Genetic causes of syndromic and non-syndromic autism

AHMET O CAGLAYAN

Kayseri Education and Research Hospital, Department of Medical Genetics, Kayseri, Turkey.

Correspondence to Dr Ahmet O Caglayan at Kayseri Education and Research Hospital, Head of Department of Medical Genetics 38010, Kayseri, Turkey. E-mail: aocaglayan@erciyes.edu.tr

PUBLICATION DATA
Accepted for publication 21st July 2009.
Published online 5th January 2010.

LIST OF ABBREVIATIONS

ASD	Autism spectrum disorder
DMD	Duchenne muscular dystrophy
FXS	Fragile X syndrome
MIM	Mendelian Inheritance in Man
PWS	Prader–Willi syndrome
SLOS	Smith–Lemli–Opitz syndrome
TSC	Tuberous sclerosis complex

AIMS Over the past decade, genetic tests have become available for numerous heritable disorders, especially those whose inheritance follows the Mendelian model. Autism spectrum disorders (ASDs) represent a group of developmental disorders with a strong genetic basis. During the past few years, genetic research in ASDs has been successful in identifying several vulnerability loci and a few cytogenetic abnormalities or single-base mutations implicated in the causation of autism.

METHOD In this study the literature was reviewed to highlight genotype–phenotype correlations between causal gene mutations or cytogenetic abnormalities and behavioural or morphological phenotypes.

RESULTS Based on this knowledge, practical information is offered to help clinicians pursue targeted genetic testing of individuals with autism whose clinical phenotype is suggestive of a specific genetic or genomic aetiology.

INTERPRETATION Comprehensive research into the molecular mechanism of autism is required to aid the development of disease-specific targeted therapies. In order to transfer this recently acquired knowledge into clinical practice, it is critical to define a set of phenotypic inclusion criteria that must be met by affected probands to justify their enrolment in a specific genetic testing programme.

WHY IS GENETICS IMPORTANT?

Autism spectrum disorders (ASDs) represent a heterogeneous group of neurodevelopmental disorders (including autism, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder – not otherwise specified [PDD-NOS]) characterized by social and communication deficits accompanied by repetitive and stereotyped behaviours, with onset before 3 years of age.[1,2] Genetic mechanisms contribute to the pathogenesis of ASDs.[3,4] The clinical heterogeneity of ASD probably reflects the complexity of its genetic profile, involving multiple genes, genetic/locus heterogeneity, genetic imprinting, uniparental disomy, epistasis, and gene–environment interactions.[4] Genetic screening represents a powerful tool when dealing with monogenic Mendelian disorders, characterized by direct genotype–phenotype correlations. In the case of complex disorders, such as ASD, widespread genetic testing would be not only expensive and time-consuming, but also generally inappropriate owing to their aetiological complexity.[4] Nonetheless, genetic testing can be successfully used in complex disorders to evaluate the degree of genetic susceptibility to a certain disease and to identify rare monogenic or cytogenetic forms of the disease. The relevant literature was reviewed to identify specific correlations between ASD-causing gene mutations or cytogenetic abnormalities and clinical ASD phenotypes (mainly behavioural and/or morphological ASD phenotypes). Hopefully this information will be useful to guide clinicians in establishing and implementing effective genetic diagnoses for those individuals with ASD whose phenotype is suggestive of a specific genetic or genomic aetiology.

INHERITED AUTISTIC DISORDERS

Recent insights show that a variety of genetic mechanisms may be involved in the aetiology of ASD, for example single-gene disorders, copy-number variations, and polygenic mechanisms. I chose to focus on the genetics of ASDs, as they constitute the neuropsychiatric disorder with the highest monozygotic twin concordance rate (73–95%) and the highest heritability (90%, as estimated by twin studies), and in addition are associated with a sizeable risk of occurrence in siblings (5/100–6/100 in the case of non-syndromic autism).[3,4] In addition, the presence of mild autistic traits in the first-degree relatives of individuals with autism points to a strong genetic component in ASD.[5]

AUTISM IN GENETIC SYNDROMES

The prevalence of autistic disorder that meets full diagnostic criteria has been estimated as 40 to 60 per 10 000 children.[6] In the past, approximately 1/100 of individuals with ASDs were diagnosed as having secondary autism, that is autism in which cytogenetic abnormalities (i.e. 15q duplication), single-gene defects (i.e. in the *RELN* and *UBE3A* genes), or a known

 DOI: 10.1111/j.1469-8749.2009.03523.x © The Author. Journal compilation © Mac Keith Press 2010

environmental agent (i.e. prenatal infections) were identified as causative.[7] However, recent studies suggest that genetic causes may play an even more important role in the aetiology of ASDs.[8] Many children with ASD have some degree of learning disability,* and genetic disorders associated with learning disability have also been associated with ASDs. The more common genetic syndromes are presented in Table SI (supporting information published online).

Fragile X syndrome

Fragile X syndrome (FXS) (Mendelian Inheritance in Man [MIM]: 300624) is the most common cause of inherited learning disability. The syndrome caused by the full mutation affects approximately 1 in 2500 males and 1 in 8000 females.[9] FXS is an X-linked dominant disorder with reduced penetrance. It is most often caused by a dynamic mutation that involves an unstable expansion of a trinucleotide CGG repeat at the 5′-untranslated region of the fragile X mental retardation 1 (*FMR1*) gene, located at Xq27.3. On the basis of the number of the CGG repeats, the allele is classified as normal (about 5–45 repeats), intermediate or grey zone (about 46–54 repeats), premutation (about 55–199 repeats), or full mutation (more than 200 repeats).[10]

Individuals with FXS may present with learning problems and a borderline normal IQ (especially in females), or moderate (IQ 35–50) to severe (IQ 20–35) learning disability. In addition, approximately 90% of male children with FXS show one or more features of autism (e.g. atypical social interaction, lack of eye contact, social anxiety and avoidance, perseverative speech, stereotypic behaviour [e.g. hand flapping], hypersensitivity to sensory stimuli, impulsive aggression, or self-injurious hand biting).[11,12] The prevalence of autism within the male FXS population is reported to range from 1.5/100 to 3.3/100, and affected individuals meet all criteria necessary for a diagnosis of autism, including impairments in social interaction, language, and communication, and a pattern of restrictive or repetitive behaviours.[13] FXS is diagnosed in almost 5/100 of individuals with autism.[14]

Several studies have investigated the relationship between factors such as IQ and sensory difficulties and the presence of autism in individuals with FXS. Hatton et al.[13] reported that the level of the fragile X protein FMRP (familial mental retardation protein) was correlated with the level of autistic behaviour as measured by the Childhood Autism Rating Scale. Loesch et al.[15] found that the level of FMRP was correlated with the degree of autism on the Autism Diagnostic Observation Schedule (ADOS).[15]

Recent reports have documented children, mostly males, with the fragile X premutation (a CGG repeat number between 55 and 200) who have cognitive deficits, behavioural problems, and/or ASDs.[16,17] A study of an older subgroup of carriers with the premutation found that some individuals had white matter disease or brain atrophy, and some eventually developed the fragile X-associated tremor–ataxia syndrome.[18] Genetic testing for this repeat expansion is diagnostic for this syndrome, and testing is appropriate in all children with developmental delay, learning disability, or autism.

*North American usage: mental retardation.

Rett syndrome

Rett syndrome (MIM: 312750) is an X-linked dominantly inherited postnatal neurodevelopmental disorder that is the second most common cause of severe cognitive impairment in females after Down syndrome, and is identified by the age of 15 years approximately in 1 in 8000 females.[19] Rett syndrome is caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2). Individuals with classic Rett syndrome appear to develop normally up to the age of 6 to 18 months (stage I), although female infants with Rett syndrome may display subtle behavioural abnormalities before this period. In stage II (age 1–4y), individuals display a developmental arrest. At this stage, social withdrawal and loss of language become apparent in addition to irritability and self-abusive behaviour. Other autistic features also manifest, including expressionless face, hypersensitivity to sound, lack of eye-to-eye contact, indifference to the surrounding environment, and unresponsiveness to social cues.

There is some stabilization of the disease during stage III (age 4–7y); however, affected individuals continue to exhibit gross cognitive and motor impairments and commonly develop epilepsy. Seizures become less frequent during stage IV (age 5–15ys and older), but motor deterioration continues. Amelioration of the social component of the autistic-like behaviour occurs between 5 and 10 years of age. Behavioural abnormalities during this postregression phase include teeth grinding, night laughing or crying, screaming fits, low mood, and anxiety episodes elicited by distressful external events. During this phase, repetitive, stereotypic hand movements replace purposeful hand use. Patterns consist of tortuous hand wringing, hand washing, clapping, patting, or other more bizarre hand automatisms, during waking hours.[20] Most females with Rett syndrome lose mobility and often become non-ambulant during the adolescent years. The condition reaches a plateau and some individuals survive up to the sixth or seventh decade of life in a severely debilitated physical condition.

Prader–Willi and Angelman syndromes

Deletions of a ~4Mb region from chromosome 15q11 to q13 produce either of two distinct clinical syndromes (although they involve different genes), depending on the parental origin of the deleted chromosome: deletions on the paternal chromosome cause Prader–Willi syndrome (PWS) whereas those on the maternal chromosome cause Angelman syndrome. PWS (MIM: 176270) occurs in 1 in 15 000 births and typically presents as neonatal hypotonia and failure to thrive. Other physical manifestations include hypogonadism, a characteristic face, small hands and feet, and hypopigmentation.[21] A well-described behavioural pattern begins in early childhood in 70 to 90% of affected individuals and includes hyperphagia resulting in severe obesity, obsessive–compulsive symptoms, disruptive behaviour, and an increased risk for mood disorders. In addition, recent evidence suggests that some individu-

als with PWS exhibit repetitive behaviour and social deficits reminiscent of ASDs, which have been diagnosed in up to 25/100 of affected individuals,[22,23] and it appears that the risk of autistic symptomatology is greater in those in whom PWS is the result of maternal uniparental disomy than in those with deletions of 15q11 to q13 on the paternal chromosome.[22]

The severity of behavioural problems increases with age and body mass index, and then diminishes in older adults.[24] The clinical phenotype of Angelman syndrome (MIM: 105830), which occurs in 1 in 15 000 births, is distinct from that of PWS and comprises microcephaly, a movement disorder with ataxia, a characteristic happy disposition, seizures, severe learning disability with either no or very little speech development, and hypopigmentation.[25] A number of characteristic features of Angelman syndrome may be seen in the context of the autistic spectrum, including virtual absence of speech, impaired use of non-verbal communicative behaviours (such as facial expression), attention deficits, hyperactivity, feeding and sleeping problems, and delays in motor development.[26] Autistic features are considered as a comorbidity.[26] A recent study found that, among children with Angelman syndrome, those with comorbid autism scored lower on measures of language, adaptive behaviour, and cognition and demonstrated a slower rate of improvement over the course of the study.[27]

Furthermore, deficits have been demonstrated in communication and socialization that mirror those observed in children with idiopathic autism.

Inv dup(15) or idic(15) syndrome

The other entity related to the 15q region is inv dup(15) or idic(15) syndrome. This is a rare, nearly always sporadic, neurogenetic disorder that occurs in 1 in 30 000 births and is characterized by early central hypotonia, developmental delay and intellectual disability, epilepsy, and autistic behaviour with no facial dysmorphic features. The distinct behavioural disorder shown by children and adolescents has been widely described as autistic or autistic-like.[28]

Down syndrome

Trisomy 21, a microscopically demonstrable chromosomal aberration occurring in 1 in 700 live births in all ethnic groups, is the most common genetic cause of moderate to severe learning disability and is characterized by distinctive phenotypic features and a well-defined natural history.[29] Complex cognitive and neurobehavioural disorders can occur in association with Down syndrome, contributing to the within-syndrome variability often seen in neurogenetic disorders.

The frequency of pervasive developmental disorder in Down syndrome have been reported to range from approximately 1/100 to 11/100.[30] Autism is 10 times more common in children with Down syndrome than in the general population. The majority of reported individuals with comorbid autism and Down syndrome are male,[31] although this may reflect underreporting by professionals who expect autism to be less common in females. The latest studies have shown that ASD manifests as a distinct behavioural phenomenon in Down syndrome and can be differentiated from typical Down syndrome by anxious behaviour and complex and unusual stereotypies; from Down syndrome with stereotypic movement disorder by social withdrawal and anxious behaviours; and from Down syndrome with disruptive behaviours by relatively simple stereotypic behaviour.[32] In Down syndrome, there appears to be a correlation between the severity of aberrant behaviour and the severity of cognitive dysfunction in general. Recent studies have shown that the co-occurrence of Down syndrome with ASD is associated with significantly higher total scores on the Aberrant Behavior Checklist and Autism Behavior Checklist, in agreement with earlier reports of a link between the degree of low cognitive function and severity of autistic-like behaviours.[30]

Finally, Molloy et al.[33] showed that, among children with trisomy 21, brain function (i.e. communication, and cognitive and adaptive behaviour skills) is significantly more impaired in those with autism than in those without autism. However, deficits in the core domains of social reciprocity and communication and the restricted and repetitive interests are not entirely explained by the more severe cognitive impairment, and this autism phenotype in children with trisomy 21, which includes an increased risk for seizures, may indicate a widespread loss of functional connectivity in the brain.[32]

Joubert syndrome

Joubert syndrome (MIM: 213300), with a prevalence of 1 in 100 000, is the most common inherited cerebellar malformation syndrome and part of the autosomal recessive cerebellar ataxia group of disorders.[34] A few children with Joubert syndrome have been diagnosed with autism, although a more recent study proposed that Joubert syndrome and autism are genetically distinct disorders with no evidence of a shared genetic liability.[35]

Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) (MIM: 162200), which occurs in 1 in 3000 to 3500 individuals worldwide, is an autosomal dominant inherited multisystem disorder due to a mutation of the *NF1* gene, which is located on 17q11.2 and which encodes the neurofibromin protein.[36] An increased risk of neurofibromatosis in an autistic population has been suggested previously.[37]

Macrocephaly and overgrowth syndromes

The macrocephaly observed in approximately 15/100 to 35/100 of individuals with autism appears to be an independent clinical trait, not related to sex, the presence of morphological abnormalities, IQ, occurrence of seizures, or the severity of autistic symptoms. It is typically not present at birth but becomes manifest at around 1 to 3 years of age.[39,40] Although macrocephaly is one of the most widely replicated neurobiological findings in autism, its pathogenesis remains unknown. Converging evidence from head circumference measurements, magnetic resonance imaging studies, and postmortem brain weight indicates that a large proportion of children with autism have an abnormal regulation of brain

growth, resulting in enlarged brains during early childhood.[42] Other studies, however, have found increased brain volume in populations of older individuals with autism,[43] so the timing of brain enlargement remains to be determined. Similarly, the pattern of enlargement across the brain lobes and cerebellum, and the involvement of grey versus white matter, is still unclear at present.

Sotos syndrome (MIM: 117550) is a childhood overgrowth syndrome characterized by cardinal features such as macrocephaly, distinctive facial features, including prominent forehead, down-slanted palpebral fissures, and pointed chin, advanced bone age, and learning disability caused by mutations or deletions of the *NSD1* gene.[38] Macrocephaly is present at birth and progresses rapidly during the first year. Affected children usually exhibit developmental delay, and speech delay is common. In addition, ASDs or autistic features have been described in a number of individuals with Sotos syndrome.[41]

The other three macrocephalic conditions with overgrowth are Simpson–Golabi–Behmel syndrome (MIM: 312870, 300209), Perlman syndrome (MIM: 267000) and Beckwith-Wiedemann syndrome (MIM: 130650). Beckwith-Wiedemann syndrome is a classical human imprinting disorder characterized by prenatal and postnatal overgrowth and variable developmental anomalies. Recently Kent et al.[44] reported that 6.8% of children with Beckwith-Wiedemann syndrome had been diagnosed with an autistic spectrum disorder (ASD).

In addition, germline *PTEN* gene mutations have been reported in children with autism and macrocephaly, and autism with no other clinical features, and it has been suggested that *PTEN* gene sequencing be included in the diagnostic work-up of these children.[45]

Timothy syndrome

Timothy syndrome (MIM: 601005) is a very rare autosomal dominant condition inherited with full penetrance. This childhood multisystem disorder is characterized by multi-organ dysfunction, including lethal cardiac arrhythmias, congenital heart disease, webbing of fingers and toes, immune deficiency, intermittent hypoglycaemia, cognitive abnormalities, and autism. Splawski et al.[46] found a significant association between ASDs and Timothy syndrome, and suggested that individuals with Timothy syndrome meet the criteria for autism or have severe deficits of language and social development. Furthermore, they suggest that abnormal Ca^{2+} signalling may contribute to such disorders.[46]

Tuberous sclerosis complex with autism

Tuberous sclerosis complex (TSC) (MIM: 191100), which occurs in 1 in 6000 births, is an autosomal dominant inherited genetic disorder caused by mutations in one of the tumour-suppressor genes *TSC1* or *TSC2*. TSC remains a clinical diagnosis, with its major and minor features outlined in consensus criteria.[47]

The co-occurrence of ASD and TSC is well established. The prevalence of TSC in the ASD population is 1/100 to 4/100, whereas features of autism are present in 25/100 to 5/10 of individuals with TSC.[48] There is an observed association of autism and TSC, but the pathogenesis underlying this association is still largely unknown. In contrast to the general population, in which the prevalence of autism is four times higher in males than in females, the incidence of autism among children with TSC does not differ between the sexes. Among children with TSC, seizure onset occurs at a significantly younger age in those who also have autism than in those with no autistic features. However, autism also develops in children with TSC who do not have seizures. The likelihood of autism is greater if the child experiences early-onset West syndrome that are difficult to control, especially if there is an epileptic focus in a temporal lobe. Bolton and Griffiths[49] found a very strong association between temporal lobe tubers and autism. In pooled studies, the incidence of autism or pervasive developmental disorder in learning disability and TSC was approximately 76%, compared with 24/100 among the population without learning disability.[50]

Turner syndrome

Turner syndrome is a neurogenetic disorder due to a numeric chromosome anomaly associated with the inheritance of a single X chromosome (45,X), and its variants. It occurs in approximately 1 in 2000 to 5000 live female births, but it is one of the most common chromosome abnormalities in spontaneous abortions and is estimated to occur in 1/100 to 2/100 of all conceptuses.[51] Turner syndrome is associated with a substantially increased risk of autism. Among affected females, the risk of ASDs is substantially higher (200 times greater than among females with intelligence in the normal range and up to 10 times higher than in males).[52] Females with Turner syndrome are known to have specific cognitive and behavioural deficits that overlap with but are also distinct from those found in children with idiopathic autism.

Williams syndrome

Williams syndrome (MIM: 194050) is an autosomally dominant inherited, neurodevelopmental disorder with a prevalence of approximately 1 in 7500 of the population. Williams syndrome results from the microdeletion of ~25 to 30 genes spanning about 1.5 megabases in the q11.23 region of chromosome 7.[53]

For the past two decades, autism (ASD) and Williams syndrome have captured the interest and imagination of cognitive neuroscientists. The most salient difference between people with ASD and people with Williams syndrome is their social behaviour. ASD is defined on the basis of profound impairments in social functioning, including difficulties interacting with others, attending to people, and decoding non-verbal cues, and impairments in social emotional reciprocity. In contrast, people with Williams syndrome show an unusually strong interest in people, including strangers; they are warm and engaging and seem highly empathetic towards others.

Smith–Magenis syndrome

Smith–Magenis syndrome (SMS; MIM: 182290), which occurs in approximately 1 in 25 000 births, is typically a spo-

radic disorder and is caused by haploinsufficiency of the retinoic acid-induced 1 (*RAI1*) gene on chromosome 17p11.2. It is characterized by complex, multiple congenital anomalies including learning disability and neurobehavioural problems.[54] Among children with SMS, there are individual case reports of some who fulfil the diagnostic criteria for autism. Many affected individuals with autistic-type behaviours have been reported.[55]

Klinefelter syndrome

Klinefelter syndrome, caused by the XXY karyotype and its variants, is the most common cause of hypogonadism and infertility in males and occurs in approximately 1 in 575 to 1000 newborn males.[56] Population-based studies investigating genetic diseases in individuals with autism have commented on the co-occurrence of autism and the XXY pattern. Recent studies have shown that, compared with males in the general population, males with Klinefelter syndrome report more distress during specific social situations and are characterized by increased levels of autistic features across all dimensions of the autism phenotype. Recently, Tartaglia et al.[57] reported a prevalence of ASDs among individuals with XXYY syndrome of 28.3/100 and showed that neurodevelopmental and psychological difficulties were a significant component of the behavioural phenotype, with developmental delay and learning disability universal but variable in severity.

XYY syndrome

XYY syndrome may arise from a meiosis II error in the father or a postfertilization mitotic event. Hyperactive behaviour, distractibility, temper tantrums, and a low frustration tolerance are reported in some males in late childhood and early adolescence. Geerts et al.[58] reported an increased frequency of language and motor development delay in this group and an increased risk of autism.

22q13.3 deletion syndrome

22q13.3 deletion syndrome (or Phelan–McDermid syndrome) (MIM: 606232) is a contiguous gene microdeletion syndrome characterized by severe neonatal hypotonia (>97%) and global developmental delay (>98%), normal to accelerated growth (95%), absent to severely delayed speech (>98%), and minor dysmorphic features with unknown prevalence. Behaviour may be autistic-like with poor eye contact, stereotypic movements, and self-stimulation. The *SHANK3* gene may be responsible for at least part of the phenotype, such as developmental delay and speech deficits.[59]

Smith–Lemli–Opitz syndrome

Smith–Lemli–Opitz syndrome (SLOS; MIM: 270400) is an autosomal recessive multiple malformation syndrome caused by a deficit of 7-dehydrocholesterol reductase (*DHCR7*) gene located on chromosome 11q12 to 13. Occurring in 1 in 20 000 to 60 000 births, SLOS is characterized by facial abnormalities, developmental delay, learning disability, and behavioural abnormalities.[60] The incidence of SLOS and other sterol disorders among individuals with ASDs is unknown, but the incidence of autism among individuals with SLOS is high, and ASD is among the most severe behavioural problems associated with SLOS. Approximately 5/10 of individuals with SLOS and a non-verbal cognitive age of 18 months or greater meet the criteria for autism.[61] A recent study reported that approximately 75% of children with SLOS met the criteria for some variants of ASD.[62] However, SLOS is a rare cause of ASD, accounting for no more than 1/100 of cases, and routine screening of children with ASD for disorders of cholesterol biosynthesis is not indicated because of their low prevalence.

Many parents have reported positive changes in the behaviour of their children with SLOS – including autistic behaviours – within days of dietary cholesterol supplementation, before any change in the plasma level of cholesterol or 7-dehydrocholesterol becomes apparent. Recently, a high prevalence (19/100) of below-normal levels of cholesterol was detected in 100 children with ASD who participated in the Autism Genetic Resource Exchange study and who had a sibling with ASD.[63] Cholesterol is essential for neuroactive steroid production, growth of myelin membranes, and normal embryonic and fetal development. Individuals with SLOS who receive cholesterol treatment display fewer autistic behaviours, infections, and symptoms of irritability and hyperactivity, and show improvements in physical growth, sleep, and social interactions.[64]

Cohen syndrome

Cohen syndrome (MIM: 216550) is a very rare autosomal recessive connective tissue disorder that results from mutations in the *COH1* gene and which has a prevalence of approximately 1 in 105 000 of the population. Diagnostic criteria for Cohen syndrome are based largely on physical characteristics, and systematic information about behaviour and social functioning is limited. However, recent studies have indicated that behavioural difficulties may occur more frequently than previously suggested and that autistic features may be relatively common.[65]

Phenylketonuria

Phenylketonuria (MIM: 261600) is an autosomal recessive genetic disorder due to deficiency of phenylalanine hydroxylase and occurs in approximately 1 in 10 000 births. In the past, phenylketonuria was frequently associated with autistic symptoms but the association has almost vanished since the introduction of early detection and treatment for phenylalanine hydroxylase deficiency. The exact percentage of individuals with phenylketonuria who display autistic symptomatology is difficult to determine, especially since the introduction of treatment. Recent studies found an autism frequency ranging from 2.7/100[66] to 5.6/100[67] in individuals with phenylketonuria.

Sanfilippo syndrome

Mucopolysaccharidosis type III (MPS III, Sanfilippo syndrome) is an autosomal recessive disorder caused by impairment of degradation of heparan sulphate, one of the

glycosaminoglycans, and its general incidence has been estimated to be about 1 in 20 000 to 50 000 live-born children.[68] As heparan sulphate accumulates in many tissues and organs, including brain, severe neurological symptoms occur in individuals with Sanfilippo syndrome. The probable diagnosis of all mucopolysaccharidosis type III subtypes is based on an increased concentration of heparan sulphate in the urine. Clinically, the syndrome is characterized by a mild somatic phenotype combined with a severe neurodegenerative illness with prominent behavioural disturbance.[68]

Adenylosuccinate lyase deficiency

Adenylosuccinate lyase deficiency (MIM: 103050) is a rare autosomal recessive disorder of de novo purine synthesis. A defect in the gene coding for adenylosuccinate lyase on chromosome 22 leads to deficiency of the enzyme, which results in the accumulation of succinylpurines in body fluids. Although the clinical presentation may vary, the disorder is characterized by a broad spectrum of neurological disorders, ranging from fatal neonatal encephalopathy with hypokinesia to mild learning disability, with autistic features in about one-third.[69]

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) (MIM: 310200) is an X-linked recessive disease and the second most common genetic disease in humans. It results from mutations in the gene coding for the protein dystrophin. The function of dystrophin in the central nervous system (CNS) is obscure, and the basis of the CNS symptoms is unknown. Dystrophin deficiency may be responsible for CNS disorders such as the cognitive impairment or psychiatric disorders, including autism related to DMD. DMD and the allelic disorder Becker muscular dystrophy are associated with a spectrum of genetically based developmental cognitive and behavioural disabilities. Males with DMD have a static cognitive impairment, with mean full-scale IQ approximately 1SD below the mean. Less is known of the cognitive profile of males with Becker muscular dystrophy, which is associated with variable alterations in the amount or size of the dystrophin protein. Recently, Hendriksen and Vles,[70] using a questionnaire-based study, assessed the parent-reported prevalence of attention-deficit–hyperactivity disorders (ADHDs), ASDs, and obsessive–compulsive disorders in a group of 351 males with DMD. They found that 3.1/100 also had ASD. They suggest that this finding, together with recent reports on the higher prevalence of cognitive and learning problems in DMD, supports the view that DMD is not only a muscular disorder but also a disorder affecting the brain.[70–72] Young et al.[73] performed a prospective cohort study in individuals with Becker muscular dystrophy. They enrolled 24 males with normal IQ according to the Wechsler Full-scale IQ. The overall frequency of behavioural problems in the clinical range was 67%, and the frequency of autism was 8.3/100.[73]

Mitochondrial cytopathies

A growing number of studies, including studies of brain metabolism abnormalities and hyperlactacidaemia, suggest that brain energy metabolism may be disturbed in autistic individuals, which might be a result of mitochondrial oxidative phosphorylation dysfunction in neuronal cells. Correia et al.[74] proposed that mitochondrial disease might be one of the most common medical conditions associated with autism. Oliveira et al.[75] found that 7/100 of children with ASD, clinically indistinguishable from other children with ASD, exhibited a mitochondrial respiratory chain disorder.[71] Finally, Weissman et al.[76] proposed that defective mitochondrial oxidative phosphorylation is an additional pathogenetic basis in a subset of individuals with autism.[76]

NON-SYNDROMIC CAUSES OF AUTISM

Many genes and environmental factors are likely to contribute to the aetiology of autism, making it difficult to isolate disease genes. There is a substantial fall-off in the risk of autism among the second- and third-degree relatives of autistic probands,[77] and some predict that alleles of 10 to 100 or more genes, each of small effect, may underlie the autistic phenotype. Accordingly, several loci have been identified, some or all of which may contribute to the phenotype. Each autosomal locus is prefixed with 'AUTS', for example AUTS1, which has been mapped to chromosome 7q22, and each genosomal (X-linked) locus is correspondingly named 'AUTSX'. Other loci have been mapped to different chromosomes (Table I).

In addition to mapping studies, functional candidate gene and proteomic approaches have identified variants in specific genes that may affect susceptibility to the development of autism, for example the glyoxalase I gene (*GLO1*) on chromosome 6p21.3 (Table II).[77] Recently, Marshall et al.,[78] using high-resolution microarray analysis, found 277 unbalanced copy number variations, including deletion, duplication, translocation, and inversion, in 189 (44/100) of 427 families with ASD which were not present in a comparison group. Of note, a copy number variation at chromosome 16p11.2 (AUTS14; MIM: 611913) was identified in 4 (1/100) of the 427 families and in none of 1652 families in the comparison group (p=0.002). Some of the autism loci were also common to learning disability loci. They concluded that structural gene variants were found in ASD, suggesting that cytogenetic and microarray analyses be considered in routine clinical work-up. However, not all children with predisposing genes develop autism, indicating that the genetic alterations should be seen not as the cause of autism, but as a major predisposing factor.[78]

SELECTED GENES FOR A MONOGENIC HERITABLE FORM OF AUTISM

NLGN3, *NLGN4*, and *NRXN1* genes

Neuroligins interact with neurexins expressed in presynaptic neurons.[79] The *NLGN3* and *NLGN4* genes, located at human chromosome loci Xq13 and Xq22.33 respectively, have been found to be mutated in 1/100 of individuals with ASD.[80] The clinical phenotype of human *NLG* mutation carriers is heterogeneous. Mutation carriers typically display no dysmorphic features but, interestingly, they can undergo

Table I: Selected candidate genes responsible for non-syndromic autism

Affected gene (OMIM)	Chromosomal locus	Protein name	Gene function	Clinical phenotype	Inheritance	Prevalence among individuals with autism
NLGN3 (300336)	Xq13.1	Neuroligin-3 precursor	Neuroligins function as ligands for the neurexin family of cell-surface receptors	Autism, Asperger syndrome, PDD-NOS	X-linked	<1%
NLGN4 (300427)	Xp22.33	Neuroligin-4, X-linked precursor	Same as *NLGN3*	Autism, Asperger syndrome, X-linked mental retardation, PDD-NOS	X-linked	<1%
SHANK3 (606230)	22q13.3	SH3 and multiple ankyrin repeat domains protein 3	Encodes a scaffolding protein found in the PSD complex of excitatory synapses,where it binds directly to neuroligins	Autism with severe language and social deficits	Unknown	1.1%
NRXN1 (600565)	2p16.3	Neurexin-1α precursor	Neurexins functionin the vertebrate nervous system as cell adhesion molecules and receptors	Autism with seizures, facialdysmorphism mild to severe spokenlanguage deficits	Unknown	<1%
MeCP2 (300005)	Xq28	Methyl-CpG-binding protein 2	A transcriptional repressor that binds to methylated CpG dinucleotides generally located at gene promoters and recruits HDAC1 and other proteins involved in chromatin repression	Autism, learning disability, Angelman syndrome phenotype, preserved speech variant of Rett syndrome	X-linked	0.8–1.3% of the female ASD population
HOXA1 (142955)	7p15.3	Homeobox protein Hox-A1	Transcription factor essential to the development of head and neck structures, including hindbrain, ear, and occipital and hyoid bones	Autism spectrum disorder susceptibility	Autosomal recessive	Very rare
PTEN (601728)	10q23.31	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase	A tumour-suppressor gene influencing G1 cell cycle arrest and apoptosis. In the central nervous system, *PTEN* inactivation results in excessive dendritic and axonal growth with increased numbers of synapses	ASD with macrocephaly has been consistently found in approximately 20% of individuals with autism recruited in independent samples	Unknown	4.7%

Data are compiled from the following standard references: gene symbol from the Human Genome Organisation (HUGO); chromosomal locus, locus name, critical region, complementation group from Online Mendelian Inheritance in Man (OMIM); protein name from Swiss-Prot. ASD, autism spectrum disorder; PDD-NOS, pervasive developmental disorder – not otherwise specified; PSD, postsynaptic density.

regression at disease onset, characterized by a loss of initially acquired social and verbal milestones.[81] The neurexin 1 gene (*NRXN1*), located at chromosome 2p16.3, encodes a neurexin 1 signal peptide variant. It is a neuronal cell-surface protein that may be involved in cell recognition and cell adhesion by forming intracellular junctions through binding to neuroligins. Neurexin gene mutations have been identified in individuals with autism.[82] Levison and El-Husseini[83] reviewed information on the role of the neuroligin–neurexin interaction on synapse maturation and functioning, and the mechanisms whereby structural defects in these proteins may lead to autism.

SHANK3 gene

Shank proteins are involved in the assembly of specialized postsynaptic structures and are required for the development of language and social communication. Recent studies have confirmed that SHANK3 mutations can cause ASD with phenotype characterized mainly by severe verbal and social deficits.[64,84]

PTEN gene

Butler et al.[85] analysed the *PTEN* gene in 18 individuals with ASDs and macrocephaly (average head circumference +4.0SD) and identified PTEN mutations in three males. Then Herman et al.[45] and Buxbaum et al.[86] reported individuals with macrocephaly and autism associated with mutations in the *PTEN* gene. Tan et al.[87] reported that most children with PTEN mutations are macrocephalic. Among individuals with autism, those with PTEN mutations can be differentiated from those without PTEN mutations by the presence of severe to extreme macrocephaly (head circumferences >+3SD) in the former.

FUTURE DIRECTIONS

Psychiatric genetics is entering a period of great promise as the identification of susceptibility genes is becoming easier as a result of recent developments in molecular genetics. The major problem in developing a unifying theory of autism is the large number of variations of the disorder. Its complex aetiology, and the fact that in most cases the

Table II: Candidate genes responsible for non-syndromic autism

Name	OMIM number	Gene map locus	Target genes	Inheritance
AUTS3	608049	13q14.2–q14.1	*MAB21L1, DCAMKL1, MADH9*	Autosomal
AUTS4	608636	15q11	*GABRB3*	Autosomal
AUTS5	606053	12q	*NRXN1*	Autosomal
AUTS6	609378	17q11	*SLC6A4*	Autosomal
AUTS7	610676	17q21	*ITGB3*	Autosomal
AUTS8	607373	3q25–q27	Unknown	Autosomal
AUTS9	611015	7q31	*MET, WNT2*	Autosomal
AUTS10	611016	7q36	*EN2*	Autosomal
AUTS11	610836	1q24.2	Unknown	Autosomal
AUTS12	610838	21p13–q11	Unknown	Autosomal
AUTS13	610908	12q14	Unknown	Autosomal
AUTS14	611913	16p11.2	Unknown	Autosomal
AUTS15	612100	7q36–q36	*CNTNAP2*	Autosomal
AUTSX1	300425	Xq13	*NLGN3*	X-linked
AUTSX2	300495	Xp22.33	*NLGN4*	X-linked
AUTSX3	300496	Xq28	*MECP2*	X-linked
Not named	–	6p21.3	*GLO1*	Autosomal

Data are compiled from the following standard references: gene symbol from the Human Genome Organisation (HUGO); chromosomal locus, locus name, critical region, complementation group from Online Mendelian Inheritance in Man (OMIM); and protein name from Swiss-Prot. (Note: the symbol 'AUTS2' has been used to refer to a gene on chromosome 7q11 [KIAA0442; MIM: 607270], and therefore is not used as a part of this autism locus series.)

underlying pathological mechanisms are unknown and autistic symptoms are found in association with many other disorders. Estimates of the frequency of such problems and conclusions about the nature of the association have differed from one research group to another. Studies that consider these comorbidities as subtypes of autism and use these disorders as the basis for developing genetic models of autism have contributed to the elucidation of the core pathologies underlying autism. Comprehensive research into the molecular mechanism of autism is needed to aid the development of disease-specific targeted therapies. For example, studies of metabotropic glutamate receptor 5 pathway antagonists in animal models of FXS have demonstrated benefits in reducing seizures, improving behaviour, and enhancing cognition. Genomic technologies are yielding information on autistic diseases at the molecular level. However, further steps are required before these data can be integrated into routine clinical practice.

ONLINE MATERIAL

The following supporting information is available for this article online:

Table SI: Genes responsible for autism in frequent syndromes

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington DC: American Psychiatric Association, 1994.
2. DiCicco-Bloom E, Lord C, Zwaigenbaum L, et al. The developmental neurobiology of autism spectrum disorder. *J Neurosci* 2006; **26:** 6897–906.
3. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics* 2004; **113:** 472–86.
4. Persico AM, Bourgeron T. Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci* 2006; **29:** 349–58.
5. Piven J, Palmer P, Jacobi D, Childress D, Arndt S. Broader autism phenotype: evidence from a family history study of multiple-incidence autism families. *Am J Psychiatry* 1997; **154:** 185–90.
6. Jones JR, Skinner C, Friez MJ, Schwartz CE, Stevenson RE. Hypothesis: dysregulation of methylation of brain-expressed genes on the X chromosome and autism spectrum disorders. *Am J Med Genet A* 2008; **146:** 2213–20.
7. Veenstra-Vanderweele J, Christian SL, Cook EH Jr. Autism as a paradigmatic complex genetic disorder. *Annu Rev Genomics Hum Genet* 2004; **5:** 379–405.
8. Schaefer GB, Lutz RE. Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. *Genet Med* 2006; **8:** 549–56.
9. Hagerman PJ. The fragile X prevalence paradox. *J Med Genet* 2008; **45:** 498–9.
10. Brunberg JA, Jacquemont S, Hagerman RJ, et al. Fragile X premutation carriers: characteristic MR imaging findings of adult male patients with progressive cerebellar and cognitive dysfunction. *Am J Neuroradiol* 2002; **23:** 1757–66.
11. Roberts JE, Weisenfeld LAH, Hatton DD, Heath M, Kaufmann WE. Social approach and autistic behavior in children with fragile X syndrome. *J Autism Dev Disord* 2007; **37:** 1748–60.
12. Koukoui SD, Chaudhuri A. Neuroanatomical, molecular genetic, and behavioral correlates of fragile X syndrome. *Brain Res Rev* 2007; **53:** 27–38.
13. Hatton DD, Sideris J, Skinner M, et al. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. *Am J Med Genet A* 2006; **140:** 1804–13.
14. Cohen D, Pichard N, Tordjman S, et al. Specific genetic disorders and autism: clinical contribution towards their identification. *J Autism Dev Disord* 2005; **35:** 103–16.
15. Loesch DZ, Bui QM, Dissanayake C, et al. Molecular and cognitive predictors of the continuum of autistic behaviours in fragile X. *Neurosci Biobehav Rev* 2007; **31:** 315–26.
16. Aziz M, Stathopulu E, Callias M, et al. Clinical features of boys with fragile X premutations and intermediate alleles. *Am J Med Genet* 2003; **121B:** 119–27.
17. Farzin F, Perry H, Hessl D, et al. Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *J Dev Behav Pediatr* 2006; **27:** S137–44.
18. Hagerman PJ, Hagerman RJ. The fragile-X premutation: a maturing perspective. *Am J Hum Genet* 2004; **74:** 805–16.
19. Laurvick CL, de Klerk N, Bower C, et al. Rett syndrome in Australia: a review of the epidemiology. *J Pediatr* 2006; **148:** 347–52.
20. Hagberg B. Rett syndrome: clinical peculiarities and biological mysteries. *Acta Paediatr* 1995; **84:** 971–6.
21. Reed ML, Leff SE. Maternal imprinting of human SNRPN, a gene deleted in Prader–Willi syndrome. *Nat Genet* 1994; **6:** 163–7.
22. Dimitropoulos A, Schultz RT. Autistic like symptomatology in Prader–Willi syndrome: a review of recent findings. *Curr Psychiatry Rep* 2007; **9:** 159–64.
23. Veltman MW, Craig EE, Bolton PF. Autism spectrum disorders in Prader–Willi and Angelman syndromes: a systematic review. *Psychiatr Genet* 2005; **15:** 243–54.
24. Dykens EM. Maladaptive and compulsive behavior in Prader–Willi syndrome: new insights from older adults. *Am J Ment Retard* 2004; **109:** 142–53.
25. Angelman H. 'Puppet' children: a report on three cases. *Dev Med Child Neurol* 1965; **7:** 681–8.
26. Williams CA, Lossie A, Driscoll D; RC Phillips Unit. Angelman syndrome: mimicking conditions and phenotypes. *Am J Med Genet* 2001; **101:** 59–64.
27. Peters SU, Beaudet AL, Madduri N, Bacino CA. Autism in Angelman syndrome: implications for autism research. *Clin Genet* 2004; **66:** 530–6.
28. Battaglia A. The inv dup (15) or idic (15) syndrome (tetrasomy 15q). *Orphanet J Rare Dis* 2008; **19:** 3.
29. Epstein CJ, Korenberg JR, Anneren G, et al. Protocols to establish genotype–phenotype correlations in Down syndrome. *Am J Hum Genet* 1991; **49:** 207–35.
30. Capone GT, Grados MA, Kaufmann WE, Bernad-Ripoll S, Jewell A. Down syndrome and co-morbid autism spectrum disorder: characterization using the aberrant behavior checklist. *Am J Med Genet* 2001; **134:** 373–80.

31. Prasher VP, Clarke DJ. Case report: challenging behaviour in a young adult with Down's syndrome and autism. *Br J Learn Disabil* 1996; **24:** 167–9.

32. Madhumita G, Amita HS, Kiran D, Kaneez FM. Behavior in children with Down syndrome. *Indian J Pediatr* 2008; **75:** 685–9.

33. Molloy CA, Murray DS, Kinsman A, et al. Differences in the clinical presentation of trisomy 21 with and without autism. *J Intellect Disabil Res* 2009; **53:** 143–51.

34. Parisi MA, Glass IA. Joubert syndrome. In: GeneReviews at GeneTests-GeneClinics: Medical Genetics Information Resource 2007 Seattle: University of Washington, http://www.geneclinics.org or http://www.genetests.org (accessed 9 October 2009).

35. Takahashi TN, Farmer JE, Deidrick KK, Hsu BS, Miles JH, Maria BL. Joubert syndrome is not a cause of classical autism. *Am J Med Genet* 2005; **132:** 347–51.

36. Friedman JM, Gutmann DH, MacCollin M, Riccardi VM. Neurofibromatosis: Phenotype, Natural History, and Pathogenesis. Baltimore, MD: Johns Hopkins University Press, 1999.

37. Gillberg C, Forsell C. Childhood psychosis and neurofibromatosis – more than a coincidence? *J Autism Dev Disord* 1984; **14:** 1–8.

38. Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. *Nat Genet* 2002; **30:** 365–6.

39. Courchesne E, Carper R, Akshoomoff N. Evidence of brain overgrowth in the first year of life in autism. *JAMA* 2003; **290:** 337–44.

40. Dementieva YA, Vance DD, Donnelly SL, et al. Accelerated head growth in early development of individuals with autism. *Pediatr Neurol* 2005; **32:** 102–8.

41. Miles JH, Hadden LL, Takahashi TN, Hillman RE. Head circumference is an independent clinical finding associated with autism. *Am J Med Genet* 2000; **95:** 339–50.

42. Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports *Biol Psychiatry* 2005; **58:** 1–9.

43. Joseph DB, Guiqing C, Gudrun N, et al. Mutation analysis of the NSD1 gene in patients with autism spectrum disorders and macrocephaly. *BMC Med Genet* 2007; **8:** 68.

44. Kent L, Bowdin S, Kirby GA, Cooper WN, Maher ER. Beckwith Weidemann syndrome: a behavioral phenotype-genotype study. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147:** 1295–7.

45. Herman GE, Butter E, Enrile B, Pastore M, Prior TW, Sommer A. Increasing knowledge of PTEN germline mutations: two additional patients with autism and macrocephaly. *Am J Med Genet A* 2007; **143:** 589–93.

46. Splawski I, Timothy KW, Sharpe LM, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004; **119:** 19–31.

47. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 1998; **13:** 624–8.

48. Iznitzer M. Autism and tuberous sclerosis. *J Child Neurol* 2004; **19:** 675–9.

49. Bolton PF, Griffiths PD. Association of tuberous sclerosis of temporal lobes with autism and atypical autism. *Lancet* 1997; **349:** 392–5.

50. Curatolo P, Porfirio MC, Manzi B, Seri S. Autism in tuberous sclerosis. *Eur J Paediatr Neurol* 2004; **8:** 327–32.

51. Powell CM. Sex chromosomes and sex chromosome abnormalities. In: Gersen SL, Keagle MB, editors. The Principles of Clinical Cytogenetics, 2nd edn. Totowa, MJ: Humana Press, 2005: 210.

52. Gillberg C, Cederlund M, Lamberg K, Zeijlon L. Brief report: 'The Autism Epidemic' The registered prevalence of autism in a Swedish urban area. *J Autism Dev Disord* 2006; **36:** 429–35.

53. Tassabehji M. Williams–Beuren syndrome: a challenge for genotype–phenotype correlations. *Hum Mol Genet* 2003; **12:** 229–37.

54. Vlangos CN, Yim DK, Elsea SH. Refinement of the Smith–Magenis syndrome critical region to approximately 950kb and assessment of 17p11.2 deletions. Are all deletions created equally? *Mol Genet Metab* 2003; **79:** 134–41.

55. Dykens EM, Finucane BM, Gayley C. Brief report: cognitive and behavioral profiles in persons with Smith–Magenis syndrome. *J Autism Dev Disord* 1997; **27:** 203–11.

56. Yoshida A, Kazukiyo M, Shirai M. Chromosome abnormalities and male infertility. *Assist Reprod Rev* 1996; **6:** 93–9.

57. Tartaglia N, Davis S, Hench A, et al. A new look at XXYY syndrome: medical and psychological features. *Am J Med Genet A* 2008; **146:** 1509–22.

58. Geerts M, Steyaert J, Fryns JP. The XYY syndrome: a follow-up study on 38 boys. *Genet Couns* 2003; **14:** 267–79.

59. Durand CM, Betancur C, Boeckers TM, et al. Mutations in the gene encoding the synaptic scaffolding protein *SHANK3* are associated with autism spectrum disorders. *Nat Genet* 2007; **39:** 25–7.

60. Kelley RI, Hennekam RCH. Smith–Lemli–Opitz syndrome. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. The Metabolic and Molecular Basis of Inherited Disease, 8th edn. New York: McGraw-Hill, 2001: 6183–201.

61. Tierney E, Nwokoro NA, Porter FD, Freund LS, Ghuman JK, Kelley RI. Behavior phenotype in the RSH/Smith–Lemli–Opitz syndrome. *Am J Med Genet* 2001; **98:** 191–200.

62. Sikora DM, Pettit-Kekel K, Penfield J, Merkens LS, Steiner RD. The near universal presence of autism spectrum disorders in children with Smith–Lemli–Opitz syndrome. *Am J Med Genet A* 2006; **140:** 1511–8.

63. Tierney E, Bukelis I, Thompson RE, et al. Abnormalities of cholesterol metabolism in autism spectrum disorders. *Am J Med Genet B Neuropsychiatr Genet* 2006; **141:** 666–8.

64. Aneja A, Tierney E. Autism: the role of cholesterol in treatment. *Int Rev Psychiatry* 2008; **20:** 165–70.

65. Karpf J, Turk J, Howlin P. Cognitive, language, and adaptive behavior profiles in individuals with a diagnosis of Cohen syndrome. *Clin Genet* 2004; **65:** 327–32.

66. Steiner CE, Guerreiro MM, Marques-de-Faria AP. Genetic and neurological evaluation in a sample of individuals with pervasive developmental disorders. *Arq Neuropsiquiatr* 2003; **61:** 176–80.

67. Baieli S, Pavone L, Meli C, Fiumara A, Coleman M. Autism and phenylketonuria. *J Autism Dev Disord* 2003; **33:** 201–4.

68. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill, 2001: 3421–52.

69. Spiegel EK, Colman RF, Patterson D. Adenylosuccinate lyase deficiency. *Mol Genet Metab* 2006; **89:** 19–31.

70. Hendriksen JG, Vles JS. Neuropsychiatric disorders in males with Duchenne muscular dystrophy: frequency rate of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and obsessive–compulsive disorder. *J Child Neurol* 2008; **23:** 477–81.

71. Wu JY, Kuban KC, Allred E, Shapiro F, Darras BT. Association of Duchenne muscular dystrophy with autism spectrum disorder. *J Child Neurol* 2005; **20:** 790–5.

72. Zwaigenbaum L, Tarnopolsky M. Two children with muscular dystrophies ascertained due to referral for diagnosis of autism. *J Autism Dev Disord* 2003; **33:** 193–9.

73. Young HK, Barton BA, Waisbren S, et al. Cognitive and psychological profile of males with Becker muscular dystrophy. *J Child Neurol* 2008; **23:** 155–62.

74. Correia C, Coutinho AM, Diogo L, et al. Brief report: high frequency of biochemical markers for mitochondrial dysfunction in autism: no association with the mitochondrial aspartate/glutamate carrier SLC25A12 gene. *J Autism Dev Disord* 2006; **36:** 1137–40.

75. Oliveira G, Diogo L, Grazina M, et al. Mitochondrial dysfunction in autism spectrum disorders: a population-based study. *Dev Med Child Neurol* 2005; **47:** 185–9.

76. Weissman JR, Kelley RI, Bauman ML, et al. Mitochondrial disease in autism spectrum disorder patients: a cohort analysis. *PLoS ONE* 2008; **3:** 3815.

77. Szatmari P, Jones MB, Zwaigenbaum L, MacLean JE. Genetics of autism: overview and new directions. *J Autism Dev Disord* 1998; **28:** 351–68.

78. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet* 2008; **82:** 477–88.

79. Lise MF, El-Husseini A. The neuroligin and neurexin families: from structure to function at the synapse. *Cell Mol Life Sci* 2006; **63:** 1833–49.

80. Lintas C, Persico AM. Autistic phenotypes and genetic testing: state-of-the-art for the clinical geneticist. *J Med Genet* 2009; **46:** 1–8.

81. Jamain S, Quach H, Betancur C, et al. Paris Autism Research International Sibpair Study. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 2003; **34:** 27–9.

82. Yan J, Noltner K, Feng J, et al. Neurexin 1alpha structural variants associated with autism. *Neurosci Lett* 2008; **438:** 368–70.

83. Levinson JN, El-Husseini A. A crystal-clear interaction: relating neuroligin/neurexin complex structure to function at the synapse. *Neuron* 2007; **56:** 937–9.

84. Moessner R, Marshall CR, Sutcliffe JS, et al. Contribution of SHANK3 mutations to autism spectrum disorder. *Am J Hum Genet* 2007; **81:** 1289–97.

85. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet* 2005; **42:** 318–21.

86. Buxbaum JD, Cai G, Chaste P, et al. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B:** 484–91.

87. Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. *J Med Genet* 2007; **44:** 594–602.