Phenotypes and epidemiology of rare neurodevelopmental disorders

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CHAPTER 1

General introduction

Advances in genetic research have allowed us to identify specific genetic aberrations associated with behavioral and intellectual developmental disorders. However it is also becoming increasingly clear that there is not a unilateral relationship between genetic deviations and their manifestations. Rather, the expression and evolution of these disorders represent a complicated dance between genetic makeup (genotype) and behaviors and characteristics (phenotype), the environment, and learning over time. The study of genetically determined syndromes associated with specific behavioral phenotypes, including autism and intellectual disability, offers an opportunity to study these interactions. Autism is a disorder that is increasingly recognized as being influenced not only by genetic factors, but also by environmental factors (Hallmayer et al., 2011). While most of the genetic syndromes associated with intellectual disability and a pronounced psychiatric dimension are rare, even extremely rare, collectively they represent a significant proportion of severe intellectual disability, where autism is likely under–identified. The study of the behavioral and intellectual development aspects of these syndromes can help us understand better the complex etiology, progression, and classification of autism spectrum disorders.

Brain–behavior relationships develop as a result of brain programming and functional connectivity within neural circuits and networks, all determined by gene expression. Gene expression affecting brain programming and function is influenced by the interplay between genes, learning behavior and social context. Thus, brain–behavior relationships are not a static given, individual experiences within environments will over the lifespan also influence the brain and may result in alternative developmental trajectories (Oliver et al., 2000; Rutter, 2005; Pennington, 2009; Saemundsen et al., 2010).

The objective of the research projects in this dissertation was to study autism as part of phenotypes in selected (ultra) rare genetic syndromes; and to examine autism within a different sociocultural environment.

Genotype of behaviorally described neurodevelopmental and psychiatric disorders

An individual's genetic make–up (as determined by DNA sequence) defines genotype. Genetic risk factors may disturb neural development and functioning of specific brain regions that serve aspects of cognition and behavior. These disruptions may ultimately lead to neurodevelopmental phenotypes such as intellectual disability and autism spectrum disorder, involving atypical social responsiveness and impaired filtering of stimuli, and language development, and/or repetitive–restrictive behaviors. Similar phenotypes that may emerge from distinctly different genetic defects (pathways) are thought to have been caused by the multidirectional interaction between genetic and environmental risks and protective factors. Conversely, a given genotype can give rise to different

phenotypes depending on environmental circumstances. Establishing the genetic underpinnings of neurodevelopmental disorders is rarely straightforward – complex behavior rarely maps to a specific gene. Even when the genes are highly deterministic, there is a range of severity, the range variations possibly reflecting environmental and other circumstances.

A well–known example of a highly deterministic disorder that may feature autism spectrum disorder as part of the behavioral phenotype is Fragile X syndrome. The study of genetic syndromes in a subset of patients with the same genetic defect/aberration, such as Fragile X syndrome, has added to our insight into the potential genetic pathways of autism spectrum disorder, while at the same time highlighting the diversity of possible outcomes without autism spectrum disorder. It has lead to the understanding that single deficit models for understanding complex developmental disorders disregard the pleiotropy of a given genetic cause and the diversity of effects that it may have on behavioral outcomes and cognitive deficits.

Many recent genetic studies have investigated chromosome regions and possible loci on various chromosomes with regard to their contribution to the cause of autism spectrum disorder, intellectual disability, and schizophrenia. Several of these studies have concluded that many of the genomic variants investigated are not disease–specific, rather they contribute to the expression of varying clinical symptoms crossing diagnostic boundaries and leading to various phenotypes such as intellectual disability, autism spectrum disorder and schizophrenia. Similar to intellectual disability, autism spectrum disorders are considered to be complex multifactorial, heterogeneous syndromes for which no single causative factor has been identified. Much research over the past few decades has focused on characterizing and describing the behaviors that are part of the core symptomatology. Increasingly, such studies have employed multiple approaches to advance our understanding.

Behavioral phenotype

A phenotype may be defined as a group of observable, measurable characteristics that are the result of interactions between genotype and environment. Many different phenotypes can be distinguished in this way, for example molecular, biochemical, physical, psychiatric, and cognitive phenotypes. Prevailing deterministic models have frequently focused on a single neurobiological cause to explain phenotypic outcome, disregarding the complex interactions among a multitude of factors in the social and nurturing environments. While genetic defects influence brain function and may lead to psychiatric problems in an individual, existing inter–individual variability can make it difficult to arrive at comparable profiles for behavior and cognition within a genetic syndrome. It is neces-

sary for such problems to be considered within the framework of developmental phase, family and life events, and social and learning environments, to determine their meaning and clinical significance for that individual. It is clear that behavioral characteristics in any genetic syndrome are not solely determined by genetics (Harris, 2010) and too strong an emphasis on the biological determinants of behavior is misleading.

Research examining cognitive profiles together with specific behavioral patterns has led to the realization that certain syndromes or chromosomal anomalies may well be characterized by specific behaviors or a specific combination of behaviors (Mazzocco & Reiss, 1994; Flint, 1995). To consider a combination of behaviors a behavioral phenotype, two conditions must be met (Flint & Yule, 1994; Turk & Hill, 1995; Dykens et al., 2000). First, the behavioral phenotype, a defined pattern of specific behaviors, must be seen in almost all cases affected with the syndrome, while rarely observed in other syndromes. Second, a direct link between genetic defect and its physical manifestations must be plausible (Flint & Yule, 1994).

Behavioral phenotypes in combination with specific cognitive strengths and weaknesses have offered clues to an underlying genetic cause for certain developmental and behavioral difficulties and have sometimes led to the definition of a (new) syndrome.

Aberrant behaviors can have a more significant impact on the life of a child and the family than the cognitive limitations associated with a syndrome. Behavioral problems may influence the quality of interactions with others, but behavior may also be determined by the reactions of others to the distinct physical features and cognitive limitations of the child. Obviously, children with a distinct genetic anomaly are also subject to social, familial, psychological, and learning experiences that shape behavior and phenotypic presentations (Dykens, 2000), which in turn will have an effect on the architecture of the brain. Interestingly, studies investigating reciprocal effects of genotype and behavior have shown that phenotypes in genetically determined syndromes do not necessarily have fixed linear outcomes, and they can be influenced by social information (Oliver et al., 2000; Dykens et al., 2006). And although causal direction remains unclear, cross–sectional studies make it apparent that a solely linear perspective on syndromally determined behaviors is insufficient to explain the social, cognitive, and environmental contributors to the phenotype and the changes that can take place over time (Pennington, 2009).

Defining intellectual disability, autism spectrum disorder and adaptive skills

Rare disorders are defined as disorders with an incidence of fewer than 2, 000 individuals per year in a population. While rare and ultra rare disorders comprise small groups of individuals with a specific genetic etiology, collectively they are a large group and represent a substantial proportion of the group with developmental disability (Hennekam,

2011). Behaviors targeted for study in this dissertation are: intellectual disability, adaptive skills, and autism spectrum disorder. These are defined in accordance with two organizations, the American Association on Intellectual and Developmental Disability (AAIDD) and the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV), of the American Psychiatric Association (APA).

The AAIDD defines intellectual disability as a disability originating before the age of 18 and characterized by significant limitations in two domains: intellectual functioning (reasoning, learning, problem solving), and adaptive behavior (covering many everyday social and practical skills). Adaptive behavior is defined by the AAIDD into three skills levels namely conceptual (e.g. language, time concepts, self–direction), social (interpersonal relationships, self–esteem, social problem solving), and daily living skills (personal care and hygiene, schedules, routines).

Autism spectrum disorders are defined as pervasive, neurodevelopmental disabilities with onset before 36 months of age and characterized by impairments in three domains: reciprocal social interactions, communication skills and behavioral abnormalities (APA, 1994).

Studying rare and ultra rare disorders associated with intellectual disability requires reframing traditional approaches to research. The prevalence of intellectual disability is estimated to be 1–4% in the total population worldwide (Roeleveld et al., 1997). Estimates for the Netherlands indicate that there are 125, 000 individuals with intellectual disability, while 2, 000 babies are born each year with an ultra–rare disorder associated with intellectual disability (Hennekam, 2011).

Any group studied in a single location will by definition be small. Affected individuals are likely to be geographically dispersed. Research must then take into consideration differences in language and health care systems. In the past this has required combining multiple sites and multinational studies to compile information on a sufficient numbers of patients. Alternatively, or in combination with standard strategies, a Wiki can be used as an online collaborative resource for compiling information from dispersed sources. In the study of extremely rare conditions, such as Marshall–Smith syndrome described in this dissertation (with less than 50 cases reported worldwide), the utility of a Wiki is an obvious tool for overcoming language barriers and/or geographical distances. It offers parents from all over the world the opportunity to add important information to the collected data and makes it possible to include their perspectives on the communication and social interaction skills, behavior, and developmental potential of their children. Thus a Wiki can be considered an efficient tool in gathering information on very rare disorders (Hu et al., 2008; Shaw et al., 2010).

The study of physical, behavioral and cognitive aspects of phenotype–genotype associations in humans may benefit greatly from studying more than one aspect of phe-

notype and from using different and multidisciplinary approaches to do so. Studies have time and time again demonstrated the pleiotropy of genes and the complexities involved in mapping gene – brain – behavior pathways. Finding the genetic defect in syndromes is only the beginning of understanding the expression and the role of the proteins involved and the effects on phenotype, since such a defect may have an impact on only some or on all (for example behavioral) traits. Therefore, careful study and detailed descriptions of behaviors and comorbid conditions over a lifetime remain crucial and continue to improve our understanding of the pathways involved (Harris, 2010).

The study of risks associated with specific genetic compositions and translating the knowledge acquired toward treatment interventions is called translational genetics. One of its principal goals is to link genetic information to phenotypic outcome and risk for disorders with the aim of eventually using this knowledge to devise treatments that will ameliorate or modify etiology–specific predisposition and vulnerability to pathology. Studying the physical characteristics in combination with the behavioral and psychiatric aspects of a genetic syndrome not only enhances our knowledge of differences among syndromes, but also sheds light on similarities, behavior clusters, and environmental effects on development and outcome.

Behavioral research within a syndrome is helpful to delineate the syndrome, as is the study of those individuals with partial variants who exhibit some, but not all features of the syndrome (Harris, 2010). Studying behavioral phenotypes in more prevalent genetic syndromes associated with intellectual disability such as Fragile X syndrome or Prader–Willi syndrome has significantly added to our understanding of the behaviors that commonly occur in people with these syndromes and the changes that may occur over time (Whittington & Holland, 2010; Arron et al., 2011).

The recognition of behavioral phenotypes and distinctive, etiology–specific behaviors in genetic syndromes has sparked a great interest in the study and description of clinically relevant issues pertaining to these behaviors. Increasingly, such studies have employed multiple approaches to advance our understanding of both genes and phenotypes.

Many genetic syndromes associated with intellectual disability share commonalities across phenotypes such as delays in speech/language development, problems within social situations and interactions, lack of imaginative play, and other characteristics which indicate similarities with the behaviorally defined DSM–IV criteria for autism spectrum disorders. While studies have found that in various syndromes with a known genetic defect, autism or other psychiatric disorders may be part of the behavioral and psychiatric phenotypes, researchers have also emphasized the difficulties in differentiating between genetically determined intellectual disability and autism spectrum disorder or other psychiatric symptoms. In spite of these difficulties, the studies remain of impor-

tance. In genetic syndromes where the cause is still unknown, investigating and accurately describing the behavioral, linguistic and social difficulties and recognizing co–morbid psychiatric symptoms can aid in the clinical diagnosis and may eventually lead to the development of effective treatment interventions.

Outline of this dissertation

This dissertation discusses several genetic syndromes associated with intellectual disability and their phenotypes.

chapter 2 reviews various distinctive behavioral characteristics in well–known syndromes associated with intellectual disability. The syndromes discussed in this chapter were selected based on their prevalence and their syndrome–associated behavioral phenotype. More in–depth review and discussion of phenotypes in genetic syndromes associated with intellectual disability and distinct behavioral abnormalities follow in chapters 3 and 4.

chapter 3 reviews the marked maladaptive and self–injurious behaviors and sleep disturbances of the behavioral phenotype in Smith–Magenis syndrome, including psychiatric and cognitive issues.

chapter 4 presents an early clinical case in which Pitt–Hopkins syndrome, a rare disorder associated with intellectual disability and breathing abnormalities, was diagnosed based on distinctive clinical manifestations of physical and behavioral phenotype.

chapter 5 discusses results of a clinical study of Pitt–Hopkins syndrome in 10 individuals, and compares the results to those found in the literature worldwide. The clinical study included assessments regarding behavior, development, adaptive and psychological functioning.

A large, international collaborative research project studying, exploring, and further delineating the developmental progression, physical and behavioral phenotype, cognition and autism in an ultra–rare disorder, Marshall–Smith Syndrome, is described in chapters 6 and 7.

Finally, chapters 8 and 9 describe the first attempt to study the prevalence and possible risk factors of treated autism spectrum disorders in the Caribbean.

chapter 8 describes the prevalence project, whose aim was to expand autism–specific epidemiologic research beyond the developed world countries, which have dominated the research literature. In chapter 9 paternal age was studied to examine the relationship between advanced paternal age and the risk of autism spectrum disorders in Aruba's distinctive sociocultural setting.

chapter 10 summarizes the studies presented in this dissertation and offers a discussion of the findings.

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CHAPTER 2

Behavioral phenotypes in syndromes with intellectual disability

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ABSTRACT

It is becoming increasingly evident that genetically determined syndromes may be characterized not only by specific dysmorphic features and congenital anomalies, but also by specific behavioral and cognitive patterns. Knowledge of such behavioral phenotypes and cognitive profiles provides the clinician new and additional tools in diagnosing and delineating different syndromes. It allows parents and other caregivers to anticipate and deal with abnormal behaviors of the child with the syndrome. Furthermore, studies of behavioral and cognitive phenotypes in syndromes may lead to a better understanding of the biological basis of human behavior. A number of frequent genetic syndromes with a specific behavioral phenotype and cognitive profile are described in brief in this review.

INTRODUCTION

Clinical genetics is often still considered a discipline primarily interested in diagnosing remarkable physical features and anatomical anomalies, and in researching their genetic causes. It has become increasingly clear over the last decade, however, that certain impulsive behaviors such as for example violent, aggressive behavior and arson may also be partly determined by genetic causes (Mazzocco & Reiss, 1994; Flint, 1995).

Research of cognitive profiles together with specific behavioral patterns has led to the realization that certain syndromes or chromosomal anomalies may well be characterized by specific behaviors or combination of behaviors (Mazzocco & Reiss, 1994; Flint, 1995). In several cases, these behavioral phenotypes in combination with certain cognitive strengths and weaknesses, have offered clues to the underlying genetic cause for the individual's developmental and behavioral difficulties. In some cases they have actually led to the delineation of a syndrome. Two conditions are required to consider a combination of behaviors and other features a behavioral phenotype (Flint & Yule, 1994; Turk & Hill, 1995). First, a behavioral phenotype is defined as a pattern of specific behaviors seen in almost all affected cases, while rarely observed in other syndromes. Second, a direct connection between genetic defect and physical manifestations is plausible (Flint & Yule, 1994).

In 1995 Turk and Hill proposed a broader definition of behavioral phenotype, one in which not only cognitive aspects of known genetic defects were included but also syndromes with as yet unknown etiology. They defined a behavioral phenotype as a pattern of behavioral and psychological characteristics present in many or most of the affected individuals. They emphasized the clinical importance of a structured approach in describing cognitive and behavioral functioning and proposed dividing these aspects and symptoms into 5 groups namely: intelligence, speech and language, attentional

defects, social impairments and other behavioral problems (Turk & Hill, 1995).

In this paper we review behavioral characteristics of some well–known syndromes associated with intellectual disability. The syndromes described here were selected on the basis of their prevalence and their syndrome based behavioral phenotype. For example, in Down syndrome there are no specific behavioral characteristics, although the syndrome occurs frequently. In Lesch–Nyhan syndrome there are striking behavioral issues, but this entity is very rare. This led us to review the selected entities: Fragile X syndrome, Rubinstein–Taybi syndrome, Prader–Willi syndrome, Velo–cardio–facial syndrome, Williams syndrome, and Cornelia de Lange syndrome.

CLINICAL DESCRIPTIONS

Fragile X syndrome

Fragile X syndrome (FXS) is characterized by intellectual disability, delay of motor development and physical features such as a long face with prominent jaw and large protruding ears, and the development of macro–orchidism during or after puberty. The defect is located on the distal end of the long arm of chromosome X (Xq27.3) and is caused by expanded repeats of a specific triplet, causing transcriptional silencing of the *fragile X mental retardation gene (FMR1)*. The absence of the associated protein FMRP as a consequence causes dysregulation of many genes, which in turn can lead to a neuropsychiatric phenotype of hyperactivity, anxiety, epilepsy and autism spectrum disorder (ASD) (Zafeiriou et al., 2007; D'Hulst & Kooy, 2009). FXS is now considered the most severe expression of *FMR1* mutation leading to gene silencing. It is part of a group of *FMR1* mutation related disorders, termed fragile X–associated disorders. These include fragile X–associated tremor/ataxia (FXTAS) and fragile X–associated primary ovarian insufficiency syndrome (Boyle et al., 2010).

Cognitive skills develop parallel to those of typically developing peers until puberty. The psychological profile shows performance skills are less developed than verbal capacities. Specific defects are found, especially in information processing, abstract reasoning, visual–spatial capacity, and auditory and visual short term memory; and these become more noticeable with age (Flint & Yule, 1994; Merenstein et al., 1994; Turk & Hill, 1995; Udwin & Dennis, 1995). From puberty on cognitive development seems to slow significantly (Flint & Yule, 1994; Turk & Hill, 1995; Udwin & Dennis, 1995). But this finding may be better explained by the fact that in different age groups different skills are examined, than by a true decline in intellectual skills. Adolescents and adults with FXS have difficulties with cognitive tasks that require skills such as abstract reasoning, sequential processing of information, and mathematics, these tasks however are increasingly part of

psychometric measurements with increasing age. In addition, longitudinal studies have shown that new skills are acquired at a slower rate, which can manifest itself as a decline in IQ scores over time (Bolton & Holland, 1994; Flint & Yule, 1994; Merenstein et al., 1994; Turk & Hill, 1995; Udwin & Dennis, 1995; Dykens et al., 2000).

Problems in speech and language may vary from a complete absence of speech to mild communication issues. Studies in patients with Fragile–X syndrome showed not only problems due to a general developmental delay, but also disorders of expressive language and perseverative speech (Bolton & Holland, 1994; Merenstein et al., 1994; Turk & Hill, 1995; Udwin & Dennis, 1995).

The observed problems in enunciation are probably due to physical anomalies, such as a highly arched palate and weakness of the temporomandibular joint. Examples of echolalia, repetitive, disorganized and perseverative speech in FXS have been described as 'cluttering', talking at a fast and fluctuating rate while speech is interspersed with repetitions of sounds, words or phrases, and sentences are often incomplete (Flint & Yule, 1994; Turk & Hill, 1995; Udwin & Dennis, 1995).

Hyperactivity, impulsivity and significant attention difficulties can be seen in 80% of men with FXS. Hyperactivity usually diminishes with advancing age, but attention deficits and impulsivity often persist into adolescence and adulthood (Turk & Hill, 1995; Udwin & Dennis, 1995). Approximately 30% of children with FXS meet criteria for autism, while another 20% can be diagnosed with a broader defined ASD (Hagerman et al., 2008). The most frequently observed symptom (in 90% of cases) with respect to autism symptomatology is difficulty in establishing and maintaining eye–to–eye contact. Self–injury is associated with repetitive and impulsive behavior in FXS (Arron et al., 2010). Stereotypies and self injurious behaviors such as hand flapping, hand biting, and head banging are as common to FXS as they are to ASDs. A notable difference between FXS patients and patients diagnosed with autism seems to be the clear wish for social interaction in FXS, although this is often hampered by anxiety and shyness (Bolton & Holland, 1994; Flint & Yule, 1994; Merenstein et al., 1994; Turk & Hill, 1995; Udwin & Dennis, 1995).

The verbal stereotypies and echolalia in expressive language seem to have an important function in attempts to initiate and maintain social interactions by FXS patients regardless of their difficulties in central processing of information (Turk & Hill, 1995; Udwin & Dennis, 1995). Other autistic behaviors in FXS are related to difficulties on the domains of social relatedness and communication. These include (social) anxiety, unusual sensory interests with a hypersensitivity to touch, impulsivity, and attention deficits (Hagerman et al., 2008).

Rubinstein–Taybi syndrome

Rubinstein–Taybi syndrome (RTS) is characterized by intellectual disability, postnatal growth retardation (with short stature, broad thumbs and broad great toes, and typical facial features with a large nose, convex nasal ridge, and protruding columella). Occurrence is usually sporadic, prevalence is 1 birth in 100, 000–125, 000 (Hennekam, 2006). In some patients the syndrome is caused by a deletion on band 16p13.3, or a mutation in gene *Cyclic AMP responsive element Binding Protein (CBP)* which is included in that part of chromosome 16. Rarely, mutations in the *E1A Binding Protein P300 (EP300)* gene are found.

A Dutch study of the syndrome reported full scale intelligence levels between 25 and 79; in a small percentage of patients IQ levels precluded formal testing and levels were estimated around 25. Mean IQ was around 35, with higher scores on performance skills than on verbal skills (Hennekam et al., 1992). Sometimes there is a complete lack of speech (Udwin & Dennis, 1995), but in most cases expressive language is limited with difficulties in complex syntax and concept formation. In spite of these, most patients make excellent use of their limited verbal skills in social communication (Hennekam et al., 1992; Udwin & Dennis, 1995). Children with RTS show a preference for adult company, most have attention deficits, startle easily at loud noises and more than half of patients exhibit stereotyped movements such as rocking, hand flapping and spinning. Resistance to change and distress caused by sudden events or unexpected changes in daily routines are reported in approximately 75% of children. Older patients often show mood swings and temper tantrums (Hennekam et al., 1992; Udwin & Dennis, 1995). Behavioral problems most frequently reported by parents include: short attention span, stubbornness, clinging behavior and sometimes aggressiveness in early adulthood (Hennekam, 2006). Significant numbers of individuals with RTS suffer from symptoms of severe over–activity, short attention span, motor stereotypies, poor coordination, mood swings, and aggressive outbursts in a cyclical pattern. Behavioral changes and exacerbation of symptoms may occur with aging and these can lead to psychiatric diagnoses of mood disorders, bipolar disorders and autism spectrum disorders (Hellings et al., 2002; Galera et al., 2009; Verhoeven et al., 2010).

Prader–Willi syndrome

Prader–Willi syndrome (PWS) is characterized by a combination of intellectual disability, hypogonadism, and obesity. Birth incidence is approximately 1: 22, 000– 1: 25, 000 (Vogels et al., 2003). Two phases can be distinguished in the clinical phenotype from neonate through to adulthood. The first phase, the neonatal phase, is characterized by

severe hypotonia, feeding difficulties, failure to thrive and delayed motor development. This is followed by a second phase commencing between the first and fourth year characterized by hyperphagia, which can lead to excessive weight gain, gross obesity and high mortality if these issues are not addressed (Whittington & Holland, 2010). Most affected patients have a chromosome 15 abnormality (e.g. deletion, uniparental disomy, structural rearrangement, methylation defects) at band q11–13 (Vogels et al., 2003). The degree of the intellectual disability can vary considerably; IQ level varies between 20 and 90. There are indications that in as many as 50% of patients, intellectual level is borderline between below–average functioning and mild mental retardation (Holm et al., 1993; Flint & Yule, 1994; Udwin & Dennis, 1995; Cassidy, 1997).

There is an unusual cognitive profile with strong visual organization and perception, but relatively poor processing of auditory and sequential information. Individuals with PWS typically perform well on tasks such as reading, development of vocabulary and doing puzzles (Holm et al., 1993; Udwin & Dennis, 1995; Cassidy, 1997). However, most patients have specific deficits in math, writing, visual and auditory short term memory and auditory attention (Turk & Hill, 1995; Udwin & Dennis, 1995; Cassidy, 1997). Motor milestones are significantly delayed due to the neonatal hypotonia. Children generally achieve independent sitting around 12–13 months, and walking independently around 24 to 28 months. The delay in speech and language development is partly due to facial anomalies and early hypotonia. Problems include mostly articulation problems and hypernasal voice (Holm et al., 1993; Cassidy, 1997).

Expressive language skills are weaker than receptive language skills. Parents often report verbal perseveration on a favorite topic as a distinctive, sometimes irritating behavioral feature (Udwin & Dennis, 1995).

Insatiable appetite, constantly requesting or seeking food, and abnormal food intake are the most characteristic clinical symptoms of the syndrome (Holm et al., 1993; Bolton & Holland, 1994; Flint & Yule, 1994; Udwin & Dennis, 1995; Cassidy, 1997; Boer et al., 1998; Whittington & Holland, 2010). The absence of a feeling of satiation causes the PWS patient to continue eating, which may lead to extreme obesity beginning before age six and an increased risk of obesity related complications in adulthood (Schrander–Stumpel et al., 2004). In approximately 30% of cases bodyweight is more than 200% of the ideal weight. It is unclear if this symptom can be attributed solely to the syndrome. There are arguments that the behavior could also be classified as learned behavior. Because food is kept out of reach from the patient and only offered at intervals, the patient 'learns' to eat as much as possible in the short period of time that the food is available (Flint & Yule, 1994). The obsession with food, as well as the continuous search for food are examples of the severity of the eating disorder, and these become more apparent beyond childhood (Holm et al., 1993; Flint & Yule, 1994; Udwin & Dennis, 1995;

Cassidy, 1997; Boer et al., 1998).

Temperament and contingent behavior in PWS are considered syndrome specific. The young child with PWS is usually described as stubborn. With advancing age patients can show temper tantrums, obsessional thoughts and obsessive–compulsive behaviors. They tend to be oppositional, rigid, manipulative and quarrelsome (Holm et al., 1993; Bolton & Holland, 1994; Flint & Yule, 1994; Turk & Hill, 1995; Udwin & Dennis, 1995; Cassidy, 1997; Boer et al., 1998). Self–injury is associated with repetitive and impulsive behaviors (Arron et al., 2010), and consists of highly prevalent (severe) compulsive skin picking and gouging. It is often seen in older children and adults with PWS (Holm et al., 1993; Flint & Yule, 1994; Bolton & Holland, 1994; Turk & Hill, 1995; Udwin & Dennis, 1995; Boer et al., 1998; Dykens & Shah, 2003). The syndrome is associated with psychotic episodes, which have been described in a small proportion of PWS patients. PWS resulting from the maternal uniparental disomy genetic subtype is strongly associated with psychotic episodes (Udwin & Dennis, 1995; Cassidy, 1997; Boer et al., 1998; Dykens & Shah, 2003; Vogels et al., 2003; Soni et al., 2007, 2008; Ingason et al., 2011). The rigidity, repetitive behaviors and restricted interests seen in PWS are similar to behaviors seen in autism spectrum disorder (Whittington & Holland, 2010). It is primarily due to the maladaptive behaviors that relatively few adult PWS patients are able to lead an independent lifestyle (Udwin & Dennis, 1995; Cassidy, 1997).

Velo–cardio–facial syndrome

Velo–cardio–facial syndrome (VCFS), the most common contiguous gene syndrome, is caused by a microdeletion on the long arm of chromosome 22, located at 22q11. The syndrome is autosomal dominantly inherited, but occurs in a majority of patients (85%) as a spontaneous mutation. The deleted region contains approximately 50 genes, some of which are implicated for psychiatric dysfunction. The gene *catechol–O–methyl transferase (COMT)* is within the deleted region for all patients with VCFS. Decreased *COMT*–activity, linked to elevated dopamine levels in the brain, predisposes for psychiatric disorders such as bipolar disorder and schizophrenia (Dunham et al., 1992; Bassett et al., 2007; Gothelf et al., 2009).

VCFS has a significant variability in phenotypic expression and no single clinical feature occurs in 100% of cases (Shprintzen, 2008). Most important physical characteristics include overt or occult submucous cleft palate, congenital cardiac abnormalities (e.g. ventricle septal defect, atrial septal defect, pulmonic atresia, tetralogy of Fallot) and a distinctive, although not obviously abnormal face with long, straight profile, prominent nasal bridge, bulbous nasal tip, narrow nasal base, and narrow palpebral fissures. Many infants with VCFS are frequently ill with hospitalizations for failure to thrive, cardiac

abnormalities and early hypotonia, chronic upper and lower respiratory complications (Swillen et al., 2000; Shprintzen, 2008).

Ryan et al. (1997) compiled cognitive information on 558 patients and discovered normal cognitive development in 32% of patients, mild mental retardation in 30% and moderate to severe intellectual disability in 18%. Of the remaining 20% of patients cognitive levels were unknown. Incidence of intellectual disability is higher in the group of familiarly occurring VCFS than within the group of de novo occurring VCFS. Other studies have shown significant numbers of VCFS patients had full scale IQ scores below 70, with lower verbal than performance IQ scores (Shprintzen et al., 1978). Notable was the fact that children with VCFS seem to perform relatively well compared to classmates when still young (<5 years of age). Learning difficulties become more apparent during later childhood and adolescence when the emphasis on abstract reasoning and conceptual learning increases, although in preschool children (aged <6 years) intelligence was found to be within normal limits with a mean full scale IQ level of around 87 (Golding–Kushner et al., 1985; Swillen et al., 1997).

In VCFS children a mild delay in speech and language development occurs with a specific developmental pattern of early unintelligibility after the onset of speech and subsequent hypernasal qualities. Children usually begin to develop first words before age 2, but do not acquire short phrases and sentences until the second or third year of life. The hypernasal voice is due more to structural anomalies of the soft palate and velopharyngeal insufficiency, than to hearing loss caused by hypoplasia of Eustachian tubes (Shprintzen et al., 1981).

VCFS is associated with alarmingly high prevalence rates for psychiatric morbidity (Jolin et al., 2006). Recent research found that psychiatric issues in VCFS seem to follow a developmental pattern, with psychotic and mood disorders rarely occurring during childhood but dramatically increasing during young adulthood. In early childhood, behavior and social relatedness are negatively affected by severe separation anxiety, simple phobias, and generalized anxiety, although it is likely that the expressive language impairment also contributes to the social withdrawal and the avoidance of verbal contact. Careful monitoring of psychiatric symptoms during childhood, adolescence and young adulthood is warranted (Shprintzen et al., 1992; Green et al., 2009).

Golding–Kushner et al. (1985) noted that patients with VCFS were socially isolated and had 'extremes of behavior' evidenced in impulsivity, distractibility, shyness and facial mannerisms with lack of expression or affect. More recent studies have noted major depressive disorders, attention deficit disorders and behavioral impairments and hypothesized that the increase of social difficulties with age could be a factor in the development of mood disorders in adolescence or adulthood (Antshel et al., 2006; Jolin et al., 2006; Aneja et al., 2007).

These and other published studies have shown that psychiatric illness should be considered a primary feature of VCFS, and although clinically there is overlap in diagnostic categories with changes during the lifetime, most reported diagnoses are: anxiety disorders, ADHD, depressive disorders, bipolar disorder, schizo–affective disorder, and schizophrenia (Shprintzen et al., 1992; Karayiorgou et al., 1995; Gothelf et al., 1997; Bassett et al., 1998; Jolin et al., 2006; Antshel et al., 2006; Aneja et al., 2007; Shprintzen, 2008; Gothelf et al., 2009).

Williams syndrome

Williams and co workers (1961) were the first to suggest an association between multiple physical features as cardiovascular abnormalities, failure to thrive, dental abnormalities and hypersensitivity to sound, mental retardation and specific behavioral features (Williams et al., 1961). Williams syndrome (WS) is caused by the deletion of approximately 25 genes on chromosome 7q11.23. The deletion includes the gene for *elastin (ELN)*, detecting the absence of one copy of the gene for *ELN* confirms the diagnosis of WS. The prevalence of WS is estimated at 1: 20, 000 (Jarvinen–Pasley et al., 2008).

Mental retardation may vary between mild and moderate. Intellectual functioning usually remains on a stable level during childhood with no apparent decline in cognitive abilities over time. Long term follow–up showed little educational progress beyond early teenage years (Udwin & Yule, 1990a; Bellugi et al., 2000). Specific areas of weakness include difficulty with abstract concepts, spatial cognition and abstract reasoning, visual–spatial construction disability, and major defects in planning and problem solving (Gosh et al., 1996; Bellugi et al., 2000; Mervis & Klein–Tasman, 2000; Jarvinen–Pasley et al., 2008; Morris, 2010). Dysmorphic facial characteristics are often difficult to recognize at a very young age, but features usually become more apparent with age. These features include puffiness around the eyes, a small upturned nose, long philtrum, wide mouth, full lips, and a small chin. Blue and green–eyed individuals with the syndrome can have a distinctly beautiful "starburst" or white lacy pattern on their iris. Early symptoms in infancy and childhood include failure to thrive, and feeding difficulties due to hypotonia. Muscle tone tends to improve with age. Developmental disabilities and cardiovascular complications can become apparent later in childhood.

A distinctive cognitive profile was described as early as 1978. It showed a significant discrepancy between verbal and performance skills resulting in relative strengths in aspects of language and facial processing, and severely impaired spatial cognition in addition to poor perceptual ability. Although this unusual neuropsychological profile is not necessarily unique to WS, it is not often seen in children with mental retardation of different origin and it is considered an important syndrome feature useful in syndrome

identification (Bennett et al., 1978; Bellugi et al., 2000; Jarvinen–Pasley et al., 2008).

Further features include selective attention to parts or details and difficulty in assembling the whole, with the exception of a particular skill in face perception and recognition (Tager–Flusberg et al., 2003). This last feature is also seen in individuals with right hemisphere damage. Such damage is consistent with relatively spared language abilities, primarily in the areas of grammar and vocabulary also found in individuals with WS. There are indications of augmented amygdala volume in WS. The amygdala has a crucial role in social cognition, and regulating responses to social–emotional stimuli (Jarvinen–Pasley et al., 2008; Morris, 2010). Bilateral damage may be linked to a lessened ability to perceive fear towards strangers (Jarvinen–Pasley et al., 2008).

Early anecdotal reports have highlighted great language ability and verbal expressions, and later studies have confirmed that although expressive language is usually fluent with an abundance of social phrases, chit–chat and clichés, the content of conversation can often be odd or out of context (Bellugi et al., 1990; Jarvinen–Pasley et al., 2008). Later research with varying outcomes to assessments of speech and language questioned whether greater than typical language ability is a consistent manifestation of the syndrome (Udwin, 2005; Mervis & Becerra, 2007).

Speech is often qualified as 'unusual' probably also as a consequence of the relatively spared language, the frequent use of neologisms (Bellugi et al., 1990) and stereotypical use of sentences, words, and adult sounding phrases (Udwin & Yule, 1990b). The voice is usually deep and hoarse.

Adverse reactions to certain sounds is present in almost all persons with WS (96%), usually manifesting itself in distressed reactions on hearing sudden loud noises (Dilts et al., 1990; Levitin et al., 2005). This causes heightened distractibility to all noises and probably explains some of the hyperactivity, attention deficits and restlessness. Additional issues reported include concentration difficulties, excessive anxiety and impairments in social relatedness with peers (Udwin & Yule, 1990a; Greer et al., 1997) and perseveration in thought processes (Greer et al., 1997).

The syndrome specific temperament in WS shows increased sociability and empathy in social interaction. Paradoxically, numerous reports over time have also emphasized maladaptive behaviors, limited social judgment, a greater interest in contact with adults than with peers and a limited ability to use skills in a general social context (Tomc et al., 1990; Plissart et al., 1996; Jarvinen–Pasley et al., 2008). Studies have shown that 2/3 of children between 3 and 7 years have a difficult or relatively difficult temperament (Tomc et al., 1990). However, concurrent with difficult behavior children with WS will also show active, social behavior, especially by seeking contact with or socially engaging the other, possibly resulting in the lessening of other, more negative aspects of temperament during short observations.

Parents have reported that their children with WS are typically unafraid of strangers (Gosch et al., 1994) and in general show a greater interest in contact with adults than with their peers. They are frequently troubled by fears and anxieties related to non–social circumstances (Mervis & Klein–Tasman, 2000; Morris, 2010). The development of adaptive behaviors, daily living skills and independent functioning is hampered by anxiety, distractibility, overfriendliness, lack of perseverance, and insufficient motor skills. It seems that adults with WS need more support and a larger social support network when compared to adults with a similar cognitive developmental level (Plissart et al., 1996; Greer et al., 1997). The domain of daily living skills such as showering and dressing is one of the least developed adaptive behavioral domains in WS (Greer et al., 1997). Common psychiatric diagnoses in WS include attention deficit hyperactivity disorder (ADHD) and clinically evident anxiety disorders such as specific phobias, generalized anxiety disorder, or separation anxiety disorder (Morris, 2010).

Cornelia de Lange syndrome

Cornelia de Lange syndrome (CdLS) was first described in 1933 by the first female professor of pediatrics in the Netherlands: Cornelia de Lange (de Lange, 1933). The incidence of CdLS is unclear, but is estimated worldwide to occur at 1 in 37, 000 to 50, 000 persons (Dorsett & Krantz, 2009).

The defect in the syndrome can be determined in about half of patients with the syndrome as a mutation in the *Nipped–B homolog (Drosophila) (NIPBL)* gene, on the short arm of chromosome 5 (5p13.2). In a small subset of male patients the syndrome is caused by a change in the *structural maintenance of chromosomes 1A (SMC1A)* gene located on the X–chromosome, and very rarely mutations in *structural maintenance of chromosomes 3 (SMC3)* are found. All genes causally implicated in the syndrome have a function in the division of individual chromosomes, but it is still unclear how this results in the characteristic syndrome symptomatology.

CdLS is characterized by mental retardation (Kline et al., 1993), short stature, limb abnormalities and distinctive facial features such as confluent eyebrows, long eyelashes, low nasal bridge and thin, down turned lips. In 65–70% of CdLS patients, a form of autism spectrum disorder has been described in which the problems in social interaction and communication, and in behavior have been significant (Bhuiyan et al., 2006).

The syndrome can be expressed in two clinical dichotomous forms, one a classic form in which intellectual disability is severe, while patients with the milder form show less retardation of cognitive development and growth. Autism spectrum disorder can be found as part of the clinic of both forms. There is no regression of skills. Most children with the syndrome are able to acquire new skills until well into their teenage years

depending on their cognitive level. Visual–spatial memory is usually well–developed.

Research has shown that those children with a combination of low birth weight (below 2, 500 grams), microcephaly, and severe anomalies of the arms tend to have a higher risk of speech and language delay. Difficulties in reciprocal social interaction are pronounced with a lack of social–emotional reciprocity, mask–like facial expressions and rejection of physical contact through body posture. Severe problems with the development of speech and language or complete lack of speech may be negatively impacted by frequent auditory issues (Jackson et al., 1993). If language and speech do occur, expressive language skills and speech are less developed than comprehension and passive language.

Stereotyped and self–injurious behaviors seem to be characteristic of the group with classic CdLS (Basile et al., 2007) and seem to be associated with repetitive and impulsive behaviors (Arron et al., 2010). The stereotypies, repetitive and self injurious behaviors consist predominantly of a fascination for own hands and hand movements, motor mannerisms, finger biting, head banging, poking behind the ear with one finger and scratching. Maladaptive behaviors in children with a severe form of CdLS have been observed and documented through videotaping. Several behavioral characteristics included, e.g. rejecting social and physical contact with the mother and unfamiliar others, the masque like face with lack of emotional expression, frequent stereotyped, repetitive and self–stimulating movements, and reacting with pleasure to vestibular stimulation. One characteristic movement that may be interpreted as rejection is bending further backwards when the child is carried horizontally. It is important for parents to understand that these behaviors should not be interpreted as rebuffs but rather these are behaviors occurring with the syndrome. Communication with others may improve with increasing age (Johnson et al., 1976). Self–injury is found more often in patients over age 12 and usually occurs in response to stress, frustration, anxiety or fear. Fascination with own hands and typical hand movements are often accompanied by grimacing and teeth grinding. It is difficult to attract the attention of the child or distract it at these times (Sarimski et al., 1997).

Other adverse behavioral issues such as aggressive episodes directed toward objects and persons and serious temper tantrums were associated with co–morbid autism spectrum disorder. In addition, there are behaviors that are also common in children with intellectual disability, such as hyperactivity, passivity and stereotypical behaviors (Sarimski et al., 1997).

Sleep disturbances are common in children with CdLS with autism spectrum disorder and clinical presentations include irregular sleep patterns, insomnia or interrupted sleep, and daytime drowsiness (Berney et al., 1999; Bhuiyan et al., 2006).

DISCUSSION

Improved knowledge of syndromically determined behavioral characteristics allows parents the possibility to anticipate this behavior, and it can improve recognition and diagnosis of the syndrome. Furthermore, a better understanding of the genetic basis of deviant behavior can also increase understanding of the biological basis of normal behavior and cognition (Mazzocco & Reiss, 1994; Flint, 1995; Turk & Hill, 1995; Walter et al., 2009).

The great inter–individual variability can make it difficult to come to concurrent profiles for behavior and cognition in the syndromes described, making it clear that behavioral characteristics in any syndrome are not solely determined by genetics (Harris, 2010). Too strong an emphasis on the biological determinants of behavior should be avoided: for example just as not every patient with Williams syndrome will have a supravalvular aortic stenosis so may a behavioral and cognitive profile of the syndrome not always be fully evident.

Behavior is also influenced by interactions with the environment and by the reactions from that environment to temperament, external features and neuropsychological deficits. Furthermore, it is possible that the variability described in the international literature could be explained by methodological differences across studies.

For parents it is of great value to realize that certain behavioral characteristics of their child are associated with the syndrome, and that his behavior should not be interpreted as a personal rejection. This realization may greatly reduce feelings of guilt, incomprehension and irritation in parents and other caregivers (Hennekam et al., 1992; Turk & Hill, 1995; Udwin & Dennis, 1995).

It is important that parents do not accept certain behaviors associated with the syndrome as inevitable and unalterable, thereby not reacting in appropriately corrective ways to behavioral abnormalities in the child with the possibility of further exacerbation ('self–fulfilling prophecy') and even stigmatization. Determining whether (child psychiatric) interventions are possible to ameliorate or manage severe behavioral problems associated with the syndrome is desirable from both a scientific and clinical perspective.

CONCLUSION

Increasingly the causes of more syndromes with specific behavioral phenotypes will be isolated with advances in cytogenetic/molecular genetics. Interdisciplinary collaboration will contribute to the development of more refined, structured measures of behavior and cognition in these syndromes, which in concert with genetic information will contribute greatly to our understanding of human behavior.

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CHAPTER 3

Severe behavioral problems in children with intellectual disability: Smith–Magenis syndrome

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Ernstige gedragsproblemen bij kinderen met een verstandelijke handicap: het Smith–Magenis syndroom
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ABSTRACT

BACKGROUND – Smith–Magenis syndrome is a genetically determined syndrome characterized primarily by unusual behavior. The syndrome is still insufficiently recognized, although it has an incidence of 1: 25,000, which is just as high as that of Prader–Willi syndrome and Williams syndrome.
AIM – To increase awareness of the syndrome among professionals by briefly summarizing the cause, the most important physical manifestations and the cognitive profile, and by describing the unusual behavioral pattern associated with the syndrome. Therapeutic aspects will also be discussed.
METHOD – Relevant literature was traced via the Pubmed database using the search terms 'Smith–Magenis syndrome' and 'deletion 17p11.2'. No exclusion criteria were used.
RESULTS – The literature search in Pubmed and through cross–references yielded 52 articles with clinical descriptions of Smith–Magenis syndrome.
CONCLUSION – Smith–Magenis syndrome is a genetically determined syndrome characterized by moderately severe mental retardation (average IQ between 40 and 55), unusual facial features (broad face, deep–set eyes, flat midface, broad mouth with down turned corners and prominent chin) and especially by behavioral problems: low frustration tolerance, sudden mood swings and excessive irritability. Highly characteristic behavior of children with Smith–Magenis syndrome includes self–hugging, polyembolokoilomania (insertion of objects into body cavities), onychotillomania (pulling out finger– and toenails) and sleep disturbances.

KEYWORDS: behavioral disorders, genetics, sleep disorders, Smith-Magenis syndrome

Part I – Peer reviewed article in 2004

Children with an intellectual disability of genetic syndromal origin are usually diagnosed based on specific physical features, sometimes in combination with internal anomalies (Gorlin et al., 2001). Sometimes, however, a specific behavior or combination of behaviors can lead to the diagnosis. Abnormal behavior can have a more significant impact on the life of the child than cognitive limitations associated with a syndrome. Behavioral problems may influence the quality of interaction with others, while conversely behavior may also be determined by the reaction of others to the distinct physical appearance and cognitive limitations (van Balkom et al., 1999).

Smith–Magenis syndrome (SMS) is an example of a syndrome that is primarily characterized by marked behavioral problems. The incidence of SMS is equal for both sexes and is estimated at 1 per 25, 000 births, which is comparable to the incidence of

Angelman syndrome, Prader–Willi syndrome and Williams syndrome. This paper summarizes cause, distinct physical features, cognitive profile, behavioral patterns and sleep disturbances associated with SMS.

METHOD

Searches were performed in Pubmed employing the search terms 'Smith–Magenis syndrome' and 'deletion 17p11.2'; no exclusion criteria were used. As no minimal diagnostic criteria are available, the inclusion criteria consisted only of the before mentioned search terms in published papers, where the diagnosis was judged as probable.

RESULTS

From the literature search method in Pubmed and through cross–referencing 52 articles were selected with clinical descriptions of SMS. None of the articles describing one or more individuals with SMS were excluded. All articles retrieved were systematically assessed. In the reference list, only those articles actually used in this paper were listed.

The salient features of SMS are summarized in Table 3.1 (physical features) and Table 3.2 (behavioral characteristics).

SMS was first described in 1982 by Ann Smith, Ellen Magenis and colleagues (Smith et al. 1982) in two patients with congenital heart defects and cleft, where the symptoms were caused by a deletion on the short arm of chromosome 17. Later, awareness of the syndrome improved mainly through studies by the clinical geneticist Frank Greenberg. Currently there are over 100 patients described in literature (Smith et al., 1982, 1986, 1998a, b; Stratton et al., 1986; Colley et al., 1990; Allen et al., 1991; Greenberg et al., 1991, 1996; Finucane et al., 1994, 2001; Dykens et al., 1997; Allanson et al., 1999; Potocki et al., 2000; De Leersnyder et al., 2001, 2003). Subsequent studies have shown that palate clefts, contrary to what was initially described, are not a main characteristic of the syndrome.

Cause

SMS has a genetic cause. Most patients have a microdeletion of chromosome 17p11.2. In determining this, use of a specific laboratory technique is needed, as the defects are often too small to be detected by routine chromosomal investigation. The cause of the microdeletions is unknown; in almost all cases the deletion was de novo – so no defect could be found in either parent. The probability of recurrence in subsequent children is

Table 3.1 Most frequent physical features in Smith–Magenis syndrome

Short stature	78%
Brachycephaly	83%
Prominent forehead	64%
Myopia	30%
Broad nasal bridge	81%
Flat midface	94%
Deep, hoarse voice	82%
Prominent chin	51%
Ear abnormalities	68%
Hearing impairments	68%
Scoliosis	65%
Brachydactyly	81%
Peripheral neuropathy	75%
Congenital heart defects	37%
Congenital renal anomalies	35%

Greenberg et al., 1991, 1996

Table 3.2 Most frequent behavioral issues and cognitive levels in Smith–Magenis syndrome

Sleep disturbances	75%
Self–injurious behaviors:	
Hand biting	93%
Head banging	55%
Trichotillomania	34%
Hitting oneself	62%
Onychotillomania	55%
Polyembolokoilomania	73%
'Self–hugging'	62%
Cognitive development:	
IQ <25	12%
IQ 25–39	16%
IQ 40–54	44%
IQ 55–69	24%
IQ 70–79	4%

Finucane et al., 1994; Smith et al.,1998a

therefore very small. If the deletion is caused by a more complicated mechanism, such as a translocation in one of the parents with one of the deleted sites also involving the 17p11.2 region, there could be an increased risk of recurrence.

Recently it has been determined that the syndrome can also be caused by a point mutation in the *Retinoic Acid Induced 1 (RAI1)* gene, which is located in the 17p11.2 region (Slager et al., 2003). This gene codes for a protein of which the function is still fairly unknown. It is thought that the protein has a function in nerve–cell–differentiation and in transcription of parts of our DNA. Children and adults with SMS caused by either a 17p11.2 deletion or a point mutation of *RAI1* cannot be identified based on facial features, behavior or development. However, heart and kidney anomalies do not occur in patients with a point mutation whereas they do occur in patients with a deletion of a larger part of chromosome 17p11.2. This finding suggests that other genes, located close to the *RAI1* gene on chromosome 17p, are responsible for these anomalies instead. So far all point mutations in *RAI1* developed anew in the patients themselves, and could not be determined in either of the parents. Therefore, it is assumed that the chance of recurrence is probably quite low, although the number of patients in whom this specific defect has been determined is still small.

Physical features

The facial features in babies are often described as cherubic with prominent rosy cheeks and wonderful smiles. Due to the social smiling and alert impression of babies the remarkable facial features usually remain unnoticed. Mothers often describe their babies as perfect children with a happy disposition. One noticeable physical feature in babies are the extra rolls of fat on the arms and legs ('Michelin doll'), which disappear as the child ages (Allen et al., 1991; Smith et al., 1998a; Allanson et al., 1999).
Distinctive facial features are noticeable in younger children: there is a wide, square face with a prominent forehead, a down–turned mouth, eyebrows that meet in midline (synophrys), deep–set eyes, a flattened midface, a wide mouth with down turned corners, fleshy everted upper lip, and a prominent chin for their age (see Figure 3.1). With increasing age the facial features become more subtle. The most significant features are brachycephaly, flattened mid–face, heavy eyebrows, broad nasal bridge and prominent lower jaw; the whole of the face can be perceived as somewhat coarse (Stratton et al., 1986; Allen et al., 1991; Greenberg et al., 1991, 1996; Finucane et al., 1994; Allanson et al., 1999). In all age groups the ears can be oddly shaped, and positioned slightly posteriorly (Greenberg et al., 1991, 1996). A cleft palate is found in 9% of patients (Greenberg et al., 1991). Velopharyngeal weakness with hypernasal speech can be found in an even higher percentage of the patients, which, together with the deformities of ears and the mid–

Figure 3.1 Patient with Smith–Magenis syndrome at 8 years

Note broad midface, small and deeply set eyes, long eyebrows, flat midface, short nose with prominent nasal tip, everted upper vermillion, and slightly malformed ears.

face hypoplasia, may lead to diagnostic confusion with velo–cardio–facial syndrome (Greenberg et al., 1996).

Patients with SMS often have eye problems, varying from myopia or strabismus to cataract, microcornea and iris anomalies (Colley et al., 1990; Allen et al., 1991; Greenberg et al., 1991, 1996; Finucane et al., 2001). Hearing impairment (conductive with/without sensorineural hearing loss) occurs in 68% of patients, possibly coinciding with a history of recurring mid–ear–infections (Stratton et al., 1986; Colley et al., 1990; Allen et al., 1991; Greenberg et al., 1996; Smith et al., 1998b; Finucane et al., 2001). Approximately 75% of the patients have signs of peripheral neuropathy, with decreased reflexes, elevated pain– and temperature thresholds, and hollow or flat feet (Allen et al., 1991; Greenberg et al., 1991, 1996; Smith et al., 1998b). Patients can also have short, wide hands (brachydactylia) and often there is growth retardation (Colley et al., 1990; Allen et al., 1991; Greenberg et al., 1991, 1996). Scoliosis is present in 65% of patients and can exacerbate with age. Congenital heart defects (37%) are usually present as ventricular or atrial septal defects and valve defects (Greenberg et al., 1991). In a multidisciplinary study by Greenberg et al.

(1996) borderline hypothyroidism and borderline hypogammaglobulinaemia were found in 25% of the patients.

Cognitive development

Evidence of non–progressive moderate to severe intellectual disability and developmental problems can be found in most patients with SMS. Cognitive impairments often warrant placement in special educational settings. In patients investigated using the Bayley Scales of Infant Development or one of the Wechsler–scales, measured intelligence levels are between 20 and 78. Most patients function in the mild to moderate range of intellectual functioning, with IQ levels between 40 and 55 (Stratton et al., 1986; Greenberg et al., 1996; Dykens et al., 1997; Smith et al., 1998a).

The cognitive profile shows weaker verbal than performance skills. In psychometric examination of 10 patients Dykens et al. (1997) found that sequential processing and short term memory were relatively weak, while long term memory and visuoperceptual abilities were relatively strong. A severe delay in development of speech–language either with or without associated loss of hearing occurs in 95% of the patients; there is a hoarse, deep voice in 82% of patients. In general, development of expressive language is more delayed than receptive language, often giving rise to frustration in the child when interacting with others. Speech therapy and sign language can be helpful in some cases (Allen et al., 1991; Greenberg et al., 1991, 1996; Smith et al., 1998a).

Behavior

A recognizable pattern of behavioral problems both at home and at school is seen in at least 60–80% of patients and often arises at a young age. The behavioral problems include low frustration tolerance, resistance to changes, sudden mood changes and temper tantrums or explosive outbursts, attention–deficit–hyperactive–disorder (ADHD), self injury, sleep disorders, bruxism, and repetitive, stereotypic, impulsive and aggressive behaviors (Smith et al., 1986, 1998a ; Allen et al., 1991; Dykens et al., 1997; Allanson et al., 1999; Finucane et al., 2001).

Smith et al. (1998a) mention a fascination for electronics, such as computers and video cameras/ recorders, while Dykens et al. (1997) noted repetitive, quick flipping of pages of books and licking finger ('lick and flip').

In contrast to children with autism spectrum disorders who have similar behavioral problems, most children with SMS have good eye–to–eye gaze and social smiling (Smith et al., 1998a). Because of their impulse regulation problems, distractibility and attention problems, children with SMS usually perform better in smaller groups within

well-structured settings. Due to the relative strength in visual perception teaching can be aided by the use of pictograms, while a predictable, structured daily routine can prevent explosive outbursts that accompany unexpected changes to the schedule. The self–injurious behaviors, in the form of head banging, hitting and biting oneself, and the constant attention seeking behaviors, can complicate the interaction of these patients with their parents, teachers and caregivers (Colley et al., 1990; Allen et al., 1991; Smith et al., 1998a).

A curious phenomenon that seems to affect many patients with SMS is the stereotypic self–hugging or hand–clasping, which mostly seems to occur as an expression of happiness or excitement. This behavior was described by Finucane et al. (1994) based on observations in an institute where it was mainly seen in children and adolescents with SMS. The behavior is described as short, serial, random 'spasms' or 'tics', often while grimacing or making noise. Two types of behavior are distinguished: the spasmodic upper–body squeeze and hand clasping at chest or chin level. This behavior was not observed in patients during tantrums or when upset. Besides self–hugging, patients also tend to repetitively and forcefully hug others (Smith et al., 1998a).

Most of the self–injurious behaviors in SMS become apparent at age 2 and are not specific for the syndrome. These behaviors mainly include biting wrists and hands, head banging, hitting oneself, scratching the skin or picking at small wounds (Smith et al., 1986, 1998a ; Colley et al., 1990; Greenberg et al., 1991; Dykens et al., 1997; Finucane et al., 1994, 2001). However, there are two self–injurious behaviors that are distinctive to the syndrome, these can be observed mostly in older patients (Greenberg et al., 1991; Finucane et al., 2001): polyemboikoilomania (inserting objects into body cavities) and onychotillomania (pulling out of finger– and toenails), seemingly without pain to the patient. It is unknown whether this high threshold for pain can be accounted for by a peripheral neuropathy, an altered emotional response to pain, or both (Greenberg et al., 1991; Finucane et al., 1994, 2001).

Most patients have already had different treatments with psychotropic medication to modify behavior before the correct diagnosis can be made. Stimulants (usually methylphenidate) and anticonvulsive (carbamazepine) medication usually prove ineffective in the long–term modification of behavioral abnormalities (Dykens et al., 1997; Smith et al., 1998a).

Sleep disorders

Significant sleep disturbances are present in almost all patients with SMS and these have a negative impact – not only on the patient, but also on parents and other family mem-

bers, who themselves can become sleep deprived. Sleep deprivation can subsequently be a factor in behavioral problems during the day, disrupted communication, high parental stress, and learning issues (Colley et al., 1990; Greenberg et al., 1991, 1996; Finucane et al., 1994, 2001; Dykens et al., 1997; Smith et al., 1998b; Potocki et al., 2000; De Leersnyder et al., 2001, 2003; Turk, 2003). Sleep disorders occurring in the syndrome include difficulties falling asleep, frequent night time awakenings and (partially as a consequence of these) excessive daytime sleepiness with more 'sleep attacks' and naps at the end of the day. Enuresis nocturna is also common (Smith et al., 1998b). Total sleeping time is reduced and REM sleep is diminished (Greenberg et al., 1991; Potocki et al., 2000; De Leersnyder et al., 2003). Inversion of the circadian rhythm of melatonin was found in most patients: during the day melatonin production was higher than at night, with paradoxical daytime secretion. Temper tantrums and tiredness occur when the melatonin level increases. Children with SMS take daytime naps or have sleep 'attacks' when melatonin production peaks in the afternoon and evening (Smith et al., 1998b; Potocki et al., 2000; De Leersnyder et al., 2001, 2003; Turk, 2003). In a Belgian study a group of children with SMS was treated with acebutolol (β–adrenerge antagonist), to reduce daytime melanin production and thus improve night time sleep. The trial showed not only a positive impact on sleep, but the medication also seemed to improve the concentration of the children during the day, while the frequency of tantrums decreased and interpersonal interactions improved (De Leersnyder et al., 2001). In a different study De Leersnyder et al. (2003) reported a positive effect of a morning dose of acebutolol accompanied by an evening dose of melatonin. Acebutolol suppressed elevated plasma melatonin levels in the morning, resulting in a decrease of restlessness, aggressive outbursts and daytime napping. The evening dose of melatonin subsequently improved sleep patterns in all tested children.

Although more research is needed, it seems likely that the sleep disorders can be effectively treated with melatonin.

CONCLUSION PART I

Since the initial description of the syndrome in 1982, biological and molecular–genetic mechanisms have become increasingly clear. The behavioral phenotype with the unusual, often severe, behavioral abnormalities, the self–injurious behavior and the sleep disturbances are usually the primary reason for referral for psychiatric evaluation and treatment. In the differential diagnosis of children with intellectual disability and a pattern of unusual behavior Smith–Magenis syndrome needs to be considered. For the assessment of distinctive physical features a clinical geneticist or pediatrician should be consulted. Subsequent molecular–genetic testing can confirm the suspected diagnosis of SMS.

In management, medication for regulating and modifying behavior and impulsiveness may have an important role, and improvement of expressive language through speech therapy and other ways to communicate such as sign language should be considered in efforts to prevent or limit frustration in interactions and communications. The use of melatonin to regulate the day–night rhythm has shown promise in research and clinical practice and may contribute not only to improved sleep but also to a subsequent decrease in behavioral problems.

Part II – Update on clinical and behavioral features in SMS

Since our publication in 2004 a number of papers have expanded our knowledge on clinical features and behavioral aspects of SMS (Sarimski, 2004; Shelley et al., 2005; Girirajan et al., 2006; Gropman et al., 2006; Madduri et al., 2006; Martin et al., 2006; Tomona et al., 2006; Andrieux et al., 2007; Edelman et al., 2007; Gropman et al., 2007; Elsea & Girirajan, 2008; Taylor & Oliver, 2008; Wolters et al., 2009). In the following paragraphs we highlight additional or new findings and evidence in SMS from these papers with respect to the subjects presented in our earlier publication.

Cause

In a study of phenotypic comparison between individuals with the 17p11.2 deletion and those with the *RAI1* mutation Girirajan and co–workers (2006) found that most of the common features associated with SMS were found in patients with haploinsufficiency of *RAI1* (Girirajan et al., 2006). Functional abrogation of the *RAI1* gene should therefore be considered primarily responsible for the most common clinical features of SMS, with other genes within the deletion interval likely accounting for the more variable features of the syndrome and adding to the overall severity of phenotype (Girirajan et al., 2006; Gropman et al., 2007; Elsea & Girirajan, 2008).

Physical features

Intellectual disability, neurobehavioral problems and significant sleep disturbances are consistently part of the clinical manifestations of the syndrome regardless of cause. In recent studies it has become more evident that the severity of the phenotype increases with increased deletion size, as is the case in those who carry 17p11.2 deletion. These individuals are more likely to have additional issues such as cardiac anomalies, severe speech and motor delay, short stature, and hearing problems (Girirajan et al., 2006; Andrieux et al., 2007; Gropman et al., 2007). Tomona et al. (2006) investigated dental and craniofa-

cial findings in SMS as part of an ongoing study of the natural history of the syndrome. They found a strikingly high incidence of two developmental dental abnormalities, tooth agenesis and taurodontism. Tooth agenesis most commonly affects the mandibular second premolars. Taurodontism, which is characterized by prism shaped molars with large pulp spaces, affects both primary and secondary teeth. Tonoma and coworkers suggest that these findings may facilitate early diagnosis in preschool children (Tonoma et al., 2006).

Cognitive development

Assessments of cognitive function in various studies since 2004 confirmed earlier findings in most SMS patients of mild to moderate intellectual disability (Madduri et al., 2006; Martin et al., 2006; Wolters et al., 2009).

Behavior

In a meta–analysis of a large group of SMS individuals to analyze genotype–phenotype differences, Edelman et al. (2007) found that those with the *RAI1* mutation were more likely to show behavioral abnormalities such as overeating, polyembolokoilomania, and self–hugging than those with the deletion on 17p11.2 (Edelman et al., 2007).

The distinctive behaviors accompanied by delays in speech and language development often lead to a diagnosis of autism in toddlerhood, although infants with SMS can seem to develop typically due to their socialization skills, friendly demeanor and the lack of behavioral problems (Gropman et al., 2007; Wolters et al., 2009). Long term follow-up has shown that many individuals with SMS eventually do attain acceptable levels of expressive language. Once verbal they are often described as interactive, sociable and communicative, which seems to support reports of relative strengths in socialization, but could also refute an earlier diagnosis of autism (Martin et al., 2006). However, many of the distinctive behaviors observable, such as stereotypic and repetitive behaviors e.g. body rocking, self–hugging, spinning objects, as well as self injurious and attention seeking, adult oriented behaviors, and intrusiveness during conversation seem to indicate that qualitative impairments on the three core domains in autism spectrum disorders (communication, social skills and behavior) persist or exacerbate with increasing age despite relative strengths noted (Sarimski, 2004; Gropman et al., 2006; Madduri et al., 2006; Gropman et al., 2007). Behavioral problems in SMS usually exacerbate with the onset of puberty, depending also on severity of intellectual disability, comorbid somatic conditions and sleep disorders (Edelman et al., 2007; Elsea & Girirajan, 2008). With increasing age, relative strengths in socialization seem to remain when compared to

adaptive functioning. Especially with respect to communication and daily living skills measured with the Vineland Adaptive Behavior Scale as shown in a study by Taylor and Oliver (2008), although their small study sample precluded statistical analysis of these findings (Taylor & Oliver, 2008).

Sleep disorders

In a study Gropman et al. (2007) found that although sleep disturbances can be found at a very early age, these can undergo developmental changes with increasing age. Manifesting in infancy first as decreased 24–h sleep in infants, in toddlers and school age children shortened sleep cycles are further complicated by frequent, prolonged night time awakenings and excessive daytime sleepiness and napping. From adolescence additional sleep disturbances reported are increased evening arousal and difficulty falling asleep, which often continue into adulthood (Gropman et al., 2007).

CONCLUSION PART II

In addition to the conclusions already mentioned in our manuscript published in 2004 we would like to conclude from studies since then, that it is likely that early recognition and diagnosis could prevent some of the disruption of development through improvement of communication skills in interactions with both adults and peers, and through early interventions with respect to sleep disturbances and maladaptive behaviors. However, despite the facial features in infancy, definitive diagnosis of Smith–Magenis syndrome is often delayed due to the infant's complacent temperament, social smiling and lack of recognizable behavioral problems until the distinctive behaviors fully emerge and significant sleep disturbances become more evident.

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CHAPTER 4

Mental retardation, "coarse" face, and hyperbreathing: confirmation of the Pitt–Hopkins syndrome

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ABSTRACT

We present a patient with distinctive clinical manifestations resembling those first described by Pitt and Hopkins in 1978 as a separate entity. Cardinal findings in this syndrome are mental retardation, "coarse" face, and an abnormal breathing pattern. The symptoms in this patient are different from those in Joubert syndrome, Rett syndrome, Rett–like variants, and of a case reported by Leifer et al. (1991). The manifestations in our patient and in the case described by Singh (1993) seem to confirm the delineation of this syndrome, the cause of which remains unknown.

KEYWORDS: mental retardation, coarse face, hyperbreathing, Pitt–Hopkins syndrome, Joubert syndrome, Rett syndrome

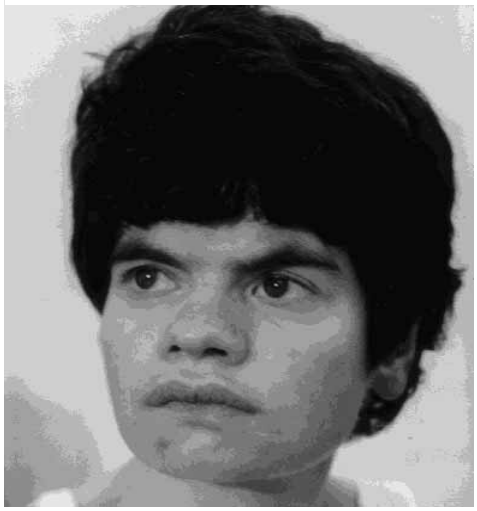
INTRODUCTION

In 1978 Pitt and Hopkins described two unrelated patients with similar clinical manifestations, mainly consisting of a wide mouth, an abnormal respiratory pattern, clubbing of the fingers, and mental retardation. Singh (1993) reported a male patient with the same abnormal breathing pattern, facial findings, and mental retardation. We report on an adult female with a similar combination of symptoms, and compare these symptoms with the earlier patients described and with other related entities.

CLINICAL REPORT

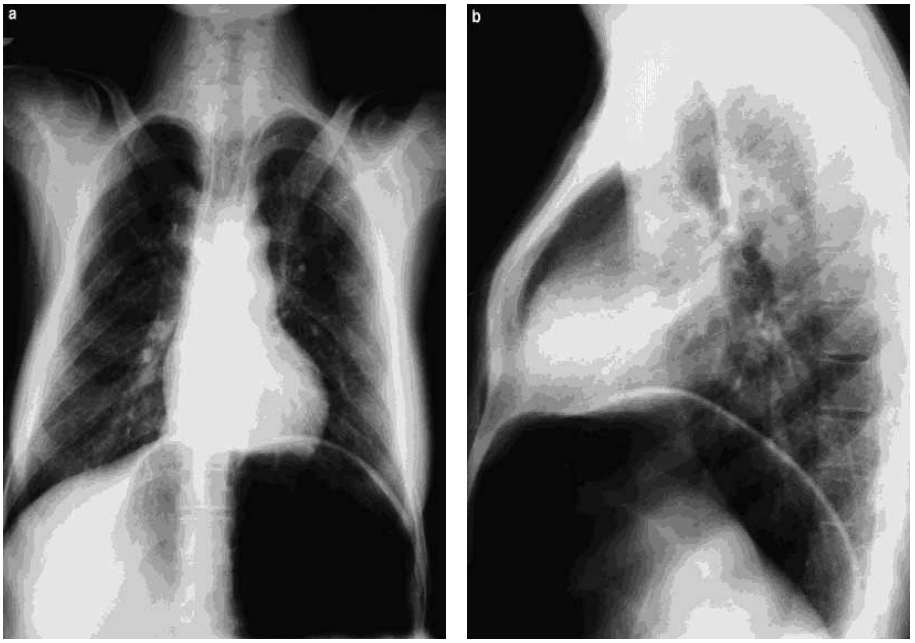
The patient was the first–born child of healthy, non–consanguineous parents. Her two brothers and a sister were healthy. The pregnancy was uneventful, and there was no known exposure to teratogens. Weight at birth was 2,750 g (10th centile); length and head circumference were not recorded. The neonatal period was complicated by prolonged feeding problems. Her motor development has always been severely delayed, without any period of regression: sitting was at 4 years of age, standing at 6, and walking at 7. There has never been any language development. She did not suffer from seizures. Age at menarche is unknown, and her menstruation pattern has been regular. At 26 years, she was operated on because of club feet. Examination at the age of 40 years showed a severely intellectually disabled woman with no expressive speech (Figure 4.1). Usually, her respiratory pattern was normal, but there was daily episodic hyperbreathing, which caused massive swallowing of air, necessitating changing to clothes of a larger size during the daytime because of abdominal distension (Figure 4.2). Height (148 cm) and head circumference (50 cm) were below the 3rd centile. She had coarse hair, heavy

Figure 4.1 Proposita at age 40 years



Note the heavy eyebrows, flared nares, wide mouth, and thick lips.

Figure 4.2 Frontal (a) and lateral (b) truncal radiographs of the proband showing massive distension of the colon

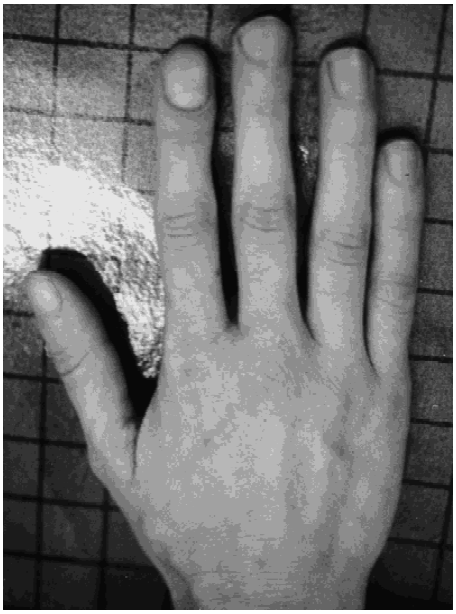


eyebrows, a broad nasal bridge, large nose, flared nares, wide mouth with thick, fleshy lips, a broad palate, and an abnormal ear with a dysplastic helix on the right side. Her shoulders were narrow, she had a mild thoracolumbar scoliosis, and thin limbs with poor muscular development and small hands (16.0 cm, below the 3rd centile). All fingers showed clubbing, which was most pronounced on the 2nd fingers (Figure 4.3). Secondary sexual characteristics were normal. The great toes were clubbed, somewhat short and proximally implanted; the other toes were normal. Acral circulation was good. Additional investigations included chest X–rays, ECG, full internal screen, and extensive urinary metabolic investigations, all with normal results. The karyotype was normal (46,XX) and molecular analysis was negative for a methylation defect on chromosome 15 (Angelman syndrome). A recent CT scan of the brain showed no cerebral malformation or atrophy, and the cerebellum was normal.

DISCUSSION

The similarity of clinical findings in the present patient and in the two cases described by Pitt and Hopkins (1978) and in the patient described by Singh (1993) suggests the existence of a specific syndrome characterized by a "coarse" face, with wide mouth, everted

Figure 4.3 Right hand, showing relatively long slender fingers



Clubbing is especially clear on the second finger.

thick lips, and large nose, severe psychomotor retardation and voluntary, episodic overbreathing (Table 4.1). The clubbing of the fingers may well be related to the unusual breathing pattern. Additional reports are needed to define all the characteristics typical of this syndrome. Several entities bear resemblance to the presently described patient. Joubert syndrome (Joubert et al., 1969; Saraiva & Baraitser, 1992) is characterized by episodic hyperpnoea, agenesis of the cerebellar vermis, abnormal eye movements, and ataxia. The abnormal respiration usually becomes apparent soon after birth, the periods of abnormal breathing intensify with stimulation, and respiratory abnormalities tend to improve with age. The absence of ataxia and the normal configuration of the cerebellum on the CT scan in our patient allows differentiation with the Joubert syndrome.

Rett syndrome (Hagberg, 1989) and atypical Rett syndrome (Hagberg & Skjeldal, 1994; Akesson et al., 1995) show some similarity, also, especially in the voluntary overbreathing. However, the present proposita showed no sequential stages of Rett syndrome, no dyspraxia, and no stereotypic hand movements. Leifer et al. (1991) reported an adult woman with mental retardation, microcephaly, minor facial anomalies, seizures, loss of ability to walk, stereotypic hand movements, and limb anomalies. A CT scan showed central atrophy with dilatation of the lateral ventricles and cerebellar atrophy. Although the minor anomalies and mental retardation resembled the findings in our patient, an abnormal breathing pattern was conspicuously absent in the patient described by Leifer et al. (1991) and further differentiation by neuroradiologic studies was possible. The cause for the combination of findings in our patient remains unknown: all cases have been isolated, there has been no report of consanguinity, the parental ages were normal, and chromosomal studies have been noncontributory.

Acknowledgments

We thank Dr. D.B. Pitt for additional information regarding his patients, and the family for their cooperation.

Table 4.1 Comparison of present patient with published cases, and with Rett syndrome, and Joubert syndrome*

	Pitt & Hopkins (1978)		Singh (1993)	Present case	Rett syndrome	Joubert syndrome
Sex	M	F	M	F	F	2M:1F
Height ø P3	–	+	+	+	–	–
OFC ø P3	–	+	–	+	+	–
Mental retardation	+	+	+	+	+	+
Poor motor development	+		+	+	+	+
No language development				+	+	–
Voluntary overbreathing	+	+	+	+	+	+
Hand stereotypies	–	–	–	–	+	–
CNS						
Atrophy/agenesis vermis			+	–	+	+
Cerebellar hypoplasia			+	–	+	+
Seizures			+	–	+	–
Hypotonia	–	–	–	–	–	+
Abnormal eye movements	–	–	–	–	–	+
Cranial						
Coarse hair				+	–	–
Heavy eyebrows			+	+	–	–
Chorioretinal coloboma	–	–	–	–	–	+
Wide nasal bridge	+	+	+	+	–	–
Prominent nose	+	+	+	+	–	–
Flared nares	+	+	+	+	–	–
Macrostomia	+	+	+	+	–	–
Thick, fleshly lips	+	+	+	+	–	–
Dysmorphic ear(s)				R[b]	–	–
Clubbing of fingers	+	+	+	+	–	–
Simian crease	L[b]			B[b]	–	–
Polydactyly	–			–	–	–
Club foot	+		+	+	–	–
Short great toes		+[a]		+	–	–
Scoliosis				+	+	–

* Findings were scored positive if specifically mentioned in the text, or if they could be reliably concluded from the pictures.
[a] Personal communication (Pitt, 1990).
[b] L = left; R = right; B = bilateral.

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CHAPTER 5

Behavior and cognition in Pitt–Hopkins syndrome

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submitted

ABSTRACT

Pitt–Hopkins syndrome (PHS) is a rare genetic syndrome characterized primarily by intellectual disability, distinctive facial characteristics, breathing abnormalities, and repetitive behaviors. Classic PHS and PH–like syndromes are caused by genetic deletions/mutations, specifically *TCF4* haploinsufficiency, *NRXN1*, and *CNTNAP2* alterations. Changes in *TCF4*, *NRXN1* and *CNTNAP2* have been implicated in intellectual disability, epilepsy, autism, and schizophrenia. Though this syndrome clearly has important developmental, cognitive, and behavioral consequences, there has been little systematic study of the psychiatric dimension of the disorder.

We assessed behavioral, adaptive, and psychological functioning and autism symptoms in 10 individuals with molecularly confirmed classic PHS via direct psychiatric and neuropsychological assessments, parental interviews, and questionnaires. Relevant literature was reviewed with specific attention to descriptions of cognition and behavior in both classic and recessive forms of PHS. We compared our findings to those found in literature.

Participants all showed (very) profound intellectual disability, amiable demeanor with minimal maladaptive behaviors, severe impairments in communication and language with failure to engage socially, and intense, frequent motor stereotypies. Autism spectrum disorder can also be a component of the phenotype of classic PHS, albeit presenting in varying degrees of severity.

Systematic collection of developmental and behavioral data in rare disorders, such as PHS, improves clinical recognition of physical, developmental, behavioral and psychiatric features. This is important for the diagnosis and prognosis of the disorder, and for adequate counseling of families. It also increases our understanding of shared etiologies, comorbid conditions, and the influence of social and learning environments on gene expression and eventual outcome.

KEYWORDS: Pitt–Hopkins syndrome, *TCF4* mutations, autism, intellectual disability, motor stereotypies

INTRODUCTION

Pitt and Hopkins first described the syndrome that bears their name in 2 unrelated patients with intellectual disability, an abnormal breathing pattern, and distinctive facial features, including a wide mouth, heavy eyebrows, and postnatal microcephaly (Pitt & Hopkins, 1978). In later publications, the phenotype of Pitt Hopkins syndrome (PHS) was further defined to include severe developmental delays in motor and speech/language

development, episodic diurnal hyperventilation with apnea, and frequent epilepsy (Singh, 1993; van Balkom et al., 1998; Orrico et al., 2001; Peippo et al., 2006). The dominant form of PHS is caused by deletions/mutations in *Transcription Factor 4 (TCF4)* on chromosome 18 in 18q21 (Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007, 2008; Andrieux et al., 2008; Giurgea et al., 2008; de Pontual et al., 2009; Takano et al., 2010). Recessive forms of a PHS–like disorder have been identified and are caused by mutations in *NeuReXiN 1 (NRXN1)* on chromosome 2 and the *CoNTactiN Associated Protein–like 2 (CNTNAP2)* on chromosome 7 (Stefansson et al., 2009; Zweier et al., 2009; Blake et al., 2010).

PHS is best known for breathing abnormalities. However, they may not be a cardinal manifestation of the syndrome, as already suggested in earlier publications (Singh, 1993; van Balkom et al., 1998; Orrico et al., 2001; Peippo et al., 2006). Not all molecularly confirmed cases show intermittent overbreathing. PHS studies have cited severe developmental delay and intellectual disability, motor abnormalities (late or absent walking, repetitive movements of hands and head), and behavioral traits such as autistic symptoms, a quiet, pleasant disposition in most cases, and in other cases sudden aggression towards others in association with sudden changes in daily routine. Some of these behaviors are consistent with the definition of an autism spectrum disorder (Giurgea et al., 2008; de Pontual et al., 2009; Zweier et al., 2009; Takano et al., 2010). To date there have been no studies focusing specifically on cognition, behavior and autism in PHS.

Though PHS and PH–like syndromes clearly have important developmental, cognitive, and behavioral consequences, there has been little systematic study of the psychiatric dimension of the disorder. Here we review behavioral and cognitive data from the literature on PHS, and the association of the genes involved in PHS and PH–like syndrome with psychiatric disorders. Subsequently we report an exploratory investigation of behavior and cognition in 10 individuals with molecularly confirmed PHS, with specific attention to possible autism spectrum disorder characteristics.

METHODS

Literature review

Relevant literature was searched for in all Ovid resources, the EMB database, and PubMed (basic and advanced searches) using as search terms: 'Pitt–Hopkins syndrome,' '*TCF4* haploinsufficiency', and 'deletion 18q21'. Papers had to have been published in peer–reviewed journals in English, German, French, or Dutch. No other exclusion criteria were used. All retrieved publications were hand–searched for further relevant papers. This search yielded a total of 30 articles (Pitt & Hopkins, 1978; Wilson et al., 1979;

Petty et al., 1987; Seshadri et al., 1992; Singh, 1993; van Balkom et al., 1998; Gustavsson et al., 1999; Orrico et al., 2001; Engelen et al., 2003; Peippo et al., 2006; Amiel et al., 2007; Brockschmidt et al., 2007; Flora et al., 2007; Zweier et al., 2007, 2008, 2009; Andrieux et al., 2008; Cisse et al., 2008; Giurgea et al., 2008; Kalscheuer et al., 2008; Kim SK et al., 2008; Ouvrier, 2008; de Pontual et al., 2009; Rosenfeld et al., 2009; Stefansson et al., 2009; Blake et al., 2010; Brzozka et al., 2010; Kato et al., 2010; Taddeucci et al., 2010; Takano et al., 2010). Only those publications that included clinical descriptions, development, and behavior of individuals or groups of individuals were selected for inclusion in Tables 5.1 and 5.2.

A similar literature search was conducted with regard to psychiatric aspects, using as search terms 'psychiatric syndromes/disorders and/or chromosome 18 and/or *TCF4*, and/or deletion 18q, and/or chromosome 2 and/or *NRXN1*, and/or chromosome 7 and/or *CNTNAP2*, and/or *TCF4* mutations and/or deletions, and/or *TCF4* haploinsufficiency'. We applied the same language criteria and no exclusion criteria. All retrieved manuscripts were again hand–searched for other relevant publications. The search in these databases and cross–references yielded a total of 49 articles (Asschauer et al., 1993; Stine et al., 1995; DeLisi et al., 1995; Fang et al., 1995; de Bruyn et al., 1996; Breschel et al., 1997; Mors et al., 1997; van Broeckhoven & Verheyen 1998; Grierson et al., 1999; Hallmayer 1999; Hampson et al., 1999; van Broeckhoven & Verheyen, 1999; Verheyen et al., 1999; Del–Favero et al., 2002; Kamnasaran, 2003; McInnis et al., 2000; Pickard et al., 2005; Walss–Bass et al., 2005; Feng et al., 2006; Hayden & Nurnberger, 2006; Strauss et al., 2006; Abrahams et al., 2007; Alarcón et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Blackwood et al., 2008; Friedman et al., 2008; Kim HG et al., 2008; Kim SK et al., 2008; Kirov et al., 2008, 2009; Vernes et al., 2008; Walsh et al., 2008; Jackman et al., 2009; Carroll & Owen, 2009; Rujescu et al., 2009; Williams et al., 2009; Zavala et al., 2009; Ching et al., 2010; Mefford et al., 2010; Newbury & Monaco, 2010; Scott–van Zeeland et al., 2010; Tan et al., 2010; Wang et al., 2010; Gauthier et al., 2011; Lennertz et al., 2011; Mühleisen et al., 2011; Nord et al., 2011; Williams et al., 2011).

Participants

Parents of 10 PHS individuals were recruited through the Dutch PHS Family Association. The Family Association knows of 21 PHS individuals; participation in the study was determined on the basis of the distance between the family residence and the research center, and the availability of the family within the time frame of the study. The study group consisted of 4 girls and 6 boys, 7 were born between 1998 – 2008, and 3 between 1987–1991. All had a molecularly confirmed *TCF4* mutation. Participating families resided in the Netherlands and in Belgium. All parents gave written informed consent, and the central

Medical Ethical Review Committee (Mental Health) gave permission to perform the study.

Test instruments

All participants were examined by the same child psychiatrist (IvB) and neuropsychologists (PJV, MF). The child psychiatrist is experienced in assessing individuals with autism and other developmental disabilities (van Balkom et al., 1998, 2002, 2004, 2009). In–person interviews with parents were used to assess past and current development, and functioning for the domains communication, (adaptive) behavior, and social–emotional development. Parents were invited to provide further information through a standardized questionnaire assessing emotional and behavioral problems. Only validated instruments to study individuals with intellectual disabilities were used to assess cognitive and behavioral functioning.

Bayley Scales of Infant Development

Mental and motor functioning was assessed using the Dutch version of the Bayley Scales of Infant Development (BSID–II) (van der Meulen et al., 2002) with Dutch norms for developmental ages between 0–48 months. The BSID–II is considered a reliable and valid instrument (Provost et al., 2000, 2004). The raw scores on the motor and mental scale were converted into age equivalents to determine level of motor and mental functioning.

Snijders–Oomen Nonverbal Intelligence Test

For participants older than 18 years, whose developmental level was likely to be greater than the 48 month cut–off of the Bayley Scales, the Snijders–Oomen Nonverbal Intelligence Test – Revised (SON–R 2½–7) was selected (Tellegen et al., 1996) to assess overall cognitive functioning, abstract and concrete reasoning, spatial ability, and visual perception. Test reliability and validity are considered good (Evers et al., 2000).

Autism Diagnostic Interview – Revised

In addition to an in–person psychiatric examination of all participants by an experienced child psychiatrist, one or both parents of 8 children were interviewed using the Autism Diagnostic Interview–Revised (ADI–R) (Lord et al., 1994; de Jonge et al., 2007); the parents of 2 participants could not be interviewed for practical reasons. The ADI–R is con-

sidered a reliable and valid instrument (Rutter et al., 2003; Le Couteur et al., 2008; Cicchetti et al., 2008). The ADI–R is a semi–structured diagnostic interview designed to collect developmental information, a history focused on autism–specific criteria, and information on actual behavior as manifested in the child's daily life. The instrument carries the risk of over classification of autism when used in the assessment of individuals whose mental age–equivalent is less than 24 months. The severity of intellectual disability associated with PHS demands that ADI–R results should be interpreted with great caution, but we considered the ADI–R a useful tool to establish a developmental history, collect data on current behaviors, and supplement the direct assessments of the participants. Indeed the ADI–R has previously been used with individuals functioning below a mental age of 24 months, as there is a dearth of adequate instruments available for individuals with severe intellectual disability and possible comorbid autism spectrum disorder (Howlin, 2000; Battaglia et al., 2010; Bruining et al., 2010; van Balkom et al., 2011).

Vineland Adaptive Behaviour Scales

The Vineland Adaptive Behaviour Scales – Survey Form (VABS) was used to assess personal and social self–sufficiency (Sparrow et al., 1984). The VABS measures the level of adaptive functioning with regard to communication, daily living skills, and socialization. These measures provide an overall adaptive composite score, allowing for a classification in adaptive levels. The VABS has good psychometric properties (Sparrow et al., 1984). Decile scores were also determined. These scores are likelihood assertions concerning the level of cognitive functioning based on a Dutch sample (n=826) of children between the ages 5 and 18 years with an IQ <70 (de Bildt & Kraijer, 2003).

Developmental Behaviour Checklist

The Developmental Behaviour Checklist–Primary Carer (DBC–P) for the children and the Developmental Behaviour Checklist for Adults (DBC–A) for those above 18 years were used to assess behavioral and emotional problems. The DBC–P is a 96–item checklist specifically developed to assess a broad range of behavioral and emotional problems in individuals with intellectual disability (ID) (Einfeld & Tonge, 2002). Parents rate items on a 3 point scale. The DBC–P is considered reliable and has been validated in a large sample of Dutch children with ID (Dekker et al., 2002; Einfeld & Tonge, 2002). The DBC–A is a 107 item instrument with similar properties but suited for adults. The questionnaire is completed by someone who knows the person well. The DBC–A has acceptable reliability, good validity and satisfactory psychometric properties (Mohr et al., 2005).

RESULTS

Literature review

The major findings in the literature for cognition and behavior in patients with molecularly confirmed PHS are summarized in Table 5.1 (deletions of *TCF4*) and Table 5.2 (mutations in *TCF4*). Among the physical manifestations only hearing and vision impairments are shown as these are considered risk factors for the development of repetitive behaviors (McClintock et al., 2003).

Classic autosomal dominant PHS is caused by a deletion on the long arm of chromosome 18 (del 18q21), resulting in haploinsufficiency of *TCF4* (Gustavsson et al., 1999; Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007; Andrieux et al., 2008; Kato et al., 2010). Normally, *TCF4* is highly expressed in the central nervous system, and deregulation of *TCF4* results in interference with brain development, cognitive functioning, and memory (de Pontual et al., 2009; Stefansson et al., 2009). Brzozka and co–workers hypothesized that while haploinsufficiency for *TCF4* causes PHS, more subtle changes at transcript level such as a trinucleotide repeat in intron 3 and a single nucleotide polymorphism (SNP) in intron 4 might be associated with increased risk for neuropsychiatric disorders in adolescence and in adulthood (Brzozka et al., 2010). Meta–analysis of several genomic–wide association studies showed SNPs in intron 3 and 4 of *TCF4* to be associated with schizophrenia (Stefansson et al., 2009; Blake et al., 2010; Lennertz et al., 2011; Williams et al., 2011). Both schizophrenia and bipolar disorder have been studied in relation to chromosome 18 alterations (Stine et al., 1995; Breschel et al., 1997; Mors et al., 1997; Blake et al., 2010; Lennertz et al., 2011; Williams et al., 2011).

A recessive form of PHS or a PH–like syndrome is caused by changes in *NRXN1*. The *NRXN1* locus is situated at 2p16.3, and codes for neurexins and associated cell–surface proteins that help neurons to adhere to one another, creating synaptic connections necessary for communication between neurons. *NRXN1* is highly expressed in the brain and plays an important role in synaptic function and specialization. Neurexins and associated cell–surface proteins mediate essential signaling between pre– and postsynaptic specializations and neurotransmitter release from pre–synaptic vesicles (Feng et al., 2006; Bucan et al., 2009; Glessner and Hakonarson, 2009; Kirov et al., 2009). Additionally, research findings have suggested that disruption of these mechanisms through Copy Number Variants (CNVs), deletions or haploinsufficiency might constitute fundamental commonalities in genetic susceptibility for schizophrenia and autism (Kirov et al., 2008; Walsh et al., 2008; Rujescu et al., 2009). Deletions and CNVs involving one or more exons in *NRXN1* have been implicated in autism spectrum disorders and intellectual disability, although

the clinical significance and range of phenotypic expression remains unclear (Feng et al., 2006; Friedman et al., 2008; Kim HG et al., 2008; Ching et al., 2010). The interpretation of the significance of disruptions is complicated by incomplete penetrance. It has been suggested that changes disrupting *NRXN1* may act as a predisposing factor for autism spectrum disorders and that additional influences (such as genetic, epigenetic, and environmental factors) are necessary to result in the complete phenotype (Guilmatre et al., 2009). Various studies have provided compelling evidence that deletions of *NRXN1* confer an increased risk of schizophrenia and autism spectrum disorders (Friedman et al., 2008; Kim HG et al., 2008; Kim SK et al., 2008; Walsh et al., 2008; Kirov et al., 2008, 2009; Rujescu et al., 2009; Gauthier et al., 2011). Other studies have added evidence suggesting that rare CNVs at numerous loci are involved in the etiology of intellectual disability, autism spectrum disorder, and schizophrenia. These three conditions share many phenotype similarities in their atypical responsiveness to environment and impaired filtering of stimuli that may disrupt information processing with regard to emotional, social, language, communication, and executive functioning abilities (Kirov et al., 2008; Cheung et al., 2010; Gauthier et al., 2011). Indeed, the phenotype of individuals with *NRXN1* deletions or mutations is variable and includes intellectual disability, autism spectrum disorders, and schizophrenia. *NRXN1* variants may also contribute to anxiety and mood disorders, and to alcohol and nicotine dependence (Hallmayer, 1999; Kim SK et al., 2008; Bucan et al., 2009; Ching et al., 2010; Wi niowiecka–Kowalnik et al., 2010; Gauthier et al., 2011).

Another autosomal recessive form of PHS or PH–like syndrome is caused by alterations involving *CNTNAP2* on chromosome 7q35–36.1 (Stefansson et al., 2009; Zweier et al., 2009; Blake et al., 2010). *CNTNAP2* encodes a synaptic protein that plays an important role in neuronal development and connectivity. It is highly expressed in the frontal lobe circuits of the brain, where it is thought to influence the development of brain structures involved in speech, language and thought (Vernes et al., 2008; Wang et al., 2010). The gene may be involved in autism spectrum disorders (Alarcón et al., 2008; Bakkaloglu et al., 2008; Tan et al., 2010). Children with autism tended to have a higher rate of thymine in a single segment of the genetic code instead of adenine, which was found more likely to have been inherited from mothers than from fathers (Arking et al., 2008). *CNTNAP2* may also be linked to developmental language disorders, intellectual disability, epilepsy, and schizophrenia (Strauss et al., 2006; Friedman et al., 2008; Vernes et al., 2008; Mefford et al., 2010). In their study of early language development in the general population, Whitehouse and collaborators found that common variants in the exon 13–15 region of *CNTNAP2* influenced early language acquisition (assessed at age 2) and proposed that these variants conferred increased risk of language disorders and autism when occurring together with other risk factors (Whitehouse et al., 2011). Genetic variation at *CNTNAP2*

Table 5.1 Summarized features *TCF4* gene deletions

	Sheshadri et al., 1992	*Gustavsson et al., 1999*	*Engelen et al., 2003*	*Amiel et al., 2007 (P1)*	*Brockschmidt et al., 2007*	*Zweier et al., 2007 (P2)*	*Andrieux et al., 2008*
Age at diagnosis (years)	2.8	6.5	1.3	4.5	7	11	12
Gender	M	F	M	F	F	M	M
Deleted chromosome region	18q21.2	18q21.1q22.3	18q21.2q21.3	18q21.1	18q21.2	18q21.2	18q21.2q21.32
Intellectual disability	moderate	+	moderate	+	+	+	+
Language	absent, words at 12 months but stopped	absent	delay	absent/limited	absent	absent	absent
Motor development			asymmetric		delay		
Hypotonia	?	+	?	?	+	?	+
Age sitting unsupported		2 yr	?	13–18 months	?	?	?
Age onset independent walking	20 months	assisted (6 yr)	19 months	absent at 4.5yr	?	? (assisted at 11yr)	6 yr
Pleasant temperament	?	?	+	+	+	+	?
Neuroradiology	?				none		
Callosal body absent/small		(+/–)	no	–/+		–/+	–/+
Wide ventricles		no	+ slightly				
Other						small hypocampi bulging ncl caudati	small vermis
Epilepsy/seizures (age onset)	none	+ (2 yr)	?	?	none	+ (8 yr)	none
Behavior							
Aggression	?	?	?	?	?	?	+
Agitation/anxiety	withdrawn	?	?	?	?	?	?
Stereotypies hands, fingers	+	+	?	+	?	?	?
Stereotypies head, trunk	+ rocking	?	?	–	?	?	?
Bouts of screaming/shouting	?	+	?	?	?	?	?
Rattling/banging/spinning objects	?	?	?	?	?	+	?
Breathing abnormalities (age onset)	?	+	?	–	+ (7 yr)	+ (6yr) daytime	–
Sleep disturbances	?	?	?	–	?	?	–
Hearing abnormalities	none	–	?	?	?	?	none
Eyes/vision	?		?			?	
Eye movements							
Strabismus		+		+			
Myopia		+ visual loss			+		+

Table 5.1 (Continued)

	Giurgea et al., 2008 (P1)	*Giurgea et al., 2008 (P2)*	*Giurgea et al., 2008 (P3)*	*Giurgea et al., 2008 (P4)*	*Rosenfeld et al., 2009 (P1)*	*Rosenfeld et al., 2009 (P2)*	*Rosenfeld et al., 2009 (P3)*	*Kato et al., 2010*
Age at diagnosis (years)	18	4	3.5	1.5	6.08	2	1.25	18
Gender	M	F	F	M	F	M	F	F
Deleted chromosome region	18q21.2–q22.1	18q21.1–q22.1	18q21.1–q22.1	18q21.1–q22.1	18q21.2	18q21.2	18q21.2	18q21.1–q21.33
Intellectual disability	+	+	+	+	+	+	–	+
Language	absent	absent	absent	absent	1 word	2 words	absent	?
Motor development								
Hypotonia	?	?	?	?	+	+	+	+
Age sitting unsupported	?	?	?	?	?	?	no	> 2 yr
Age onset independent walking	8 yr	absent at 4yr	absent at 3.5 yr	absent at 1.5 yr	absent at 6 yr	absent at 2 yr	absent at 1 yr	?
Pleasant temperament	+	+	+	+	+	+	–	?
Neuroradiology	?	?	?	?	?	none	?	
Callosal body absent/small								–/–
Wide ventricles					+			
Other								
Epilepsy/seizures (age onset)	+	none	none	none	none	none (staring spells)	none	?
Behavior								
Aggression	–	–	+ (self injury)	–	?	?	?	?
Agitation/anxiety	–	–	–	–	?	?	?	?
Stereotypies hands, fingers	+	+	+	+	+	+	–	?
Stereotypies head, trunk	+	+	+	+	?	?	–	?
Bouts of screaming/shouting	?	?	?	?	?	?	?	?
Rattling/banging/spinning objects	?	?	?	?	?	?	?	?
Breathing abnormalities (age onset)	+	–	+	+	–	–	–	?
Sleep disturbances	–	–	?	+	?	?	?	?
Hearing abnormalities	?	?	?	?	?	?	?	?
Eyes/vision								
Eye movements		nystagmus	nystagmus	nystagmus				
Strabismus	+	+	+	+	–	+	–	+
Myopia	+	+	+	+	+	–	–	

Table 5.2 Summarized features *TCF4* mutations

	Amiel et al., 2007 (P2)	*Amiel et al., 2007 (P3)*	*Amiel et al., 2007 (P4)*	*Zweier et al., 2007 (P1)*	*Zweier et al., 2007 (P3)*	*Zweier et al., 2007 (P4)*
Age at diagnosis (years)	6.5	10	4.5	14	8	12
Gender	F	M	M	M	M	F
Mutated chromosome region	mutation missense	mutation missense	mutation missense	mutation missense	mutation missense	mutation missense
Intellectual disability	+	+	+	+	+	+
Language	absent/limited	absent/limited	absent/limited	absent	single words	absent
Motor development						
Hypotonia	?	?	?	+	+ severe	+ severe
Age sitting unsupported	13–18 months	13–18 months	13–18 months	no	?	?
Age onset independent walking	–	–	–	assisted	assisted	+ ataxic (5 yr)
Pleasant temperament	+	+	+	+	+	+
Neuroradiology						
Callosal body absent/small	(–/+)	(–/+)	(–/–)	(–/+)		
Wide ventricles					+	
Other				bulging ncl caudati		bulging ncl caudati
Epilepsy/seizures (age onset)	?	?	?	+ (9 yr)	none	none
Behavior						
Aggression	?	?	?	?	?	?
Agitation/anxiety	?	?	?	?	?	?
Stereotypies hands, fingers	+	+	+	?	?	?
Stereotypies head, trunk	+	+	–	?	?	?
Bouts of screaming/shouting	?	?	?	+ shouting	?	?
Rattling/banging/spinning objects	?	?	?	+	?	?
Breathing abnormalities (age onset)	+	+	+	+ (5 yr) daytime	–	+ (8 yr) daytime
Sleep disturbances	+	–	–	–	?	?
Hearing abnormalities	?	?	?	–	?	?
Eyes/vision						?
Eye movements						
Strabismus	+	+	+	?	+	
Myopia				+		

Table 5.2 (Continued)

	Zweier et al., 2007 (P5)	*Zweier et al., 2007 (P6)*	*Giurgea et al., 2008 (P5)*	*Giurgea et al., 2008 (P6)*	*Giurgea et al., 2008 (P7)*	*Giurgea et al., 2008 (P8)*	*Giurgea et al., 2008 (P9)*	*Giurgea et al., 2008 (P10)*
Age at diagnosis (years)	29	29	18	6	16	8	8	18
Gender	M	F	F	M	F	F	F	M
Mutated chromosome region	mutation missense	mutation missense	mutation	mutation	mutation	mutation	mutation	mutation
Intellectual disability	+	+	+	+	+	+	+	+
Language	absent	absent	absent	absent	absent	absent	absent	absent
Motor development								
Hypotonia	+	+	?	?	?	?	?	?
Age sitting unsupported	?	?	?	?	?	?	?	?
Age onset independent walking	+ ataxic (14 yr)	+ wide base (7 yr)	+ (10 yr)	+ (5 yr)	–	+ (5 yr)	+ (5 yr)	+ (9 yr)
Pleasant temperament	+ unmotiv.laughter	+	+	+	+	+	+	+
Neuroradiology	none	none	?	?	?	?	?	?
Callosal body absent/small								
Wide ventricles								
Other								
Epilepsy/seizures (age onset)	none	none	none	none	?	none	+	+
Behavior								
Aggression	+ (self injury)	?	+ (self injury)	–	–	+ (self injury)	–	+ (self injury)
Agitation/anxiety	+	?	+	–	–	+	–	+
Stereotypies hands, fingers	?	?	+	+	+	+	+	+
Stereotypies head, trunk	?	?	+	+	+	+	+	+
Bouts of screaming/shouting	?	?	?	?	?	?	?	?
Rattling/banging/spinning objects	?	?	?	?	?	?	?	?
Breathing abnormalities (age onset)	+ (2 yr)	+ (5 yr)	+	–	+	+	+	+
Sleep disturbances	?	?	–	–	–	+	–	+
Hearing abnormalities	?	?	?	?	?	?	?	?
Eyes/vision		?						
Eye movements								
Strabismus	+		+	+	+	+	+	+
Myopia			+	+	+	+	+	?

Table 5.2 (Continued)

	Zweier et al., 2008 (P1)	*Zweier et al., 2008 (P2)*	*Zweier et al., 2008 (P3)*	*Zweier et al., 2008 (P4)*	*Zweier et al., 2008 (P5)*	*Zweier et al., 2008 (P6)*	*Zweier et al., 2008 (P7)*	*Zweier et al., 2008 (P8)*
Age at diagnosis (years)	18	17	2	7	20	17	20	4
Gender	F	M	M	M	F	F	F	M
Mutated chromosome region	mutation	mutation	mutation	mutation	mutation	mutation	mutation	mutation
Intellectual disability	+	+	+	+	+	+	+	+
Language	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited
Motor development								
Hypotonia	+	+	+	+	+	+	+	+
Age sitting unsupported	?	?	?	?	?	?	?	?
Age onset independent walking	–	assisted	?	+ ataxic	?	?	?	+ (8 yr)
Pleasant temperament	+	+	+	+	–	+	+	+
Neuroradiology	none	none			none	?		none
Callosal body absent/small			(–/+)					
Wide ventricles				+ mild				
Other							underdeveloped frontal& parietal areas	
Epilepsy/seizures (age onset)	none	none	none	+ neonatal	none	none	+ (9 months)	+ (3 yr)
Behavior	?	?	?	stereotypies		?	?	stereotypies
Aggression	?	?	?	?	+ outbursts	?	?	?
Agitation/anxiety				?	?			
Stereotypies hands, fingers				?	?			
Stereotypies head, trunk				?	?			
Bouts of screaming/shouting				?	?			
Rattling/banging/spinning objects				?	?			
Breathing abnormalities (age onset)	–	–	–	+ (4.5 yr)	+	+ (10 yr)	+ neonatal	+ (3 yr)
Sleep disturbances	?	?	?	?	?	?	?	?
Hearing abnormalities	?	?	?	?	?	?	?	?
Eyes/vision	?	?	?	?	?	?		?
Eye movements								
Strabismus							+	
Myopia							+	

Table 5.2 (Continued)

	Zweier et al., 2008 (P9)	*Zweier et al., 2008 (P10)*	*Zweier et al., 2008 (P11)*	*Zweier et al., 2008 (P12)*	*Zweier et al., 2008 (P13)*	*Zweier et al., 2008 (P14)*	*Zweier et al., 2008 (P15)*	*Zweier et al., 2008 (P16)*
Age at diagnosis (years)	16	10	17	2.9	1.2	1.5	1.9	2.9
Gender	M	M	M	M	M	F	F	F
Mutated chromosome region	mutation	mutation	mutation	mutation	mutation	mutation	mutation	mutation
Intellectual disability	+	+	+	+	+	+	+	+
Language	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited	absent/limited
Motor development								
Hypotonia	–	–	–	+	+	+	+	+
Age sitting unsupported	?	?	?	?	?	?	?	?
Age onset independent walking	?	?	?	?	?	+ ataxic	?	?
Pleasant temperament	+	+	+	+	+	+	+	+
Neuroradiology		none	?		none	none	+	+
Callosal body absent/small	(+/–)			(–/+)				
Wide ventricles								
Other				bulging ncl caudati				
Epilepsy/seizures (age onset)	+ (5 yr)	+ (4 yr)	–	none	none	none	none	+ (4 months)
Behavior	?	?	?	?	stereotypies	stereotypies	?	?
Aggression	?	?	?	?	?	?	?	?
Agitation/anxiety								
Stereotypies hands, fingers								
Stereotypies head, trunk								
Bouts of screaming/shouting								
Rattling/banging/spinning objects								
Breathing abnormalities (age onset)	+ plays breath	+	+ (17 yr)	–	–	–	–	?
Sleep disturbances	?	?	?	?	?	?	+	?
Hearing abnormalities	?	?	?	?	?	?	?	?
Eyes/vision	?	?	?		?			?
Eye movements								
Strabismus						+		
Myopia				+		+	+	

Table 5.2 (Continued)

	Rosenfeld et al., 2009 (P4)	*Rosenfeld et al., 2009 (P5)*	*Rosenfeld et al., 2009 (P6)*	*Rosenfeld et al., 2009 (P7)*
Age at diagnosis (years)	1.75	11.25	0.9	19.4
Gender	M	F	F	F
Mutated chromosome region	18q21.2 intragenic deletion or truncating mutation	18q21.2 intragenic deletion or truncating mutation	18q21.2 intragenic deletion or truncating mutation	18q21.2 intragenic deletion or truncating mutation
Intellectual disability	+	+	+	+
Language	absent	absent	babbles	absent
Motor development				
Hypotonia	+	+	+	+
Age sitting unsupported	sits	?	bears weight	?
Age onset independent walking	?	assisted	?	assisted
Pleasant temperament	+	–	–	+
Neuroradiology	none	+	+	none
Callosal body absent/small				
Wide ventricles				
Other		underdeveloped frontal& parietal areas	delayed myelination	
Epilepsy/seizures (age onset)	none (staring spells)	none	none	none
Behavior				
Aggression	?	?	?	?
Agitation/anxiety	?	?	?	?
Stereotypies hands, fingers	+	+	–	?
Stereotypies head, trunk	+	+	–	?
Bouts of screaming/shouting	?	?	?	?
Rattling/banging/spinning objects	?	?	?	+
Breathing abnormalities (age onset)	–	+ heavy breathing	–	+holds breath
Sleep disturbances	?	?	?	?
Hearing abnormalities	?	?	?	?
Eyes/vision				
Eye movements				
Strabismus	+	–	+	+
Myopia	–	?	+	+

Table 5.2 (Continued)

	Taddeucci et al., 2010	*Takano et al., 2010 (P1)*	*Takano et al., 2010 (P2)*
Age at diagnosis (years)	3.5	7	17
Gender	M	M	M
Mutated chromosome region	mutation balanced translocation	mutation frameshift	mutation missense
Intellectual disability	+	+	+
Language	absent	2 words	2 words
Motor development			
Hypotonia		+ mild	+
Age sitting unsupported		+ (1 yr)	?
Age onset independent walking	+ (2yr)	+ wide based (3 yr)	+ ataxic (4 yr)
Pleasant temperament	+	+	?
Neuroradiology	none	none	?
Callosal body absent/small			
Wide ventricles			
Other			
Epilepsy/seizures (age onset)	+ (>3.2 yr)	none (staring spells)	+ (10 yr)
Behavior			
Aggression	?	+ (towards others)	–
Agitation/anxiety	?	–	–
Stereotypies hands, fingers	+	+	–
Stereotypies head, trunk	?	?	–
Bouts of screaming/shouting	?	?	?
Rattling/banging/spinning objects	?	+	?
Breathing abnormalities (age onset)	+ (3.2)	?	+ wakefulness
Sleep disturbances	?	?	?
Hearing abnormalities	?	?	?
Eyes/vision	?		
Eye movements			
Strabismus		–	+
Myopia		–	?

impacts brain connectivity, especially in the frontal lobe (Hallmayer, 1999; Strauss et al., 2006; Abrahams et al., 2007; Alarcón et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Vernes et al., 2008; Scott–van Zeeland et al., 2010; Tan et al., 2010).

In summary, while the genetic origin of PHS and related syndromes may vary, they have similar effects, e.g., intellectual disability, autism, schizophrenia.

Clinical study

Results of the present clinical study including extensive descriptions of child assessments with observations of interaction and behavior, measurements of cognitive and adaptive functioning, assessments of past and current development, and assessments of behavioral and emotional problems are included in this paper. Table 5.3 compares frequently reported features of *TCF4* deletions with findings in the present study.

Table 5.3 Comparison of literature cases with *TCF4* deletions and *TCF4* mutations to patients with Pitt–Hopkins syndrome in the present study

	Literature cases with *TCF4* deletions and mutations*	Present study
Number of cases	52	10
Number of males (M), females (F)	27M, 25F	6M, 4F
Severe intellectual disability	94%	100%
Severely limited/absent language	96%	90%
Pleasant temperament	83%	90%
Unassisted walking	35%	40%
Self–injury	10%	50%
Aggression towards others	6%	40%
Stereotypies hands / fingers	42%	100%
Stereotypies head/ trunk / body	29%	50%
Breathing abnormalities	58%	60%
Epilepsy	27%	10%
Nystagmus	6%	0%
Strabismus	48%	0%
Myopia	48%	20%

* Seshadri et al., 1992; Gustavsson et al., 1999; Engelen et al., 2003; Amiel et al., 2007; Brockschmidt et al., 2007; Zweier et al., 2007, 2008; Andrieux et al., 2008; Giurgea et al., 2008; Rosenfeld et al., 2009; Kato et al., 2010; Taddeucci et al., 2010; Takano et al., 2010

Clinical narrative descriptions

In this section we present narrative descriptions of individual child psychiatric assessments, and clinical observations of interaction and behavior.

Case 1

Case 1 was a toddler, but seemed younger due to her lack of active interaction. She had no somatic complaints, with the exception of constipation for which she has medication. Her mother mentioned that her breathing would become irregular when angry, this was noticed from a very young age. There had been one incident of overbreathing when she was visiting her grandparents. At second meeting she sat clutching a puffed rice cake in one hand and had little eye–to–eye gaze; and little reciprocity. In addition there was little integration of gaze, facial expression, vocalization and gesture. Her mother mentioned that she did have eye contact with her daughter, but that it was always of brief duration. She would cuddle up with her mother, sometimes biting her mother's neck. If unhappy she could cry uncontrollably and become extremely upset, sometimes ending up having a temper tantrum. She would smile and laugh without obvious cause, sometimes giving the impression of laughing at others. She liked staring into lamps. Both spontaneous expressive language and comprehension of verbal communication were severely limited. She had less than 5 words, but was able to vocalize sounds in differing intonations and would sometimes scream loudly when excited or happy. For up to 5 minutes, her capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was very short; she would lose interest quickly after bringing the object to her mouth, drop it from her hand and stare off in the distance. She enjoyed manipulating toys with sounds. Most motor milestones had not been reached, she was not able to walk independently, but would stand and step along while holding on to parents' hands with both her own. She would frequently flap her hands or clap them, and sometimes also rocked her upper body back and forth. There was no head banging. She could hold her bottle with both her hands and drink from it while lying on her back. Her parents were currently trying to teach her to drink while in a sitting position. Her mood was usually pleasant; she smiled and laughed often although the cause of it was not clear. Her mother mentioned that she was an easy sleeper but always needed a pacifier, and she enjoyed her food.

Case 2

Case 2 was a withdrawn, but active toddler with a pleasant demeanor. He had no current somatic complaints, but had been prescribed glasses from age 1 due to severe myopia (–15). Bowel control had not been achieved, although he would sometimes indicate that he wanted a diaper change by hitting the back of one hand with the other hand. No breathing abnormalities had been noticed by his mother. His eye–to–eye gaze was limited, and he showed little reciprocity or spontaneous initiation of contacting or engaging the other. At home he would get upset and fearful when hearing sharp and loud sounds, covering his ears when the hair dryer or the mixer were used. His mother noted that he insisted aspects of the daily routine remained the same, for example if his usual bedtime was delayed he could be difficult for the rest of the week. He liked staring into lamps and enjoyed looking at spinning objects. He did not have spontaneous expressive language, but would make some sounds while occasionally screaming or yelling. There seemed to be no comprehension of verbal communication. He had no understanding of the meaning of simple words, like 'yes' or 'no'. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was short, he was restless and overactive. When presented with a new toy he would first carefully touch the toy, instead of grabbing it immediately, and then bring it to his mouth. He would subsequently rapidly lose interest (within seconds). He did not show any attempts to imitate the other. His mother mentioned that he enjoyed listening to the same music over and over again, and he enjoyed looking at the same books. He would fiddle toys and objects repetitively, and bobbed his head when listening to music. He frequently used both hands to hit on the table or on toys that were in his vicinity. This behavior would sometimes occur when he was enthusiastic, but also sometimes for no apparent reason. He tried to put every object he would get his hands on in his mouth. Most motor milestones had not been reached. He was not able to walk independently, but demonstrated great flexibility and dexterity with his fingers when he played with his own hands, although his grasp of objects showed immature motor skills. He regularly flapped his hands and rocked his body, sometimes hitting himself, this behavior would increase when he was excited. His mood was usually happy, he would laugh and giggle without obvious cause.

Case 3

Case 3 was an alert boy of preschool age with a pleasant demeanor. While he extended his hand at first meeting when prompted by his mother to shake hands, he did not make

eye contact when doing so. He had no somatic complaints, except for recurring constipation. His mother had not noticed any breathing abnormalities. He was fitted with lower leg splints to aid leg function for walking. He smiled without obvious cause and without making eye contact with the examiner. There was some reaction to his own name, but not consistently. There was little visible response to the examiner's facial expression, orientation or smiles. His eye–to–eye gaze was limited, and there was little reciprocity or spontaneous initiation of contacting or engaging the other. He would often raise his face, glance at the ceiling and stare into lamps, according to his mother this behavior had been more prominent at a younger age. His mother mentioned that he would put up his arms to be lifted; he had little response to the examiner's attempts to draw his attention to distant objects although he had an obvious interest in a ball when it was close. When the ball was thrown out of his eyesight he would not search for it with his eyes. His mother mentioned that he understood many words, including names of familiar people, food items, and toys and he was able to follow verbal instructions e.g. when instructed to 'go get a cookie from the drawer' he would go, open the drawer and get the cookie. While his spontaneous expressive language was limited, he did use at least five different words every day and was able to vocalize sounds in differing intonations. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was short, he was easily distracted by outside noise and would quickly lose interest. He would handle the object, bring it to his mouth and then hurl it away. He would sometimes reach with open hand for a toy, but would not point to it to indicate a desire to play with it. His mother said at home he liked watching television. He would handle toys put near him, often bringing these to his mouth and then throwing them, but would not point. He regularly flapped his arms and hands, this behavior would increase when he was excited. Walking independently had not been achieved yet, he moved around the house easily by hopping up and down on his bottom. His mood was usually happy, he would laugh when physical games such as tickling and romping about were initiated by his parents and siblings. His mother mentioned that he could also become very angry sometimes without apparent reason and could lash out angrily hitting, biting or pulling hair of siblings or companions at school.

Case 4

Case 4 was an alert boy of preschool age with a pleasant, but withdrawn demeanor at first meeting, his mouth was open and he drooled a bit. Although he did make eye contact with his parents while producing sounds, his eye–to–eye gaze with others was limited. He wore glasses to correct myopia, and used medication for hyperbreathing. His

mother noticed that he would still sigh regularly. He had also used medication, since age 3, to reduce his hyperactive, impatient behavior. Bowel and bladder control had not been achieved. He showed little reciprocity or spontaneous initiation of contacting or engaging the other. He had a tendency of standing too close to others, sometimes rocking his body back–and–forth while standing. At home he would get upset at hearing unexpected, loud noises. His mother noted that he would sometimes eat non–food items, such as dirt or grass. He did not have expressive language, but would spontaneously hum, yell or scream. His mother had noticed a decrease in his screaming and yelling with use of medication. There seemed to be little to no comprehension of verbal communication. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was short, he was restless and impatient. He would get up and move around, bring objects to his mouth without looking at them before losing interest altogether and flinging them away. He was fascinated by door knobs, and light switches and he would also stare into lamps. He seemed interested in the feel of different surfaces. His play was mostly linked to stereotyped use of parts of toys, and he would play repetitively with toy cars by first bringing them to his mouth and then spinning their wheels. He moved to music and enjoyed listening to favorite songs over and over again. Most motor milestones had not been reached. He was not able to walk independently, but did crawl in a peculiar fashion by first moving both hands forward and then following on both knees simultaneously. He regularly bit his hand, according to his mother this behavior would increase when he was frustrated and she had noticed that he seemed to have a high threshold for pain. He clapped with his fists together and flapped his hands regularly. He would sometimes lash out, kicking or hitting the other, but his mood was usually happy.

Case 5

Case 5 was of primary school age, at second meeting she sucked a pacifier and her mother mentioned that she would grab it from the table at every opportunity to stick it into her mouth. Her tongue regularly protruded from her mouth, sometimes she closed her eyes while moving her tongue. She had no somatic complaints, although she suffered from constipation sometimes, and used no medication. Bowel and bladder control had not been achieved. Her mother mentioned that she would sometimes 'gasp' for breath when panicked or upset. She had little eye–to–eye gaze; and little reciprocity with little integration of gaze, facial expression, vocalization and gesture. Her mother mentioned that she did sometimes have eye contact with her daughter, but it was mostly of brief duration. Her mother had noticed from an early age that she did not follow with her eyes and that she lacked responsiveness to her surroundings. She had pulled her own hair and

banged her head for a short period when younger. She would smile often without obvious cause, and would sometimes smile when seeing her parents or grandmother. She tended to stare into lighted lamps for prolonged periods of time, although this behavior had diminished somewhat with advancing age. Both spontaneous expressive language and comprehension of verbal communication were severely limited. She had less than 5 words, but she had some comprehension of the word 'no' and seemed to understand names of favorite objects or words within familiar routines (e.g. the word 'toothbrush' for brushing teeth). For up to 5 minutes her capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was short; she would tilt her head to look at objects from different angles but would lose interest quickly after 1 minute and stare off into the distance. While she would grab building blocks, she did not construct anything with them or try to imitate when shown. She seemed interested in the feel of different surfaces, e.g. often licking the table. She enjoyed manipulating musical toys or books with crinkly sounds. She enjoyed individual attention, liked to go swimming and would become visibly happy when listening to music or singing. When approached by others she sometimes reacted by wildly and unexpectedly waving her arms. Most motor milestones had not been reached, she was not able to walk independently, but she had just started to stand and step along while holding on to her parents' hands. She would frequently flap her hands when excited, and sometimes also rocked her upper body back and forth. She tended to rub one hand over the other repetitively. Her mood was usually happy; although she could become grumpy and start pinching or biting the other when the social situation was unclear to her.

Case 6

Case 6 was of primary school age and had a withdrawn demeanor, drooling a little at second meeting. He had no current somatic complaints and used no medication, but he had suffered from constipation before his first birthday and hearing in one ear was found to be reduced. Bowel and bladder control had not been achieved. No breathing abnormalities were noticed by his mother. His mother thought him a very easy, contented baby, not even crying to be fed. During assessments he stared into ceiling lamps for prolonged periods of time and showed little reaction to attempts to engage his attention. He would repeatedly slap his hands against his own face, wring or flap his hands and grind his teeth. There was little eye–to–eye gaze during examination and observation; and although reciprocity was limited he did sometimes show a reaction to his own name. From a very young age he could get somebody to do something for him by smiling winningly and his mother also mentioned that he would sometimes take her hand to pull her towards

something of interest without using words, and without pointing or coordinating his action with eye gaze. Sometimes he would bite the table, but he did not lick objects. He liked to open and close doors repetitively. Although spontaneous expressive language was severely limited with no daily use of words, his mother mentioned that his comprehension of verbal communication included names of familiar persons, food items, and simple instructions such as 'wait your turn', 'another time' and 'get ready for bed'. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that he had a very short attention span, and while he would extend his hand to receive an object he would mouth it for a short time and then hurl it away within one minute. He reacted to every sound but lost interest quickly. He would repetitively play and fiddle with toys. He walked independently from approximately age 6, his gait was broad based. Fine motor skills were immature, he would grab a piece of bread with the whole hand and hold it in his fist. He almost continuously showed hand and finger movements, and often rocked his body. His mood was hard to gauge at the assessments, as there seemed to be little emotional reciprocity or visible affect, but his mother mentioned that he would laugh when physical games such as tickling, hide–and–seek, running and football were played with him.

Case 7

Case 7 was of primary school age and had a pleasant demeanor at second meeting, he sat in a wheelchair with one leg atop the other bended at the knee. He announced his arrival by continuously clapping his hands in the corridor and stamping his feet on his wheelchair footboard. He had no current somatic complaints, he used medication to prevent constipation. Hearing and vision had been found to be normal. Bowel and bladder control had not been achieved. His mother noticed that he would sigh when happy, while at other times he seemed to hold his breath for brief periods. His mother had worried about his development from a very early age, noting how he showed little initiative to move, was unable to roll over at 12 months and tended to repetitively flap hands or move legs. He had at some time been able to hold a cookie in one hand and bring it to his mouth, but seemed to lose this ability around 11 months. Mother mentioned that he would repeatedly bang his hands against his own chin when frustrated. During assessments there was little eye–to–eye gaze, he would glance off in the distance and reciprocity was limited. His mother noted that he was able to look her directly in the face, but this direct gaze was usually of short duration and seemed to have little communicative purpose. He would smile when his grandmother visited and seemed to recognize her face. Spontaneous expressive language was severely limited with no daily use of

words, his mother mentioned that his comprehension of verbal communication was also limited although he did have some understanding of 'no', names of familiar persons, and food items. He was able to vocalize different sounds with differing intonations, his mother mentioned that he seemed to make one distinct sound when he was unhappy. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that he had a poor attention span, and could not attend to one activity or object for any length of time. He was also easily distracted by outside sounds. He enjoyed swimming and horseback riding according to his mother, but he showed no spontaneous imaginative play nor imitated others. When aged 4 he had played with cars by turning these upside down and repetitively spinning the wheels. He now liked to clap his hands excitedly when others sang, would cry at sad melodies, and enjoyed watching TV. If he was close enough with his wheelchair he would repetitively flick light switches on and off when given the chance. He liked to snuggle and hug indicating this by inclining his head forward. He was sometimes responsive when approached by other children, but could react in unpredictable ways suddenly pulling the other's hair, hitting or flapping his arms. He disliked holding objects in his hand, would almost continuously flap his hands and frequently grinded his teeth. When younger he had also frequently shown midline wringing hand movements, but these were infrequent now according to his mother. Walking independently had not been achieved yet, although he could walk short distances with his mother walking behind him and holding both his hands. He could not wave goodbye. His mood was mostly happy, he tended to giggle and laugh without clear cause and his mother thought that he had a full range of facial expressions.

Case 8

Case 8 was an adolescent with a withdrawn, but amiable demeanor. He extended his hand at second meeting when prompted by his parents to shake hands, but did not make eye contact when doing so. He had no current somatic complaints, he had no hyperbreathing but would sometimes noticeably sigh. Hypoplasia of the corpus callosum had been confirmed at an early age. Bowel and bladder control had not been achieved. His mother thought him a contented baby, not even crying to be fed and lying quietly when awake. He used lower leg splints to aid leg function for walking. There was little visible response to the examiner's facial expression, orientation or smiles, although he sometimes seemed to cock his head to listen. Both his eye–to–eye gaze and range of facial expressions were limited, and there was little reciprocity or spontaneous initiation of contacting or engaging the other. His mother considered him very sociable at a young age, he smiled from the age of 3 months and was quick to smile at a camera. Both spon-

taneous expressive language and comprehension of verbal communication were severely limited. He had 1 word, and his production of sounds was also limited. For up to 5 minutes, his capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was sufficient, he especially enjoyed spinning the wheels on a toy car with one hand and kept doing that until the car was removed from his grasp. There was no play involving others. He was able to drink from a covered cup with one hand; to sip water with a straw. He had no unprompted spontaneous attempts to point to objects of interest. His mother mentioned that he would handle objects, bringing them to his mouth, but not biting or licking them. His mother said he liked musical toys and enjoyed watching television. He also loved to take the other's hands and clap them together, often not realizing his own strength and clapping them very hard. He would often make rapid stereotyped movements with his head, sometimes completing a figure–8, sometimes just rapidly going back and forth. There was no head banging. His parents mentioned that he could make movements within a contextualized setting, such as lifting his arms high when his father announced that he was going to remove the coat. He repetitively clasped his hands together in the midline and also had frequent hand and finger movements. He could walk independently, but would need to grasp one finger of his Dad's hand to get up from the chair and start moving. When he was unsure of his surroundings he would stop walking and stand. Sometimes he was hesitant when walking and he could suddenly grab onto somebody standing close by. He was usually even–tempered, and he always slept well and enjoyed his food.

Case 9

Case 9 was a self–absorbed young adult with her tongue protruding from her mouth. She sat quietly in her chair while playing with musical toys at first meeting. She had no visible reaction to the introduction, did not make eye contact nor extended her hand when prompted. She received medication for epilepsy, but otherwise had no somatic complaints. She would sigh, and she regularly overbreathed during short periods with quick breaths interspersed with very slow ones. Bowel and bladder control had not been achieved. There was little integration of gaze, facial expression, vocalization and gesture. Her mother mentioned that her range of facial expressions was limited, usually giving a neutral impression while she had a blank stare. Although she had grinded her teeth repetitively when younger, this behavior had lessened over time. There was no spontaneous expressive language and comprehension of verbal communication was also severely limited. She had no words, but was able to vocalize some sounds, sometimes screaming or yelling. Her capacity to attend to different tasks (such as toys or objects)

was observed for up to 5 minutes, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was very short; she would repeatedly bring the object to her mouth, drop it from her hand and stare off in the distance. She had a preference for musical toys with pulling cords, choosing these toys from a basket next to her chair. She would sometimes pull the cord with great strength, disrupting the musical mechanism and drop one toy on the floor with a quick right handed gesture, then grab another with the same hand. Her mother mentioned that she could also play the whole day with the same musical toy, repetitively pulling the cord to start the music. She was able to walk independently from age 4, but her mother and sibling described her as mostly passive and prone to sit by herself without interacting with others. She would frequently rock her upper body back and forth. There was no head banging. She could hold her uncovered drinking cup in one hand and sip from it. Her mood was hard to gauge, her mother and sibling often wondered if she was happy. Her mother mentioned that she slept well and enjoyed her food, she also often ate non–food items such as sand or grass.

Case 10

Case 10 was a boisterous young adult at second meeting, willingly shaking hands when prompted by her parents and talking repetitively about the car drive. She made a restless impression and tended to keep moving around within the room, sitting down for only short periods of time. She had no somatic complaints. No breathing abnormalities had been noticed by her parents. Daytime bladder control had been achieved around age 10. Nighttime bladder control and bowel control had been achieved around 12 years. Her parents considered her sociable from an early age, but also mentioned that she always sought the other's attention and would need to be entertained. She would sometimes stand too close to others and she could be stubborn, bossy and uncooperative. Eye–to– eye gaze was sufficient and she seemed interested in making contact with others although this included little reciprocity and could largely be determined as attention seeking behavior. She would repeatedly interrupt her father's conversation. She grinded her teeth repetitively. There was spontaneous expressive language and comprehension of verbal communication included understanding more than 50 words, names of familiar others, toys and food items. She had babbled from the age of 20 months, and had started short sentences around age 11, usually indicating a wish for food or need to visit the toilet. She tended to speak loudly, but she would modulate her voice when encouraged to do so. Her father mentioned that she could sit on the sofa and could repetitively and relentlessly call for his attention and continuing this behavior even when she was corrected and told to wait. After correction she would sometimes start calling her Mom

repetitively. She would offer videos that she would like to see on the TV or sometimes asked her parents to inquire if she could go to tea at a friend. For up to 5 minutes, her capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that her attention span was poor, she could not attend to one activity or object for any length of time and she was continuously distracted by her own or outside sounds. She tended to flit from one object to the next, unable to stay on task. At home she enjoyed going for walks outside and liked to watch favorite DVDs. She sometimes repeated parts of sentences she heard in TV commercials. She was able to walk independently from age 7, would frequently flap her hands and sometimes banged her head. She could keep moving around the room with no apparent purpose. Her mood was mostly happy.

Child assessments

Bayley Scales of Infant Development

The scores for mental age and motor development as measured using the BSID–II are shown in Figure 5.1. As participants had severe intellectual disability and a chronological age above the norms of the BSID–II, only age–equivalent scores are shown and no standard scores. The chronological age of the participants lies between 32 and 289 months and the developmental age between 3.5 and 15 months for the mental scale and between 4 and 19 months for the motor scale. With the exception of one young child, all participants performed better on the motor scale than on the mental scale.

Snijders–Oomen Nonverbal Intelligence Test (SON–R)

As none of the participants had a developmental level beyond 48 months, the SON–R was not used.

Autism Diagnostic Interview – Revised (ADI–R)

Highest scores for all participants were found on the domain of social interactions and play. Eight subjects scored at or above cut–off scores on social and communication domains (Table 5.4). Subjects 6 and 10 did not score above cut–off for the behavioral domain. These ADI–R scores in themselves should not be interpreted as conclusive for autism or indicative of symptom severity, especially since mental age equivalents in this group were lower than minimum developmental level described in the ADI–R manual. However, they add to and corroborate other findings.

Figure 5.1 Developmental level of mental and motor functioning, measured by the BSID, compared to chronological age

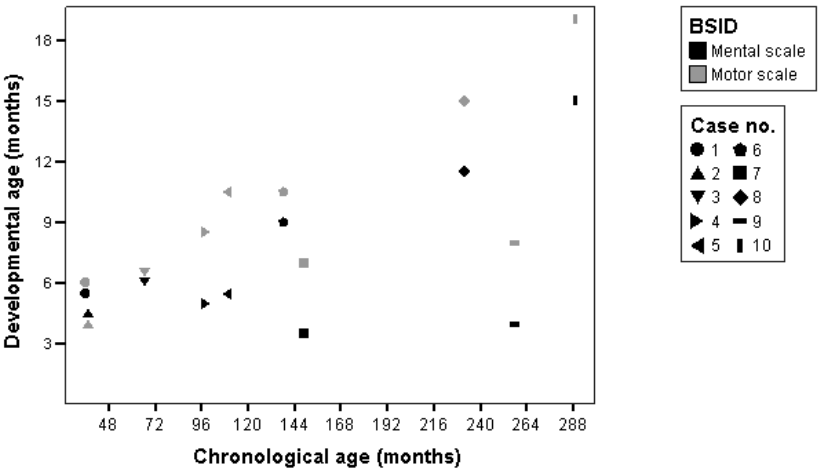


Table 5.4 Item scores on the three domains of the Autism Diagnostic Interview – Revised

		Participant #									
Test domain	Cut–off	1	2	3	4	5	6	7	8	9	10
Social skills and play	≥10	15	X	15	25	X	22	17	23	26	16
Communication (verbal & non–verbal)	≥8	NS	X	8	NS	X	NS	NS	NS	NS	18
Communication (non–verbal only)	≥7	10	X	NS	8	X	10	12	14	14	NS
Behavioral abnormalities	≥3	6	X	4	4	X	2	4	6	4	0

NS = no score; X = not measured

Vineland Adaptive Behavior Scales (VABS)

VABS results (Figure 5.2) were determined with age–equivalent scores. None of the participants, except the eldest, performed beyond a developmental age of 20 months. The domains of daily living skills and communication appear to be relative strengths,

Figure 5.2 Developmental level on the three domains and total adaptive behavior score of the Vineland, compared to chronological age

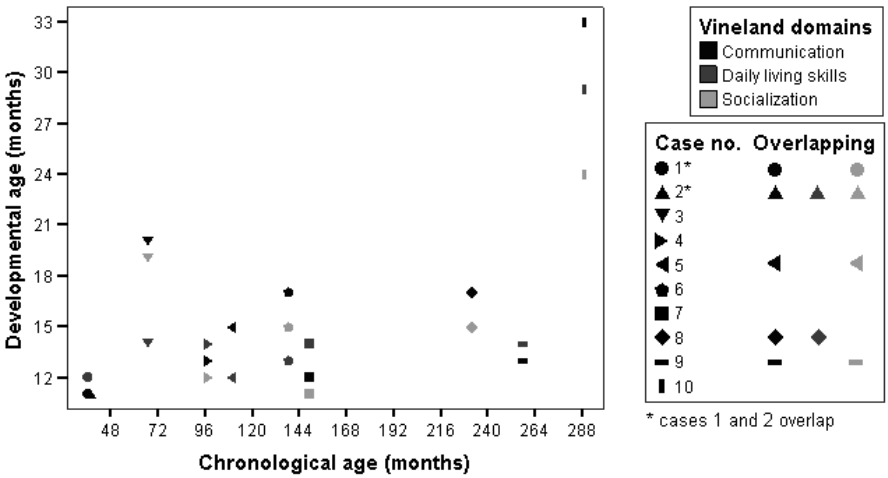


Table 5.5 Likelihood assertions concerning level of cognitive functioning

Participant	Total score	Decile scores	Description
1	42	1 (too young)	(very profound ID)
2	38	1 (too young)	(very profound ID)
3	84	2	profound ID
4	55	1	very profound ID
5	62	1	very profound ID
6	67	1	very profound ID
7	50	1	very profound ID
8	75	1 (norm table 14–18)	(very profound ID)
9	59	1 (norm table 14–18)	(very profound ID)
10	140	1 (norm table 14–18)	(very profound ID)

de Bildt & Kraijer, 2003

with weaker functioning in the domain of socialization. It also seems that with increasing age very little progress in adaptive functioning could be accomplished.

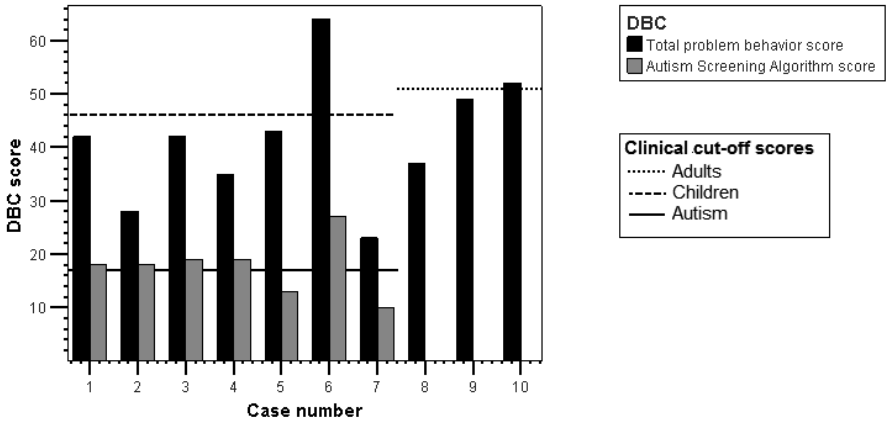
The decile scores in the present study showed a very profound intellectual disability in 7 of 8 participants and profound disability in one participant (Table 5.5). In the case of 2 participants, their young age prevented calculation of a decile score. The 3 participants >18 years were categorized as category 1 (lowest category), although they fall outside the age range of 14 – 18 years. However, because they are older and fall within category 1 it is unlikely that we are underestimating their cognitive functioning.

Developmental Behaviour Checklist (DBC)

The DBC assessment showed 2 participants (cases 6 and 10) with scores above the clinical cut–off level for problem behaviors for age group (Figure 5.3). Clinical cut–off scores for the age group below 18 (at 46) and for the age group above 18 (at 51) are shown in Figure 5.3 as separate dotted lines. Total problem behavior in case 6 was caused by a high score on the Self–Absorbed scale, while case 10 had high scores on the Communication Disturbance and Disruptive Behavior scales.

All participants had high scores on self–absorption. Five of the 7 subjects below 18 years scored just above threshold on the DBC Autism Screening Algorithm. This algorithm is not available for adults using the Developmental Behaviour Checklist for Adults.

Figure 5.3 Total problem behavior scores and autism screening algorithm scores with their cut–off lines, measured with the Developmental Behaviour Checklist



DISCUSSION

This is the first study of cognition and behavior in classic PHS. Results from this exploratory study show that all subjects share (very) profound intellectual disability, severe impairments in social interactions, severe impairments in communication and language, and highly frequent, intense stereotyped behavior consisting primarily of repetitive hand and finger flapping/twisting and/or rocking. Findings show that 90% of participants are functionally nonverbal, and breathing abnormalities are present in 60% and range from overbreathing and breath holding spells to gasping or sighing. Aggression towards self is present in 50%, towards others in 40%. Most participants have an amiable demeanor, but also show high levels of self–absorption and failure to engage socially. In comparison to an earlier study of Marshall–Smith syndrome with a similar methodology (van Balkom et al., 2011), the findings in this study indicate that in classic PHS not only the difficulties in engaging and communicating with others are more pronounced, but the individuals with PHS also show a much higher occurrence and level of severity of repetitive motor stereotypies. Stereotypies in our group are also more prevalent than reported in several genetic studies of PHS (see Table 5.3), suggesting that these behaviors may be less recognized as a distinct characteristic of PHS. Higher levels of repetitive motor behaviors may be associated with the lower levels of adaptive and cognitive skills found in our sample, or may be part of a phenotype of autism spectrum disorder. Severity of intellectual disability is considered a risk factor for difficulties in communication and social interactions, sometimes resulting in behavioral problems (McClintock et al., 2003; Szatmari et al., 2006). Previous publications have emphasized the increased vulnerability to co–morbid psychopathology to which individuals with developmental disability are subject (Dykens, 2000; Leyfer et al., 2006; Matson & Shoemaker, 2009). Co–morbidities associated with intellectual disability include a high prevalence of epilepsy, behavioral, psychiatric, and sensory disorders. Higher prevalence and severity of co–morbid disorders is closely related to lower levels of intellectual functioning (Matson & Shoemaker, 2009; Saemundsen et al., 2010). In addition, when intellectual disability is highly prevalent in one specific diagnostic group, clinician expectation of an individual's developmental potential may be biased. This fact, combined with the lack of suitable instruments for severe intellectual disability and associated behavioral problems, may prevent more thorough evaluations of cognitive and adaptive functioning in both clinical and research settings (Sanz et al., 2010). In the study of genetic syndromes, differentiating between deficits related to intellectual disability with severe developmental delay and deficits related to autism remains difficult (Percy et al., 1990; Mazzocco et al., 1998; Howlin, 2000; Cohen et al., 2005; Leyfer et al., 2006; Hagerman & Harris, 2008; Battaglia et al., 2010). Specific brain regions serve aspects of cognition and

behavior, and neural development and functioning of these regions may be disturbed due to genetic risk factors. Brain–behavior relationships develop as a result of brain programming and functional connectivity within neural circuits and networks determined by gene expression. Findings in recent years have increased our understanding that causal effects in brain–behavior relations are neither unidirectional nor invariant. These brain–behavior relations may change over the course of development, contingent also on the effects of experiences within rearing environments, learning and social contexts (Oliver et al., 2000; Rutter, 2005; Pennington, 2006; Guilmatre et al., 2009; Karmiloff–Smith, 2009; Pennington, 2009; Saemundsen et al., 2010).

Similar phenotypes emerging from distinctly different genetic defects are thought to be caused by the multidirectional interaction between etiological risk and protective factors from both genetic and environmental perspectives. Conversely, a given genotype can give rise to different phenotypes depending on environmental circumstances. A single genetic alteration will often affect more than one neural system, subsequently influencing the development and function of other neural systems downstream. These neural systems may in turn be influenced by interactive processes in the social and physical environment and have eventual effects 'upstream' on the way genes work, affecting different regions to a greater or lesser degree and changing overall developmental outcome (Bateson et al., 2004; Pennington, 2006: Blackwood et al., 2008; Geschwind, 2008; Diamond, 2009; Karmiloff–Smith, 2009).

Many recent genetic studies have investigated chromosome regions and possible loci on various chromosomes regarding their possible contribution to the cause of autism spectrum disorder, intellectual disability, and schizophrenia. Several of these studies concluded that the genomic abnormalities investigated were not disease specific. Rather they contribute to the expression of various overlapping neurodevelopmental phenotypes, and challenge longstanding ideas of how disorders can be delineated and differentiated from one another. Research into the involvement of Copy Number Variants (CNVs) in intellectual disability, autism spectrum disorders, and schizophrenia has also suggested outcome similarity and overlap with regard to synaptic formation, function, and neurotransmission. The chromosomes involved in PHS and PH–like syndromes have all been investigated for their association with neurodevelopmental and psychiatric disorders. Structural changes, deletions, and mutations in *TCF4*, *NRXN1*, and *CNTNAP2* have been implicated in brain dysfunction, and they may contribute to neuronal networks that lead to psychiatric phenotypes (Kirov et al., 2008, 2009; Walsh et al., 2008; Rujescu et al., 2009; Stefansson et al., 2009; Zweier et al., 2009; Blake et al., 2010). In a meta–analysis of datasets of brain imaging, Cheung et al. (2010) found that in schizophrenia and autism there are structural concordances with abnormalities of the limbic loop (cingulated, striatum, and thalamus), suggesting shared etiologies and partly explaining shared socio–emotional symptoms.

Schizophrenia and autism differ in the localization of lower grey matter volume (autism: left putamen; schizophrenia: left fronto–striatal–temporal region).

NRXN1 and *CNTNAP2* play important roles in creating effective connections for signals between neurons (Feng et al., 2006; Bucan et al., 2009; Glessner & Hakonarson, 2009; Kirov et al., 2009; Stefansson et al., 2009; Zweier et al., 2009; Blake et al., 2010). As *CNTNAP2* is highly expressed in the frontal lobes, it may influence the development of brain structures involved in speech, language, and thought, and may thus be instrumental in reducing gray and white matter volume in particular brain regions, and increasing susceptibility for autism spectrum disorders, language disorders, intellectual disability, and epilepsy (Strauss et al., 2006; Alarcón et al., 2008; Bakkaloglu et al., 2008; Tan et al., 2010). Comparable impairments in social communication in autism, intellectual disability, and schizophrenia may be caused by impaired filtering and information processing at brain level, and by atypical responsiveness to social and learning environments at the behavioral level. It has been hypothesized that these effects may be determined at different levels within mirror neuron networks that impact learning behaviors, resulting in deficits in gestures and language, and in imitative capabilities which are important in learning (Frith & Frith, 2010; King & Lord, 2011). Researchers have also postulated that functional connectivity deficits in key brain networks and their effects on long–range interactivity with other regions may underlie shared phenotypes, regardless of the initial starting point at the genetic level (Oliver et al., 2000; Pennington, 2009; Ching et al., 2010; King & Lord, 2011). The impact of alterations in these genes includes outcome effects on, among others language, thought, social cognition, and memory. This effect can be understood as a multilevel and long–range influence on neuronal development and connective functioning in the brain and primarily affects the frontal lobe, and gray and white matter.

The study of PHS and PH–like syndromes shows that different genomic alterations can result in similar phenotypes, and it is clear that there is still much to learn to improve our understanding of the delineation between typical and atypical behavior and about the significance of genomic changes with regard to the expression of overlapping phenotypes and their diagnostic boundaries.

Strengths and limitations of the present clinical study

Major strengths of our study are that participants comprised a diagnostically homogenous group with a diagnosis of PHS caused by *TCF4* alterations, that all subjects were directly assessed through individual psychiatric examinations and a robust, comprehensive battery of tests, and that they had a wide (chronological) age distribution, which allowed assessments from toddler– to young adulthood. Nonetheless, the following limitations regarding the present study also need to be considered. First, our sample of

10 participants is relatively small, although it could be considered substantial in light of the rarity of the syndrome. Second, the lack of suitable instruments to measure cognitive functioning directly in individuals with severe intellectual disability required an *a priori* judgment of approximate cognitive level through clinical psychiatric assessment. In our study, all subjects scored within developmental levels that could be measured by our instrument of first choice (Bayleys), and the use of the other instrument (SON–R) was not necessary. Similarly, it should be noted that use of the ADI–R to assess individuals whose mental age–equivalent is below a developmental level of 24 months carries the risk of over–classification of autism. However, in this study the results of the ADI–R were used to add to other data collected through individual psychiatric assessments, informant reports, and individualized standardized testing.

Conclusion

This first exploratory study of cognition and behavior in classic PHS shows (very) profound intellectual disability, severe impairments in communication and language with failure to engage socially and very frequent and intense motor stereotypies. We conclude that autism spectrum disorder may be part of the phenotype of classic PHS, albeit presenting in varying degrees of severity.

Changes in *TCF4*, *NRXN1* and *CNTNAP2* in PHS and PH–like syndromes have been implicated in outcomes of intellectual disability, epilepsy, autism, and schizophrenia, through their impact on the development and function of neuronal networks. Continued studies of rare genetic disorders will eventually, through longitudinal data, allow for improved recognition of shared etiologies and co–morbid conditions. They will increase our understanding of significant contributions from social and learning environments, shed more light on individual and group level developmental trajectories, on changes over time, and suggest possibilities to improve outcomes.

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CHAPTER 6

Phenotype and natural history in Marshall–Smith syndrome

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ABSTRACT

Marshall–Smith syndrome (MSS) is a distinctive entity of unknown etiology with fewer than 50 patients described in the medical literature to date. Through an International collaboration and use of an online wiki to facilitate data collection and sharing, we further delineate the phenotype and natural history of this syndrome. We present 15 new patients, the oldest being 30 years, provide an update on four previously published cases, and compare all patients with other patients reported in literature. Main clinical features are moderate to severe developmental delay with absent or limited speech, unusual behavior, dysharmonic bone maturation, respiratory compromise secondary to upper airway obstruction, short stature, and kyphoscoliosis. Facial features are characteristic with high forehead, underdeveloped midface, proptosis, anteverted nares, and everted lips. Minor abnormalities of brain morphology such as hypoplasia of the corpus callosum are common. Mortality from respiratory complications is high, but airway support increasingly allows survival into adulthood. Array–CGH was performed on 12 of the cohort and no copy number variants of clear clinical relevance were identified. The present study is the first reported use of an online wiki to aid delineation of a genetic syndrome, and illustrates its value in collecting detailed data in rare conditions.

KEYWORDS: Marshall–Smith syndrome, mental retardation, dysostosis, kyphoscoliosis, natural history, wiki

INTRODUCTION

In 1971, the physicians R.E. Marshall, C.B. Graham, C.R. Scott, and D.W. Smith reported two unrelated male infants with unusual facial features, failure to thrive, developmental delay, and what was described as marked early acceleration of osseous maturation (Marshall et al., 1971). The facial appearance was very similar in both and characterized by prominent eyes, thick eyebrows, depressed nasal bridge, and a small upturned nose with prominent nares. Both patients had respiratory difficulties, and one of them had died at 20 months of age. To date, at least 43 cases with this phenotype have been described in the literature, and the entity has become known as the Marshall–Smith syndrome (MSS). The majority of reported cases died in infancy or early childhood, but prolonged survival of some cases especially due to improved management of the respiratory difficulties, suggested such early demise is not inevitable.

The majority of previous reports have been of single patients, with the largest published series comprising 5 new cases (Adam et al., 2005), collated through an international collaboration. Meaningful study of ultra–rare phenotypes such as MSS, necessitates

large–scale collaboration between clinicians. The apparent difficulty in amassing sizable cohorts to date may be compounded by inefficient means of effective data sharing, inconsistent data–sets, and difficulty tracing patients who are not under active follow–up. The use of evolving web–based data sharing methods such as a wiki, may provide a solution to some of these problems and aid delineation of rare phenotypes. Wikis are easy–to–use text–based data repositories that can be accessed through a web browser and allow any individual with world–wide–web access to read the content and add their own text. Wikis may be open–access or available only to registered users and can easily be created using a number of free open–source or commercial software products.

Here we provide the phenotype and natural history of 15 new and 4 previously published patients on whom data were in–part collected and shared using a secure online wiki resource. Three patients are aged over 16 years and allow us to further describe the adult phenotype of MSS.

METHODS

A literature search was performed using "Marshall–Smith" as search term. The reference lists of all manuscripts thus retrieved were searched manually for further reports.

Patients were referred to us by colleagues around the world and through the international Marshall–Smith Support group. All patients referred have been personally evaluated by at least one of the authors. In addition to medical assessment and clinical examination, personal history and additional information on the patients were assimilated using an online wiki. An early draft of this paper consisting of the general description of the syndrome and medical complications, was re–written in lay language and translated into French, German, Dutch, Norwegian, Portuguese, Spanish, and Croatian. The translated text was uploaded to a secure wiki website, accessible to registered clinicians and members of the International MSS patient support group (www.marshallsmith.org). Families were encouraged to read the text and add their own data and comments.

Agilent Technologies 244 K genome–wide arrays were used for the patient testing. In brief, genomic DNA from the patient and from a single sex–matched reference were double–digested using the restriction endonucleases AluI and RsaI (Promega, Wisconsin) and purified using Microcon centrifugal filter devices (Millipore Corporation, Massachusetts). 1.5 mg of the digested products were differentially labeled by random priming with Cy3–dUTP and Cy5–dUTP (Perkin Elmer, Massachusetts) and co–hybridized to the arrays for 48 hr at 65°C in a rotating oven (Agilent Technologies, Inc., Illinois). Hybridized arrays were washed according to Agilent Technologies, Inc. protocols (www.agilent.co.uk) with the exception that the final stabilization step was not performed. Hybridized arrays were scanned at 5 mM resolution immediately following

washing using an Agilent DNA Microarray Scanner. Image data were extracted using Agilent Feature Extraction software version 8.5 and analyzed using Agilent CGH Analytics software version 3.4 (z–score method setting). Potential genome imbalances were recorded if 4 or more consecutive oligonucleotide probes gave values that fell outside the log10 Cy–dye threshold ratios. This gave an average resolution of 40 kb. The positions of proximal and distal oligonucleotides showing potential imbalances were noted and the regions queried both in the Database of Genomic Variants (Iafrate et al., 2004) and the laboratory's own database. Approval from the NHS (UK) National Research Ethics Service was obtained prior to the study commencement.

RESULTS

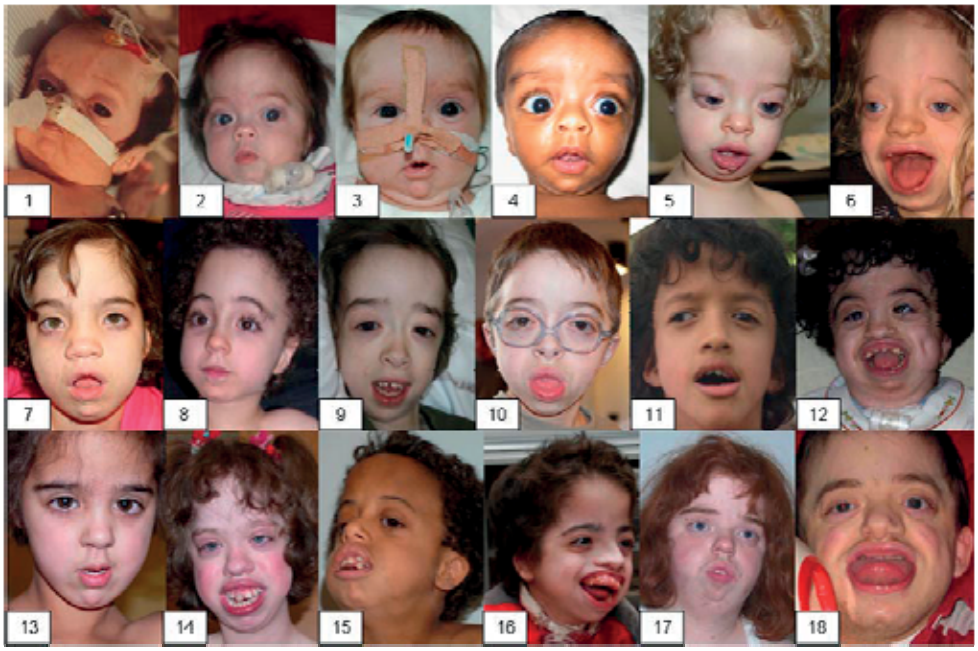
Clinical data on all patients are summarized in Table 6.1, and patients 1–18 are illustrated in Figure 6.1. A detailed description of the oldest patient, aged 30, is provided below and she is illustrated in Figure 6.2. Four patients have been previously described in the medical literature: Patient 13 (Deshpande et al., 2006), Patient 14 (Adam et al., 2005), Patient 15 (Dernedde et al., 1998), and Patient 17 (Williams et al., 1997).

Mean maternal age at birth was 29.3 years, and mean paternal age at birth was 33.2 years. The mean parental ages for normal populations vary year by year and by country. Although comparison of the parental age for each patient with published data on mean paternal and maternal age for the corresponding year of birth is difficult due to the varying countries of origin, it is unlikely that these data are significantly deviated from the mean, suggesting no parental age effect in the cohort. Mean birth weight for term deliveries was 2,936 g for males and 3,229 g for females. Mean and median times to conception were 5 and 1 month, respectively.

Respiratory problems were present in 14 patients. The majority presented at birth or shortly after with upper airway obstruction or apneas. Laryngomalacia was not uncommon (four subjects), but in most patients the obstruction appeared secondary to the combined changes to craniofacial anatomy, where retrognathia, an underdeveloped midface, narrow choanae, and anteriorly placed larynx reduced airway patency. Treatment was by tracheostomy in five subjects, nasopharyngeal airway in six subjects and positive pressure ventilation in one patient. In two individuals, surgery was performed to relieve the obstruction. Obstructive sleep apnea was common in older children and adults (nine subjects) including those who did not experience respiratory problems in infancy (two patients).

Spastic quadraparesis presented in the first year of life in two patients, secondary to dysplasia of the upper cervical vertebrae. Both patients recovered fully following cervicomedullary decompression.

Figure 6.1 Facial pictures of the presented patients with Marshall–Smith syndrome



Patients are identified by their number in the figure. Age at imaging is as follows:
Patient 1, 2 weeks; Patient 2, 6 months; Patient 3, 3 months; Patient 4, 2 years;
Patient 5, 20 months; Patient 6, 4 years; Patient 7, 6 years; Patient 8, 5 years;
Patient 9, 5 years; Patient 10, 6 years; Patient 11, 8 years; Patient 12, 7 years;
Patient 13, 6 years; Patient 14, 12 years; Patient 15, 13 years; Patient 16, 13 years;
Patient 17, 16 years; Patient 18, 20 years.

Figure 6.2 Changing phenotype over time in patient 19 from 3 weeks to 30 years

Age at imaging is shown in the figure (w, weeks; m, months; y, years).

Table 6.1 Clinical characteristics of present 19 patients with Marshall–Smith syndrome

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
Epidemiology																				
Gender	M	F	F	M	M	F	F	F	F	M	M	F	F	F	M	M	F	M	F	8 M/11 F
Age	3 wk [a]	6 m	6 m	26 m	3 yr	5 yr	7 yr	7 yr	7 yr	7 yr	8 yr	8 yr	8 yr	14 yr	13 yr	14 yr [a]	16 yr	21 yr	30 yr	3 wk to 30 yr
Mat/Pat age (yr)	26/28	36/37	18/23	22/32	30/31	24/32	23/31	32/36	32/51	27/29	24/31	34/32	20/21	33/40	35/33	26/32	28/28	38/39	27/27	
Growth																				
Birth weight (g)	2,600	3,400	3,570	2,950	2,975	2,170		1,590	4,030	3,230	2,400	2,183	3,630	2,990	2,000	2,270	2,800	3,860	2,977	
Gestation	term	term	term	term	term	36 wk	31 wk	32 wk	41 wk	term	35 wk	term	term	term	term	34 wk	term	term	term	
Weight (kg)	2.97	5		9.1	15	13.8	18		17	21	28	14.5		30	22	19	35	41	32	
Height (cm)	55	68		82	100	107	118	103	120	120	136	100		138	120	122	131		127	
Height centile	75	64		3	10	10	20	7	38	30	72	<0.4	85	0.2	<0.4	<0.4	<0.4	<0.4	<0.4	
(SDS if centile <2)												(–4.95)		(–2.90)	(–4.9)	(–5.6)	(–4.6)	(–6)	(–6)	
Development																				
Degree of delay	N/A	N/A	N/A	sev	mod	mod-sev	mod-sev	mod	mod-sev	mod	mod	sev	mod	mod	sev	mod-sev	sev	sev	mod-sev	
Walked	N/A	N/A	N/A	–	–	–		–	–	3 yr	3 yr	–	2 yr	4.5 yr	never	never	never	never	9 yr	
First words	N/A	N/A	N/A	–	–	60 m		60 m	42 m	36 m	–	–	–	48 m	none	none	none	none	10 yr	
Craniofacial features																				
High forehead	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Proptosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Underdeveloped midface	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	18/19
Short nose	+	+	+	+	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	15/19
Anteverted nares	+	+	+	+	+	–	+	–	+	+	–	+	–	+	–	+	–	–	–	11/19
Prominent premaxilla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Short philtrum	+	–	–	–	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	13/19
Everted lips	–	–	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	13/19
Irregular dentition	N/A	N/A	N/A		+	–		–	–	+	+	–	–	+	+	+	+	–	+	8/14
Gum hypertrophy	–	+		+	+	–		–	–	+	–	–	–	+	+	+	–	–	–	7/17
Retrognathia	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	17/19
Low-set ears	–	–		+	+	+	+	–	–	+	+	+	–	–	+	+	+	–	–	10//18
Eyes																				
Myopia	–	–		–	–14	–2.5	–6 /–5	–12/–9	–2/–7	–	–2	–8	–	–	+	–7/–8	–	–	–	9/18
Blue sclerae	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	+	+	+	+	15/19
Glaucoma	–	–		–	+	+		–	–	–	–	–	–	–	+	–	–	–	–	3/17
Optic nerve hypoplasia	–	–		+	–	–		–	–	–	–	+	+	–	–	+	+	–		5/16

Table 6.1 (Continued)

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
Respiratory																				
Choanal stenosis	–	+	+	–	–	+		–	–	+	–	–	–	+	+	–	–	–	–	6/18
Respiratory problems	+	+	+	–	+	+	+	–	–	+	–	+	+	+	+	+	–	+	+	14/19
Obs sleep apnea	N/A	–		–	+	+	–	–	+	+	+	N/A (trach)	+	+	+	N/A (trach)	–	+	–	9/15
Neurology																				
High tone	–	–		–	–	–		–	–	–	–		–	+	+		+	+	–	4/15
Brisk reflexes	–	–		–	–	–		–	–	–	–		+	+	+		+	+	–	5/15
Cervical cord compression	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	2/19
Brain MRI		Pachygyria hypoplasia callosal body	Small cerebellum	CT scan: N	Hypoplasia callosal body	Delayed myelination		N	N	N	Hypoplasia callosal body	Hypoplasia callosal body	N	N	N	Dilated cerebral ventricles	Dilated cerebral ventricles		N	
Skeletal																				
Abnormal bone maturation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	19/19
Craniosynostosis	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	1/19
Bone fractures	–	–	–	–	1	–	–	–	4	4	1	–	–	–	–	–	–	–	–	4/19
Kyphoscoliosis	–	–	–	–	–	+	+	–	–	+	–	+	–	+	+	+	+	+	+	10/19
Other																				
Cardiac defect	–	–		–	–	–		VSD	–	–	–	–	–	–	–	–	VSD	–	–	2/17
Pulmonary hypertension	–	–		–	–	–		–	–	–	–	–	–	–	–	+	–	–	–	1/17
Hearing loss	+	+		–	+	+	–	–	+	+	–	–	–	–	+	+	+	–	–	9/18
Umbilical hernia	–	+		–	–	–		–	–	+	–	–	–	–	–	–	–	–	–	2/17
Cryptorchidism	–	N/A	N/A	–	+	N/A	N/A	N/A	N/A	–	+	N/A	N/A	N/A	–	+	N/A	–	N/A	3/8
Hypertrichosis	–	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	16/19
Fetal finger pads	+	–		+	+	+		+	+	–			–	+	–		–	+	–	8/14
Miscellaneous		IgA deficiency vesico-ureteral reflux		Abnormal pinnae	Hypo-spadias					Anteriorly placed anus; pyloric stenosis		Choroid plexus cyst antenately; tethered spinal cord		Vascular skin naevus	Pyloric stenosis	No secondary dentition	Wilms tumor aged 4			

Fields are left blank if no data on a feature are available.
[a] deceased
M, male; F, female; d, day; wk, week; m, month; yr, year; SDS, standard deviation score; N/A, not applicable; sev, severe; mod, moderate; N, normal; VSD, ventricular septal defect

Patient 14 had asymptomatic narrowing of the cervical spine noted on imaging performed as surveillance. Corneal scarring occurred peri–operatively in three patients secondary to proptosis and incomplete eye closure. All subjects had moderate to severe mental retardation with limited or absent speech. Parents frequently reported a strong attachment to a favorite toy which remained for years. More detailed evaluation of the neurocognitive profile will be presented elsewhere (van Balkom et al., 2011).

Clinical report

This 30–year–old woman was diagnosed with MSS at age 2 months. There were no antenatal concerns and she breathed spontaneously at birth with no airway support required. She had feeding difficulties in the neonatal period with a weak suck, taking over an hour to complete a feed. She developed upper respiratory tract obstruction as an infant and eventually required an emergency tracheostomy at 13 months. Her feeding problems and neurocognitive development improved substantially afterwards. The tracheostomy remained in place until 4 years and there have been no further respiratory problems since. Menarche occurred at 14 years and was normal. She had a single seizure at the age of 6. She had very narrow ear canals and had a canaloplasty aged 8 years. Facial hirsutism became marked aged 16, and has been successfully treated with laser removal. She walked unaided from 9 years on but in the last years her mobility reduced and she developed severe osteoarthritis. She was continent from the age of 3. Her first words were at 10 years, but she had only 3 or 4 words in total. She communicated well through pointing and leading the way. She was a happy and sociable lady who enjoyed music, visiting family and shops. Linear growth was normal in childhood, but she stopped growing at around 13 years. She lost height due to scoliosis and current adult height is 127 cm. Bone age at 2 months was approximately 4 years, and at 8 chronological years was 10 years.

She always had typical facial features (Figure 6.2). Her eyebrows and eyelashes were particularly thickened and coarse. She had a wide mouth, protruding tongue, irregular teeth, and everted, prominent lips, and depressed nasal bridge. She had a soft, supple skin with hypertrichosis on areas that have not received depilatory treatment. She had a scoliosis of 60 degrees, marked thoracic kyphosis, and a cautious gait with externally rotated hips. Her muscle tone was high and she had strong power. She appeared shy with gaze avoidance, but smiled, laughed and enjoyed company.

Array–CGH results

Genomic DNA samples from Patients 1, 3, 5, 6, 7, 8, 10, 13, 14, 15, 17, and 18 were available for aCGH testing. For patients 3, 5, 6, 7, 10, 13, 14, 15, and 17 only genome

imbalances/CNVs that have been noted in the Database of Genomic Variants (DGV) (http:// projects.tcag.ca/variation/), or observed many times in our own sample sets, were identified. In patients 1, 8, and 18, several putative genomic imbalances were identified, but follow–up studies using a combination of FISH, MLPA, and study of parental samples, suggested none of the changes were likely to be of clinical significance.

DISCUSSION

We found 43 patients with MSS or a very similar phenotype described in the literature (Marshall et al., 1971; Nabrady & Bozalyi, 1973; Tipton et al., 1973; Visveshwara et al., 1974; De Toni et al., 1976; Hassan et al., 1976; Perrin et al., 1976; Iafusco et al., 1977; Ferran et al., 1978; Flatz & Natzschka, 1978; LaPenna & Folger, 1982; Johnson et al., 1983; Menguy et al., 1986; Roodhooft et al., 1988; Yoder et al., 1988; Smyth et al., 1989; Charon et al., 1990; Eich et al., 1991; Pappas & Rekate, 1991; Sperli et al., 1993; Sharma et al., 1994; Endo et al., 1995; Cullen et al., 1997; Williams et al., 1997; Antila et al., 1998; Chatel et al., 1998; Dernedde et al., 1998; Seidahmed et al., 1999; Summers et al., 1999; Moon et al., 2002; Sumiya et al., 2002; Wang, 2002; Diab et al., 2003; Watanabe et al., 2003; Butler, 2004; Adam et al., 2005; Deshpande et al., 2006; Travan et al., 2008). A summary of the major manifestations of 39 published cases (excluding the 4 that have been updated here) is shown in Table 6.2. We have excluded five possible cases due to difficulty interpreting language or insufficient information to confirm the diagnosis (de la Torre Cecilia et al., 1989; Moon et al., 2002; Watanabe et al., 2003; Kubota et al., 2005; Mandim et al., 2007). Some additional cases cited in the literature are likely to have alternative diagnoses such as Marshall–Stickler syndrome (Cooley et al., 2004) and Weaver syndrome (Jalaguier et al., 1983).

The major manifestations of MSS from patients described in the literature and the present studied cohort are summarized in Table 6.3. Features described in most patients are the moderate to severe developmental delay, severe respiratory difficulties, distinctive facial features (high forehead; proptosis; anterverted nares; retrognathia), abnormal bone ossification, and failure to thrive. We consider these findings, in particular the abnormal radiographs, required to make the diagnosis. Other highly prevalent features are blue sclerae, hypertrichosis, gingival hypertrophy, and the development of kyphoscoliosis in later childhood and adolescence. The six oldest individuals in the cohort (aged over 13 years) and one 8–year–old had short stature (SDS < 2.0) ` suggesting this is also a consistent feature of the adult phenotype, compounded by kyphoscoliosis.

Table 6.2 Major characteristics of 39 patients with Marshall–Smith syndrome from literature compared to a summary of the present series

	Marshall et al., 1971 (P1)	*Marshall et al., 1971 (P2)*	*Nabrady & Bozalyi, 1973*	*Tipton et al., 1973*	*Visveshwara et al., 1974*	*De Toni et al., 1976*	*Hassan et al., 1976*	*Perrin et al., 1976*
Epidemiology								
Gender	M	M	M	F	M	M	F	M
Age	20 m [a]	10 m	8 m	13 d [a]	3 m [a]	3 yr	10 wk [a]	6 m [a]
Growth								
Birth weight (g)	3,300	4,500	3,800	2,595	2,468	3,580	3,800	3,100
Gestation (wk)	term	term	term		term	term	term	term
Failure to thrive	+	+			+	+		+
Psychomotor delay	+	+	+			+		+
Craniofacial features								
High forehead	+	+	+	+	+	+	+	+
Proptosis	+	+	+	+	+	+	+	+
Short nose	+	+	+	+	+	–	+	+
Anteverted nares	+	+	+	+	+	+	+	+
Prominent premaxilla	+	+	+	–	+	+	+	–
Short philtrum	–	–	–	–	–	–	–	–
Retrognathia	+	+	+	+	+	+	+	+
Eyes								
Blue sclerae	+	+	+			+		–
Glaucoma					–			–
Respiratory problems	+	+	+	+	+	+	+	+
Callosal body underdevelopment	–							–
Skeletal								
Abnormal bone maturation	+	+	+	+	+	+	+	+
Craniosynostosis				–	–		–	+
Kyphoscoliosis	+	+		–			–	–
Bone fractures				–			–	–
Cardiac defect	–	–		PDA			ASD	PDA
Umbilical hernia	+	+	+		+	–	+	–
Hearing loss								
Hypertrichosis	–	–			+	–	+	+

Table 6.2 (Continued)

	Iafusco et al., 1977	*Ferran et al., 1978*	*Flatz & Natzschka, 1978*	*LaPenna & Folger, 1982*	*Johnson et al., 1983 (P1)*	*Johnson et al., 1983 (P2)*	*Menguy et al., 1986*	*Roodhooft et al., 1988*
Epidemiology								
Gender	F	M	F	F	M	F	F	F
Age	7 d [a]	4 wk [a]	18 d [a]	2 yr	2 m [a]	16 m [a]	7 d	4 yr
Growth								
Birth weight (g)	2,500	3,900	2,450	2,950	2,400	1,750	2,490	3,850
Gestation (wk)	42	45	term	term	35	34	term	term
Failure to thrive		–		+	+	+		+
Psychomotor delay				+		+		+
Craniofacial features								
High forehead	–	+	+		+	+	+	
Proptosis	+	+	+	+	+	+	+	–
Short nose	+	–	+	+	+	+	+	+
Anteverted nares	–	+	+	+	+	+	+	+
Prominent premaxilla	+		–		+	+	+	+
Short philtrum	–		–		–	–	–	
Retrognathia	+	+	+	+	+	+	+	+
Eyes								
Blue sclerae			+		+	+		
Glaucoma								–
Respiratory problems	+	+	+	+	+	+	+	–
Callosal body underdevelopment					–	–		–
Skeletal								
Abnormal bone maturation	+	+	+	+	+	+	+	+
Craniosynostosis		–			+	–		–
Kyphoscoliosis					–	–		
Bone fractures					–	–		
Cardiac defect		–		–	–	PDA	–	–
Umbilical hernia					–		–	
Hearing loss					+			
Hypertrichosis	+		+	+	+			

Table 6.2 (Continued)

	Yoder et al., 1988	*Smyth et al., 1989*	*Charon et al., 1990*	*Eich et al., 1991 (P1)*	*Eich et al., 1991 (P2)*	*Eich et al., 1991 (P3)*	*Pappas & Rekate, 1991*	*Sperli et al., 1993*	*Sharma et al., 1994*
Epidemiology									
Gender	F	F	F	M	F	M	M	M	F
Age	3 m [a]	2 yr	7 wk [a]	7 wk [a]	3 yr [a]	1 d [a]	2 yr	5 yr	2 m[a]
Growth									
Birth weight (g)	3,420		2,530	3,400	3,710	2,300		3,780	3,200
Gestation (wk)	term	term	34	term	term	term		term	term
Failure to thrive	+	+	+	+	+			+	+
Psychomotor delay		+	+		+		+	+	
Craniofacial features									
High forehead	+	+	+	+			+	+	+
Proptosis	+	+	+	+		+		+	+
Short nose	+	+	+	+		+	+	+	–
Anteverted nares	+	+	+	+				+	
Prominent premaxilla	–	+	+	+				+	
Short philtrum	–	–	–	–				+	–
Retrognathia	+	+	+	+	+	+	+	+	+
Eyes									
Blue sclerae	+	+						+	+
Glaucoma		–	–						
Respiratory problems	+	+	–	+		+		–	+
Callosal body underdevelopment	–		–	–	–	–		+	
Skeletal									
Abnormal bone maturation	+	+	+	+	+	+		+	+
Craniosynostosis	–	–	–	–	–	–		–	
Kyphoscoliosis	–		–	–	–	–			
Bone fractures			–		–		2		
Cardiac defect	–	–	–	–		–			
Umbilical hernia								–	
Hearing loss		–	–		+				
Hypertrichosis			+					+	

Table 6.2 (Continued)

	Endo et al., 1995	*Cullen et al., 1997*	*Antila et al., 1998*	*Chatel et al., 1998*	*Seidahmed et al., 1999*	*Summers et al., 1999 / Butler, 2004*	*Sumiya et al., 2002*	*Wang, 2002*
Epidemiology								
Gender	F	F	M	F	F	M	F	M
Age	8 m	5 m [a]	7 m	1 d [a]	4 m [a]	4 yr	7 yr	6 yr
Growth								
Birth weight (g)	2,500	2,760	3,890	2,150	2,400	3,060	2,680	2,850
Gestation (wk)	36	term	term	33	term	term	term	term
Failure to thrive	+					+	+	+
Psychomotor delay	+				+	+	+	+
Craniofacial features								
High forehead	+	+	+	+	+	+	+	+
Proptosis	+	+	+	+	+	+	+	+
Short nose	+	+	+		+	+		
Anteverted nares	+	+	+	+	+	+	+	+
Prominent premaxilla		+	+					+
Short philtrum		–	–			+		+
Retrognathia	+	+	+	+	+	+	+	+
Eyes								
Blue sclerae	+		+	–	+	–	+	
Glaucoma								+
Respiratory problems	+	+	+	+	+	+	+	+
Callosal body underdevelopment	+			–	+	–	–	–
Skeletal								
Abnormal bone maturation	+	+	+	+	+	+	+	+
Craniosynostosis	–	–				+	+	
Kyphoscoliosis		–				+	+	
Bone fractures	–	–				2		
Cardiac defect	–			–				
Umbilical hernia	–		+	+		–	+	
Hearing loss							+	+
Hypertrichosis	+			+	+	+	+	

Table 6.2 (Continued)

	Diab et al., 2003	*Adam et al., 2005 (P1)*	*Adam et al., 2005 (P2)*	*Adam et al., 2005 (P4)*	*Adam et al., 2005 (P5)*	*Travan et al., 2008*	*Total literature*	*Total current cases*
Epidemiology								
Gender	F	F	M	M	M	F	18M:21F	8M:11F
Age	7 yr	2 yr	19 yr [a]	2 yr	2 yr	16 d [a]	1 d – 19 yr	3 wk – 30 yr
Growth								
Birth weight (g)	2,255	3,250	3,100	3,400		2,250	term mean 3,144	term mean 3,085
Gestation (wk)	36	term		37		term		
Failure to thrive	+		+		+	+	24/25	14/14
Psychomotor delay	+	+	+	+	+		23/23	16/16
Craniofacial features								
High forehead	+	+	+	+	+	+	34/35	19/19
Proptosis	+	+	+	+	+	+	36/37	19/19
Short nose	+					+	28/31	15/19
Anteverted nares	+	+	+	+		+	33/34	11/19
Prominent premaxilla	+						19/23	19/19
Short philtrum	+				+		5/25	13/19
Retrognathia	+	+	+		+	+	38/38	17/19
Eyes								
Blue sclerae	+	+	+		+		19/22	15/19
Glaucoma	+						2/7	3/17
Respiratory problems		+	+	–	+	+	32/36	14/19
Callosal body underdevelopment	–	–	–	–	–	+	4/23	4/16
Skeletal								
Abnormal bone maturation	+	+	+	+	+	+	38/38	19/19
Craniosynostosis							4/19	1/19
Kyphoscoliosis		+	+		+		7/18	10/19
Bone fractures	15	4					4/13	4/19
Cardiac defect							4/18	2/17
Umbilical hernia							8/15	2/17
Hearing loss		+	+				6/8	9/17
Hypertrichosis							14/17	15/18

Data are indicated only if a feature was stated positive or negative in the article or clearly visible in the figures.
[a] deceased
M, male; F, female; d, day; wk, week; m, month; yr, year; ASD, atrial septal defect; PDA, patent ductus arteriosus.

Table 6.3 Most common manifestations of Marshall–Smith syndrome

Manifestation	Literature (n = 39)	Present study (n = 19)	Total
Dysharmonic bone maturation	100%	100%	100%
Psychomotor delay	100%	100%	100%
Typical facial appearance [a]	100%	100%	100%
Failure to thrive	96%	100%	97%
Respiratory problems	89%	74%	84%
Blue sclerae	86%	79%	83%
Hypertrichosis	82%	83%	83%
Kyphoscoliosis	39%	53%	46%
Gum hypertrophy	—	41%	41%
Umbilical hernia	53%	12%	31%
Cardiac defect	22%	12%	17%

[a] High forehead, proptosis, underdeveloped midface, anteverted nares, and retrognathia

Facial morphology

The typical facial phenotype consists of a high and prominent forehead, shallow orbits, flat midface, prominent premaxilla, and small and retracted mandible. The nose is frequently short, with upturned tip and anteverted nares, the philtrum may be long in infancy but in time may become short and everted. In older children the lips are frequently full and everted making the gingival hypertrophy and markedly irregularly placed teeth well visible in most patients. Two of the adult patients had a protruding tongue, but it is uncertain whether this is a frequent feature of the adult phenotype. The ears may be low set and minor anomalies of morphology are common. Facial hair is normal, including secondary hair in males.

Ophthalmology

The eyes are large and the orbits shallow, which both contribute to the proptosis. High myopia is present but glasses are frequently not tolerated which impairs visual development. Glaucoma, when present, is due to congenital anomalies of morphology of the anterior chamber or trabecular meshwork and affects about 30% of patients. Optic nerve hypoplasia has been found in some with glaucoma, but also in absence of glaucoma suggesting it to be a primary phenomenon. Several patients experienced corneal ulceration peri–operatively due to incomplete eye closure, and this should be highlight-

ed as a preventable complication. Patients should have regular ophthalmologic evaluation due to the range of pathologies, the difficulty of patients to self–report symptoms, and the importance of early intervention to reduce secondary phenomena.

Respiratory complications

The frequent and significant respiratory difficulties in MSS result from a combination of pathologies, mainly upper airway obstruction (retrognathia; choanal stenosis; abnormal larynx), and aspiration pneumonia (secondary to underdeveloped epiglottis and pharyngeal incoordination). Retrognathia is a frequent sign in MSS and contributes to both upper airway obstruction and poor visualization of the anatomy on laryngoscopy. Choanal stenosis occurred in six of our cohort and in four additional cases from literature (Tipton et al., 1973; Visveshwara et al., 1974; Flatz & Natzschka, 1978; Summers et al., 1999) suggesting an incidence of 5–10%. It presents later than classical choanal atresia, and other cases have been reported with partial stenosis making passage of feeding tubes difficult (Perrin et al., 1976; Menguy et al., 1986) suggesting that the stenosis features a spectrum of expression and is possibly caused by midface underdevelopment. Analysis of the laryngeal features in MSS is hampered by the variety of terms used to describe similar findings such as laryngomalacia, laryngeal stenosis, glottic stenosis, anteriorly placed larynx, and rudimentary epiglottis. In some patients, the larynx is described as anatomically normal, but with a functional obstruction. Irrespective of the cause the upper airway obstruction leads to an increase in negative thoracic inspiratory pressure, increasing the risks of aspiration and increasing pulmonary venous return contributing to increased pulmonary vascular pressure. Pulmonary hypertension with evidence of right ventricular hypertrophy has been reported in four cases in the literature and one of our series, and has a poor prognosis (LaPenna & Folger, 1982; Johnson et al., 1983; Yoder et al., 1988; Adam et al., 2005).

Airway support is required in the majority of cases either via tracheostomy or a tube keeping the nasopharyngeal airway open. This is most commonly required in the first week of life and may be required for several years, or even lifelong. Several patients have had reconstructive surgery incorporating mandibular distraction to improve airway competence, with varying degrees of success. Once no longer dependent on such airway support, many patients have continued to experience airway incompetence, usually presenting as obstructive sleep apnea. This may require airway support into adulthood, either with positive pressure ventilation or nasopharyngeal airway at night. General anesthesia appears safe in experienced hands with several techniques adopted to aid intubation, including ketamine induction, use of a laryngeal mask, and use of a nasopharyngeal airway (Antila et al., 1998; Dernedde et al., 1998; Machotta & Hoeve, 2008).

Hearing

Minor anomalies of external ear morphology and narrow ear canals are common. Many patients have sensorineural or mixed conductive hearing loss in the moderate range. Inner ear malformations have not been noted.

Bone and connective tissue

The bone age is invariably reported as advanced at birth and in childhood. Full skeletal surveys however, do not show an advanced bone age elsewhere and only mild abnormal bone maturation in the long tubular bones (wide epiphyses). In the hand, the carpus appears more advanced in age than the phalanges. Therefore it seems more justified to state bone maturation in MSS is abnormal instead of advanced. We consider it as being a dysostosis. Typically the proximal and middle phalanges are wide, bullet shaped or rectangular and terminal phalanges short and narrow (Figure 6.3).

MSS has been considered as an example of an overgrowth syndrome. However, stature is typically normal in infancy and early childhood, and in the second decade height progressively diverges from normal so that final height is >6 standard deviations below the mean. This is compounded to some degree by (kypho)scoliosis. There does not appear to be a growth spurt associated with puberty (the timing of which is normal). Thoracic kyphoscoliosis becomes evident in childhood and appears universal by adulthood. No structural abnormalities of the vertebral bodies are usually seen. Surgical rod implants impair already limited growth and mobility, but make lifting and handling easier. Non–traumatic fractures and osteopenia have been reported in some however several patients have sustained significant trauma without fracture, and osteopenia is not universal. Blue–gray sclerae are evident in two thirds of cases, and all patients with non–traumatic fractures had this feature.

Umbilical hernia occurs in around 30% of cases but herniation at other sites are not widely reported. One patient had recurrent herniation after abdominal surgery suggesting a possible defect in connective tissue healing. Scar formation however appears to be normal, and although skin texture is frequently described as soft, there is no evidence of a tendency to bruise easily, and no reports of abnormal bleeding. Joint laxity may be present in the periphery in younger patients, although mild contractures and high muscle tone may also occur. Pes planus appears universal. Gingival hyperplasia is frequent and present in 40%. It may require surgery to maintain oral hygiene. Histology has not been reported so the etiology of this manifestation is unclear.

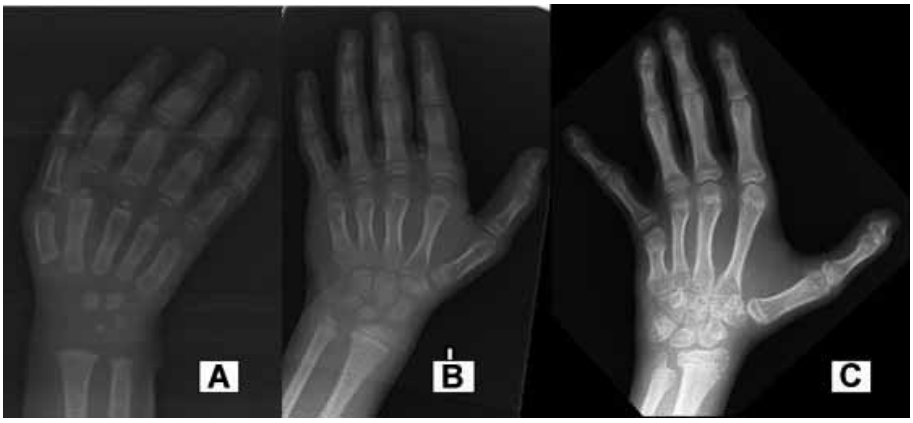
Abnormalities of the upper cervical spine and skull base have been noted with appearances of hyperostosis, dysplasia, and sclerosis. Radiological evaluation of the cer-

vical spine and skull base with flexion/extension views or other imaging modalities is warranted. Neurological complications are discussed below.

Development and behavior

Patients show a moderate to severe cognitive deficit, with several behavioral characteristics that were common to many in the cohort. Subjects mostly have a happy demeanor and especially enjoy social interactions with friends and family (van Balkom et al., 2011). A fascination for a favorite toy with which they tend to play in a repetitive, stereotypical manner, appears a common phenomenon. This is often a toy designed to stimulate several senses at once, perhaps appealing to children with impaired hearing and vision. Speech milestones are markedly delayed with many subjects never attaining spoken language, presumably in part due to anomalies of laryngeal and facial anatomy. Motor milestones are also severely delayed with several patients remaining non–ambulant.

Figure 6.3 X–rays of hands



(A) newborn (Patient 4) (B) 5 years (Patient 8) (C) 12 years (Patient 14)

Neurology

MSS patients have usually truncal hypotonia and peripheral hypertonia with brisk deep tendon reflexes. This phenotype is present from childhood and appears non–progressive. Drooling of saliva is common and may stem in part from oromotor dysfunction, but

is compounded by facial anatomy promoting an open mouth. Two patients developed spastic tetraparesis in infancy secondary to cervical spine compression and another patient had asymptomatic cervical spine stenosis noted on MRI. Neuroradiological imaging has shown a number of structural anomalies such as absent or underdeveloped callosal body; ventriculomegaly; pachygyria; polymicrogyria; and septo–optic dysplasia. Occasional seizures occur but they are not common and no patient is receiving anti–convulsant therapy. We recommend brain imaging in infants presenting with MSS and there should be awareness of the risk of cervicomedullary compression.

Other findings

Two male patients have developed hypertrophic pyloric stenosis, with a classical presentation at around one month of age. The finding of pyloric stenosis in 2 out of 19 cases may be coincidence, or may be related to other common findings in infants with MSS, such as advanced carpal bone maturation and gingival hypertrophy. One patient of the present cohort developed unilateral Wilms tumor at the age of 4 years. No other patient has been reported with any type of malignancy, but most cases were very young when reported. Further long–term follow–up and cohort studies will be required to establish whether individuals with MSS have an increased susceptibility to Wilms tumor or other forms of cancer. No screening is currently warranted. Craniosynostosis occurred in one patient and is reported in three from the literature. The affected sutures were the metopic suture in three patients and the posterior segment of the sagittal suture in one. All patients have a thin build with reduced muscle bulk.

Adult phenotype

The general adult phenotype is characterized by moderate to severe mental retardation, including little or no speech and limited mobility. Adult height and weight are significantly reduced but head circumference is normal. The facial features become more obvious, especially in the proptosis, short nose with anteverted nares, and thick, everted lips. The mouth is often held open showing prominent and irregularly placed teeth and thick gingiva. The tongue may be large and protuberant and drooling is common. Individuals of both sexes are hirsute, particularly on the limbs and back. Adults are cheerful and pleasant in nature, although stubbornness and obsessive traits also occur. Medical problems identified in adulthood are obstructive sleep apnoea, aspiration pneumonia, pulmonary hypertension, and early onset osteoarthritis.

Differential diagnosis

Much debate can be traced in medical literature whether Marshall–Smith and Weaver syndromes are distinct entities, in part because both syndromes were first described around the same time with advanced skeletal maturation as a principal feature. Careful delineation of the phenotype however, with particular regard to the facial features, radiological findings and natural history, suggests significant differences (Fitch, 1980). Other syndromes with overlapping phenotypes include Desbuquois chondrodystrophy, Fine–Lubinsky syndrome, pyknodysostosis, Antley–Bixler syndrome, Ehlers–Danlos type VII, galactosyltransferase I deficiency and Lysyl hydroxylase 3 deficiency (Hennekam et al., 2010). The combination, however, of the distinctive radiological findings, facial dysmorphism, and upper airway pathology, make MSS an easily recognisable and unique entity.

Etiology

All definite cases of MSS have occurred sporadically with, no familial recurrence or parental consanguinity. The gender ratio of reported cases is roughly equal, and there is not an increased prevalence of sub–fertility or miscarriage in the parents of affected individuals. Although one report in the literature described a brother and sister with features suggestive of MSS (Jalaguier et al., 1983), we posit that the clinical features are more suggestive of Weaver syndrome than MSS. One patient with a phenotype suggestive of MSS was found to have an inverted duplication of chromosome 2q (Seidahmed et al., 1999), but other patients with trisomy for this region did not resemble MSS, and no other chromosome abnormalities have been reported. In the present cohort paternal or maternal age at conception was not advanced beyond that of the general population.

The analysis of 12 patient samples by array–CGH did not identify any recurrent pathogenic CNVs within this sample set. These results indicate that at the resolution tested, MSS is not a genomic disorder caused by a recurrent pathogenic CNV.

Marshall–Smith syndrome wiki

The term wiki is derived from the Hawaiian phrase for quick, and is used for an online collaborative resource for compiling information from numerous authors. MSS is an extremely rare condition with less than 50 cases reported worldwide, and traditional methods of collating a large series of patients are hampered by geographical distances, underdeveloped healthcare systems in developing countries, and language differences. Compiling anonymous phenotype data on a wiki allowed parents and carers to add com-

ments on aspects of the phenotype or natural history based on their own experiences, thus giving a deeper insight into the natural history of the syndrome and facilitating dialogue between clinicians and families that were spread across 11 countries in Europe and the Americas. This technique also aided recognition of common traits, as sharing experiences allowed families to remember important or significant facts that they had forgotten to report to their clinician. Responses from all families were compiled and used as a basis for re–writing of the final draft of this manuscript. Using the wiki facilitated the development of a much more complete and consistent data–set than would have been possible using retrospective case–note review. It may therefore be a useful adjunct if evaluation of all subjects by a single observer is impractical due to the geographical spread of the patients. Wikis are starting to be used in many areas of science, as a way of more efficiently utilizing collective expertise and sharing information that would otherwise remain hidden in personal files or memories (Hu et al., 2008). We recommend this technique for future studies attempting to describe the phenotype and natural history of (very) rare diseases.

Conclusion

We present a relatively large series of patients with MSS. By including previously reported cases, adults and information obtained from families using a wiki resource, we could further delineate this distinctive and severe multisystem disorder, have gained insight into the natural history of the entity and suggested recommendations for management. Discovery of the molecular cause and evaluation of the long–term physical and medical consequences will further aid medical management, lead to potential treatments and reveal important biological mechanisms in human development and function.

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CHAPTER 7

Development and behavior in Marshall–Smith syndrome: an exploratory study of cognition, phenotype and autism

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ABSTRACT

BACKGROUND – Marshall–Smith syndrome (MSS) is an infrequently described entity characterized by failure to thrive, developmental delay, abnormal bone maturation and a characteristic face. In studying the physical features of a group of patients, we noticed unusual behavioral traits. This urged us to study cognition, behavioral phenotype and autism in six patients.
METHODS – Information on development, behavioral characteristics, autism symptoms, and adaptive and psychological functioning of six MSS children was collected through in–person examinations, questionnaires, semi–structured interviews of parents and neuropsychological assessments.
RESULTS – Participants showed moderate to severe delays in mental age, motor development and adaptive functioning, with several similarities in communication, social interactions and behavior. There was severe delay of speech and motor milestones, a friendly or happy demeanor and enjoyment of social interactions with familiar others. They exhibited minimal maladaptive behaviors. Deficits in communication and social interactions, lack of reciprocal social communication skills, limited imaginary play and the occurrence of stereotyped, repetitive behaviors were noted during assessments.
CONCLUSIONS – Systematic collection of developmental and behavioral data in very rare entities such as MSS allows recognition of specific patterns in these qualities. Clinical recognition of physical, developmental and behavioral features is important not only for diagnosis, prognosis and counseling of families, but also increases our understanding of the biological basis of the human physical and behavioral phenotype.

KEYWORDS: autism, behavioral phenotype, cognition, intellectual disability, Marshall–Smith syndrome

INTRODUCTION

In studying genetic syndromes, clinicians and researchers have described difficulties in examining psychological and behavioral features of the syndromes, and how they might be causally related to underlying genetic conditions (Skuse, 2000; Cassidy & Morris, 2002). Studying syndromes that commonly occur with severe intellectual disability (ID) is further complicated by the lack of adequate instruments to directly measure individual cognitive levels. Although correlations between biological and behavioral variables do not necessarily imply causation, and methodological differences across studies have often limited our ability to draw conclusions, many researchers have recognized the importance of cross–disciplinary collaboration in studying samples of patients with

genetic defects in an effort to improve our understanding of normal and abnormal behaviors (Finegan, 1998). Careful clinical assessment and description are therefore crucial steps in eventually determining clinical relevance.

Marshall–Smith syndrome (MSS) is an infrequently described malformation syndrome first reported by Marshall et al. (1971) and characterized by ID, abnormal bone maturation, failure to thrive, severe respiratory problems and unusual facial features. To date, some 45 cases with this syndrome have been reported internationally in various languages, usually as single case reports or small groups (Marshall et al., 1971; Nabrady & Bozalyi, 1973; Tipton et al., 1973; Visveshwara et al., 1974; DeToni et al., 1976; Hassan et al., 1976; Perrin et al., 1976; Iafusco et al., 1977; Ferran et al., 1978; Flatz & Natzschka, 1978; LaPenna & Folger Jr, 1982; Johnson et al., 1983; Menguy et al., 1986; Roodhooft et al., 1988; Yoder et al., 1988; Smyth et al., 1989; Charon et al., 1990; Eich et al., 1991; Pappas & Rekate, 1991; Sperli et al., 1993; Sharma et al., 1994; Endo et al., 1995; Cullen et al., 1997; Williams et al., 1997; Antila et al., 1998; Chatel et al., 1998; Dernedde et al., 1998; Seidahmed et al., 1999; Summers et al., 1999; Moon et al., 2002; Sumiya et al., 2002; Wang, 2002; Diab et al., 2003; Watanabe et al., 2003; Butler, 2004; Adam et al., 2005; Deshpande et al., 2006; Travan et al., 2008; Shaw et al., 2010).

A recent genetic study reported on mutations in *transcription factor nuclear factor I (NFIX)* resulting in MSS (Malan et al., 2010). At present, the specific function of *NFIX* remains unclear, but *NFIX* must have an important role in human brain development and skeletogenesis.

Recently, we reviewed the physical features of a group of 19 patients and compared these to all earlier reported cases (Shaw et al., 2010). In addition to medical assessment and clinical examination, personal history and additional information on the patients have been assimilated using an online Wiki. Through this resource, parents and carers had secure access to a lay translation consisting of the general description of the syndrome and medical complications, and could add comments on aspects of the phenotype or natural history, based on their own experiences (Shaw et al., 2010). During the study, we noticed unusual behavioral traits in several patients not reported before. Some behavioral features showed resemblance to autism. Earlier reports on children with MSS had described delays in psychomotor development (Sumiya et al., 2002; Butler, 2004; Adam et al., 2005), and absence of speech/language development (Sperli et al., 1993), but no other behavioral characteristics. This urged for a more detailed cognitive and behavioral assessment.

Here, we report an exploratory investigation of behavioral and psychological profiles in six children with MSS. Our general aim was to describe their behavior patterns, development and cognitive abilities, using in–person clinical assessments and a dedicated test battery. A specific aim was to investigate if an autism symptom profile could be part of the syndrome.

MATERIALS AND METHODS

Exploratory study

In accordance with the clinical impression during the study of the natural history in MSS mentioned before (Shaw et al., 2010), we wanted to conduct an exploratory study. In this exploratory study, we focused on autism symptomatology and distinctive behavioral features in MSS children at different ages and developmental stages, while at the same time systematically assessing and describing the behavior and development of the children.

Participants

The total study group of MSS patients participating in the natural history study consisted of 19 children from 11 countries (Belgium, Brazil, Croatia, France, Germany, India, Mexico, the Netherlands, Norway, UK and USA). Of these, six MSS patients could be assessed: a personal assessment of the other children was impossible, due to a language barrier between children, families and the examiners, death of children, or because of the distance to their country of residence.
The six participating MSS children, three girls and three boys, were born between 1994 and 2006. Three resided in the Netherlands, two in the UK and one in France.
All parents gave written informed consent, and the Medical Review Ethics Committee gave permission to perform the study.
A summary of the major physical characteristics of the six patients compared to those of all known patients with MSS is provided in Table 7.1. A more detailed description of physical manifestations can be found elsewhere (Shaw et al., 2010).

Test instruments

All children in the study were clinically examined by the same child psychiatrist (IvB) and neuropsychologist (PJV). The child psychiatrist was trained in the Netherlands, where she did residencies in pediatrics, genetics, psychiatry and child psychiatry. She has more than 15 years of clinical experience and has expertise in developmental and genetic syndromes. She is certified in the use of standardized assessment instruments for research diagnosis of autism spectrum disorders (van Balkom et al., 1998, 2002, 2009).

One subject (patient 6) could not be fully assessed with the complete test battery due to language problems and geographical distance. Only instruments valid and reliable in studying individuals with limited verbal abilities were chosen to assess cognitive functioning. In–person interviews with parents were used to assess past and current

Table 7.1 Main physical characteristics of the presently studied six patients with Marshall–Smith syndrome, compared to those in Marshall–Smith syndrome in general

Patient		**1**	**2**	**3**	**4**	**5**	**6**	**Feature reported in literature cases**
Epidemiology	Gender	F	F	M	F	M	M	equal M : F ratio
	Age (years)	14	7	3	8	13	7	0–19
Growth	Birth weight (g)	2990	1590	2975	3630	2000	3230	term mean 3144
	Gestation	term	32 wks	term	term	term	term	term
	Weight (kg)	30		15	26	22	21	n/a
	Height (cm)	138	103	100	133	120	120	n/a
	Height centile (SDS if centile<2)	0.2 (–2.90)	7	10	50	<0.4 (–4.9)	30	n/a
Development	Degree of (cognitive) disability	severe	severe	severe	severe	severe	not measured	moderate–severe
	Walked	4.5 years	–	–	2 years	never	3 years	delayed
	First words	48 months	60 months	–	–	none	36 months	delayed
Typical craniofacial features		+	+	+	+	+	+	+
Eyes	Myopia	–	–12 / –9	–14	–	+	–	+
	Glaucoma	–	–	+	–	+	–	N/A
	Optic nerve hypoplasia	–	–	–	+	–	–	N/A
Respiratory problems		+	–	+	+	+	+	+
Neurology	High tone	+	–	–	–	+	–	N/A
	Brisk reflexes	+	–	–	+	+	–	N/A
	Brain MRI	normal	normal	hypoplasia callosal body	normal	normal	normal	N/A
Skeletal	Abnormal bone maturation	+	+	+	+	+	+	+
	Bone fractures	–	–	1	–	–	4	+
	Scoliosis	+	–	–	–	+	+	+
Other	Cardiac defect	–	VSD	–	–	–	–	+
	Hearing loss	–	–	+	–	+	+	+
	Umbilical hernia	–	–	–	–	–	+	+
	Hypertrichosis	–	+	+	+	+	+	+
NFIX Mutation found		–	+	+	–	–	+	

F=female; M=male; N/A=not available; SDS=standard deviation score; MRI=magnetic resonance imaging; VSD=ventricular septal defect

development, and functioning on three major domains: communication (adaptive) behavior, and social–emotional development. Through standardized questionnaires, additional information was gathered about other symptoms and psychological functions, such as aggression, attention and mood.

Assessment of intellectual capabilities

Mental and motor functioning was assessed using the Dutch version of the Bayley Scales of Infant Development, 2nd Edition (BSID–II; Van der Meulen et al., 2002). The mental scale consists of items assessing level of visual and auditive information processing, hand–eye coordination, imitation, language development, memory and problem solving skills. The motor scale assesses level of fine and gross motor development. The BSID–II is considered a reliable and valid instrument (Provost et al., 2000, 2004). The raw scores on the motor and mental scale were converted into age equivalents to determine level of motor and mental functioning. The BSID–II was administered according to the manual of the test.

Child psychiatric examination and Autism Diagnostic Interview

An experienced child psychiatrist (IvB) performed psychiatric examinations of each of the children and also interviewed one or both parents of each child with the Autism Diagnostic Interview – Revised (ADI–R) (Lord et al., 1994). The ADI–R is considered a reliable and valid instrument (Rutter et al., 2003; Cicchetti et al., 2008; Le Couteur et al., 2008). It is a semi–structured diagnostic interview designed to collect developmental information, a history focused on autism–specific criteria, and information on actual behavior as it has occurred in the child's daily life, as a basis for a lifetime diagnosis of pervasive developmental disorder. The ADI–R yields individual item scores (normal, possible abnormality, definite abnormality) and domain scores in the areas of social skills and play, communication and behavioral abnormalities. While there were concerns about how level of ID might affect interpretation of the results, we still considered the ADI–R an appropriate standardized instrument to collect data on development given the lack of available measurements for individuals with severe ID (Howlin, 2000; De Bildt et al., 2004; Bruining et al., 2010).

Adaptive functioning

To assess the degree of personal and social self–sufficiency, the Vineland Adaptive Behavior Scales – Survey Form (VABS) was used (Sparrow et al., 1984). The VABS sup-

plies measures of the level of adaptive functioning on three domains: communication, daily living skills and socialization. These measures provide an overall adaptive composite score, allowing for a classification in adaptive level (in five levels, high to low), and separate composite scores on the three domains. The psychometric properties of the VABS are considered to be good (Sparrow et al., 1984). The interview was conducted by two experienced clinicians (PJV, MF).

Behavioral characteristics

Problem behaviors and competencies of the children were assessed using the Child Behavior Checklist (CBCL; Achenbach, 1991a,b). Kostentausta et al. have found that the CBCL may be less reliable for those with moderate to severe ID, possibly because many of its items may not reflect problem behaviors in children with ID, and may fail to reveal all psychiatric issues (Kostentausta et al., 2004). De Ruiter et al. have studied the developmental course of psychopathology in children with and without ID using the CBCL. They found that, while children with ID (ranging from mild to moderate levels of ID) showed increased risk for problem behaviors across all ages when compared to typically developing children, developmental trajectories in both groups were quite similar (De Ruiter et al., 2007). The CBCL has previously proven its usefulness in studying populations of children with severe ID, for example, Rubinstein–Taybi syndrome (Hennekam et al., 1992), Williams syndrome (Graham et al., 2005) and Costello syndrome (Axelrad et al., 2004).

The CBCL is completed by the parents or primary caregivers and gives insight into problem behaviors. The questionnaire is informative on eight specific domains and problem behaviors: aggressive behavior, mood, attention, delinquent rule–breaking behavior, social problems, somatic complaints, thought problems and withdrawal. Total scores for internalizing problem behavior (withdrawal, somatic complaints and anxious/depressed) and externalizing problem behavior (delinquent rule–breaking behavior, and aggressive behavior) are obtained as well as a total problem score by summing all eight specific problem behaviors.

RESULTS

We present first a narrative description of individual clinical assessments and behavioral observations. Subsequently, we present measures of cognition, development, adaptive functioning and behavior. Because patient 6 could not be assessed with the complete test battery, his findings are included only for those items that could be studied (child psychiatric exam; ADI–R).

Individual child psychiatric assessments, clinical observations of interaction and behavior

Patient 1

Patient 1 was of middle school age and had a lively, friendly demeanor. She had little initial reserve at first contact, showed no anxiety and immediately tried to actively and spontaneously engage the examiner in play, by running back and forth and talking incessantly or by pulling hands. There was sufficient eye–to–eye gaze during examination; and although reciprocity was limited, she visibly enjoyed the interaction and play with the other. She was able to engage in conversation, but back–and–forth interchange was limited. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient. These observations showed that she had difficulty completing tasks. Probably because she did not understand some of them but also because her attention span was short and she was easily distracted by sounds, movements and her own wishes. She clapped her hands when she was complimented on her efforts in trying to stay on task and during the examination she repeated this action in a ritualized manner. She made her wishes for play clearly and insistently known; she demanded participation while directing the actions of the other, laughing the whole time. There was little joint interactive or collaborative play. She walked independently at age 4, her gait broad based. Her mood appeared happy; she often smiled without clear cause.

Patient 2

At second examination, patient 2 was of primary school age. She made a friendly, active impression. She was diagnosed with a significant refractive error, but only recently started training to wear glasses at school. There was some eye–to–eye gaze of brief duration and there was little integration of gaze, facial expression, vocalization and gesture. When younger she seemed interested in her surroundings, and explored her environment primarily through turning, biting, chewing or licking objects. She had a tendency of staring into lamps. Her mother mentioned that she was sensitive to noises at a young age, she startled easily and would panic and cry loudly, but this behavior had improved. She would usually cover her ears when her mother vacuumed. Her production of spontaneous language and her comprehension of verbal communication are limited. She had less than 10 words but was able to vocalize sounds in differing intonations. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/sufficient.

These observations showed that her attention span was short; she was easily distracted by sounds or movements. She enjoyed playing with building blocks, and she was able to slowly stack these or hand them to her mother. Some motor milestones had not been reached, she was not able to walk independently, but would stand and walk holding her parent's hand. Recently, she had started imitating her parents by drinking independently from a mug, although she would do so messily with one hand. Her mood was usually happy; she smiled and laughed often although the cause of it was not always clear. She sometimes smiled while looking at people, but her smiles were generally not reciprocal. Her mother mentioned that she would have difficulty falling asleep, and would cry loudly to be allowed out of bed.

Patient 3

Patient 3 was an alert toddler who had a friendly demeanor. He had marked vision problems and a history of recurrent ear infections. He smiled often without obvious cause and without making eye contact with the examiner. There was little visible reaction to his own name, nor did he respond to the examiner's facial expression, orientation or smiles. His eye–to–eye gaze was limited, and there was little reciprocity or spontaneous initiation of contacting or engaging the other. His parents mentioned that he would put up his arms to be lifted or pull their hand to get attention; he had little response to the examiner's attempts to draw his attention to distant objects. His mother mentioned that he enjoyed playing 'calling on the phone', making prattling sounds but no words. He startled easily at unexpected sounds or movements; and he would become quite upset and start crying by more pronounced sounds as, for example, organ music in church. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was sufficient, although he showed little interest in his surroundings beyond what was right in front of him. He had played with one favorite musical toy for the past year and a half, enjoying its crinkly sounds. He would sometimes reach with open hand for a favorite toy, but did not point to it to indicate a desire to play with it. He could spontaneously initiate a game of peek–a–boo by pulling a cloth over his face and waiting for his father to pull it away. Walking independently had not been achieved yet, but he started crawling at 2.5 years and could pull to standing at 3.5 years. His mood was happy; he would laugh when physical games such as lifting, jumping up–and–down and tickling were initiated by his parents.

Patient 4

Patient 4 was of primary school age and seemed shy and hesitant at first contact; she had a friendly facial expression. At first, eye–to–eye gaze was of brief duration, but this improved during the examination, and there was some integration of gaze, vocalization and gesture. It was, however, difficult for the examiner to draw her attention to a distant object through eye contact and facial orientation. She made a specific vocalization, which according to her mother she would always use to indicate the dog. She had no clear words, but would vocalize some sounds in differing intonations. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether her attention span was deemed short/ sufficient. These observations showed that her attention span was short; she was easily distracted by sounds or movements. During the examination she was restless, active and kept moving around the room. Her mother mentioned that she was usually 'on–the–go'. She had difficulty staying on task, even when the task was very structured (such as drawing a shape) and she tended to flit from one thing to the next. She enjoyed playing with her doll, would take it out of a toy buggy and hug it. She would recognize and point to herself in family pictures when invited to do so. When looking at a photo album she was not easily distracted by ringing toys, but persisted in turning the pages to continue looking at pictures. Her mother would find her quite active at home, often imitating play activities initiated by her younger sister. Although she enjoyed imitating play activities she had difficulties initiating and organising new games herself. She was able to walk independently, her gait was broad based and her gross motor skills were clumsy. Fine motor skills were immature. She walked around the room, pointed out the dog and walked closer to hug him. Her mood was usually happy; she would smile frequently and sometimes put her hand in front of her mouth to indicate surprise.

Patient 5

Patient 5 was of middle school age and had a passive and withdrawn demeanor at first contact; he drooled a bit. He wore a brace and was wheelchair–bound, but able to operate his wheelchair. He was diagnosed with many health problems, which included glaucoma and severe scoliosis. He kept his head down a great deal, and although there was some eye–to–eye gaze, there was little integration of gaze, facial expression and gesture. He had little reciprocal response to the examiner's facial expressions or smiles, and there was no attempt to spontaneously engage in social interaction with the examiner through eye gaze. He vocalized sounds, but had no words. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed. These obser-

vations showed that his attention span was sufficient. He did react to being touched by turning his head towards the person, he would smile and laugh when he was tickled, and clearly enjoyed physical interaction and play, inviting the other to continue by re–extending his hands or arms after tickling. He would also extend his hand to grab and would gesture purposively when drumming on a favorite toy drum. He drummed on the plastic side of the toy and not on the drum itself. His mother mentioned that he only wanted this particular toy drum of a certain style and color, and that he would accept no other replacements. Although his motor skills were limited by his physical disabilities, patient 5 had recently swum small distances in a pool independently from his helper, had walked a small distance in the pool and had shown increasing confidence in the water. He would turn from a sitting position on the sofa and get down from it when verbally requested to do so. His mood was usually happy and stable, but sometimes he would show frustration, for example, when waiting for his food, by throwing things on the floor to get the attention of his helpers.

Patient 6

Patient 6 was a lively, active, primary school age boy at first contact; he was comfortable in the presence of his mother. He wore spectacles and had hearing aids in both ears. Initially, he averted his gaze, but during the continued examination there was intermittent eye–to–eye gaze. There was limited response to the examiner's facial expressions or smiles and little reciprocity in social interaction with the examiner, but he frequently spontaneously engaged with his mother trying to get her attention to help him with tasks and play. His spontaneous language and communication were limited, and although he vocalized sounds there were few discernible words. Some of these were understood by his mother, but not by many others. For 5 to 10 min, the child's capacity to attend to different tasks (such as toys or objects) was observed, to conclude whether his attention span was deemed short/sufficient. These observations showed that his attention span was short: he was fidgety and had difficulty staying on task, tending to flit from one object or activity to the other. When he was interested in the task or the object, his perseverance improved. When interested in play he would draw his mother's attention primarily through sounds and by pulling her hand towards the object; his mother mentioned that he could be very insistent when trying to have his way. Gross motor skills were sufficient; fine motor skills were immature. His mother mentioned that he was able to ride a bicycle, but was prone to fall and he would see no dangers. During examination his mood was happy; he enjoyed trying to color a drawing. He got up just as happily when the examination was finished and rushed to exit the room before his mother. Often his behavior at home would be challenging, he would tend to be insistent

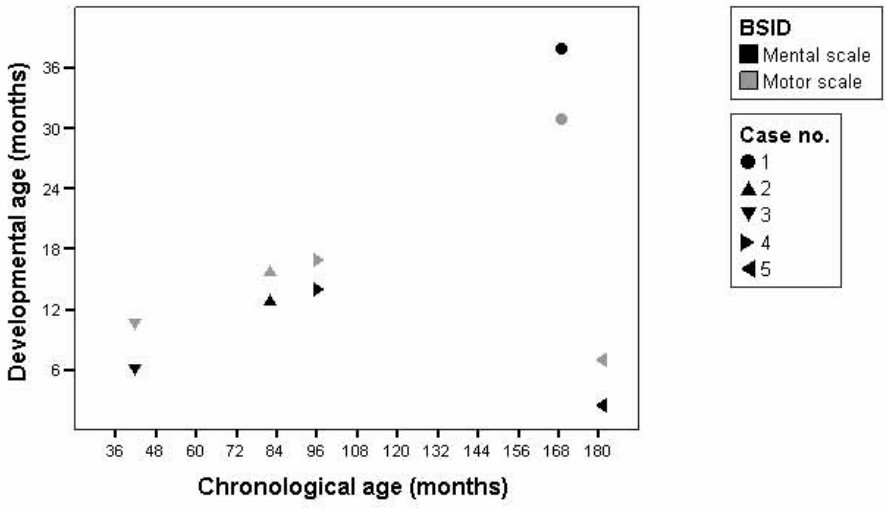
and quite irritable when things would not go as he expected. When irritable he could scream loudly; in general he demanded a lot of attention, and his mother mentioned that it would take a lot of effort to distract and calm him. At night, he used an oxygen mask; he would often be anxious and have difficulty falling asleep.

Cognitive assessment and cognitive function

Bayley Scales of Infant Development

Scores on mental age and motor development can be seen in Figure 7.1. In view of their ID combined with the fact that chronological age of most participating children was above that for norms of the BSID–II, we present results in Figure 7.1 as age equivalents and omit standard scores. The graph indicates that generally a progression in mental age and motor development can be expected with increasing age, but in a single patient (patient 5) cognitive and motor development remains severely delayed.

Figure 7.1 Developmental level of mental and motor functioning, measured by the Bayley Scales of Infant Development (BSID), compared to chronological age



Development and autism symptomatology

Autism Diagnostic Interview – Revised

On the three domains of the ADI–R (social skills and play, communication and behavioral abnormalities) all children scored above the cut–off, with the exception of patient 6, who did not score above cut–off on behavioral abnormalities (Table 7.2).

Table 7.2 Item scores on the three domains of the Autism Diagnostic Interview – Revised

		Patient #					
Test domain	Cut–off	**1**	**2**	**3**	**4**	**5**	**6**
Social skills and play	≥10	14	21	16	16	11	14
Communication (verbal & non–verbal)	≥8	13	NS	NS	NS	NS	14
Communication (non–verbal only)	≥7	NS	10	7	12	8	NS
Behavioral abnormalities	≥3	3	4	3	4	6	2

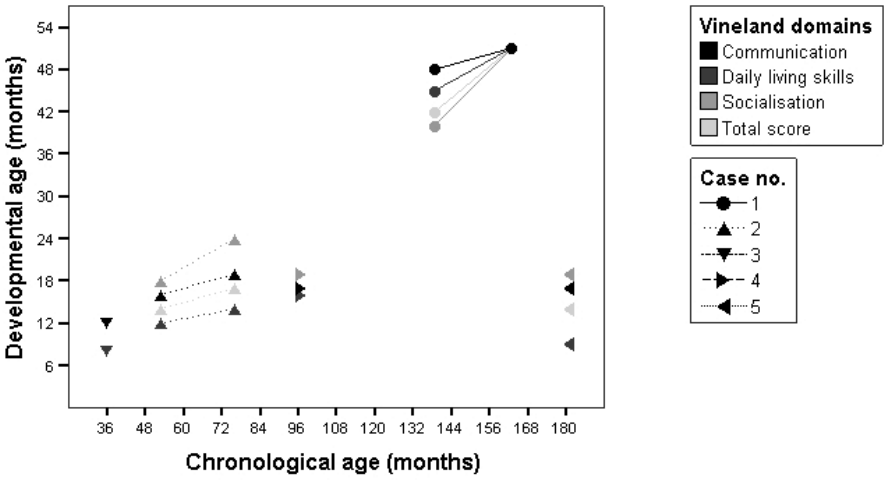
NS = no score

Adaptive functioning

Vineland Adaptive Behavior Scales

Patients 1 and 2 were assessed with the VABS twice during the study, with an interval of 2 years, which allowed for a limited follow–up perspective on their adaptive functioning and development (Figure 7.2). For the other subjects, no earlier assessments were available, due either to their young age or to practical considerations, especially a geographical barrier. For these subjects, first measurements are also shown in Figure 7.2. The following observations with respect to development, strengths and weaknesses can be made on adaptive functioning based on results of the VABS. First, we see gradual improvements on all adaptive scales of the Vineland over time, when comparing the children with each other (with the exception of patient 5) as well as within themselves (patient 1 and 2). Patient 2 showed progress in all domains at second measurement, although one more gradually than the other, with scores overlapping. This seems to indicate that, although children with MSS are considerably delayed on adaptive functioning,

Figure 7.2 Developmental level on the three domains and total adaptive behavior score of the Vineland, compared to chronological age



they do have learning potential and seem to follow their own slow developmental trajectory. Second, the domain of socialization appears to be somewhat better developed, with parents reporting, for example, that their children do show affection to familiar persons, anticipate when they are about to be picked up by their parents or caregivers and imitate simple proceedings of adults. Third, the domain of communication seems to be a weaker domain. Children with MSS score positive on questions like 'understands the meaning of at least 10 words' or 'listening attentively to instructions', but they fail on questions that imply mastering (the beginning of) expressive language like 'has a vocabulary of at least 50 words' or 'uses sentences of at least 4 words'. Fourth, in most children, daily living skills are the weakest domain. This domain contains questions regarding skills such as 'can drink without any help from a cup' or 'alerts the parent that he/she has to go to the toilet'.

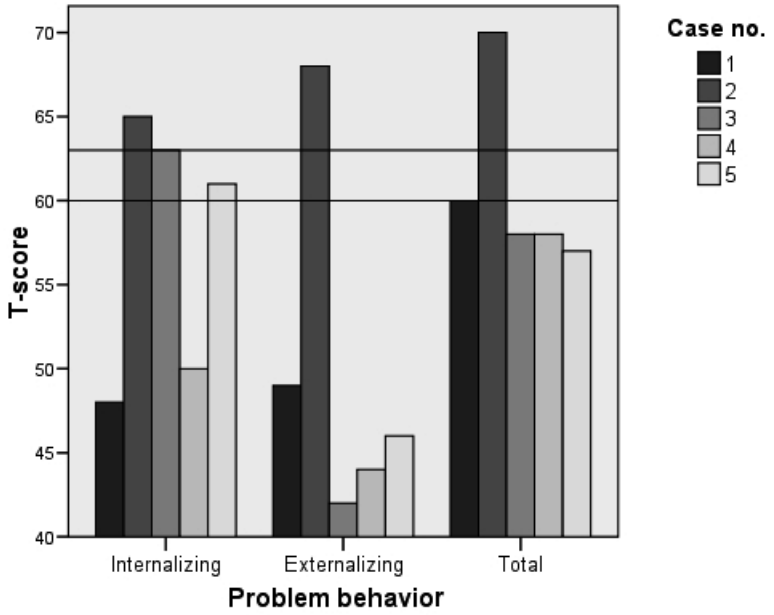
Again, results for patient 5 are an exception, as is also visible in Figure 7.1 of the BSID scales. Patient 5's somatic condition could partly explain his scores.

Behavioral issues

Child Behavior Checklist

The subjects show hardly any externalizing problem behavior with the exception of patient 2 (Figure 7.3), whose externalizing problems are the result of scores in the clinical range on attention problems and scores in the borderline range on aggressive behavior.

Figure 7.3 T–scores on internalising, externalising and total problem behavior, measured by the Child Behavior Checklist, in five patients with Marshall–Smith Syndrome



Three patients scored above the borderline or clinical range on internalizing problems: one patient (patient 5) did so because of a high score on somatic complaints (see case description); a second subject (patient 3) scored in the clinical range due to borderline scores on emotionally reactive behavior and withdrawn behavior; and the third subject (patient 2) scored in the clinical range on emotionally reactive behavior.

DISCUSSION

A structured clinical and interdisciplinary approach towards syndrome characterization and delineation includes the integration of information regarding developmental issues, cognitive skills and behavioral characteristics. Only a limited number of studies of rare syndromes which feature considerable ID have directly assessed cognition and behavior by examining the child with a structured test battery. More frequently, assessment was performed indirectly by interviewing the parents or based on observations by researcher or clinician. In the present study, we have combined direct evaluation of the

child (BSID; psychiatric assessment), with indirect information gathered from parents with structured interviews and questionnaires (VABS; ADI–R; CBCL).

In only a proportion of patients with MSS, a mutation involving the gene *NFIX* is found, suggesting that there may be other factors involved in patients with MSS where the mutation has not been determined. The significance of *NFIX* mutations, however, is still unclear as there is insufficient information on the effects which alterations in the gene may have. Further studies to find other gene(s) involved in the etiology for MSS are underway at present.

Cognitive and motor functioning in our sample of six cases with MSS is characterized by marked delays in individual development. The chronological age of the present MSS children lies between 42 and 181 months, while the developmental age as assessed by the BSID lies between 7 and 31 months on the mental scale and between 2.5 and 38 months on the motor scale respectively. When examining adaptive functioning, results from the VABS show social functioning as a relative strength and seem to indicate that in the presence of a slow individual development, progress in adaptive functioning, communicative, social and motor skills could be accomplished with increasing age. Decile scores were calculated based on the manual of the Dutch version of the VABS (De Bildt & Kraijer, 2003). Likelihood concerning the level of cognitive functioning could not be asserted for one participant due to young age. Within the category of severe ID, two of the participants were categorized as profoundly intellectually disabled, while two others were asserted as having moderate ID.

The children examined in the present study all showed significant delays in the development of speech and language or acquired no language at all. Language and social cognition are closely linked in development (Tecumseh Fitch et al., 2010). Language plays an important role in understanding social interactions, which is part of social cognition. Social cognition in turn is necessary to acquire language. Social cognition includes the capacity to follow the other's gaze to objects of interest, imitate the other and understanding the meaning of the other (Frith & Frith, 2010; Tecumseh Fitch et al., 2010). Communication between humans is determined both by speech and language abilities, and by non–verbal expressions such as eye gaze, joint attention, facial expressions, gestures and postures. Typically developing infants rapidly learn in their first year of life that the gaze and emotional expressions of others provides socially important information (Striano et al., 2006). The ability to detect emotional signals from others, interpret their meaning and adjust behavior accordingly is an important characteristic in social interactions and necessary for the development of social competence. Social competence may be defined as the ability to socially interact and understand others in an effective, responsive and appropriate way, and this is evident in typically developing children even before the onset of spoken language. Examples of socially competent behaviors may be

apparent in (developmentally) young children through non–verbal social interactions such as joint attention, smiling, approaching others, imitating another, imaginative play, imaginative play with peers and/or group play. An inability to interact this way may indicate an important deficit in the social domain as can be seen in autism spectrum disorders (Frith & Frith, 2008, 2010; Hoehl et al., 2009).

There were many similarities in social interactions and behavior between the children investigated in this study. Most prominent deficits in social interactions were: limited eye–to–eye gaze, lack of either initial reserve or aloofness, lack of reciprocity. Most important behaviors were: inflexibility with or without temper tantrums, repetitive and stereotypical play and limited imaginative play. In contrast to these findings is the determination that socialization may be a relative strength in MSS, as these children are able to show affection to familiar persons, anticipate when they are about to be picked up by their parents or caregivers and imitate simple proceedings. Scores from assessments and interviews with parents showed that the severe delays in development of speech/language, social skills, and levels of communicative and adaptive functioning may be consistent with autism symptomatology, although social functioning could be considered a relative strength in comparison with other domains of adaptive functioning. Differentiating between deficits related to ID/developmental delay and deficits related to (subtle) autism symptomatology proved too difficult to accomplish with certainty in the small sample of the present study. This is consistent with the difficulties described in other published studies of genetic syndromes with significant ID/developmental delay with autism (Percy et al., 1990; Mazzocco et al., 1998; Cohen et al., 2005).

It is well possible that the autism–like behavioral features found in the present study are influenced by the various significant medical issues. Furthermore, we need to also take into account the higher frequency of repetitive, stereotyped behaviors found in individuals with severe ID reported in various studies (Bodfish et al., 2000; Moss et al., 2009). Therefore, we hesitate to draw inferences about the association of an autism symptom profile with MSS based on the findings of this first exploratory study of behavior, cognition and development in the syndrome. Continued careful case descriptions with documentation and long–term follow–up of somatic, behavioral and cognitive phenotypes will eventually help determine their clinical relevance, and increase our understanding of diverse clinical presentations with or without autism symptomatology in this syndrome.

Conclusion

Results from our study make it clear that the children with MSS showed moderate to severe delays in mental age, motor development and adaptive functioning, with several

similarities in communication, social interactions and behavior. Speech and motor milestones were found to be severely delayed. Subjects mostly have a friendly or happy demeanor and seemed to enjoy social interactions that include familiar others, and they exhibited minimal maladaptive behaviors. Deficits in communication, social interactions, lack of reciprocal social communication skills appropriate for developmental level and stereotyped, repetitive behaviors were noticeable during in–person psychiatric and psychological assessments. There was limited imaginary play; subjects tend to play in a repetitive, stereotypical manner with a favorite toy they are fascinated with. These characteristics may fit the definition of an autism spectrum disorder, but it remains unclear how developmental progress over time might influence this determination.

By using a standardized research protocol through a dedicated test battery and re–examining children with genetic syndromes over time, we improve our ability to detect specific behavioral characteristics of syndromes such as autism or autism–related symptomatology, and gather information on the long–term natural history. Integrating interdisciplinary information contributes significantly to the development of more refined, structured measures of behavior and cognition in syndromes.

Clinical recognition of both physical and developmental and behavioral manifestations of syndromes is important for diagnosis, prognosis and counseling of the families involved, and coupling this with molecular genetic data will increase our understanding of the biological basis of the human physical and behavioral phenotype.

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CHAPTER 8

Prevalence of treated autism spectrum disorders in Aruba

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ABSTRACT

To study autism outside of a narrow range of settings previously studied, and in a particularly distinctive setting in the Caribbean. The aim of the Aruba Autism Project was to determine the prevalence of autism spectrum disorders (ASDs) in birth years 1990–1999 in Aruba. A record review study was conducted; cases were ascertained from children treated at the Child & Adolescent Psychiatry Clinic of Aruba, the first and only child psychiatry service on the island. In these 10 birth years we found a prevalence for autistic disorder (AD) of 1.9 per 1,000 (95% CI 1.2–2.8) and for autism spectrum disorders (ASDs) of 5.3 per 1,000 (95% CI 4.1–6.7). Comparison analysis with a cumulative incidence report from the UK, showed a similar cumulative incidence to age five in Aruba. Prevalence of ASDs in birth years 1990–1999 and cumulative incidence to age five in Aruba are similar to recent reports from the United Kingdom and the United States.

KEYWORDS: autism, epidemiologic study, prevalence, cross-cultural

INTRODUCTION

Autism spectrum disorders (ASDs) are developmental disorders, characterized by impairments in social functioning, communication and behavior. Reports of worldwide prevalence figures since the 1990's contributed to intensified research efforts (Fombonne, 2003; Fombonne, 2009), but the descriptive epidemiology of ASDs remained incomplete, as concern over potential environmental causes continued to increase (Kolevzon et al., 2007).

For decades available data derived from prevalence studies in developed countries conducted in a narrow range of settings (Fombonne, 2003). Current prevalence estimates of ASDs in these settings fall in the range of 3–12 per 1,000 (Baird et al., 2006; Fombonne et al., 2006; Petersen et al., 2006; Centers for Disease Control and Prevention (CDC), 2007a, b). Autism specific epidemiologic research outside of the narrow range of these first world high-income countries has only recently been addressed (Ellefsen et al., 2007; Ghanizadeh, 2008; Oliveira et al., 2007). The current project contributes to the expansion of autism specific epidemiologic research in increasingly diverse settings.

This study is the first attempt to study the epidemiology of ASDs in the Caribbean, using methods that allow comparisons with other studies. Aruba is uniquely suited for this purpose, as it has a culturally distinct, heterogeneous, multilingual and ethnically mixed population.

Furthermore, Aruba has a well-established health care system, one centralized child psychiatry clinic and a population registry providing both the means to identify disabled

children, and to enumerate the island population.

Previous psychiatric epidemiologic research in rare disorders in the same region (the Netherlands Antilles) has shown that such research is feasible (Hoek et al., 1998; Hoek et al., 2005).

Aims of the study were to determine the prevalence for ASDs in birth years 1990–1999 in Aruba, and to conduct a comparison analysis with a cumulative incidence report from the UK. We performed the study because examining prevalence of autism across diverse settings might provide clues to either genetic or environmental etiologies.

MATERIAL AND METHODS

Area and population

Aruba, a Caribbean island 17 miles off the coast of Venezuela, is a separate, autonomous member of the Kingdom of the Netherlands. Since 1990, the population of Aruba increased nearly 37% through immigration to 90,506 inhabitants in 2000. The population of Aruba is predominantly of Amerindian (Arawak), Dutch, and Spanish ancestry (Toro-Labrador et al., 2003). While there may be social distinctions based on race, these are nowhere documented, and race is officially considered a continuously distributed trait.

In some ways Aruban health characteristics such as life expectancy, leading causes of death, and infant mortality are similar to those of the UK, the Netherlands, and the US (Pan American Health Organization, 2002; United States Census Bureau, 2002; World Health Organization, 2005).

During the 1990's health insurance was nearly universal for legal residents, although access to specialty services was limited. After the introduction of a mandatory universal health insurance system in 2001 for legal residents, access to health care in Aruba improved further. Children are entitled to health care based on legal residency of parents. The insurance premium is income-dependent up to a certain maximum and paid by employers, employees and the government.

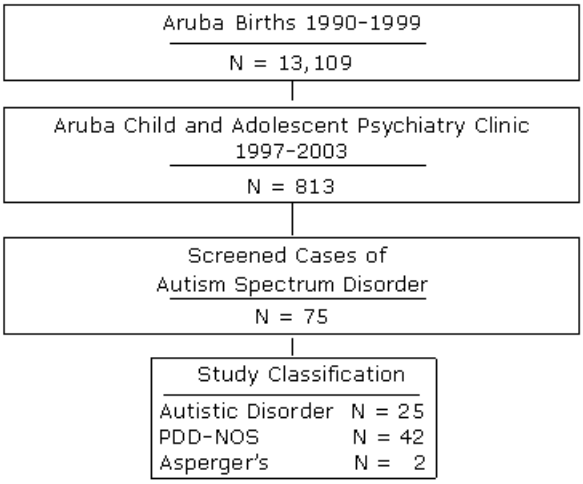
Study population

The Aruba Autism Project was carried out at the Child and Adolescent Psychiatry (CAP) Clinic of Aruba, an outpatient clinic established in 1997. The clinic was the first and only child psychiatry service on the island. Before its establishment no child psychiatry expertise or services were locally available to the community. Children could be referred to the service by general practitioners, pediatricians or other medical specialists. Virtually all Aruban-born children within the psychiatry service were legal residents.

This study is based on children born in Aruba from January 1, 1990 through December 31, 1999 and seen at the Child and Adolescent Psychiatry Clinic between May 1, 1997 and December 31, 2003.

All clinical files for the period from the establishment of the clinic from May 1, 1997 until December 31, 2003 were reviewed for the study. In this six and a half year period the clinic evaluated a total of 1,543 patients, including 813 Aruban children born in the targeted years (see Figure 8.1).

Figure 8.1 Study sampling



Case ascertainment

Clinic charts of children born in the targeted birth years (N = 813) were systematically screened, and the records of potential cases abstracted (N = 75). Study diagnoses were assigned based on abstracted data.

Clinical records

Clinical notes and DSM-IV symptoms were recorded by the one clinic child psychiatrist (IvB) over the entire study period. The clinic psychiatrist was trained as a child psychiatrist in the Netherlands, where she did residencies in pediatrics, genetics, psychiatry and child psychiatry. She has expertise in developmental and genetic syndromes (van Balkom et al., 1992, 1998, 2002), and is certified in the use of standardized assessment

instruments for research diagnosis of ASDs. Standardized forms were completed on every child at intake. Intake included collection of medical, developmental, school and family histories; as well as information on current clinical symptoms. Diagnostic assessments were rarely concluded in one visit. Child psychiatric assessments and behavioral observations would typically take place at second and third follow-up visits. Results of routine psychological assessments performed at intake or during the course of treatment were also recorded, as were notes from consultations with other experts.

At the clinic a 'suspected' ASD diagnosis was given when clinical symptoms did not (yet) meet all the criteria necessary for a definite diagnosis of a pervasive developmental disorder. A 'suspected' diagnosis made support and intervention possible, while allowing parents time to adjust, and the symptomatology to fully emerge over time (Charman et al., 2005).

For the study the clinical cases with a 'suspected' ASD diagnosis were subject to review and not automatically included in the numerator of prevalence figures. If a suspected case was assigned an ASD study diagnosis— based on the presence of DSM symptoms in the chart notes—then he/she was included as a case in the prevalence figure.

Charts with an ASD diagnosis (Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified, Rett's Disorder, or Childhood Disintegrative Disorder), or an ASD diagnosis "suspected" with no subsequent diagnosis ruling out spectrum diagnoses, were flagged and abstracted by a Dutch resident of psychiatry (MV).

Record review and study diagnosis

Evidence of DSM-IV symptoms was abstracted from the charts; subsequently a computer algorithm was applied. The algorithm was consistent with DSM-IV symptom list ratings for ASDs. Study inclusion was based on standardized chart abstractions; a study diagnosis was assigned in accordance with standardized diagnostic criteria.

A study diagnosis of Autistic Disorder (AD) required chart evidence of two or more social criteria, one or more communication criteria, and one or more behavioral criteria for autism, totaling six or more criteria across the three symptom domains, with a delay or abnormal functioning onset before age three in at least one of three areas—social interaction, language used in social communication, symbolic or imaginative play. The Asperger's Disorder (AS) classification required chart evidence of two or more social criteria for autism, one or more behavioral criteria for autism, normal language development (single words by 24 months, phrase speech by 36 months), and absence of mental retardation and autistic disorder. Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) classification required one or more social criteria, and one or

more communication criteria for autism or one or more behavioral criteria for autism in the absence of other diagnosable autism spectrum disorders. An Autism Spectrum Disorder (ASD) classification was also applied to those classified with AD, AS or PDD-NOS.

Mental retardation

Mental retardation (MR) was diagnosed based on chart records of IQ measurements. When children were unequivocally MR (N = 15), they received a clinical diagnosis of MR and were not tested (22%). Measurements were available in 54 of the study diagnosed cases (78%): in 40 cases the children had a normal test-based IQ, while 14 children (20%) had been tested as mentally retarded (IQ <70). In total 29 of the 69 cases were mentally retarded (42%).

Validation study

To validate study classification of ASD, the Autism Diagnostic Observation Schedule (ADOS) was used. The ADOS is a semi-structured, standardized assessment of communication, social interaction and imaginative play for individuals suspected of having an Autism Spectrum Disorder (Lord et al., 1989, 2000).

The subjects included 24 children with a study diagnosis of ASD, and six clinic children diagnosed with other disorders. Selection of non-ASD clinic children was based on random identification in the computerized patient list. This list was restricted to active patients, excluding children who had previously screened positive for our study. To prevent possible selection bias the secretary of the clinic invited parents from a list of children with regular follow-up visits to the clinic in preceding weeks, working down the list until six children were selected. The selected children were born 1993–1999.

Most subjects in the validation study were assessed by an independent ADOS certified rater from the neighboring island of Curaçao. When this rater was not available, children were assessed by the first author.

Confidentiality

In keeping with Dutch medical ethical guidelines for the conduct of record review studies, personal information was treated confidentially. Only the treating child psychiatrist and the research psychiatrist had access to the medical charts. Data were entered into a statistical database without identifying information.

Population data

Data on registered births and population characteristics were obtained from the Central Bureau of Statistics, Aruba. All births to legal residents are registered. During the years 1990–1999 there were 13,109 registered births (6,755 males and 6,354 females) (Central Bureau of Statistics (CBS), 2003).

ANALYSIS

Main prevalence analysis

Prevalence estimates were calculated as the number of cases identified among children born in Aruba between 1990–1999 divided by total registered live births 1990–1999. We used the Poisson distribution to calculate 95% confidence intervals (STATA, 2003).

Statistical comparison of the proportion with mental retardation among the diagnostic groups (AD versus PDD- NOS) was assessed with Pearson Chi Square.

Comparison analysis of cumulative incidence

The published study most similar to the Aruba study in methodology and birth years was conducted by Powell et al. 2000 in two areas of the West Midlands, UK (Powell et al., 2000). To compare our data to those described by Powell et al., 2000, we calculated cumulative incidence of AD and ASDs in children with first service contact prior to age five, and born in the period January 1, 1996 through December 31, 1998. Children in these birth years had access to the psychiatric service at least from ages one through 5 years. The cumulative incidence is calculated by the number of Aruban born children 1996–1998 with an intake prior to age five assigned a study diagnosis of ASD, divided by the total number of children born in Aruba between 1996–1998.

RESULTS

Characteristics of the screened positive children

A total of 813 children born in Aruba from 1990 through 1999 were identified in the Child and Adolescent Psychiatry Clinic records; of these 75 children screened positive.

Among the screen positive 60% of children were referred by GP's, 30.7% were referred by pediatricians and 9.3% by other specialists. The most common reasons for referral were behavioral problems (61.3% of children) and speech and/or language delay

(45.3% of children). Other reasons for referral were impaired relatedness (34.7%), mental retardation (4%), attentional problems, eating problems, sleeping disorder, or anxiety. In total 54.6% of children had more than one reason for referral.

Main prevalence findings

Sixty-nine of the screen positive children were assigned a study classification of ASD. 25 (36.2%) were classified as AD, 2 (2.9%) were classified as AS, and 42 (60.9%) were classified as PDD-NOS. No cases with regression in development, Childhood Disintegrative Disorder or Rett's Disorder were identified. The overall prevalence of ASDs was 5.3 (95% CI 4.1–6.7) per 1,000 births. Details concerning prevalence are shown in Table 8.1.

Table 8.1 Prevalence per 1,000 births

Diagnosis	Male	95% CI	Female	95% CI	Total	95% CI
AD	3.3	2.0–4.9	0.5	0.1–1.4	1.9	1.2–2.8
PDD–NOS	5.5	3.9–7.5	0.8	0.3–1.8	3.2	2.3–4.3
Asperger	0.1	0.0–0.8	0.2	0.0–0.9	0.2	0.0–0.6
Total ASD	8.9	6.8–11.4	1.4	0.6–2.7	5.3	4.1–6.7

Case characteristics

Clinical characteristics of the 69 cases are presented in Table 8.2. The proportion of study-defined MR in AD was 64.0%, in PDD-NOS 29.3% and overall ASDs 41.2%. The difference in percentages of children with mental retardation between AD and PDD-NOS is significant (2 =7.670; df = 1; p <.01). Boys outnumbered girls by 7.3:1 for AD, and 7.4:1 for PDD- NOS. Mean age at intake overall was 5.5 years (SD = 2.2). In children born from 1990–1994 (minimum possible intake age in the first year the clinic was opened: 3–7 years) the mean age at intake was 7.2 years (SD = 2.1). In this group, there was no significant difference in age at intake between children classified as AD and children classified as PDD- NOS. For children born 1995–1999 (minimum possible intake age in the first year the clinic was opened: 0–2 years) the mean age at intake was 4.5 years (SD = 1.5). In this group, children classified as AD were significantly younger than children classified with PDD-NOS (3.9 years versus 5.1 years; t = –2.67; df = 41; p <.05).

Table 8.2 Case characteristics

	AD (n=25)	PDD–NOS (n=42)	ASDs (n=69)
Symptoms (range)	Mean (sd)	Mean (sd)	Mean (sd)
Social (0–4)	3.8 (0.5)	2.7(1.0)	3.1(1.0)
Communication (0–3)	2.2(0.7)	1.5(0.8)	1.7(0.9)
Repetitive behaviors (0–4)	2.2 (1.1)	0.3(0.6)	1.0(1.2)
Total symptoms	8.2 (1.6)	4.5 (1.3) [a]	5.8 (2.3)
Age at intake in years	4.6 (2.3)	6.0 (1.9)	5.5 (2.2)
Birth cohort 1990–1999			
Mental retardation in %	64.0%	29.3%	41.2%

[a] Only one case meeting study criteria of PDD–NOS had the minimum number of two symptoms; all other cases had three or more symptoms.

Validation study

The subjects for the validation study included 24 children with a study diagnosis of ASD, and six clinic children diagnosed with other disorders. The independent rater was blinded to diagnostic information prior to the assessment, and assessed 17 of the 24 (70%) of ASD study cases with the ADOS, while the remaining seven ASD subjects were examined by the first author (IvB). All except one (95.8% of 24) of the study diagnoses of ASD were confirmed by the ADOS rating. None of the children diagnosed with other disorders scored for ASD on the ADOS algorithm.

Comparison analysis of cumulative incidence

To compare our data to those described by Powell et al., 2000, we calculated the cumulative incidence in children born in the period January 1, 1996 through December 31, 1998, with intake prior to age five (Powell et al., 2000). The cumulative incidence for AD was 2.4 per 1,000 (95% CI 1.1–4.4) and for all ASDs it was 4.5 per 1,000 (95% CI 2.7–7.0). Powell reported a cumulative incidence to age five of 1.6 per 1,000 (95% CI 1.1–2.4) for AD, and 3.4 per 1,000 (95% CI 2.5–4.4) for ASDs.

DISCUSSION

This is the first report of the prevalence of autism spectrum disorders in a Caribbean country. In the Aruba birth years 1990–1999 we found a prevalence for autistic disorder of 1.9 per 1,000 (95% CI 1.2–2.8) and for autism spectrum disorders of 5.3 per 1,000 (95% CI 4.1–6.7). These prevalence estimates should be considered minimum prevalence. Centralized psychiatric services with excellent coverage and penetration, notwithstanding, it is possible that ASD cases have escaped detection within the study period. Children who have left the frame of observation may have been missed cases, but they still were included in the denominator. Higher functioning cases and young children (i.e. year of birth in the late nineties) may not have been referred.

The prevalence found in the present study is in the mid range of estimates reported for similar birth years in studies conducted in the US and Europe, using diverse methodologies (Baird et al., 2000, 2006; Bertrand et al., 2001; Yeargin-Allsopp et al., 2003; Chakrabarti et al., 2005; Fombonne et al., 2006; Gillberg et al., 2006; Petersen et al., 2006; CDC, 2007a, b). In Table 8.3 we present selected autism prevalence studies published from 2000 reporting on children born during the same time period, but diagnosed using varied methodologies.

Table 8.3 A comparison of selected descriptive epidemiology studies of autism

	Powell et al., 2000	Baird et al., 2000	Bertrand et al., 2001	Yeargin-Allsop et al., 2003	Chakrabarti & Fombonne, 2005	van Balkom et al., Present study
Population	16,012[b]	16,235	8,896	289,456	10,903	13,109
Country	UK	UK	US	US	UK	Aruba
Age	1–4 years	7 years	3–10 years	3–10 years	4–6 years	4–13 years
Diagnosis[a]	RD	DA	DA	RRD	DA	RRD
Prevalence AD	1.6[b]	3.1	4.0	–	2.2	1.9
Prevalence ASDs	3.4[b]	5.8	6.7	3.4	5.9	5.3
Proportion	48%	53%	60%	–	38%	36%
AD/all ASDs	(26/54)	(50/94)	(36/60)		(24/64)	(25/69)
Male : Female ASDs	5.7:1	7.5:1	2.8:1	4:1	6.1:1 (est)	6.7:1
% MR: AD	–	40%	58%	–	67%	64%
% MR: ASDs	–	22%	49%	64%	30%	42%

Legenda
[a] DA = Direct Assessment; RD = Record Diagnosis; RRD = Record Review Diagnosis
[b] cumulative incidence single birth year ≈ lifetime prevalence to age 5 for birth year

The Aruban findings are consistent with these reports in two additional respects: the proportion of autism spectrum cases with AD (25/69 = 36.2%), and the proportion of cases with comorbid mental retardation (41% ASDs, 64% AD). The sex ratio (87.0% males) is also within the range of previous reports (Fombonne, 2003, 2006; Gillberg et al., 2006; CDC, 2007a, b).

The validation study showed a rate of agreement between study diagnosis and ADOS that was higher than expected at 95.8%. For example, Gray et al. showed that the overall agreement between ADOS and clinical diagnosis was .87 (95% CI .81–.91) in a group of young children (aged 20–55 months) (Gray et al., 2008). A possible explanation for the higher agreement found in the present study could be the preponderance of AD (16 of 24 subjects), and a higher age distribution; both conditions contribute to a better performance of the ADOS (de Bildt et al., 2004; Gray et al., 2008).

A recent epidemiological study investigating children aged 3–9 years within different health services in Venezuela (Montiel-Nava et al., 2008) yielded a treated prevalence of 1.7 per 1,000 (95% CI 0.1–2.0) for all ASDs, and 1.1 per 1,000 (95% CI 1.0–1.4) for autism. There could be various explanations for the markedly lower prevalence estimates in Venezuela, especially for all ASDs, compared to our study. Aruba is distinctly different from Venezuela, not only in terms of availability and access to health care, but also with respect to socioeconomic and population characteristics. One explanation is a lower degree of service coverage and penetration in the population compared to the Aruba study, where 6% of all children born in Aruba between 1990–1999 were evaluated at the clinic. As mentioned by the authors, a possible lack of awareness of autism and treatment options in the general population could have resulted in underrecognition and lower referral levels for higher functioning ASD cases. Of course, lower prevalence estimates can also reflect lower prevalence in the underlying population.

Because epidemiologic findings with respect to autism spectrum disorders are particularly sensitive to study methodology, the comparison analysis was undertaken in which we drew a direct comparison of cumulative incidence to age five of ASDs in Aruba to that reported by a study conducted in two areas of the West Midlands, UK (Powell et al., 2000). In this UK study case ascertainment methods are similar to the present study: children were identified through Child Developmental Centres' treatment records, and similar diagnostic criteria were in use during the period of case detection. Powell reported a cumulative incidence (to age five) of 1.6 per 1,000 for AD, and 3.4 per 1,000 for ASDs. We estimated the cumulative incidence to age five of AD and ASDs to be 2.4 per 1,000, 4.5 per 1,000 respectively, at the high end of the confidence intervals of the UK study. This difference may be one of methodology.

In the UK study onset was defined as the age at which a definite or probable diagnosis of ASD was first communicated to the child's family, whereas in the present study

we used date of first contact. However, it is uncertain whether this slightly higher cumulative incidence could be accounted for by this difference.

The ideal study upon which to base comparisons in prevalence and cumulative incidence across cultures would use the same rigorous methods at all research sites. However, in reality the development of comparable prevalence estimates is hampered by methodological issues, and differences across countries and services.

It was therefore surprising that in spite of stated differences we found, using similar methods, that the prevalence estimate for ASDs previously reported in a narrow range of countries, also pertains in a place as distinctive as Aruba.

Strengths and limitations of the study

The strength of evidence derives from the coverage and penetration of the health care system, the quality of diagnostic services, and the ability to accurately enumerate the population at risk. During the 1990's, health insurance was nearly universal for legal residents, but access to specialty services was limited. From 2001 forward, access to child psychiatry services was effectively universal; over the study period, six percent of all children born in Aruba from 1990 to 1999 were assessed at the clinic.

The consistency and reliability of diagnosis upon which the prevalence estimates are based also contribute to the strength of the study findings. All children were fully assessed by the clinic psychiatrist and detailed clinical notes were systematically collected and included in charts. Study inclusion was based on standardized chart abstractions; a study diagnosis was assigned in accordance with standardized diagnostic criteria. In an effort to validate study classification of ASD the ADOS was used to examine 35% (24/69) of ASD subjects included in the study. This showed confirmation of study classification in all cases, but one.

Finally, the population of Aruban births 1990–1999 was enumerated based on population registry data. Because virtually all births in Aruba are attended (Pan American Health Organization, 2002), registry data should include the births of all legal Aruban-born children. All children identified with ASDs reported here are legal Aruban residents.

The limitations of this study are those common to record-based prevalence studies, and fall into two principal categories: factors affecting case ascertainment and factors affecting diagnosis. With respect to case ascertainment, a fundamental limitation of record review methodology is that prevalence will only include children who presented for clinical assessment, and who elicited clinical suspicion of falling within the autism spectrum. In past studies, reliance on a single source for identifying cases has yielded low estimates (Yeargin-Allsopp et al., 2003). In this Aruban context, diagnostic assessment and treatment is centralized in the first and only child psychiatry service on the

island; competing diagnostic services do not exist.

Other ascertainment effects are specific to segments of the cohort, and are only relevant in the context of the main prevalence analysis. Some cases among children born in the earliest birth years and in the latest birth years may not have been referred to the child psychiatric service. Because the clinic opened in 1997, it is possible that cases born in the early 1990s emigrated in search of services prior to the clinic's opening and thereby escaped detection. It is also possible that higher functioning cases born in the late 1990s have not attained a sufficient age for referral and are therefore underrepresented in this study.

Another ascertainment issue may be relevant to both the main prevalence analysis and the comparison analysis, that is that ascertainment of children with prominent comorbidities, especially mental retardation, may also have been limited. Interviews with directors of Aruban schools and day-care programs for the disabled concerning the diagnostic distribution in their institutions, however, lead us to believe that few lower functioning children were overlooked.

With respect to diagnosis, as in any record-based study, the findings are limited by the absence of in-person standardized research interviews and assessments of every study classified case. Due to restraints in time and finances only 24 of the 69 children (almost 35%) with a study classification of ASD were assessed with the ADOS. One study classified ASD case was not confirmed by the ADOS rating.

A potential for misdiagnosis specific to this population arises from the multilingual environment. It is possible that some children with late language development and behavioral disturbances (e.g., ADHD) present with ASD-like profiles at some point in their development.

In conclusion, it is clear that interest in the distribution of ASDs is intensifying, as concern over possible environmental contributions to the occurrence of these disorders continues to grow (Kolevzon et al., 2007). Standardizing future research methodology would permit geographic cross-cultural com- parisons. Finding areas of high and low contrast will also motivate additional international epidemiologic investigations. In addition, each epidemiologic study will contribute to local appreciation of the magnitude of ASDs impact on local public health resources and services.

This study shows that the prevalence of ASDs in Aruba is similar to previous prevalence reports from a narrow range of developed countries. We hesitate to draw inferences about the causes of autism based on findings from a single setting. However, as studies in diverse settings accumulate, we believe that the emerging picture will provide important clues to some causes and help to rule out others. The significance of these findings for Aruba is clear. Aruba joins the developed world in needing to respond with services and care for a significant number of seriously disabled individuals.

Significant Outcomes:

•This first epidemiologic study on ASD in the Caribbean shows prevalence estimates and gender distribution similar to those reported in recent studies in the UK and US.
•Comparison analysis with a study of cumulative incidence of AD and ASD in the UK showed a cumulative incidence rate in the youngest age group in Aruba at the high end of the confidence interval of that in the UK.

Limitations:
•Only children who presented for clinical assessment and elicited clinical suspicion of falling within the autism spectrum are included in the prevalence estimate.
•Cases born in the early 1990s may have emigrated in search of services prior to the clinic's opening.
•Higher functioning cases born in the late 1990s may not have attained a sufficient age for referral.

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CHAPTER 9

Paternal age and risk of autism in an ethnically diverse, non-industrialized setting: Aruba

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ABSTRACT

OBJECTIVE – The objective of this study was to examine paternal age in relation to risk of autism spectrum disorders (ASDs) in a setting other than the industrialized west.
DESIGN – a case-control study of Aruban-born children (1990-2003). Cases (N=95) were identified at the Child and Adolescent Psychiatry Clinic, the only such clinic in Aruba; gender and age matched controls (N=347) were gathered from public health records. Parental age was defined categorically (≤29, 30-39, 40-49, ≥50y). The analysis used conditional logistic regression.
RESULTS – Advanced paternal age was associated with increased risk of ASDs in offspring. In comparison to the youngest paternal age group (≤29y), risk of autism increased 2.26 times for children born with fathers in their thirties, 2.70 times for fathers in their forties, and 3.24 thereafter.
CONCLUSION – This study, part of the first epidemiologic study of autism in the Caribbean, contributes additional evidence, from a distinctive sociocultural setting, of the risk of ASD associated with increased paternal age.

KEYWORDS: paternal age, autism risk, case-control study

INTRODUCTION

Major studies showing that advanced paternal age elevates risk of autism in offspring have been conducted in predominantly high-income countries (the U.S. (California), Denmark, Israel, Western Australia, Sweden, the Netherlands, the UK) (Glasson et al., 2004; Lauritsen et al., 2005; Reichenberg et al., 2006; Croen et al., 2007; Grether et al., 2009; Hultman et al., 2010; Shelton et al., 2010; Buizer-Voskamp et al., 2011).

The mechanisms underlying advanced parental age/autism risk association are not yet fully understood. The leading hypothesis is that with advancing paternal age, de novo genomic alterations and/or changes in gene expression regulation levels increase the risk of autism. (Sebat et al., 2007; Alter et al., 2011). Alternatively, delayed parenthood could reflect subtreshold autistic traits in individuals leading them to parent at advanced ages (Constantino & Todd, 2005; Puelo et al., 2008). There are also suggestions that sociocultural determinants of age at parenting may better explain the finding. Sociocultural factors which influence age at parenting differ across countries and include factors such as immigration, access to family planning services, educational attainment, and socioeconomic status (Bongaarts, 2003; Larsson et al., 2005; Cheslack-Postava et al., 2011; Leonard et al., 2011). The significance of these sociocultural factors is difficult to evaluate due to the lack of sociocultural diversity of the major studies to date. Studies of autism

in a greater diversity of settings are underway or have recently been published (Sansafar et al., 2010; Zhang et al., 2010). Among the first of these was a prevalence study of treated autism spectrum disorders in Aruba (van Balkom et al., 2009). In the current study we examined paternal age and risk for ASD.

METHODS

Area and population

Aruba is a Caribbean island 17 miles off the coast of Venezuela (population 90,506 in 2000) The native-born population of Aruba is predominantly of Amerindian (Arawak), Dutch, and Spanish ancestry (Toro-Labrador et al., 2003). In conjunction with an economic transition in the 1990s, Aruba absorbed a large number of immigrants. Since 2000, immigrants have constituted at least 30% of the population (CBS, 2002). Although social distinctions based on race may exist, these are nowhere documented, and race is officially considered a continuously distributed trait. During the 1990s health insurance was nearly universal for legal residents; in 2001 access to health care in Aruba improved further with the introduction of mandatory health insurance. All children of legal residents are entitled to health care (van Balkom et al., 2009).

Study design

This study is a population-based case-control study using clinic and public health records. Our aim was to examine the hypothesis that advanced paternal age increases risk of autism in the non-industrial, ethnically diverse setting of Aruba. The sampling frame includes all births in Aruba between 1990 and 2003 recorded in the Aruba public health records. Autism in children born between 1990-1999 had previously been identified in the Aruba Autism Project, a prevalence study of Autism Spectrum Disorders (ASDs) in Aruba (van Balkom et al., 2009). This earlier prevalence study was extended to include children born from 1990 to 2003, from clinic records of assessments recorded until January.1, 2006. Controls were selected from the public health records (well-baby clinics records and adolescent health preventative clinic records) matching on date/month/year of birth and gender.

Case identification

Records from the Aruba Child and Adolescent Psychiatry Clinic, the first and only child and adolescent psychiatry service on the island, were screened for diagnosed and sus-

pected cases of ASD in children born in Aruba from 1990 to 2003. At the clinic a 'suspected' ASD diagnosis was given as a working diagnosis, when clinical symptoms did not (yet) meet all the criteria necessary for a definite diagnosis of a pervasive developmental disorder. In this way support and intervention were possible, while allowing parents time to adjust, and ASD symptomatology to fully emerge over time (Charman, 2005). Charts of all potential cases were abstracted; a study diagnosis was assigned based on abstracted chart evidence of symptoms in accordance with DSM-IV symptom criteria. Autism Spectrum Disorders were defined to include Autistic Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified. In total, 101 cases of ASDs were identified by these methods and included.

Control identification

Data on controls were abstracted from the centralized computer records of the Aruba public health clinics, which serve all Aruban children from infancy to age 10 to 11 years. Public Health clinic files for selected controls were retained in one of two locations (the centralized archive or home clinic) depending upon birth years. Clinic files include immunization history, visit notes, and in most instances parental characteristics including parents' place of birth, date and/or year of birth, maternal parity, and parental occupation. Parental characteristics were abstracted for each control using a standardized abstraction form. Only anonymized data were extracted from the clinic records.

A minimum of three and a maximum of five controls, matched to each subject classified with an ASD for date of birth and gender, were randomly selected from the public health records. With these methods 469 controls were identified for the 101 ASD subjects. Characteristics of the study sample are shown in Table 9.1.

Six of the cases classified as ASD for this study were excluded due to missing data on mother and/or father's age along with their 26 matched controls. An additional 96 controls were excluded due to missing data on mother and/or fathers age. The final sample consisted of 95 cases and 347 controls.

Validation

The study-assigned diagnosis of 24 randomly chosen children identified as having ASD (N=95), along with 6 clinic patients with other disorders randomly chosen from the computerized clinic patient list, was validated with the Autism Diagnostic Observation Schedule (ADOS) by a certified independent rater from the neighboring island of Curaçao. The ADOS is a semi-structured, standardized assessment of communication, social interaction, and imaginative play for individuals suspected of having an ASD (Lord et al., 1989, 2000).

Table 9.1 Characteristics

	Controls N (%)	Cases N (%)
Paternal Age		
≤ 29	149 (42.9)	23 (24.2)
30-39	159 (45.5)	55 (57.9)
40-49	36 (10.4)	15 (15.8)
≥ 50	4 (1.2)	2 (2.1)
Maternal Age		
≤ 29	211 (60.8)	42 (44.2)
30-39	130 (37.5)	47 (49.5)
40-49	6 (1.7)	6 (6.3)
Preterm birth		
Yes	29 (8.4)	10 (10.5)
No	304 (87.6)	76 (80.0)
Missing	14 (4.0)	9 (9.5)

When the independent rater was not available, children were assessed by the first author. The independent rater was blinded for diagnostic information prior to assessment and assessed 17 of 24 (70%) randomly chosen subjects with a study diagnosis of ASD, while the remaining 7 were examined by first author (IvB). All except one of the study diagnosed ASD cases were confirmed by the ADOS rating (95.8%). The sole exception was a young child rediagnosed as having ADHD, two years after his initial working diagnosis of 'suspected' ASD. None of the randomly selected clinic children diagnosed with other disorders scored for ASD on the ADOS algorithm (van Balkom et al., 2009).

Variables

Parental ages were categorized in 10 year increments: ≤29= age group 1 (reference category), 30–39= age group 2, 40–49= age group 3, and ≥50= age group 4.

Four potential confounders of the age-autism association under consideration were identified a priori, and then examined in association with paternal age variable and the outcome. These confounders were: age of other parent at birth, low birth weight,

preterm birth and parental immigrant status. The first potential confounder considered was maternal age. Studies examining maternal age effects on risk of ASD in offspring have reported mixed findings (Croen et al., 2007; Durkin et al., 2008; Grether et al., 2009; Shelton et al., 2010). In this study we categorized maternal ages in 10 year increments, resulting in the following three age groups: ≤29=age group 1 (reference category), 30–39=age group 2, and 40–49=age group 3.

Because previous studies have suggested that low birth weight (<2500 grams) (LBW) and preterm birth (≤ 37 weeks pregnancy) may be associated with increased risk of autism (Larsson et al., 2005; Buchmayer et al., 2009) we addressed both these variables as potential confounders. High risk pregnancies in Aruba with risk of preterm birth and/or low birth weight, are usually referred to the neighboring island of Curacao for labor and delivery. These children are excluded from our sample, because they are not Aruban born. Nonetheless, there are children of LBW in our sample (N=11) and children born after ≤ 37 weeks pregnancy (N= 39). Finding no association with either exposure or outcome for LBW, this confounding variable was dropped from consideration.

In various studies parental immigrant status has been implicated in risk for ASDs in offspring (Lauritsen et al., 2007; Hultman et al., 2010; Buizer-Voskamp et al., 2011), and as it may impact on age at reproduction, we also addressed this as a potential confounder, classifying parental place of birth as Aruba/ not Aruba (+/-), and four categories of combined parental place of birth (AA, AĀ, Ā A, Ā Ā). Both parents Aruban born (ĀA) is the referent category for combined place of birth. When adjusting for parental immigrant status did not reveal an association with exposure or ASD we dropped this variable from consideration also.

Analysis

The data were analysed using STATA version 9. We used conditional logistic regression for matched case-control groups with STATA's "clogit" command to examine paternal age effects of increased risk in ASDs in offspring unadjusted, and while controlling for maternal age effects, and while controlling for maternal age and preterm birth effects.

Confidentiality

The Aruba medical ethical review committee gave permission to perform the study. All data were entered into a statistical database without identifying information.

RESULTS

Mean paternal age in cases was 33.5 (sd=6.8), and in controls, 31.1 (sd=7.1); mean maternal age in cases was 30.2 (sd=5.7), and in controls, 27.6 (sd=5.6).

Advanced paternal age was associated with increased risk of ASDs in offspring (Table 9.2). In comparison to the youngest paternal age group (≤29), the risk of autism increased significantly to 2.18 times for children with fathers in their thirties, and to 2.71 in their forties. Adjusting for maternal age, paternal age effects were significant for fathers in their thirties, compared to younger fathers. However effects were rendered non-significant for other paternal age groups. When adjusting for confounding variables maternal age and preterm birth, fathers in their thirties and forties have a significantly increased risk for ASDs in their offspring compared to the reference group.

Table 9.2 Odds ratios for paternal age adjusted for maternal age and preterm birth

	Unadjusted	Adjusted for maternal age	Adjusted for maternal age and preterm birth
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Paternal age *			
30-39	2.18 (1.29,3.72)	1.85 (1.03,3.29)	2.16 (1.15,4.04)
40-49	2.71 (1.27,5.78)	2.00 (0.87,4.61)	2.67 (1.07,6.68)
≥50	3.22 (0.55,18.68)	2.24 (0.36,13.87)	2.38 (0.37,15.40)
Maternal age *			
30-39		1.41 (0.83,2.40)	1.51 (0.86,2.67)
40-49		3.39 (0.92,12.49)	3.45 (0.84,14.10)
Preterm birth •			
< 37 weeks			1.08 (0.50,2.37)

* = reference category: age group ≤29 years;
• = reference category "not preterm"

DISCUSSION

In this case-control study in a total population Aruban birth cohort (1990-2003) we found that advanced paternal age, in comparison to the youngest paternal age group (≤29), was associated with increased risk of ASDs in offspring. Aruba has a multicultural, ethnically mixed population, including a substantial proportion of at least 30% immigrants since 2000 (CBS, 2000). Its one and only centralized child psychiatry service ensured not only a high degree of service coverage and penetration of the population, but also the capture and rigorous assessment of all cases of ASD by the same clinician (IvB).

The need to understand the distribution of autism spectrum disorders and the role of environmental factors in the occurrence and etiology of autism spectrum disorder remains urgent and requires studying autism in diverse environments (Kolevzon et al., 2007). Examining the association between paternal age effects and risk of autism in populations of different sociocultural and ethnic origin, embodying different influences on age at parenting, will advance our understanding of the significance of these environmental effects. To date, the significance of these factors remains difficult to appreciate due to the lack of sociocultural diversity of the major studies.

The present study examined the paternal age contribution to risk of ASDs in offspring in a socioculturally diverse population. It is likely that social, cultural, and ethnic influences on age of reproduction in this environment are affected by the transitional economy of Aruba and the rapid influx of immigrants, changing the meaning of older ages at parenting. In our study we found that the risk of autism increased significantly for children with fathers in their thirties, and their forties compared to younger fathers. After adjusting for maternal age as a confounding variable the relationship persisted only for fathers in their thirties when compared to the reference age group. We found that fathers in their thirties and forties have a significantly increased risk for ASD in their offspring when adjusting for both maternal age and preterm birth, suggesting that it is paternal age per se that contributes to increased risk of autism in offspring. Although certain limitations were imposed by the relatively small sample size of fathers in the older age groups, the patterns of risk remained across paternal age categories when adjusting for maternal age in categorical analysis.

Our finding, in this distinct sociocultural setting, is consistent with that of previous studies in western countries (Glasson et al., 2004; Lauritsen et al., 2005; Reichenberg et al., 2006; Croen et al., 2007; Grether et al., 2009; Hultman et al., 2010; Shelton et al., 2010; Buizer-Voskamp et al., 2011). It is also consistent with the findings of a recent case control study in Iran, in which a significant association between paternal age and an increased risk of autism, independent of maternal age, was described (Sasanfar et al., 2010).

Other possible risk factors have been examined recently. In a study on birth spacing

in California, Cheslack-Postava et al. (2011) suggested that children born after shorter intervals between pregnancies had an increased risk of autism spectrum disorder, with the highest risk found in pregnancies spaced <1 year apart. The authors suggest two reasons for closely spaced births, namely unintended pregnancies and delayed childbearing by choice (Cheslack-Postava et al., 2011). Additionally, we suggest that delayed childbearing may also reflect subtreshold autistic traits leading to childbearing at advanced ages in both women and men. In another recent study of twins Hallmayer et al. (2011) found a greater non-inherited contribution to risk of autism than was described in previous studies, thereby suggesting that the influence of environmental factors (whether biological or social) may be larger than previously thought. Additional studies examining these factors in different environment may offer clues to the etiology of ASD and elucidate the meaning of the paternal age/autism association.

Strengths and limitations

Major strengths of the study include access to rigorously defined cases arising in the population of Aruban births 1990-2003, ascertainment through the only child psychiatry clinic within a well-established universal health care system, and accurate enumeration of the population at risk through the population registry.

Nonetheless, the limitations of the present study also need to be considered, especially one common to record-based methodology. Findings with respect to assigning a study diagnosis, as in any record-based study, are usually limited by the absence of in-person standardized research interviews and direct clinical assessments of the study classified cases. However, in our study we were able to validate 24% (23/95) of study classified ASD cases. Another limitation was the fact that the sample size of oldest paternal age groups (>40y, N=57) was relatively small, a limitation inherent to research in small populations.

Conclusion

The study contributes additional evidence, from a distinctive sociocultural setting, to the literature on the relationship between paternal age and risk of ASDs, and it emphasizes the importance of replicating these findings across environments since increased paternal age may encapsulate both biological and sociocultural risk factors for adverse neurodevelopmental outcomes in offspring. As more studies in diverse settings, with a focus on meaningful distinctions in the geography of autism, are carried out and findings accumulate, it is likely that the new results will provide important clues to some causes and help to rule out others.

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CHAPTER 10

General discussion

INTRODUCTION

The objective of the research projects in this dissertation was to study autism as it manifests itself within (ultra) rare genetic syndromes; and to examine autism within a different sociocultural environment. In recent years the definition of autism has been hotly debated. The criteria used to define autism as well as the theories of possible causes have changed radically from a psychological to a biological–genetic explanation, and from narrowly defined criteria to broader criteria of atypical development and aberrant behavior. Recognizing autism where it occurs is important; how it is defined and evaluated is equally important.

The most widely used definition in clinical practice is probably the pervasive developmental disorder diagnostic algorithm presented in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM IV–TR). This algorithm encompasses twelve criteria which evaluate communication and social interaction skills as well as behavior, and allows for classification into one of the subcategories of the pervasive developmental disorders group. However this algorithm is not very helpful for evaluating individuals with genetic syndromes associated with severe intellectual disability, in which autism is probably under–recognized. Intellectual disability is a condition which is often associated with features analogous to autism: severe language impairments, social interaction difficulties, and behavioral issues. Many of these symptoms defy strict categorization; this is one of the main reasons diagnosis should be constructed upon careful clinical observations and descriptions. In addition, clinical diagnosis should be based on a careful evaluation of relevant symptoms and their significance, e.g., impairment or distress, within the framework of the individual's developmental phase, family, and other relevant milieus, and elicited from multiple informants.

The central topic of autism was addressed within two contexts, first through the study of autistic features within the context of genetic syndromes, to investigate whether these features can be considered autism; second, through the study of autism in a different geographic locale to investigate whether prevalence and environmental risk factors for autism are comparable to those found elsewhere.

Methodological challenges

Limitations of the studies presented in this thesis have to do with the following methodological issues: selection method and case ascertainment, factors affecting diagnosis, sample size, and instruments used in individual assessments. These issues are discussed here in two parts, those pertaining to the design of the study of genetic syndromes and those pertaining to the design of the study of autism spectrum disorder in Aruba.

With respect to the design of the study of genetic syndromes

Affected individuals were first identified through their membership in a syndrome–specific Family Association and invited to participate through the Family Association. This may have led to a disproportionate inclusion of a subgroup of (already diagnosed) individuals with more severe clinical and behavioral characteristics. Sample sizes were necessarily small, but given the rarity of the syndromes studied, can be considered substantial.

A serious limitation was the lack of suitable instruments to directly measure cognitive functioning in individuals with severe intellectual disability and varying chronological ages. Proper evaluation and interpretation of the target behaviors requires standardized assessments not only of cognitive levels, but also of behavior and motor skills, adaptive functioning levels, speech and language development, and learning difficulties. To avoid misattribution, social interaction, communication, social and family environment, and behaviors in different situations should also be weighed and considered at the same time.

Measuring cognition required an *a priori* evaluation of approximate cognitive level by means of a clinical psychiatric assessment. In these studies, all subjects scored within developmental levels that could be measured by the instrument of first choice (Bayleys). Assessing autistic features with the ADI–R (Autism Diagnostic Interview–revised) in individuals whose mental–age equivalent is below a developmental level of 24 months carries the risk of over–classifying autism. There have also been several publications showing that the use of the ADI–R at age 24 months was less successful in predicting eventual outcome than the clinical diagnosis of an experienced clinician. In the studies described in this thesis, the results of the ADI–R were used to add to other data collected through individual psychiatric assessments, informant reports, and individualized standardized testing.

With respect to the design of the study of autism spectrum disorders in Aruba

Prevalence estimated by means of record review can only include children who are presented for clinical assessment and who arouse clinical suspicion of falling within the autism spectrum. Other ascertainment difficulties are specific to particular segments of the cohort. Some cases among children born in the earliest birth years and in the latest birth years may not yet have been referred to the centralized child psychiatric service in Aruba. Because the clinic opened in 1997 and no child psychiatric services existed before that time, it is possible that prior to the clinic's opening, children born in the early 1990s emigrated in search of services and thereby escaped detection. It is also possible that higher–functioning cases born in the late 1990s had not attained a sufficient age for

referral and are therefore underrepresented in this study. Autism in some children with prominent comorbidities, particularly intellectual disability, may not have been recognized, although interviews concerning the diagnostic distribution within the institutions caring for the disabled indicated that few lower functioning children were overlooked. Findings with respect to assigning a study diagnosis, as in any record-based study, are usually limited by the absence of in-person standardized research interviews and direct clinical assessments of the study classified cases. However, in our study we were able to validate a proportion of the study classified ASD cases.

Other methodological challenges

Variability of phenotypes within same genotype, variability of genotype within same phenotype

Given the heterogeneity and pervasiveness of both intellectual disability and autism spectrum disorder, the study of behavioral phenotypes associated with genetic syndromes is challenging and complex. The phenotypic similarities between intellectual disability and autism spectrum disorder are obvious, and affected individuals may share many features with an early onset, such as impairments in language development, difficulties in social interaction and communication, and stereotyped behaviors.

Genetic syndromes associated with intellectual disability have significant developmental, cognitive, and behavioral consequences, and although these have been described in various studies, there has been little systematic study of the psychiatric dimension. Unfortunately, no biological or psychological markers exist for delineating and validating psychiatric disorders and intellectual disability complicates clinical assessments. This is considered a risk factor for lower levels of communicative, adaptive and cognitive skills, and can lead to difficulties in social interactions within family, learning and social environments. All these circumstances constitute the multiple genetic and environmental interactions that both influence the architecture of the brain and are influenced by it. Consistent with a spectrum concept, there may be many different genetic pathways that lead to an outcome of intellectual disability and autism spectrum disorder. Several studies have concluded that genomic abnormalities investigated were not disease–specific, but contributed to the expression of various similar neurodevelopmental phenotypes. This challenges longstanding ideas of how disorders can be delineated and differentiated from one another, more so in the case of psychiatric disorders, which are defined by observable behaviors. For example, it could be possible that given the continuous nature of features and impairments, at the most disabling end of the spectrum, autism spectrum disorder and intellectual disability co–occur.

The influence of time and environment

Gene–behavior interactions are multidirectional, complex, and dynamic. They are developed, shaped, and expressed over time, beginning at conception and over time influenced by the external environment and by social information. Environmental factors may be defined in many ways; for example they can be social, cultural, or biological. To complicate matters for research, the effects of any defect on any level is inevitably influenced by environmental and social information, which in turn may impact eventual individual outcome and determine the need for services by the patient and family. Identifying relevant genetic and environmental factors and understanding the pathways to expression remains challenging, and the interrelatedness of phenotypic outcomes complicates clinical recognition and delineation.

Diagnosis and classification

In clinical practice diagnosis is inherently different from classification. In the DSM–IV (APA, 1994), disorders are restrictively categorized by aberrant behavior (ascribed to individual pathology) and diagnostic thresholds are fixed; significant other factors, such as family environment or developmental phase, may be lost. The significance of behavior, however, must always be considered within different environments, as behavior per se does not necessarily indicate impairment. While classifying psychiatric disorder according to the DSM–IV classification system enables communication between clinicians, researchers, and policy makers, guides research, and determines access to services, it is seldom helpful in terms of determining what individual treatment interventions are needed.

GENERAL DISCUSSION

There is a long tradition in medicine of observing, describing, and comparing physical signs and symptoms. Identifying groups of similar clinical presentations (phenotypes) for further study has offered clues to the underlying genetic causes (genotype) and spurred advances. Examining behavioral phenotypes in genetically determined syndromes provides a unique opportunity to investigate similarities and differences in behavior as expressions of gene alterations. As in studies of physical symptoms and specific anomalies, these behavioral phenotypes (including autistic features or autism spectrum disorder) in combination with certain cognitive strengths and weaknesses and profiles of adaptive skills, have offered clues to the underlying genetic cause for the indi-

vidual's developmental and behavioral difficulties. In some cases, studies of behavioral phenotypes have actually led to the delineation of a syndrome and the realization that certain syndromes or chromosomal anomalies may be primarily characterized by specific behaviors or combination of behaviors (Mazzocco & Reiss, 1994; Flint, 1995). Conversely, many subsequent studies have shown that although a particular genetic variation may be the same, the behavioral outcome is not necessarily completely predictable or unalterable. The great inter–individual outcome variability seen in clinical practice makes it clear that behavioral characteristics in any syndrome are not solely determined by genetics and that too strong an emphasis on biological determinants should be avoided (Harris, 2010). Behavior is also influenced by interactions with the environment and by the reactions from that environment to a child's temperament, external features, and neuropsychological deficits.

We would argue that defining child psychiatric disorders in clinical practice as categorical entities does not do justice to the continuum of varying behavioral and cognitive outcomes. The same argument holds true for defining genetic syndromes. These are often also regarded as fixed, categorical definitions, with severe clinical cases usually first identified and considered prototypical, and similar outcomes of lesser severity often subsequently described as syndrome–like phenotypes. In fact, like psychiatric disorders, genetic syndromes usually exist along a continuum of varying physical and neurodevelopmental severity. Clinicians evaluating syndromes associated with intellectual disability may be biased with respect to their expectations of a child's developmental potential (Sanz et al., 2010), and may make inferences of long–term behavioral outcomes without taking changes over time into account. That said, it is likely that deficits in social, communication, and behavioral domains defined in autism spectrum disorder exhibit higher levels of intense, frequent, and severe presentations in intellectually disabled individuals with co-morbid autism spectrum disorder than in intellectually disabled children without autism spectrum disorder. These clinical presentations should therefore be carefully considered. It is also likely that behavioral presentations with autism spectrum disorder change less over time than those that are primarily associated with intellectual disability without autism. This hypothesis can only be made with follow–up, and may shed light on developmental trajectories into adulthood.

The need to understand the distribution of autism spectrum disorders and the role of environmental factors in the occurrence and etiology of autism spectrum disorder remains urgent and requires studying autism within different environments (Kolevzon et al., 2007). In contrast to the study of autism within the context of genetic syndromes, the research focus here is on meaningful differences between different geographic locations where autism occurs rather than on similarities. As more studies in diverse settings are carried out and findings accumulate, it is likely that the new results will provide

important clues to some causes and help to rule out others. A recent study (Hallmayer et al., 2011) has suggested that the influence of environmental factors (whether biological or social) may be larger than previously thought.

Future directions

Longitudinal approaches and Wiki

Evaluating syndrome–specific behavioral features at a single point in time does not provide a complete picture of developmental changes that occur from childhood to adulthood and it may lead to inaccurate projections of eventual outcomes. There are few longitudinal studies that examine the neuropsychological and behavioral profiles of children with genetic syndromes associated with intellectual disability, but it is likely that the impairments associated with intellectual disability and adaptive functioning persist into adulthood. While some symptoms may diminish, others may exacerbate and become more incapacitating as time progresses.

Adopting a longitudinal approach in which individuals are repeatedly assessed over time with the use of a standardized research assessment protocol would allow a more precise description of how patterns of behavioral and cognitive deficits within a genetic syndrome change, and may reveal important syndrome–specific differences. Studying patterns of behaviors within phenotypes associated with intellectual disability can help determine their importance in clinical practice and in developmental trajectories which include autism spectrum disorder. One interesting field of study may be the study of repetitive, stereotyped behaviors found in many individuals with severe intellectual disability, to determine how to differentiate between intellectual disability without autism spectrum disorder and intellectual disability with co-morbid autism spectrum disorder (Bodfish et al., 2000; Moss et al., 2009; Arnott et al., 2010).

Assessments over time should help identify possible improvement or slowed progress in performance, domains in which there may be a loss of skills, and continued areas of developmental concern, in affected individuals.

Using an online resource such as a Wiki in research in (ultra) rare disorders has shown itself to be very effective. It may serve two purposes: one, as a tool to gather and collate parental information, and expertise from families which may be widely dispersed geographically, and two, it may be useful in functioning as a virtual center of expertise for the dissemination of information on the disorder in question (Hennekam, 2011).

Next–generation gene sequencing and translational genetics

The increase of genetic studies linking genes and their relevant biological (cellular/biochemical) function to outcome and risk for disorder holds great promise for psychiatric genetics. The use of next–generation sequencing technology to sequence the genes of large patient groups with behaviorally defined psychiatric disorders (phenotype) so that those with the same gene modifications can be identified and grouped more homogenously (genotype) will transform future studies, and will make it possible to better examine similarities and differences between psychiatric disorders.

Eventually, future developments in translational genetics will involve devising informed clinical interventions to modify genetic predispositions to pathology.

Next–generation diagnostic criteria

The current system for classifying psychiatric disorders is unnecessarily restrictive and disregards clinical reality. Less reliance on narrow and rigid categorical definitions and fixed diagnostic thresholds, and more on careful lifelong evaluation of impairments and of the significance of symptoms will improve our understanding of the variations in normal development and the variations in clinical thresholds of specific disorders. This in turn will lead to better diagnostic criteria and more effective clinical decisions. Hopefully the new dimensional approach of the DSM–V, which is expected to emphasize lifetime perspectives and assessment of severity and significance of symptoms in treatment decisions, will promote this objective (Achenbach, 2009; Rutter, 2011).

Significance for families

Knowledge of behavioral phenotypes and cognitive profiles provides the clinician with new and additional tools for diagnosing different genetic syndromes. In addition, understanding the significance and effects of these behaviors and cognitive characteristics for each individual patient may be helpful for families. It allows parents and other caregivers to anticipate and deal with the abnormal behaviors of the individual with the syndrome and adjust rearing and learning environments to benefit that individual's development. Understanding what the affected individuals are communicating, whether or not they use language to do so, requires careful and thoughtful effort on the part of all those involved in their lives. For parents it may be of great value to realize that certain behavioral characteristics are associated with the syndrome, and that these symptoms should not be taken personally, as a rejection. This realization may reduce feelings of stress, guilt, incomprehension, and irritation in parents and other caregivers. Conversely, it is

equally important that parents not accept certain behaviors associated with the syndrome as inevitable and unalterable. Trying to understand the meaning of certain behaviors and reacting appropriately to correct either adverse environmental factors or specific aberrant behaviors may prevent further exacerbation and stigmatization. Meaningful positive experiences improve daily living skills and enhance communicative abilities, regardless of impairment. From a scientific and clinical perspective, it is desirable to determine whether psychiatric interventions may be helpful in managing behavioral problems associated with the syndrome. From the individual's perspective, defining the need for services at a certain point in time is necessary, but this definition should be customized to reflect individual changes and development over time to enable improved and adapted services to meet changing needs.

Conclusion

There is a growing body of evidence to suggest that while psychiatric phenotypes in genetic syndromes are typically diagnosed through behavioral observations, these disorders are closely associated with underlying disruptions in brain development, structure, and function. Genetic syndromes associated with complex behavioral disorders such as intellectual disability and autism spectrum disorder, for which no single causative factor can offer a valid explanation, exemplify the interaction of multiple risk and protective factors, whether genetic or environmental, and demonstrate how these interactions change an individual's development and eventual outcome. Studying phenotypes of rare and ultra–rare genetic syndromes associated with severe intellectual disability has made it clear that while individual outcomes may arise from genetic differences, the expression of genes affecting structure and function of the brain is also influenced by the interplay between genes, learning, and social context. Studies investigating how the interactions between genetic and environmental factors increase the likelihood of developing the disorder seem promising, especially if these studies also trace developmental trajectories over the lifespan to investigate changes in phenotypic profiles within and across syndromes.

Such approaches increase our understanding of how phenotypical features may be linked to specific genetic substrates, but more importantly, reveal how genes and environment interact in unique ways to predict outcomes. Eventually these studies may lead to therapeutic interventions that will improve the quality of life of affected individuals and their families.

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APPENDIX

Summary

The objective of the research projects in this dissertation was to study autism as it manifests itself within (ultra) rare genetic syndromes; and to examine autism within a different sociocultural environment. The research projects in this thesis review, describe and examine three sets of behaviors: intellectual disability, autism spectrum disorder, and adaptive skills.

Chapters 2 and 3 review the published literature regarding the phenotypes of intellectual disability and behavioral abnormalities associated with genetic syndromes with a known cause. Genetically determined syndromes may be characterized by specific dysmorphic features and congenital anomalies, but in clinical practice, the behavioral and cognitive patterns associated with them can be as important. Awareness of such phenotypes provides the clinician with additional tools for diagnosing and differentiating these syndromes. It also allows parents and other caregivers to anticipate and deal with abnormal behaviors. Several genetic syndromes with distinct behavioral and cognitive phenotypes that occur frequently are reviewed in chapter 2. An example of a genetic syndrome associated with intellectual disability that can be clinically recognized by the unusual behavioral phenotype, is Smith–Magenis syndrome. The highly characteristic behaviors such as self–hugging, sleep disturbances and severe self injury are reviewed in chapter 3. The severity of the behavioral abnormalities is usually the primary reason for referral for psychiatric evaluation.

An early clinical case description of specific behaviors and intellectual disability in an individual suspected of having an undefined genetic syndrome is presented in chapter 4. Findings in this patient were compared to signs and symptoms found in patients with known genetic defects described in other studies. However, these descriptions suggested the symptoms found in this patient had a different genetic origin. The marked clinical similarities with two cases described by Pitt and Hopkins (1978) and one case described by Singh (1993) led to the hypothesis of a syndrome specifically characterized by typical facial features, severe intellectual disability, and communication problems including a lack of expressive language, and an abnormal pattern of voluntary, episodic overbreathing. At the time the cause of the syndrome was still unknown; discovery of the gene involved did not take place until 2007, this disorder is now recognized as Pitt–Hopkins syndrome.

Pitt–Hopkins syndrome (PHS) is a rare genetic syndrome with important developmental, cognitive, and behavioral consequences. Classic PHS and PH–like syndromes are caused by genetic deletions/mutations, specifically *Transcription Factor 4 (TCF4)* haploin-

sufficiency and *NeuReXiN1 (NRXN1)* and *CoNTactiN Associated Protein–like 2 (CNTNAP2)* alterations. Mutations in *TCF4*, *NRXN1*, and *CNTNAP2* have been implicated in intellectual disability, epilepsy, autism, and schizophrenia. Assessments of behavioral, adaptive, and psychological functioning and autism symptoms in 10 individuals with molecularly confirmed classic PHS are presented in chapter 5. Findings were compared to those found in the literature. Participants all showed (very) profound intellectual disability, an amiable demeanor with minimal maladaptive behaviors, severe impairments in communication and language, coupled with a failure to engage socially, and intense, frequent motor stereotypies. The psychiatric dimension of the phenotype of the syndrome includes autism spectrum disorder, albeit presenting in varying degrees of severity.

Marshall–Smith syndrome (MSS) is an ultra–rare genetic syndrome, with fewer than 50 patients described in the medical literature to date. Its main clinical features are moderate to severe developmental delay with absent or limited speech, unusual behavior, abnormal bone maturation, respiratory compromise secondary to upper airway obstruction, and characteristic facial features. Hypoplasia of the corpus callosum is common. Mortality from respiratory complications is high, but interventions to support the airway increasingly allow survival into adulthood. A relatively large group of patients with Marshall–Smith syndrome was examined and assessed through an international collaborative effort and the use of an online Wiki to further delineate the phenotype and to gain insight into the developmental progression of the syndrome. These findings are presented in chapter 6. At the time of publication the etiology of the syndrome was still unknown. Since then mutations in *transcription factor Nuclear Factor I (NFIX)* have been implicated in MSS. At present the specific function of *NFIX* remains unclear, but it is assumed that *NFIX* has an important role in human brain development and in skeletogenesis.

In the course of studying the physical features of a group of patients with Marshall–Smith syndrome, unusual behavioral traits were observed. The study of these behavioral traits in 6 children is described in chapter 7. Participants showed moderate to severe intellectual disability, severe delay in the attainment of speech and motor milestones, a friendly or happy demeanor. They enjoyed social interactions with familiar others and exhibited minimal maladaptive behaviors. Although during clinical assessments we observed deficits in communication and social interaction, and stereotyped, repetitive behaviors, these characteristics were ultimately not categorized as autism spectrum disorder because the impact of various significant medical issues and the influence of developmental progress over time remained unclear. Interestingly, only a proportion of the participants showed the mutation involving the gene *NFIX*, suggesting that there may be as yet undefined etiologic factors involved in MSS.

Chapter 8 describes a study of autism spectrum disorders in Aruba, a context in which autism had not previously been studied. The objective of the study was to determine the prevalence of treated autism spectrum disorders in children born in Aruba between 1990 and 1999. All cases were ascertained from record review of children treated at the Child & Adolescent Psychiatry Clinic of Aruba, the first and only child psychiatry service on the island. This first epidemiologic study on autism spectrum disorder in the Caribbean showed prevalence estimates and gender distribution similar to those reported in recent studies in the UK and US.

Converging evidence suggests that higher paternal and maternal age elevate the risk of autism in offspring. The findings of a case–control study in a group of Aruban–born children (1990–2003), consisting of 95 cases and 347 controls matched for age and gender, are presented in chapter 9. The objective of this study was to examine whether the association between higher paternal age and increased risk for autism spectrum disorder in offspring could also be found in Aruba, whose population has a different sociocultural and ethnic composition than those of western populations studied heretofore. Results showed that higher paternal age was indeed also associated with increased risk of autism spectrum disorder in offspring in Aruba.

Chapter 10 offers a discussion of the findings and concluding remarks.

Samenvatting: Fenotypes en epidemiologie van zeldzame syndromen met ontwikkelingsproblemen

In de onderzoeksprojecten van deze dissertatie stond onderzoek naar autisme zoals het zich voordoet bij zeldzame genetische aandoeningen en binnen een andere sociaal-culturele context centraal.

Drie soorten gedrag werden in de literatuur bestudeerd, klinisch onderzocht en beschreven: intellectuele beperking, autisme spectrum stoornis en aanpassingsvermogen.

In de hoofdstukken 2 en 3 wordt de bestudeerde literatuur over verschijningsvormen (fenotypes) van intellectuele beperking en gedragsproblemen, geassocieerd met genetische syndromen met een bekende oorzaak, beschreven. Genetisch bepaalde syndromen kunnen gekarakteriseerd worden door bijzondere uiterlijke kenmerken en aangeboren afwijkingen, maar voor de klinische praktijk kunnen de erbij voorkomende gedrags- en cognitieve patronen net zo belangrijk zijn. De clinicus die op de hoogte is van dergelijke verschijningsvormen heeft extra mogelijkheden om syndromen te diagnosticeren en van elkaar te onderscheiden. Dergelijke kennis maakt het ook mogelijk voor ouders en verzorgers te anticiperen op en om te gaan met afwijkend gedrag. Verschillende genetische syndromen met kenmerkend gedrag en cognitief profiel worden beschreven in hoofdstuk 2. Een voorbeeld van een genetisch syndroom samengaand met intellectuele beperking, dat klinisch herkenbaar is door het bijkomende ongewone gedrag is Smith-Magenis syndroom. De typische gedrags- en andere verschijnselen bij dit syndroom, zoals zichzelf omhelzen, slaapstoornissen en ernstige zelfverwonding worden beschreven in hoofdstuk 3. De ernst van de gedragsafwijkingen is vaak de belangrijkste reden om te verwijzen voor (kinder)psychiatrische beoordeling.

Een vroege klinische gevalsbeschrijving van bijzonder gedrag en intellectuele beperking bij een niet-gedefinieerd genetisch syndroom wordt beschreven in hoofdstuk 4. De verschijnselen werden vergeleken met klinische verschijnselen bij andere syndromen, beschreven in de literatuur, waarvan de oorzaak wel bekend was. Bij deze vergelijkingen werd duidelijk dat de verschijnselen in deze patiënt een andere genetische oorzaak moesten hebben. De overeenkomsten tussen deze patiënt en twee gevallen, beschreven door Pitt en Hopkins in 1976, en een geval beschreven door Singh in 1998 leidde tot de hypothese van een syndroom gekenmerkt door typische gezichtskenmerken, ernstige intellectuele beperking met ontbreken van spraak, en een abnormaal ademhalingspatroon met vrijwillig en periodiek over-ademen. Ten tijde van de publicatie van deze klinische beschrijving was de oorzaak nog onbekend, het betrokken gen

werd pas in 2007 ontdekt en deze combinatie van afwijkingen staat nu bekend als Pitt-Hopkins syndroom.

Pitt-Hopkins syndroom (PHS) is een zeldzaam genetisch syndroom met belangrijke gevolgen voor de ontwikkeling, de intelligentie en het gedrag. Klassiek PHS en PH-achtige syndromen worden veroorzaakt door genetische defecten of veranderingen in *Transcription Factor 4 (TCF4)* en door veranderingen in *NeuReXiN1 (NRXN1)* en *CoNTactiN Associated Protein-like 2 (CNTNAP2)*. Veranderingen in *TCF4*, *NRXN1*, en *CNTNAP2* zijn betrokken bij intellectuele beperking, epilepsie, autisme en schizofrenie. In hoofdstuk 5 worden de uitkomsten besproken van de onderzoeken naar het gedrag, aanpassingsvermogen en psychologisch functioneren in 10 individuen, waarbij PHS moleculair werd aangetoond, beschreven en vergeleken met eerdere beschrijvingen in de literatuur. Alle deelnemers aan het onderzoek hadden een (zeer) ernstige intellectuele beperking, een vriendelijke uitstraling met weinig gedragsproblemen, ernstige beperkingen in communicatie en spraak, gecombineerd met problemen in de sociale interactie en intense, vaak voorkomende motorische stereotypieën. Geconcludeerd werd dat bij de verschijningsvorm van dit syndroom autisme spectrum stoornis kan voorkomen, maar dat de ernst van de autistische symptomen varieert.

Marshall–Smith syndrome (MSS) is een ultra-zeldzaam genetisch syndroom, dat tot nu toe bij minder dan 50 patiënten in de wereld beschreven werd. De belangrijkste klinische kenmerken zijn matig tot ernstige ontwikkelingsachterstand met weinig of geen spraak, ongewoon gedrag, abnormale botrijping, ademhalingsmoeilijkheden door luchtwegproblemen en bijzondere gezichtskenmerken. Onderontwikkeling van het corpus callosum komt vaak voor. Er is een hoge sterfte door de ademhalingsmoeilijkheden, hoewel overleving tot in de volwassenheid steeds vaker mogelijk is wanneer door medisch ingrijpen de luchtwegproblemen worden verminderd.

Een relatief grote groep patiënten met Marshall-Smith syndroom werd binnen een internationaal samenwerkingsproject en met gebruik van een online Wiki lichamelijk onderzocht. Doel was het fenotype verder af te grenzen en inzicht te krijgen in de ontwikkelingsvoortgang van het syndroom. De uitkomsten van deze onderzoeken worden beschreven in hoofdstuk 6. Ten tijde van de publicatie was de oorzaak van het syndroom nog onbekend. Daarna werd ontdekt dat veranderingen in *transcription factor Nuclear Factor I (NFIX)* mogelijk een rol spelen. De precieze functie van *NFIX* is nog steeds onduidelijk, maar aangenomen wordt dat het een belangrijke rol heeft in de ontwikkeling van het menselijk brein en in de ontwikkeling van het skelet.
Gedurende het onderzoek naar de lichamelijke kenmerken van een groep patiënten met Marshall-Smith syndroom werden ook enkele bijzondere gedragingen geobserveerd.

Het onderzoek naar deze gedragingen in een groepje van 6 kinderen met Marshall-Smith syndroom wordt beschreven in hoofdstuk 7. De kinderen hadden matig tot ernstige intellectuele beperkingen, ernstige achterstand in de ontwikkeling van taal en motoriek. Zij hadden een vriendelijk, vrolijk temperament, weinig gedragsproblemen en ze genoten van sociale activiteiten met bekende anderen. Ondanks dat er gedurende de onderzoeken ook tekortkomingen in het sociale contact en de communicatie werden gezien, en stereotype motorische bewegingen, konden deze gedragskenmerken uiteindelijk toch geen autisme spectrum stoornis genoemd worden. Vooral omdat de invloed van ernstige lichamelijke problemen en eerdere ziekenhuisopnames onduidelijk was, en omdat er met het voortschrijden van tijd nog steeds voortgang in de ontwikkeling van contact, communicatie en motoriek leek te kunnen optreden. Opvallend was dat maar een deel van de onderzochte kinderen de verandering in het gen *NFIX* bleek te hebben. Het is dus aannemelijk dat er andere, nog niet ontdekte factoren een rol spelen in het ontstaan van MSS.

In hoofdstuk 8 wordt de studie van autisme spectrum stoornissen in Aruba beschreven, een context waarin nog niet eerder onderzoek naar autisme werd gedaan. Het doel van de studie was de prevalentie te bepalen van autisme spectrum stoornissen bij in Aruba geboren kinderen, die behandeld werden bij de Polikliniek Kinder- en Jeugdpsychiatrie in Aruba. Alle gevallen werden gevonden door middel van een studie van de dossiers van de Polikliniek Kinder- en Jeugdpsychiatrie, de eerste en enige kinderpsychiatrische voorziening op het eiland. Bij deze eerste epidemiologische studie van autisme spectrum stoornissen in de Caribische regio werd aangetoond dat de prevalentie en geslachtsverdeling van autisme spectrum stoornissen vergelijkbaar zijn met de resultaten uit studies in de Verenigde Staten en het Verenigd Koninkrijk.

Er zijn steeds meer aanwijzingen uit internationale onderzoeken dat het risico op autisme van een kind toeneemt door een hogere leeftijd van vader en moeder bij de geboorte ervan. In hoofdstuk 9 worden de bevindingen van een case-control studie in een groep van in Aruba geboren kinderen (1990-2003), bestaande uit 95 cases en 347 controles geselecteerd op leeftijd en geslacht, beschreven. Het doel van deze studie was te onderzoeken of de associatie tussen een hogere leeftijd van de vader en toegenomen risico voor autisme voor het kind ook gevonden kon worden in Aruba. In Aruba heeft de populatie een andere sociaal-culturele en etnische samenstelling dan de westerse populaties die eerder werden onderzocht. Uit de resultaten van dit onderzoek werd duidelijk dat ook in Aruba een hogere leeftijd van de vader samenhangt met een toegenomen risico voor autisme in het kind.

In hoofdstuk 10 wordt een discussie van de bevindingen gepresenteerd met enkele afsluitende opmerkingen.

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Van Balkom, I. D. C., Shaw, A., Vuijk, P. J., Franssens, M., Hoek, H. W. & Hennekam, R. C. M. (2011). Development and behaviour in Marshall-Smith syndrome: an exploratory study of cognition, phenotype and autism. Journal of Intellectual Disability Research, 55, 973-987.

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Curriculum Vitae

Inge van Balkom is a native of Oranjestad, Aruba. She received her medical degree in Groningen (December 1988), doing her first residencies in Pulmonology & Internal Medicine (1989), and Pediatrics (1990). She was trained as a psychiatrist in Amsterdam (Valeriuskliniek, professor W. van Tilburg) between 1990-1994, and continued her training as a child- and adolescent psychiatrist (Amsterdam Medical Center, professor W.B. Gunning) from 1994-1997, including a residency in Clinical Genetics (Amsterdam Medical Center, professor R.C.M. Hennekam).

Early 1997 she returned to Aruba and founded the Child and Adolescent Psychiatry Clinic, the first pediatric psychiatry service on the island, serving more than 2000 families until her departure in November 2006. As consulting child psychiatrist she regularly saw children and families from the islands of the Netherlands Antilles. She frequently offered free workshops to general practitioners, pediatricians, other health care professionals, social workers and teachers in Aruba, Curaçao and St Maarten, and presentations to parents and the general public in an effort to raise awareness on mental health issues. Between 1999-2001 she completed training as a family therapist (NISTO, Joep Choy). She served as president of the Aruba Mental Health Foundation (SGGA) from 1999-2002, and on the board of the Association of Medical Specialists Aruba (VMSA) between 2004-2006. She encouraged parents dealing with autism to organize themselves in the parent association Fundacion Autismo Aruba (FAA). She serves on the scientific advisory board of the Dutch Fetal Alcohol Syndrome Foundation (since 2004), and is on the advisory board of two foundations in Curaçao: the Parenting assistance for Disabled Children Foundation (SOKH, since 2000), and the Foundation for children with autism (Stichting Het Savaanhuis, since 2006). She continues to return to Aruba and Curaçao to offer workshops, follow-up on many of her former patients, and to see new patients.

From 2006 to date Inge is employed as medical director of Jonx, the child- and adolescent psychiatry service of Lentis Psychiatric Institute in Groningen, the Netherlands. She represents Lentis on the advisory board of the Dutch Leo Kanner Foundation (since 2009), and is currently a member of the Global Partnerships in the Epidemiology of Developmental Disabilities (GPEDD) of the CDC-National Center on Birth Defects and Developmental Disabilities (Atlanta, USA) (since 2010).

Inge has been happily married to Harold since 1992, they have two wonderful daughters: Eliana and Graciela. In addition she is also a proud second mom to Lotte, Nori and Leonie.