinically diagnosed PWS but normal methylation patterns were reviewed, with special attention paid to the presence or absence of marker chromosomes. Where no chr15q11-q13 mutation is found associated with the PWS-type phenotype, several other disorders could be considered as potential explanations for the clinical profile of the PWS-like group (Section 2.3.3.5).

5.10 Mortality

In the past, the mortality rates for institutionalised persons with ID were considerably higher than those found in the general population. For instance, the mortality rate for people with ID in a Greek institution between 1965 and 1995 equated to 59.2 deaths/1000 person-years, which was 20-150 times higher than age/sex-specific rates for the rest of Greece at that time (Perakis *et al.*, 1995). Over the thirty-year study period, 22% of patients died within one year of admission to the institution. The death rate was more frequent in the age range 1-4 years than for older people in the study, possibly due to the particular need of children with ID for high levels of care, which were unmet in those circumstances (Perakis *et al.*, 1995).

In Finland, disease mortality rates for people with ID have fallen to similar levels to those in the general population after the age of 40 years, but they still tend to be somewhat higher prior to that age, suggestive of the healthy survivor effect (Patja *et al.*, 2000; Patja *et al.*, 2001). A study in the U.S.A. found that men with ID who survived to 90 years or older are likely to have higher levels of cognitive function than either middle-aged ID men or ID women, which was accepted as further evidence of the differential survival of less severely affected individuals (Perls *et al.*, 1993).

The presence of epilepsy at any time of life has been shown to increase the relative risk of death to any person, irrespective of the level of ID of the individual (Patja *et al.*, 2000). However, Dutch children who functioned within the normal range of IQ had no increased mortality rate in connection to epilepsy (Callenbach *et al.*, 2001). Epilepsy increases the standardised mortality ratio (SMR) of those with ID from 1.6 times the rate for the general population to 5.0 times, and cerebral palsy increases the SMR 8.4-fold (Strauss *et al.*, 1999; Morgan *et al.*, 2001). Autistic individuals normally have an overall SMR of 2.4, but autistic people who also suffer from epilepsy have a SMR of 33-38, as the combination of the two disorders seems to greatly magnify the adverse effects of both conditions (Shavelle *et al.*, 2001).

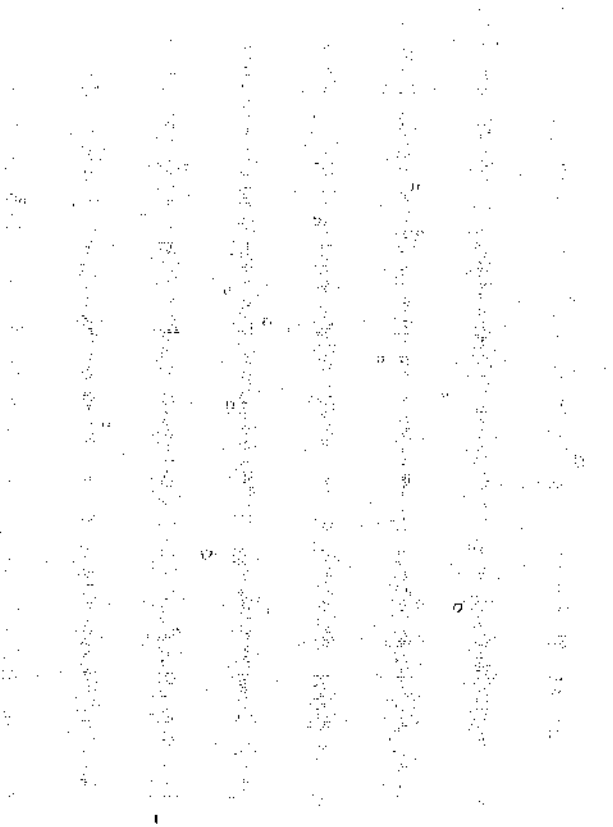
Among individuals with ID, deaths from epilepsy as a primary or secondary cause are found to occur at younger ages (mean age at death = 29.8

years) than those who die from causes other than epilepsy (mean age at death >50 years) (Patja *et al.*, 2001). However, over the last half century there has been a decrease in the proportion of ID individuals who die from *status epilepticus*, as improved medication has increased the degree of control of their seizures (Chaney & Eyman, 2000; O'Callaghan *et al.*, 2004). Only one AS patient from the present study cohort had died of epilepsy. In Australia, individuals with severe cerebral palsy are much more likely to also have severe ID and epilepsy, both of which are associated with greatly increased mortality, compared to those with a moderate or mild phenotype (Strauss *et al.*, 1999; Reddihough *et al.*, 2001; Camfield *et al.*, 2002). This is particularly evident in persons from younger age groups.

Respiratory complaints are regarded as significant primary causes of death among individuals with ID, as are diseases of the circulatory system (Beange & Lennox, 1998; Janicki *et al.*, 1999; Strauss *et al.*, 1999; Chaney & Eyman, 2000; Patja *et al.*, 2001; Reddihough *et al.*, 2001). One person with PWS and one with AS from the present study cohort had died of pneumonia, and two PWS individuals died from cardiovascular failure. Both a Finnish and a U.S.A. study have found that cardiovascular disorders are the most frequent cause of death among people with ID in those countries (Janicki *et al.*, 1999; Patja *et al.*, 2001).

The same research groups found that cancers of all types are slightly less likely to be the primary cause of death in people with ID, regardless of age or level of handicap, than in the general population (Janicki *et al.*, 1999; Patja *et al.*, 2001). This is in concurrence with the present study in which none of the individuals died from cancer, with all three carcinomas being successfully treated. However, 15% of 4028 people with cerebral palsy in a Californian study died from carcinoma, often in infancy or adolescence, and cancers raised the SMRs of autistic individuals in the same state to 1.9-2.9 times that of the general population (Strauss *et al.*, 1999; Shavelle *et al.*, 2001). Older cerebral palsy patients in the Californian study population appeared not to have any increased susceptibility to cancers, which may be a reflection of the lifestyles of people with ID, who are expected to have lower levels of exposure to carcinogenic agents over their lifetimes than the general population. For example, both smoking and alcohol consumption are much less widespread among individuals with ID, and workplaces for those with ID are less likely to contain chemicals, dust or other

carcinogens (Robertson *et al.*, 2000). Some carcinomas are not associated with home- or work-based carcinogenic agents. Therefore, there may be some degree of under-diagnosis of cancers in the ID population due to lack of screening, as suggested by Sullivan *et al.* (2003). Previously reported low rates of cancers could also have been influenced by the reduced life-span of ID individuals in earlier generations.



6. FUTURE DIRECTIONS

The study has served to highlight different genetic and clinical aspects of Angelman syndrome, Prader-Willi syndrome, and the Prader-Willi-like disorder diagnosed in a minority of the patients investigated. In this concluding section, directions for future work will be considered.

6.1 Care requirements

The range of physical, neurological and behavioural problems experienced by individuals with ID suggest that the vast majority need some degree of supervision or carer attendance. The extent of carer involvement is varied and depends on many factors, e.g., level of ID, physical health, mental health, adaptive skill level, and degree of socialisation (McGrother *et al.*, 1996). Individuals who have relatively high functional ability may not require continuous supervision, but there is likely to be some need for occasional help with non-standard matters, such as financial or legal business. Formal guardianship arrangements also may be necessary as the person ages, or if they become incapable of managing their own affairs and no appropriate family member is available (Mizano & Nanba, 2003).

The majority of individuals in the present study were living in home environments. However, the average age of the individuals in residential care was much higher than that of patients staying at home. Thus it must be supposed that there will be an increased need for sheltered accommodation when parents or other carers become unable to provide home care through age or other incapacity. This will increase the burden on the State Disability Services budget and available resources. In addition, currently there are limited numbers of the trained support staff who would be needed to equip the greater future numbers of hostels and group homes (Megahey, 1996).

Many health issues are specific to the elderly, even those within the normal range of intellectual function, and as individuals age they often become more reliant on carers for a number of functions. The need for assistance with medication management is very common, and an estimated 82% of persons of average intellectual capacity living in a personal care environment, i.e., a level of

care between living at home and a nursing home, need this type of aid (Quinn *et al.*, 1999). Other areas where support is often required are: personal hygiene (69%), visual (42%) and hearing (60%) impairment, arthritis and rheumatism (43%), incontinence (42%), mental health conditions (43%), mobility limitations (39%), and hypertension (30%). Most of these difficulties require assistance from carers to prevent further deterioration of the health of the patient (Quinn *et al.*, 1999). As these conditions are found at similar or higher rates in the ID population (Reid & Ballinger, 1995; Thompson & Reid, 2002), the consequent need for care assistance is even greater among the disabled.

Hearing and visual impairments are liable to be under-diagnosed in the intellectually disabled population, often due to the failure of the individual and/or their carers to recognise the signs of impairment. Unusual behaviours, such as inactivity, irritability, self-injury, or autism-like symptoms may be indicative of sensory impairment (Nagalzaam & Vink, 1998). Up to half of all Down syndrome individuals have been found to have some degree of hearing impairment, and many also suffer from visual disorders (Kapell *et al.*, 1998; Saxena, 2001; Harvey, 2004). In the U.K., 11-13% of ID people followed over a 26-year period were visually impaired. The numbers of individuals from this study who were hearing impaired, incontinent, and/or had mobility problems all increased overtime (Reid & Ballinger, 1995; Cooper, 1998b; Thompson & Reid, 2002).

Progressive loss of mobility with ageing is common to both the general population and those with ID, as are incontinence and chronic constipation (Evenhuis, 1997). In addition, as individuals grow older they are likely to recover more slowly and less completely from fractures, resulting in permanent loss of mobility in many cases and a concomitant increase in the level of care required (Beange & Lennox, 1998; Center *et al.*, 1998).

Although a range of mental health problems are common in the elderly, dementia is found in less than 6% of the general population over 65 years old, however it is present in approximately 25% of persons who are between 80 and 85 years old. In individuals with ID, 15% of those aged between 65 and 74 years and 70% of those older than 85 years have been reported to have signs of dementia (Cooper, 1997; van Schrojenstein Lantman-de Valk *et al.*, 1997; Cooper, 1998a).

When compared to those without dementia, individuals with dementia are more likely to be older, female, non-smokers, with poorly controlled epilepsy, and/or with a higher number of additional physical disorders (Cooper, 1998a). Down syndrome carries a disproportionate risk for early onset dementia, especially Alzheimer's disease (van Schrojenstein Lantman-de Valk *et al.*, 1997; Beange & Lennox, 1998; Bittles & Glasson, 2004).

None of the present study group had evidence of dementia. However, the oldest member of the cohort was 48 years 4 months of age, which probably was not old enough for early onset dementia to become manifest. There were no reports in the patient files of increased rates of early onset dementia in the individuals with either Prader-Willi or Angelman syndrome, such as is found in people with Down syndrome.

6.2 Where to from here?

As discussed previously (Section 5.2) there were a number of limitations associated with the data collection for this study, in particular the quality and quantity of data recorded in many patients' files. To produce a comprehensive overview of the phenotypes and ageing characteristics of individuals with AS or PWS, it would be necessary to expand the scope of the project to include access to Medical Practitioners' files, Medicare data, and hospital outpatient records.

As noted by Holman *et al.* (1999), General Practitioner records and Medicare details are held by the Australian Commonwealth Government, and during the study period it was not possible to link these data to the WA Data Linkage Unit. The linkage of WA residents with the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Schedule (PBS) was approved in mid-2004. Any future project examining the two syndromes would benefit greatly from this additional data linkage, as all visits to General Practitioners and specialist physicians, and all medications prescribed (since 1984 for the MBS, and 1990 for the PBS) will be recorded in these datasets, thus allowing a significant expansion of detailed information on the morbidities associated with each syndrome.

The use of comprehensive questionnaires and/or interviews, aimed at the families and carers or the clients themselves, would also be a valuable ancillary

resource to extend the range of information available on individuals with AS or PWS. Specific instruments such as the Functional Independence Measure for Children or WeeFIM (Msall *et al.*, 1994), the Food-Related Problems Questionnaire (Russell & Oliver, 2003), and the Quality of Life Questionnaire (Schalock *et al.*, 2002) could be used to assess particular aspects of the lifestyle and care needs of persons with Angelman or Prader-Willi syndromes. There are also questionnaires designed to elicit information on levels of carer stress and the effects, both positive and negative, of having a family member with an ID, such as the Family Stress and Coping Interview (Nachshen *et al.*, 2003), the Carers Assessment of Difficulties Index (Nolan *et al.*, 1990) , and the Carers Assessment of Satisfaction Index (Grant *et al.*, 1998).

Specific data on the influence of a particular genotype on the presenting phenotype would require that the majority of AS and PWS patients undergo comprehensive genetic testing. At present there are substantial numbers of patients who have not participated in this testing, and so their status with regard to specific mutations within chr15q11-q13 remains unknown. Personal approaches, including home visits, stressing the benefits to the family in terms of accurate recurrence forecasting, and to the individuals with respect to morbidities which might be avoided or mitigated by early intervention, could encourage greater participation in the testing process. There is also some evidence that diagnostic certainty is of psychological benefit to mothers of children with Down syndrome, enabling better use of coping strategies and improved emotional stress levels (Lenhard *et al.*, 2004). Future cases could also potentially benefit via neonatal therapy or other early treatment to alleviate the various manifestations of the syndromes.

The ability to gain access to individuals who are not registered with DSC, particularly intellectually able persons with PWS, would broaden the case ascertainment and give a more accurate picture of the complete phenotypic range of both syndromes. The relevant AS and PWS Support Associations, both National and State, are excellent potential sources of case ascertainment, as are the WA Education Department, Catholic Education and the Association of Independent Schools (Leonard *et al.*, 2003).

Western Australian and interstate molecular and cytogenetic laboratories could similarly be of assistance in identifying people who had undergone genetic tests for chromosome 15 abnormalities, regardless of the outcome. The ability to track DSC clients who had moved out of WA would assist the extension of the database, especially in terms of information on deaths and morbidities, but this is not currently available. In addition to the continuing enlargement of the database as records become available, any extra information from such sources would be very helpful in providing a clearer and more comprehensive perspective on the phenotypic variation and ageing issues associated with Prader-Willi or Angelman syndromes in Western Australia.

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8. APPENDICES

Appendix I: DSC file cover page

CLIENT FILE HEAD SHEET

Date Head Sheet completed:

Client File No: Pension No:

Name (In full):

Date of Birth: Sex: Status:

Non-English Speaking:

If YES state language:

Client address:

Postcode: Phone:

Parent or Next of Kin Title: Surname:

Address:

Postcode: Phone:

Father's name: DOB:

Mother's name: DOB:

Maiden name:

Date of Referral: Date of First Contact:

Medical Practitioner:

Current Medical Problems (Major diagnosis/allergy etc):

Service Coordinator	Service Area & Region	Date
1.		
2.		
3.		

Residential Placement	Date	Day Placement
1.		
2.		

Appendix II: **DSC diagnostic data form**

DISABILITY SERVICES COMMISSION
DIAGNOSTIC DATA FORM (Original Med. File)
(Copy) . Data 2. Appointments)

Date of Assessment: / /
File No: □□ - □□□
REGISTERED FAMILY NAME
FORENAME:
DIAGNOSIS
Code

1.		
2.		
3.		

MALFORMATIONS	Code		Code
1.		6.	
2.		7.	
3.		8.	
4.		9.	
5.		10.	

GENETIC	□ None	□ Multifactorial	□ Sex Linked	□ Dominant	
COMPONENT	□ Recessive	□ Chromosomal	□ Uncertain		
SECOND CRANIAL ANOM.	□ None	□ Hydrocephaly	□ Microcephaly	□ Other	
HEARING HANDICAP	□ None	□ Mild	□ Moderate	□ Deaf	□ Not Assessed
VISUAL HANDICAP	□ None	□ Mild	□ Moderate	□ Blind	□ Not Assessed

CONVULSIVE DISORDER:
Frequency:
□ More than 1 per week □ Less than 1 per week □ Less than 1 per year
Medication & Control:
□ No Medication & Not Controlled □ No Medication & Controlled
□ On Medication & Not Controlled □ On Medication & Controlled
Type:
□ None □ Generalised (Grand Mal) □ Absence (Petit Mal)
□ Partial (Focal) □ Myoclonic (Akinetic) □ Lennox Syndrome
□ No Further Specification

PSYCHIATRIC IMPAIRMENT:
□ None □ Behav. Reaction □ Neurotic Reaction □ Psychotic Reaction

CONSANGUINITY □ Yes □ No

MOTOR DYSFUNCTION FIRST PROBLEM
□ Rt Spastic Hemiplegia □ Lft Spastic Hemiplegia □ Spastic Diplegia
□ Spastic Quadriplegia □ Ataxia □ Dyskinetic (Athetoid)
□ Dyskinetic (Dystonic) □ Mixed □ None

MOTOR DYSFUNCTION SECOND PROBLEM
□ Rt Spastic Hemiplegia □ Lft Spastic Hemiplegia □ Spastic Diplegia
□ Spastic Quadriplegia □ Ataxia □ Dyskinetic (Athetoid)
□ Dyskinetic (Dystonic) □ Mixed □ None

DOMINANT PROBLEM:	□ First	□ Second Problem	□ Both	
SEVERITY:	□ Mild	□ Moderate	□ Severe	

INTELLECTUAL HANDICAP LEVEL:
□ Borderline □ Mild □ Moderate □ Severe □ Profound
□ Unspecified □ Not intellectually handicapped □ Not Seen

NAME OF COMPLETING OFFICER DATE: / /

Appendix III: **Proforma used to record data from DSC client files**

DSC file number:

Date of first contact:

Date of birth:

Level of ID:

Obesity:

Suck:

Age at sitting:

Speech:

Colouring:

Diabetes:

2° sex development:

Stature:

Scoliosis:

Epilepsy:

Inappropriate laughter:

Genetic testing:

Diagnosis:

Age at diagnosis:

Gender:

Hypotonia:

Hyperphagia:

Cry:

Age at walking:

Head shape/size:

Strabismus:

Hyperactivity:

Menses:

Skin picking:

Temper/aggression:

EEG:

Ataxia:

Family history:

Medical history:

Appendix IV: **DSC initial medical record form**

INITIAL MEDICAL RECORD

FILE NO _____ DATE _____

NAME (In full) _____

DATE OF BIRTH _____ SEX _____

HOME ADDRESS _____

_____ POSTCODE _____

PHONE _____ RACE _____

REFERRED BY _____

GENERAL PRACTITIONER _____

_____

LAC/SERVICE COORDINATOR _____

FATHER'S NAME _____ DOB _____

MOTHER'S NAME _____ DOB _____

MAIDEN NAME _____

PRIMARY DIAGNOSIS _____

HEBERCODE _____

DATE	SECONDARY PROBLEMS	MEDICAL PLAN

INITIAL PHYSICAL EXAMINATION Date --/--/----

DOB--/--/--- (Age _____ Years _____ Months _____ Days)
Height_____cms (P ____) Weight_____ Kgs (P_____) Head Circ _____cms (P ____)

General Appearance _____

_____

_____

Development/Nutrition/Gait _____

_____

_____

MajorDefects

1. _____
2. _____

Minor Defects/Dysmorphic Features

1. _____
2. _____
3. _____
4. _____

Posture _____
Skullshape _____ Earshape _____
Skin _____
Hair _____ Nails _____
Dentalcondition _____
ENTTongue _____ Palate _____
Ears _____
LymphNodes _____
Thyroid _____
Thorax _____ Spine _____
Cardiovascular _____ BP _____

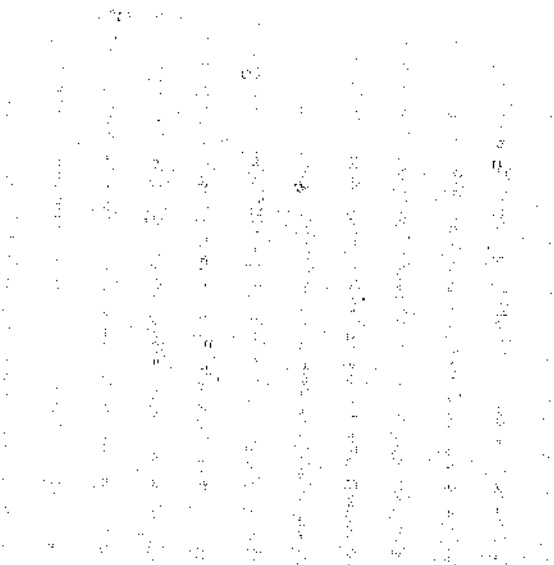
_____

Peripheral Circulation _____
Respiratory System _____
Abdomen _____ Hernia _____
Genital Development _____

Extremities
Arms/Hands _____
Legs/Feet _____

PEDIGREE

Consanguinity Y/N



Annotation

Other Family History (e.g. sensory or motor defects, epilepsy, intellectual handicap, congenital malformation)

Condition	Relationship to client	Sex	ICD Code	Ref

ANTENATAL HISTORY

PREGNANCY

General Health Satisfactory	Yes/No	
Threatened Abortion	Yes/No	
Preeclampsia/Eclampsia	Yes/No	
Ultrasound	Yes/No	
Prenatal Tests	Yes/No	
Maternal Serum Screen	Yes/No	
Amniocentesis/CVS	Yes/No	
APH Plac Praevia	Yes/No	
Abrupto	Yes/No	
Other	Yes/No	
Isoimmunisation	Yes/No	
Diabetes	Yes/No	
Heart Disease	Yes/No	
Renal Disease	Yes/No	
Rubella	Yes/No	
Other Infection	Yes/No	
Alcohol	Yes/No	
Cigarettes	Yes/No	
Anticonvulsants	Yes/No	
Other drugs/radiation	Yes/No	
Duration weeks	Yes/No	

DELIVERY

Hospital of Birth _____

Complications

None _____
Precipitate _____
Foetal Distress _____
Prolapsed _____
Cord tight round neck _____
Other _____
Hypoxia/Asphyxia _____
Resuscitation Needed _____

Presentation

Vertex _____
Breech _____

Labour

Spontaneous _____
Induced _____
Assisted _____
Normal _____
Vacuum _____
Forceps _____
Caesarean Section _____

Plurality

Single _____
1st twin _____ 2nd twin _____
Other _____

Birthweight _____ Birth length _____ Head Circumference _____

Apgars 1 minute _____ 5 minutes _____

Neonatal condition

_____

_____

_____

_____

_____

DEVELOPMENT/MILESTONES

Feeding

Smiled at

Sat alone at

Crawled at

Walked at

First words at

Fed self at

Dresses self at

Toilet trained at

Dentition

Menarche

Abnormality (nature and when first noticed)

Current Medical concerns

Past Medical History and Investigations

Past Surgical History

IMMUNISATION	Original Series	Booster
Tetanus		
Pertussis		
Diphtheria		
Poliomyelitis		
Measles/Mumps/Rubella		
Hep B		
Reactions and allergies		

PRESENT CONDITION OF

A. Hearing

B. Vision

C. Speech

Expressive

Comprehensive

D. GIT

Feeding/Appetite

Bowels

Weight/changes

E. Dressing

F. Toilettraining

G. Menses

H. Locomotion

Gross Motor

Fine Motor

I. Epilepsy

Age at onset _____ Date of last fit _____

Type

Frequency

Present condition

Medication(s)

J. Behaviour Disorder

Nature

Age at onset

Treatment

Present situation and medication

K. Medication/Alternative Therapies

Appendix V: DSC client referral form

DISABILITY SERVICES COMMISSION – CLIENT REFERRAL FORM

NEW REFERRAL FILE NO. INITIAL REFERRAL DATE

1st Bring-up Date 2nd Bring-up Date

FORENAMES:
SURNAME:
ALIAS FORENAMES:
ALIAS SURNAME:
ADDRESS:

TELEPHONE:
REGION/DIVISION:
LOCAL GOVT. AREA:
LOCAL AREA CO-ORD:
GENDER: MARITAL STATUS:
DATE OF BIRTH: CURRENT AGE:
OCCUPATION – CURRENT: PREVIOUS:

STATE WARD: WARDSHIP CEASES:
GUARDIAN APPOINTED: GUARDIAN CEASES:
ESTATE ADMINISTRATOR: EAT ADMIN CEASES:

COUNTRY OF BIRTH: YEAR ARRIVED IN AUSTRALIA:
IS AN INTERPRETER REQUIRED: HOME LANGUAGE:
PERMANENT RESIDENT: ETHNICITY:
ABORIGINAL/TORRES STRAIT ISLANDER

NEXT OF KIN RELATIONSHIP:
NEXT OF KIN NAMES 1:
2:
ADDRESS:

TELEPHONE:

NEXT OF KIN REGION I.Q.A.:

FATHERS YEAR & COUNTRY OF BIRTH:
MOTHERS YEAR & COUNTRY OF BIRTH:

OTHER FAMILY MEMBERS KNOWN TO DSC:

File No.	Client Name	Relationship	DOB

REFERRING PERSON:
POSITION:
AGENCY:
PRESENTING CONDITION:

REASON FOR REFERRAL:

Appendix VI: DSC referral: clinical information

DSCReferral: Clinicalinformation

Person referring:

Name: _____ Institution: _____ date of referral --/--/----

Person referred:

Surname:_____ Given name/s:_____

Countyofbirth: WAyes/no: other Australian state: _____ other country: _____

Male ☐ Female☐ Date of birth:--/--/---- Hospital of birth _____

Mother's Surname:_____ Mother's givenname/s: _____

Mother's maiden name: _____ Mother's date of birth: --/--/----

Level of Intellectual Disability:

IQ Test results if available

Test Type	Date	Full scale score	Verbal	Performance
Griffiths				
Bayley				
WPPSI				
WISC				
Leiter				
Stanford/Binet				
Other				

Adaptive Behaviour test results if available

Test Type	Date	Composite score
Vineland		
Scales of independence behaviour		
Other		

If test scores unavailable plea e estimate level of Intellectual disability

Mild (IQ score55-69) ☐ Moderate (IQ score 40-54)☐ Severe (IQ score <40)☐

Underlying diagnosis (if known): _____

Please give method/s of diagnosis (tick all relevant boxes)

Clinical ☐ cytogenetic ☐ molecular☐ neuro-Imaging☐

other ☐ name

Is there any known family history of developmental problems or intellectual disability? yes/no

If yes please specify

Is there a clear cause/s of intellectual disability? yes/no

If yes describe

Were there any events which may have contributed to the intellectual disability? yes/no
If yes describe
antenatal yes/no

perinatal yes/no

postnatal yes/no

Associated conditions or features: (If yes please describe)

Cerebral Palsy	yes/no	_____
Abnormal neurological signs	yes/no	_____
Autism	yes/no	_____
Significant mental disorder	yes/no	_____
If yes DSM-IV diagnosis		_____
Visual Impairment	yes/no	_____
Hearing Impairment	yes/no	_____
Epilepsy yes/no	age at onset	_____ type_____
Evidence of regression	yes/no	_____
Birth Defects	yes/no	_____
Dysmorphic features	yes/no	_____

Growth: Height _____ cm date:-/-/---- Weight _____gm date:-/-/----
Head Circumference ____ cm date:-/-/----

Tests performed: If yes please enclose copy of results.

Cytogenetic	yes/no:
FISH:	yes/no:
Molecular:	yes/no:
Metabolic:	yes/no:
Imaging:	yes/no:
Other tests:	yes/no:

Please specify other clinicians/clinics/therapists involved with investigations/management of developmental problems.

DSC clients:

Heber Diagnosis

Name	Number
1.	
2.	
3.	

Appendix VII: DSC medical review form

MEDICAL REVIEW

DATE.....
FILE NO.....
D.O.B.....AGE.....
LAC.....
GP.....

NAME:.....
ADDRESS:.....
.....PHONE:.....
WORK/SCHOOL/OTHER:.....
PRIMARY DIAGNOSIS:.....
.....
GENETIC UPDATE:.....
SECONDARY PROBLEMS:.....
.....
NEW PROBLEMS:.....
.....
VISION:.....
HEARING:.....
SPEECH:.....
EATING:.....TEETH:.....
TOILETING:.....DRESSING:.....
MOBILITY:.....
FINE MOTOR:.....
EPILEPSY:.....
MENSES/CONTRACEPTION:.....
BEHAVIOUR/FAMILY SITUATION:.....
MEDICATION:.....
.....
PAST SURGICAL HISTORY:.....
ALLERGIES:.....IMMUNIZ:.....CDA/DSP/IPS:.....
HT:.....(.....P) WT:.....(.....P) HC.....(.....P).
CLINICAL CHANGES (PTO if needed).....
GENERAL:.....
CNS – III/AFFECT:.....
CNS – VISION:.....
CNS – TONE/POWER/REFLEXES:.....
ENT/RS:.....
CVS/BP:.....
GIT:.....
GUS:.....
MSS:.....

DATE/REASON FOR NEXT REVIEW.....

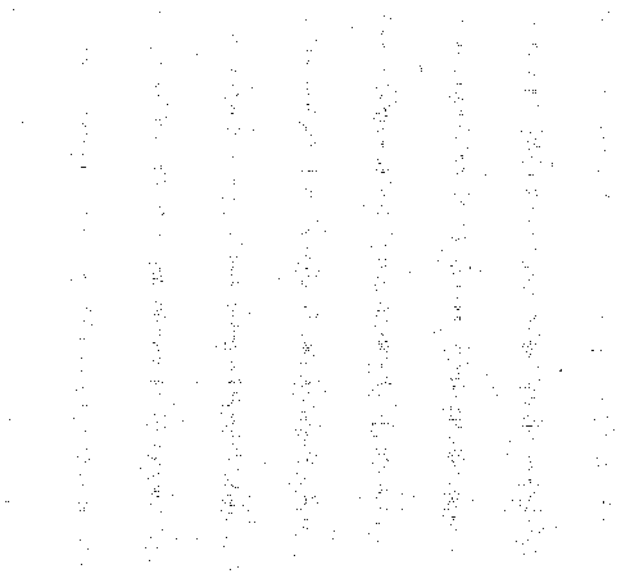
Signed.....Date.....

Appendix VIII: List of variables used in the *SPSS* database

File number

DSC identification number	Date of first contact
Level of ID	Age at dingnosis
Methylation negative	Diagnosis
Heberl	Heberlv
Heher2	Hebcr2v
Heher3	Heber3v
Deceased/not	Date of death
DSC region	Last entry date
Gender	Date of birth
Age category	Age to censor date or death
Country of birth	Residence
Indigenous/not	Hypotonia present
Degree of hypotonia	Obesity present
Age obesity noted	Hyperphagin
Sucking reflex	Crying character
Age at sitting	Age at walking
Speech development	Presence of eye defect
Type of eye defect	Presence of diabetes
Development secondary sex	Menses
Stature compared to relatives	Molecular tests done
Type of test done	Methylation negative
Deletion positive	Test results
Skin lesions/skin picking	Presence/degree of scoliosis

Temper/aggression	Epilepsy
Control of epilepsy	EEG
Ataxia	Laughter/smiling
Hyperactivity	Family history
Medical information	General notes
Number of hospital admissions	Diagnoses on admission
Further diagnoses on admission	Psych outpatient number visits
Psych outpatient diagnosis	Psych admissions no. days
Psych admissions diagnosis	Hospital procedures



Appendix IX: Record sheet for AS clinical criteria

ANGELMAN SYNDROME

Name

Fileno

DOB

Region MO

DIAGNOSTIC FEATURES

Psychomotor development

Feeding problems in infancy	YES / NO / DON'T KNOW
Delayed psychomotor development Sat unsupported _____ months	YES / NO / DON'T KNOW
Able to walk without assistance Walked alone _____ months	YES / NO / DON'T KNOW
Absent speech or use of <6 words	YES / NO / DON'T KNOW
Able to use sign language	YES / NO / DON'T KNOW
Severe mental retardation IQ (if known) _____	YES / NO / DON'T KNOW
Regression (loss of acquired skills)	YES / NO / DON'T KNOW

Neurological features / movement disorders

Seizures	YES / NO / DON'T KNOW
Truncal ataxia / hypotonia	YES / NO / DON'T KNOW
Limb hypertonia	YES / NO / DON'T KNOW
Jerky / ataxic movement	YES / NO / DON'T KNOW
Tongue thrusting	YES / NO / DON'T KNOW
Hand flapping	YES / NO / DON'T KNOW

Behaviour

Happy disposition	YES / NO / DON'T KNOW
Easily provoked / inappropriate laughter	YES / NO / DON'T KNOW

Physical features

Dysmorphic facies

Prominent jaw / mandible	YES / NO / DON'T KNOW
Widely spaced teeth	YES / NO / DON'T KNOW
Large mouth	YES / NO / DON'T KNOW

Deep set eyes YES/NO/DON'TKNOW

Small head (<25th percentile) YES / NO / DON'T KNOW

Hypopigmentation (fair hair / skin compared to other family members) YES/NO/DON'T KNOW

OTHER STUDIES /RESULTS

EEG YES/NO/DON'T KNOW

Result_____

Cytogenetic studies

Dateoftest __/__/__

Laboratory where test performed_____

Test result:

Karyotype _____

FISH studies _____

Molecular studies

Methylation studies _____

Uniparental disomy _____

Other investigations _____

Additional comments or information (including relevant family history)

_____

_____

_____

Appendix X: Record sheet for PWS clinical criteria

PRADER-WILLI SYNDROME

Name
File No.
DOB
Region MO

CLASSICAL FEATURES 1 point each

- Infantile hypotonia YES / NO / DON'T KNOW
- Infantile feeding problems: YES / NO / DON'T KNOW
  tube fed YES/NO/DON'T KNOW
- Hypogonadism: YES/NO/DON'T KNOW
  genital hypoplasia/pubertal deficiency
- Rapid weight gain 1-6 years YES / NO / DON'T KNOW
  age ____ percentile ____
- Characteristic facial features YES / NO / DON'T KNOW
- Developmental delay / intellectual disability YES / NO / DON'T KNOW
  age ____ MILD / MODERATE / SEVERE

MINOR CRITERIA ½ point each

- Decreased fetal movements YES / NO / DON'T KNOW
- Typical behaviour problems YES/NO/DON'T KNOW
- Sleep disturbance / sleep apnoea YES/NO/DON'T KNOW
- Short stature for family by age 15 YES/NO/DON'T KNOW
  age ____ percentile ____
- Hypopigmentation YES/NO/DON'T KNOW
- Characteristic fat distribution YES/NO/DON'T KNOW
- Small hands and feet for height & age YES/NO/DON'T KNOW
  age ____
- Narrow hands with straight ulnar border YES / NO / DON'T KNOW
- Estropia / myopia YES/NO/DON'T KNOW
- Thick viscous saliva YES/NO/DON'T KNOW
- Speech articulation defects YES/NO/DON'T KNOW
- Skin picking YES / NO / DON'T KNOW

Supportive criteria

High pain threshold, decreased vomiting, temperature control problems, scoliosis/kyphosis, early adrenarche, ostoeporosis, unusual skill with jigsaws, normal neuromuscular studies.

Poor motor coordination	YES/NO/DON'T KNOW
Head size	MICROCEPHALY/ NORMAL/ MACROCEPHALY
Head circumference _____ age _____ percentile _____	
Seizures	YES/NO /DON'T KNOW
Other	

DIAGNOSTIC TESTS

Cytogenetics	Performed	Results
Standard karyotype	YES/NO	
Expanded karyotype	YES/NO	
FISH	YES/NO	
Molecular		
Uniparental disomy	YES/NO	
Expression / methylation	YES/NO	