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The Neuroscience of Autism Spectrum Disorders

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Chapter 2.1

Etiological heterogeneity in autism spectrum disorders: role of rare variants

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Abstract

Autism spectrum disorders (ASD) encompass a group of behaviorally defined developmental disabilities characterized by marked clinical and etiological heterogeneity. There is increasing evidence that ASD can arise from rare highly penetrant mutations and genomic imbalances. There are at present over 100 disease genes and 50 recurrent genomic imbalances implicated in the etiology of ASD. These genes and loci have so far all been causally implicated in intellectual disability, indicating that these two neurodevelopmental disorders share common genetic bases. Similarly, many genes involved in epilepsy can also result in ASD. These observations indicate that these genes cause a continuum of neurodevelopmental disorders that manifest in different ways depending on other genetic, environmental or stochastic factors. Increased recognition of the etiological heterogeneity of ASD will expand the number of target genes for neurobiological investigations, reveal functional pathways and assist the development of novel therapeutic approaches.

Key words: autism; genetic syndrome; intellectual disability; epilepsy; metabolic disorder; mutation; copy number variation; deletion; duplication

Introduction

Autism spectrum disorders (ASD) encompass a group of behaviorally defined developmental disabilities characterized by marked clinical and etiological heterogeneity. ASD can be associated with intellectual disability (ID) of varying degrees (~70%), epilepsy (~30%), dysmorphic features and congenital malformations (~20%) (Coleman and Gillberg, 2012). ASD can thus be considered syndromic (i.e., associated with dysmorphic, neuromuscular, metabolic or other distinctive clinical features, including structural brain abnormalities) or nonsyndromic, similar to the division of ID into syndromic and nonsyndromic forms (Gecz *et al.*, 2009).[1]

The genetic architecture of ASD is highly heterogeneous (Abrahams and Geschwind, 2008; Betancur, 2011; State, 2010). About 20% of individuals have an identified genetic etiology. Cytogenetically visible chromosomal aberrations have been reported in ~5% of cases, involving many different loci on all chromosomes. The most frequent abnormalities are maternally derived 15q11-q13 duplications involving the imprinted Prader-Willi/Angelman region, detected in ~1%. ASD can also be due to mutations of numerous single genes involved in autosomal dominant, autosomal recessive and X-linked disorders. The most common single gene defect identified in ASD is fragile X syndrome (*FMR1*), present in ~2% of cases (Kielinen *et al.*, 2004) (Chapter 4.5). Other monogenic disorders described in ASD include tuberous sclerosis (*TSC1*, *TSC2*) (Chapter 4.8), Angelman syndrome (*UBE3A*), Rett syndrome (*MECP2*) (Chapter 4.6), and *PTEN* mutations in patients with macrocephaly and autism (Chapter 4.8). Rare mutations have been identified in multiple synaptic genes, including *NLGN3*, *NLGN4X* (Jamain *et al.*, 2003), *SHANK3* (Durand *et al.*, 2007), and *SHANK2* (Berkel *et al.*, 2010; Pinto *et al.*, 2010) (Chapter 4.7). Recent genome-wide microarray studies in large ASD samples have highlighted the important contribution of rare submicroscopic deletions and duplications, called copy number variation (CNV), to the etiology of ASD, including *de novo* events in 5%–10% of cases (Marshall *et al.*, 2008; Pinto *et al.*, 2010; Sanders *et al.*, 2011; Sebat *et al.*, 2007) (Chapter 2.2). Most recently, the first whole-exome sequencing studies in ASD have shown an increased rate of rare *de novo* point mutations and confirmed a high degree of locus heterogeneity (Neale *et al.*, 2012; O'Roak *et al.*, 2011; O'Roak *et al.*, 2012; Sanders *et al.*, 2012) (Chapter 2.4).

The constantly increasing number of distinct, individually rare genetic causes of ASD and the substantial contribution of *de novo* events indicates that the genetic architecture of ASD resembles that of ID, with hundreds of genetic and genomic disorders involved, each accounting for a very small fraction of cases. In fact, all the known genetic causes of ASD are also causes of ID, indicating that these two neurodevelopmental disorders share common genetic bases.

We recently performed an exhaustive review of all the genetic and genomic disorders reported in subjects with ASD or autistic behavior, and identified 103 disease genes and 44 recurrent genomic imbalances (Betancur, 2011), and the numbers have continued to grow. These findings are in stark contrast to a persisting claim among the autism research community that we know very little about the etiology of autism and that there are only a modest number of autism loci known. Here, rather than listing all the genetic and genomic disorders involved in ASD, we review what can we learn about

[1] Note that the term 'syndromic' autism refers to the clinical presentation of the patient and not to the fact that a genetic disorder or syndrome has been identified in the patient. Genetic defects can be associated with syndromic or nonsyndromic clinical presentations. Furthermore, note that the term 'idiopathic' autism means that a specific etiology has not been identified in that patient (i.e., unexplained autism); the term 'idiopathic' should not be used in lieu of nonsyndromic or isolated autism. Finally, the use of the terms 'primary' and 'secondary' autism to refer to nonsyndromic and syndromic forms, respectively, is inappropriate, since all cases of autism, regardless of the associated phenotype, are secondary to disruption of normal brain development.

the profound etiological heterogeneity underlying ASD.

The most obvious conclusion we can draw is that, when examined from an etiological perspective, ASD is not a single disease entity but a behavioral manifestation of many hundreds of single gene and genomic disorders. In addition, it is emerging that *de novo* variants are an important part of the architecture of ASD, consistent with purifying selection against deleterious genetic variants of major effect. One of the most important observations is that there is considerable overlap in high-risk genes and loci for ASD, ID, and epilepsy. Similarly, many of the rare recurrent CNVs identified recently have been found to confer risk for a broad range of neurologic and psychiatric phenotypes, including not only ID, ASD, and epilepsy, but also schizophrenia and attention deficit hyperactivity disorder (ADHD). This highlights how disruption of core neurodevelopmental processes can give rise to a wide range of clinical manifestations and that greater attention should be placed on the neurobiological processes of brain development and function rather than on the precise behavioral manifestation. Finally, we show how some of the genes implicate specific pathways, subcellular organelles, or systems in the pathophysiology of ASD, which can lead to biological and neurobiological insights into disease mechanisms.

Genetic disorders strongly associated with ASD

Table 1 shows genetic and genomic disorders in which ASD is a common manifestation. For some of these disorders, ASD is among the clinical hallmarks, including Phelan-McDermid syndrome (22q13 deletion syndrome/*SHANK3* mutations), maternal 15q11-q13 duplications, Rett syndrome (*MECP2*) and *MECP2* duplication syndrome, fragile X syndrome (*FMR1*), tuberous sclerosis (*TSC1*, *TSC2*), adenylosuccinate lyase deficiency (*ADSL)*, Timothy syndrome (*CACNA1C*), cortical dysplasia-focal epilepsy syndrome (*CNTNAP2*), Smith-Lemli-Opitz syndrome (*DHCR7*), Smith-Magenis syndrome (17p11.2 deletion, *RAI1* mutations), and Potocki-Lupski syndrome (17p11.2 duplication) (see Table 1 for references). Another disorder strongly associated with ASD is the recently described 2q23.1 microdeletion syndrome, caused by haploinsufficiency of the methyl-CpG-binding domain 5 (*MBD5*) gene. An analysis of 65 individuals with deletions or translocations involving *MBD5* reported that all had "autistic-like" behaviors (Talkowski *et al.*, 2011). If these findings were confirmed using standardized diagnostic assessments, this would constitute the first genetic disorder exhibiting fully-penetrant ASD. However, this appears unlikely, given that none of the disorders implicated in ASD to date are associated with ASD in 100% of cases, reflecting the variable expressivity of many genetic conditions.

Other disorders with common ASD manifestations are brain creatine deficiency (*SLC6A8*, *GAMT*, *GATM*), Cornelia de Lange syndrome (*NIPBL*, *SMC1A*), CHARGE syndrome (*CHD7*), Cohen syndrome (*VPS13B*), Joubert syndrome and related syndromes (*AHI1, NPHP1, CEP290, RPGRIP1L*), myotonic dystrophy type 1 *(DMPK),* X-linked female-limited epilepsy and ID (*PCDH19),* 2q37 deletion syndrome, Cri du Chat syndrome (5p deletion), Williams syndrome (7q11.23 deletion), 7q11.23 duplication syndrome, 8p23.1 deletion syndrome, WAGR syndrome (11p13 deletion), Angelman syndrome (maternal 15q11-q13 deletion), 16p11.2 microdeletion, and 22q11 deletion syndrome (velocardiofacial/DiGeorge syndrome).

In other disorders, ASD appear to be somewhat less frequent but still much higher than in the general population, such as in *PTEN* related syndromes, Kleefstra syndrome (9q subtelomeric deletion syndrome/*EHMT1* mutations), Prader-Willi syndrome (paternal 15q11-q13 deletion), 15q24 microdeletion syndrome, and 16p11.2 microduplication. Finally, certain chromosomal aneuploidies

are associated with an increased risk for ASD, including Down syndrome, Klinefelter syndrome (XXY), XYY syndrome, and XXYY syndrome.

Note that for most genetic disorders, no reliable estimates of the frequency of ASD among affected individuals or the frequency of the disorder among patients with ASD are available. Even in disorders for which such studies have been conducted, the samples are usually quite small and few are population-based. While it is assumed that these genetic syndromes are rare, some could be underdiagnosed, since only a minority of patients with ASD has been screened for most of these conditions. Several genetic disorders have been described only recently and their prevalence is unknown. Furthermore, the methods employed to diagnose ASD in these studies are very variable, and in some instances no standardized diagnostic assessments were used. Clearly, more data is needed on the prevalence of specific genetic disorders in ASD, and of ASD in genetic disorders, using reliable diagnostic assessment tools in large samples. The frequencies cited in Table 1 should serve to give an idea of the association between ASD and certain genetic disorders but should not be considered precise. Most of the disorders associated with a high risk for ASD are rare or very rare; apart from fragile X syndrome (~2%), only a few account for at most ~0.5%–1% of ASD cases (Table 1).

Genetic overlap between ASD and intellectual disability

Like ASD, ID is a common and highly heterogeneous neurodevelopmental disorder, affecting 2%–3% of the population. Like in ASD, chromosomal abnormalities detected with conventional karyotyping account for about 5% of cases of ID, while novel microarray-based methods have a diagnostic yield of 10%-15%, underscoring the major role of submicroscopic CNVs as causes of ID. Down syndrome (trisomy 21) is the most frequent chromosomal cause of ID, and has also been identified as a relatively frequent cause of autism in several epidemiological studies (Table 1). The most common single-gene defect in male patients with ID is fragile X syndrome, with full mutations identified in 2.6% of patients; the combined frequency in males and females with ID is 2% (Michelson *et al.*, 2011), like in ASD. In females with moderate to severe ID, *MECP2* testing is diagnostic in 1.5% (Michelson *et al.*, 2011). At least 93 genes have been identified that are implicated in X-linked ID; 52 are associated with syndromic ID, while 41 genes have been found to be associated with nonsyndromic ID (Figure 1) (Gecz *et al.*, 2009; Ropers, 2010). The distinction between syndromic and nonsyndromic ID is not precise, and many genes, initially identified in syndromic conditions, were later reported in subjects with nonsyndromic forms. Among the 93 genes involved in X-linked ID, 45 have also been implicated in ASD (Figure 1), demonstrating the profound etiologic overlap between these phenotypes. In addition, numerous autosomal genes, either due to dominant, usually *de novo* mutations or to recessive gene defects, have been implicated in ID (and ASD), but many more remain unidentified.

Table 2 shows several recently identified recurrent microdeletions and microduplications reported in individuals with ID, ASD and other neurodevelopmental or neuropsychiatric disorders (Chapter 2.2). Some of these novel recurrent CNVs have a recognizable phenotype, such as the 17q21.31 microdeletion syndrome, with a distinctive facial dysmorphism. Others, such as CNVs at 1q21.1, 15q13.3, 16p13.11 and 16p11.2, give rise to less consistent phenotypes (variable expressivity) and have been identified in cohorts of patients ascertained for ID, epilepsy, ASD, or schizophrenia, blurring the current nosological boundaries of these disorders. Several of these aberrations show incomplete penetrance, as demonstrated by their presence in clinically unaffected relatives and in controls. These CNVs have been studied in very large samples of subjects with various neurocognitive and neuropsychiatric conditions, and there appears to be a clear increased frequency in affecteds versus

controls for some of them, suggesting that they act as risk factors; for other CNVs, particularly those that appear to be relatively more frequent in controls, the clinical significance is still uncertain (e.g., 15q13.3 and 16p13.11 duplications).

When reviewing these studies, it is clear that not all 'intellectual disability genes and loci' are necessarily associated with ID. As shown in Box 1, several genetic and genomic disorders have been reported in individuals with higher function ASD (Asperger syndrome). Similarly, not all genetic defects involved in the etiology of ID and ASD are identified in individuals presenting with marked dysmorphic features or other congenital malformations. In fact, many disease genes implicated in ASD can be associated with nonsyndromic presentations (Box 2).

It should be clear when looking at the genetic and genomic disorders for which ASD is a manifestation that variable expressivity is the rule rather than the exception, and none will invariably present with ASD. This point is important to consider from a neurobiological perspective. There is, for example, an emphasis on studying ASD-like behaviors in rodent and primate models of ASD; if mutations in the underlying genes do not reliably lead to ASD in humans, other intermediate neurobiological phenotypes are perhaps equally or even more relevant to understanding disease pathogenesis (Chapter 4).

Genetic overlap between ASD and epilepsy

Epilepsies are common and etiologically heterogeneous disorders, affecting up to 3% of the population. About 30% of children with epilepsy have ASD, and conversely, epilepsy is observed in about a third of ASD individuals. Many well-known genetic disorders share ID, ASD, and epilepsy as prominent phenotypic features, including fragile X syndrome, tuberous sclerosis, Rett syndrome and Angelman syndrome. In addition, monogenic forms involving mutations in genes encoding voltage-gated or ligand-gated ion channels, referred to as "channelopathies" have been identified in epilepsy, and increasingly in ASD, such as the neuronal voltage-gated sodium channel genes *SCN1A* and *SCN2A* (Table 3). Both genes have been implicated in various forms of epilepsy, including early-onset epileptic encephalopathies. This group of severe epilepsies is characterized by progressive intellectual deficits or regression, and includes West syndrome (infantile spasms), Dravet syndrome (severe myoclonic epilepsy of infancy), and Ohtahara syndrome (early infantile epileptic encephalopathy with burst-suppression) (Mastrangelo and Leuzzi, 2012; Paciorkowski *et al.*, 2011). Table 3 shows several genes involved in early infantile epileptic encephalopathies that can also manifest with ASD (e.g., *ARX*, *CDKL5*, *MECP2*, *MEF2C*, *FOXG1*, *STXBP1,* and *PCDH19*).

Like *MECP2*, mutations in the X-linked cyclin-dependent kinase-like 5 (*CDKL5*) gene are more common in girls and are associated with a Rett-like phenotype with infantile spasms and ID; several cases have been described with autism (Table 3). Another X-linked gene, protocadherin 19 (*PCDH19*), was recently implicated in "epilepsy and mental retardation limited to females", a familial disorder with an unusual mode of inheritance, since only heterozygous females are affected and transmitting males are asymptomatic. *PCDH19* mutations, mostly occurring *de novo*, have also been shown to be a frequent cause of sporadic infantile-onset epileptic encephalopathy in females, and have been reported in females with epilepsy without cognitive impairment (Depienne and Leguern, 2012). ASD or autistic features appear to be frequent among patients with *PCDH19* mutations, with rates varying between 22%-38% (Table 1). Interestingly, a *PCDH19* mutation was reported in a female with Asperger syndrome and normal IQ, with a history of infantile onset seizures (Hynes *et al.*, 2010). The female-limited expression is explained by a phenomenon called cellular interference; random X inactivation in

mutated females leads to tissue mosaicism, with PCDH19-positive and PCDH19-negative cells, with altered interactions between the two populations (Depienne and Leguern, 2012). In contrast, complete absence of the protein, as seen in mutated males, is not deleterious. The only affected male reported to date was shown to be mosaic for the *PCDH19* deletion in skin fibroblasts (Depienne and Leguern, 2012).

In addition to the genes involved in early onset epilepsy and ASD listed in Table 3, many other genes implicated in ASD and ID are associated with epilepsy, including those involved in metabolic disorders (Table 3), Joubert syndrome and related disorders (Table 3), and disorders of the RAS/mitogen activated protein kinase (MAPK) pathway (Table 4). Moreover, several recently discovered recurrent CNVs associated with ID and ASD, such as 15q13.3 and 16p13.11 deletions, increase risk for various forms of epilepsy (Table 2). Large, rare non-recurrent CNVs also play a role in the genetic etiology of epilepsy (Mulley and Mefford, 2011), similar to what has been observed in ID, ASD and other neuropsychiatric disorders.

The strong association between ASD and epilepsy suggests that they share common mechanisms of synaptic dysfunction. From the neurobiological perspective, understanding this shared vulnerability is an important direction and the model of excitatory/inhibitory imbalance, first developed in epilepsy, is now being considered in forms of ASD (Chapter 3.9).

Metabolic disorders associated with ASD

Several metabolic disorders have been associated with an autistic phenotype (Table 3). Although inborn errors of metabolism are rare and probably account for a small proportion of individuals with ASD, their diagnosis is important because some are potentially treatable. Metabolic disorders may be suspected on the basis of parental consanguinity, affected family members, early seizures, episodic decompensation, developmental regression, and coarse facial features. However, many recently described disorders can present as nonsyndromic ID and/or ASD and should therefore be considered in the etiological diagnosis of ASD (Kayser, 2008).

Phenylketonuria was identified as a relatively common cause of ASD in older studies, but since the introduction of newborn screening programs and with early dietary intervention, affected children can now expect to lead relatively normal lives (Baieli *et al.*, 2003). Unfortunately, phenylketonuria is still identified among patients with ASD in emerging countries without neonatal testing or among subjects born before these screening programs were started (Steiner *et al.*, 2007).

Cerebral creatine deficiency syndromes may be due to two disorders of creatine synthesis, arginine:glycine amidinotransferase deficiency (*GATM*) and guanidinoacetate methyltransferase deficiency (*GAMT*), inherited as autosomal recessive traits, or to creatine transporter deficiency (*SLC6A8*), an X-linked disorder (Longo *et al.*, 2011). All three deficiencies are characterized by ID, severe speech impairment, epilepsy and autistic behavior (Table 3). Although *GATM* and *GAMT* mutations are very rare, creatine transporter deficiency could account for up to 1% of unexplained ID in males (Clark *et al.*, 2006). Because the presentation is nonsyndromic and autistic behavior is common, this condition could be underdiagnosed in populations of lower functioning males with ASD.

Autism may also occur in the context of mitochondrial disorders, resulting either from mutations in mitochondrial DNA or, more commonly, in nuclear DNA genes encoding mitochondrial-targeted proteins (see Chapter 2.5). Mitochondrial disorders can present with a vast range of symptoms, severity, age of onset and outcome, with a minimum prevalence estimated at 1:5000.

Understanding how metabolic disorders affect brain development and function can lead to a better

understanding of the pathophysiology of ASD. At the same time, the frequently indirect nature of this relationship may make such studies more challenging than, for example, studying how synaptic genes alter brain functioning. However, because many metabolic disorders are treatable, understanding the range of metabolic disorders associated with ASD and testing for them can provide immediate clinical benefits, and allow for genetic counseling.

Other examples of etiological subgroups associated with ASD

Joubert syndrome is a clinically and genetically heterogeneous group of disorders characterized by a distinctive cerebellar and brainstem malformation, cerebellar ataxia, ID and breathing abnormalities, sometimes including retinal dystrophy and renal disease. ASD is a relatively frequent finding in individuals with Joubert syndrome, present in 13%-36% of patients (Table 1). Sixteen genes have been implicated in Joubert syndrome, the majority very recently; thus, it is not surprising that so far only 4 of these genes have been reported to be mutated in subjects with ASD/autistic traits (Table 3). Joubert syndrome and related disorders arise from ciliary dysfunction and are collectively termed ciliopathies. Other ciliopathies reported in subjects with ASD include Leber congenital amaurosis and Bardet-Biedl syndrome, both of which exhibit phenotypic overlap with Joubert syndrome (Table 3). The means by which cilia are involved in neurodevelopmental processes, and by which ciliopathies lead to neurodevelopmental disorders, are areas of active research. One exciting emerging finding is that primary (or nonmotile) cilia, found on most neurons and astrocytes, play roles as modulators of signal transduction during both brain development and homeostasis (Lee and Gleeson, 2011). The primary cilia can mediate signaling through sonic hedgehog, wingless, planar cell polarity and fibroblast growth factor pathways.

Another group of disorders that can be associated with ASD is muscular dystrophies (Table 3). Duchenne and Becker muscular dystrophies are caused by deficient expression of the cytoskeletal protein dystrophin, coded by the *DMD* gene on chromosome Xp21.2-p21.1. One-third of the children with Duchenne muscular dystrophy and about 12% of those with the Becker type also have ID. A small subgroup of these boys with both of these disorders also have ASD, with frequencies varying between 3% and 19% (Hinton *et al.*, 2009; Kumagai *et al.*, 2001; Wu *et al.*, 2005). Several maternally-inherited exonic duplications of *DMD* have been identified in males ascertained for ASD, with no documented muscle disease (Pagnamenta *et al.*, 2011; Pinto *et al.*, 2010), suggestive of the mild end of the spectrum of dystrophinopathies seen in Becker muscular dystrophy, with later onset or subclinical muscle involvement. Another form of muscular dystrophy that includes cases with autistic features is myotonic dystrophy type 1, also known as Steinert disease, caused by expansion of a CTG trinucleotide repeat in the 3'-untranslated region in the *DMPK* gene (Table 3). The clinical findings span a continuum from mild to severe. In a study of 57 children with myotonic dystrophy type 1, 49% were found to have ASD; the more clinically severe the myotonic dystrophy, the higher the frequency of children with autistic features (Ekstrom *et al.*, 2008). This may be an underdiagnosed disease entity in autistic populations (Coleman and Gillberg, 2012).

Dysregulation of the RAS/MAPK cascade is the common molecular basis for multiple congenital anomaly syndromes known as neuro-cardio-facio-cutaneous syndromes and characterized by a distinctive facial appearance, heart defects, musculocutaneous abnormalities, and ID, including Noonan syndrome, LEOPARD syndrome (Lentigines, Electrocardiogram abnormalities, Ocular hypertelorism, Pulmonic valvular stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness), cardio-facio-cutaneous syndrome, and Costello syndrome (Table 4) (Samuels *et al.*, 2009).

These overlapping phenotypes can arise from heterozygous mutations in many genes, including *PTPN11*, *BRAF*, *RAF1*, *KRAS*, *HRAS*, *MAP2K1*, *MAP2K2*, *SOS1* and *SHOC2*. Neurofibromatosis type I and neurofibromatosis type I-like syndrome, which are caused by loss-of-function mutations of *NF1* and *SPRED1*, respectively, can also be included in the same disease entity (Aoki *et al.*, 2008). As shown in Table 3, all these disorders have been reported in subjects with ASD. In particular, ASD was observed in 8% of 65 children with Noonan syndrome (Pierpont *et al.*, 2009), as well as in several patients with cardio-facio-cutaneous syndrome or Noonan syndrome with *BRAF*, *KRAS* or *MAP2K1* mutations (Nava *et al.*, 2007; Nystrom *et al.*, 2008).

Myriad biological pathways

When considering genes involved in autism, neurobiologists usually think about synaptic genes such as those coding for the postsynaptic cell adhesion molecules neuroligins 3 and 4 (*NLGN3*, *NLGN4X*), their presynaptic partner neurexin 1 (*NRXN1*), and the postsynaptic scaffolding proteins *SHANK2* and *SHANK3* (Betancur *et al.*, 2009). In addition to this pathway (described in Chapter 4.7), further evidence implicating synaptic dysfunction in the pathogenesis of ASD has come from the study of genetic disorders with increased rates of ASD, such as fragile X syndrome (*FRM1*), Rett syndrome (*MECP2*), tuberous sclerosis (*TSC1* and *TSC2*) and Angelman syndrome (*UBE3A*). Rare mutations in numerous other genes encoding pre- and postsynaptic proteins have also been reported in ID and ASD, including *STXBP1*, *SYNGAP*, as well as the X-linked genes *AP1S2*, *ARHGEF6*, *CASK*, *GRIA3*, *FGD1*, *IQSEC2*, *IL1RAPL1*, *OPHN1*, *RAB39B,* and *SYN1* (Figure 1) (for references implicating these genes in ASD, see Betancur, 2011; for a general review, see van Bokhoven, 2011).

Although the focus on the synaptic pathway in recent years has contributed to our understanding of the pathophysiology of autism, there are dozens of other non-synaptic genes that have been implicated in ASD and which encompass a wide range of biological functions and cellular processes. Mechanisms by which such genes disrupt brain and neuronal development and function will provide a deeper understanding of ASD pathogenesis. Some examples of biological pathways and organelles recurrently implicated in ASD are highlighted in Tables 3 and 4. In addition to the genes involved in ciliopathies (Table 3) and the RAS/MAPK signaling pathway (Table 4) mentioned above, Table 4 shows genes involved in channelopathies, genes coding for cell-adhesion molecules and genes implicated in the protein kinase mammalian target of rapamycin (mTOR) signaling pathway. Hyperactivation of mTOR as a consequence of loss-of-function mutations in the genes *TSC1*, *TSC2*, and *PTEN* is responsible for the development of tuberous sclerosis, *PTEN* hamartoma-tumor syndrome (including Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome), and macrocephaly/autism syndrome (for review, see (de Vries, 2010)). Molecularly-targeted treatments using mTOR inhibitors (such as rapamycin) are currently in clinical trials, providing great promise and hope.

Another emerging pathway involves ASD/ID genes that encode regulators of chromatin structure and of chromatin-mediated transcription (for review, see van Bokhoven and Kramer, 2010). Table 4 shows the genes mutated in ASD involved in epigenetic regulation of neuronal gene expression. Prominent examples of epigenetic ASD/ID genes include *MECP2*, *CHD7* (CHARGE sydrome), *EHMT1* (Kleefstra syndrome), and the recently implicated gene *MBD5* (2q23.1 microdeletion syndrome), all listed in Table 1 as being frequently associated with ASD.

Conclusion

The findings discussed in this review clearly indicate that autism represents the final common pathway for hundreds of genetic and genomic disorders. Despite the abundant evidence, this etiological heterogeneity is still not widely recognized by autism researchers, and most studies fail to take it into account. The genetic overlap and the frequent comorbidity of ASD, ID and epilepsy indicate that the disruption of essential neurodevelopmental processes can give rise to a wide range of manifestations, where the final outcome is likely modulated by the genetic background of each individual as well as other factors including possibly environmental and stochastic factors. Increased understanding of the common genetic, molecular, and cellular mechanisms underlying these neurodevelopmental disorders may provide a framework for novel therapeutic interventions.

Chromosome microarray analysis has revolutionized the molecular diagnostic process in ASD and other neurodevelopmental conditions and is now recommended as a first-line test in the genetic workup of these children, providing an etiological diagnosis in 10 to 15% of cases. Novel high-throughput whole-exome and whole-genome sequencing technologies have hugely accelerated the mutation finding process for Mendelian disorders in the past two years, and hopefully will soon become a first-line approach in the etiological exploration of patients with ASD, replacing targeted sequencing of candidate disease genes (Chapter 2.4).

Currently the most applicable benefit of genetic testing is family planning. A prospective longitudinal study of 664 infants with an older biological sibling with ASD found that 18.7% developed ASD (Ozonoff *et al.*, 2011). Although many of the mutations associated with autism so far identified are *de novo*, future siblings are at risk in the cases where the variant is inherited from a parent, such as in autosomal dominant disorders with variable expressivity inherited from mildly affected parents (e.g., tuberous sclerosis, *PTEN* related syndromes, 22q11 deletion syndrome), autosomal recessive disorders or maternally-transmitted X-linked disorders (or even a paternally-transmitted X-linked disorder, as for *PCDH19*). Germinal mosaicism in one of the parents can also explain rare instances of familial recurrence. This mechanism has been implicated in a surprising number of cases of siblings with ASD carrying apparently *de novo* mutations, not found in the parents' DNA (e.g., *SHANK3* mutations and deletions, *NRXN1* deletions, *NLGN4X* mutation, 16p11.2 deletion, 2q23.1 deletion, Rett syndrome and tuberous sclerosis) and may remain unrecognized in sporadic cases in small families.

An etiologic diagnosis has important benefits for the patients with ASD and their families. For the patients, it can help anticipate and manage associated medical and behavioral comorbidities. For the parents, the benefits include relieving anxiety and uncertainty, limiting further costly or invasive diagnostic testing, improving understanding of treatment and prognosis, genetic counseling regarding recurrence risk as well as preventing recurrence through screening for carriers and prenatal testing. A specific disease diagnosis can be empowering to parents who wish to become involved in more targeted support and research groups. For the medical and research community, each child who is accurately diagnosed adds to our presently limited understanding of the pathological cascades which result in autistic features; undoubtedly new findings will include previously unrecognized disease mechanisms. For the neurobiologist especially, the myriad genetic findings in ASD offer a rich source of targets for further study, providing a window into brain and neuronal development and function. The deeper understanding of these brain and neuronal processes will ultimately lead to better outcomes in ASD and other neurodevelopmental disorders.

References

Abrahams, B. S., and Geschwind, D. H. (2008). Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet* **9**, 341-355.

Addington, A. M., Gauthier, J., Piton, A., Hamdan, F. F., Raymond, A., Gogtay, N., Miller, R., Tossell, J., Bakalar, J., Germain, G., Gochman, P., Long, R., Rapoport, J. L., and Rouleau, G. A. (2011). A novel frameshift mutation in UPF3B identified in brothers affected with childhood onset schizophrenia and autism spectrum disorders. *Mol Psychiatry* **16**, 238-239.

Adegbola, A., Gao, H., Sommer, S., and Browning, M. (2008). A novel mutation in JARID1C/SMCX in a patient with autism spectrum disorder (ASD). *Am J Med Genet A* **146A**, 505-511.

Alliman, S., Coppinger, J., Marcadier, J., Thiese, H., Brock, P., Shafer, S., Weaver, C., Asamoah, A., Leppig, K., Dyack, S., Morash, B., Schultz, R., Torchia, B. S., Lamb, A. N., and Bejjani, B. A. (2010). Clinical and molecular characterization of individuals with recurrent genomic disorder at 10q22.3q23.2. *Clin Genet* **78**, 162-168.

Antshel, K. M., Aneja, A., Strunge, L., Peebles, J., Fremont, W. P., Stallone, K., Abdulsabur, N., Higgins, A. M., Shprintzen, R. J., and Kates, W. R. (2007). Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). *J Autism Dev Disord* **37**, 1776-1786.

Aoki, Y., Niihori, T., Narumi, Y., Kure, S., and Matsubara, Y. (2008). The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. *Hum Mutat* **29**, 992-1006.

Archer, H. L., Evans, J., Edwards, S., Colley, J., Newbury-Ecob, R., O'Callaghan, F., Huyton, M., O'Regan, M., Tolmie, J., Sampson, J., Clarke, A., and Osborne, J. (2006). CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet* **43**, 729-734.

Assumpcao, F., Santos, R. C., Rosario, M., and Mercadante, M. (1999). Brief report: autism and Aarskog syndrome. *J Autism Dev Disord* **29**, 179-181.

Aziz, M., Stathopulu, E., Callias, M., Taylor, C., Turk, J., Oostra, B., Willemsen, R., and Patton, M. (2003). Clinical features of boys with fragile X premutations and intermediate alleles. *Am J Med Genet B Neuropsychiatr Genet* **121B**, 119-127.

Baieli, S., Pavone, L., Meli, C., Fiumara, A., and Coleman, M. (2003). Autism and phenylketonuria. *J Autism Dev Disord* **33**, 201-204.

Balciuniene, J., Feng, N., Iyadurai, K., Hirsch, B., Charnas, L., Bill, B. R., Easterday, M. C., Staaf, J., Oseth, L., Czapansky-Beilman, D., Avramopoulos, D., Thomas, G. H., Borg, A., Valle, D., Schimmenti, L. A., and Selleck, S. B. (2007). Recurrent 10q22-q23 deletions: a genomic disorder on 10q associated with cognitive and behavioral abnormalities. *Am J Hum Genet* **80**, 938-947.

Ballif, B. C., Theisen, A., Coppinger, J., Gowans, G. C., Hersh, J. H., Madan-Khetarpal, S., Schmidt, K. R., Tervo, R., Escobar, L. F., Friedrich, C. A., McDonald, M., Campbell, L., Ming, J. E., Zackai, E. H., Bejjani, B. A., and Shaffer, L. G. (2008). Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. *Mol Cytogenet* **1**, 8.

Barnett, S., Reilly, S., Carr, L., Ojo, I., Beales, P. L., and Charman, T. (2002). Behavioural phenotype of Bardet-Biedl syndrome. *J Med Genet* **39**, e76.

Battini, R., Leuzzi, V., Carducci, C., Tosetti, M., Bianchi, M. C., Item, C. B., Stockler-Ipsiroglu, S., and Cioni, G. (2002). Creatine depletion in a new case with AGAT deficiency: clinical and genetic study in a large pedigree. *Mol Genet Metab* **77**, 326-331.

Baynam, G., Goldblatt, J., and Townshend, S. (2006). A case of 3q29 microdeletion with novel features and a review of cytogenetically visible terminal 3q deletions. *Clin Dysmorphol* **15**, 145-148.

Ben-Shachar, S., Lanpher, B., German, J. R., Qasaymeh, M., Potocki, L., Nagamani, S. C., Franco, L. M., Malphrus, A., Bottenfield, G. W., Spence, J. E., Amato, S., Rousseau, J. A., Moghaddam, B., Skinner, C., Skinner, S. A., Bernes, S., Armstrong, N., Shinawi, M., Stankiewicz, P., Patel, A., Cheung, S. W., Lupski, J. R., Beaudet, A. L., and Sahoo, T. (2009). Microdeletion 15q13.3: a locus with incomplete penetrance for autism, mental retardation, and psychiatric disorders. *J Med Genet* **46**, 382-388.

Berkel, S., Marshall, C. R., Weiss, B., Howe, J., Roeth, R., Moog, U., Endris, V., Roberts, W., Szatmari, P., Pinto, D., Bonin, M., Riess, A., Engels, H., Sprengel, R., Scherer, S. W., and Rappold, G. A. (2010). Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. *Nat Genet* **42**, 489-491.

Betancur, C. (2011). Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. *Brain Res* **1380**, 42-77.

Betancur, C., Sakurai, T., and Buxbaum, J. D. (2009). The emerging role of synaptic cell-adhesion pathways in the pathogenesis of autism spectrum disorders. *Trends Neurosci* **32**, 402-412.

Bhuiyan, Z. A., Klein, M., Hammond, P., van Haeringen, A., Mannens, M. M., Van Berckelaer-Onnes, I., and Hennekam, R. C. (2006). Genotype-phenotype correlations of 39 patients with Cornelia De Lange syndrome: the Dutch experience. *J Med Genet* **43**, 568-575.

Bi, W., Sapir, T., Shchelochkov, O. A., Zhang, F., Withers, M. A., Hunter, J. V., Levy, T., Shinder, V., Peiffer, D. A., Gunderson, K. L., Nezarati, M. M., Shotts, V. A., Amato, S. S., Savage, S. K., Harris, D. J., Day-Salvatore, D. L., Horner, M., Lu, X. Y., Sahoo, T., Yanagawa, Y., Beaudet, A. L., Cheung, S. W., Martinez, S., Lupski, J. R., and Reiner, O. (2009). Increased LIS1 expression affects human and mouse brain development. *Nat Genet* **41**, 168-177.

Bishop, D. V., Jacobs, P. A., Lachlan, K., Wellesley, D., Barnicoat, A., Boyd, P. A., Fryer, A., Middlemiss, P., Smithson, S., Metcalfe, K., Shears, D., Leggett, V., Nation, K., and Scerif, G. (2011). Autism, language and communication in children with sex chromosome trisomies. *Arch Dis Child* **96**, 954-959.

Blondis, T. A., Cook, E., Jr., Koza-Taylor, P., and Finn, T. (1996). Asperger syndrome associated with Steinert's myotonic dystrophy. *Dev Med Child Neurol* **38**, 840-847.

Borck, G., Molla-Herman, A., Boddaert, N., Encha-Razavi, F., Philippe, A., Robel, L., Desguerre, I., Brunelle, F., Benmerah, A., Munnich, A., and Colleaux, L. (2008). Clinical, cellular, and neuropathological consequences of AP1S2 mutations: further delineation of a recognizable X-linked mental retardation syndrome. *Hum Mutat* **29**, 966-974.

Bruining, H., Swaab, H., Kas, M., and van Engeland, H. (2009). Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. *Pediatrics* **123**, e865-870.

Brunetti-Pierri, N., Berg, J. S., Scaglia, F., Belmont, J., Bacino, C. A., Sahoo, T., Lalani, S. R., Graham, B., Lee, B., Shinawi, M., Shen, J., Kang, S. H., Pursley, A., Lotze, T., Kennedy, G., Lansky-Shafer, S., Weaver, C., Roeder, E. R., Grebe, T. A., Arnold, G. L., Hutchison, T., Reimschisel, T., Amato, S., Geragthy, M. T., Innis, J. W., Obersztyn, E., Nowakowska, B., Rosengren, S. S., Bader, P. I., Grange, D. K., Naqvi, S., Garnica, A. D., Bernes, S. M., Fong, C. T., Summers, A., Walters, W. D., Lupski, J. R., Stankiewicz, P., Cheung, S. W., and Patel, A. (2008). Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. *Nat Genet* **40**, 1466-1471.

Brunetti-Pierri, N., Paciorkowski, A. R., Ciccone, R., Mina, E. D., Bonaglia, M. C., Borgatti, R., Schaaf, C. P., Sutton, V. R., Xia, Z., Jelluma, N., Ruivenkamp, C., Bertrand, M., de Ravel, T. J., Jayakar, P., Belli, S., Rocchetti, K., Pantaleoni, C., D'Arrigo, S., Hughes, J., Cheung, S. W., Zuffardi, O., and Stankiewicz, P. (2011). Duplications of FOXG1 in 14q12 are associated with developmental epilepsy, mental retardation, and severe speech impairment. *Eur J Hum Genet* **19**, 102-107.

Bruno, D. L., Anderlid, B. M., Lindstrand, A., van Ravenswaaij-Arts, C., Ganesamoorthy, D., Lundin, J., Martin, C. L., Douglas, J., Nowak, C., Adam, M. P., Kooy, R. F., Van der Aa, N., Reyniers, E., Vandeweyer, G., Stolte-Dijkstra, I., Dijkhuizen, T., Yeung, A., Delatycki, M., Borgstrom, B., Thelin, L., Cardoso, C., van Bon, B., Pfundt, R., de Vries, B. B., Wallin, A., Amor, D. J., James, P. A., Slater, H. R., and Schoumans, J. (2010). Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. *J Med Genet* **47**, 299-311.

Burd, L., Stenehjem, A., Franceschini, L. A., and Kerbeshian, J. (2000). A 15-year follow-up of a boy with pyridoxine (vitamin B6)-dependent seizures with autism, breath holding, and severe mental retardation. *J Child Neurol* **15**, 763-765.

Butler, M. G., Dasouki, M. J., Zhou, X. P., Talebizadeh, Z., Brown, M., Takahashi, T. N., Miles, J. H., Wang, C. H., Stratton, R., Pilarski, R., and Eng, C. (2005). Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet* **42**, 318-321.

Buxbaum, J. D., Cai, G., Chaste, P., Nygren, G., Goldsmith, J., Reichert, J., Anckarsater, H., Rastam, M., Smith, C. J., Silverman, J. M., Hollander, E., Leboyer, M., Gillberg, C., Verloes, A., and Betancur, C. (2007). Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am J Med Genet B Neuropsychiatr Genet* **144B**, 484-491.

Cario, H., Bode, H., Debatin, K. M., Opladen, T., and Schwarz, K. (2009). Congenital null mutations of the FOLR1 gene: a progressive neurologic disease and its treatment. *Neurology* **73**, 2127-2129.

Carney, R. M., Wolpert, C. M., Ravan, S. A., Shahbazian, M., Ashley-Koch, A., Cuccaro, M. L., Vance, J. M., and Pericak-Vance, M. A. (2003). Identification of MeCP2 mutations in a series of females with autistic disorder. *Pediatr Neurol* **28**, 205-211.

Ching, M. S., Shen, Y., Tan, W. H., Jeste, S. S., Morrow, E. M., Chen, X., Mukaddes, N. M., Yoo, S. Y., Hanson, E., Hundley, R., Austin, C., Becker, R. E., Berry, G. T., Driscoll, K., Engle, E. C., Friedman, S., Gusella, J. F., Hisama, F. M., Irons, M. B., Lafiosca, T., LeClair, E., Miller, D. T., Neessen, M., Picker, J. D., Rappaport, L., Rooney, C. M., Sarco, D. P., Stoler, J. M., Walsh, C. A., Wolff, R. R., Zhang, T., Nasir, R. H., and Wu, B. L. (2010). Deletions

of NRXN1 (neurexin-1) predispose to a wide spectrum of developmental disorders. *Am J Med Genet B Neuropsychiatr Genet* **153B**, 937-947.

Chiyonobu, T., Hayashi, S., Kobayashi, K., Morimoto, M., Miyanomae, Y., Nishimura, A., Nishimoto, A., Ito, C., Imoto, I., Sugimoto, T., Jia, Z., Inazawa, J., and Toda, T. (2007). Partial tandem duplication of GRIA3 in a male with mental retardation. *Am J Med Genet A* **143A**, 1448-1455.

Clark, A. J., Rosenberg, E. H., Almeida, L. S., Wood, T. C., Jakobs, C., Stevenson, R. E., Schwartz, C. E., and Salomons, G. S. (2006). X-linked creatine transporter (SLC6A8) mutations in about 1% of males with mental retardation of unknown etiology. *Hum Genet* **119**, 604-610.

Clifford, S., Dissanayake, C., Bui, Q. M., Huggins, R., Taylor, A. K., and Loesch, D. Z. (2007). Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *J Autism Dev Disord* **37**, 738-747.

Coleman, M., and Gillberg, C. (2012). "The Autisms". Oxford University Press, New York.

Cooper, G. M., Coe, B. P., Girirajan, S., Rosenfeld, J. A., Vu, T. H., Baker, C., Williams, C., Stalker, H., Hamid, R., Hannig, V., Abdel-Hamid, H., Bader, P., McCracken, E., Niyazov, D., Leppig, K., Thiese, H., Hummel, M., Alexander, N., Gorski, J., Kussmann, J., Shashi, V., Johnson, K., Rehder, C., Ballif, B. C., Shaffer, L. G., and Eichler, E. E. (2011). A copy number variation morbidity map of developmental delay. *Nat Genet* **43**, 838-846.

Coppieters, F., Casteels, I., Meire, F., De Jaegere, S., Hooghe, S., van Regemorter, N., Van Esch, H., Matuleviciene, A., Nunes, L., Meersschaut, V., Walraedt, S., Standaert, L., Coucke, P., Hoeben, H., Kroes, H. Y., Vande Walle, J., de Ravel, T., Leroy, B. P., and De Baere, E. (2010). Genetic screening of LCA in Belgium: predominance of CEP290 and identification of potential modifier alleles in AHI1 of CEP290-related phenotypes. *Hum Mutat* **31**, E1709-1766.

Cossee, M., Demeer, B., Blanchet, P., Echenne, B., Singh, D., Hagens, O., Antin, M., Finck, S., Vallee, L., Dollfus, H., Hegde, S., Springell, K., Thelma, B. K., Woods, G., Kalscheuer, V., and Mandel, J. L. (2006). Exonic microdeletions in the X-linked PQBP1 gene in mentally retarded patients: a pathogenic mutation and in-frame deletions of uncertain effect. *Eur J Hum Genet* **14**, 418-425.

D'Amico, A., Tessa, A., Bruno, C., Petrini, S., Biancheri, R., Pane, M., Pedemonte, M., Ricci, E., Falace, A., Rossi, A., Mercuri, E., Santorelli, F. M., and Bertini, E. (2006). Expanding the clinical spectrum of POMT1 phenotype. *Neurology* **66**, 1564-1567.

de Baulny, H. O., Benoist, J. F., Rigal, O., Touati, G., Rabier, D., and Saudubray, J. M. (2005). Methylmalonic and propionic acidaemias: management and outcome. *J Inherit Metab Dis* **28**, 415-423.

de Vries, P. J. (2010). Targeted treatments for cognitive and neurodevelopmental disorders in tuberous sclerosis complex. *Neurotherapeutics* **7**, 275-282.

de Winter, C. F., van Dijk, F., Stolker, J. J., and Hennekam, R. C. (2009). Behavioural phenotype in Borjeson-Forssman-Lehmann syndrome. *J Intellect Disabil Res* **53**, 319-328.

Depienne, C., Heron, D., Betancur, C., Benyahia, B., Trouillard, O., Bouteiller, D., Verloes, A., LeGuern, E., Leboyer, M., and Brice, A. (2007). Autism, language delay and mental retardation in a patient with 7q11 duplication. *J Med Genet* **44**, 452-458.

Depienne, C., and Leguern, E. (2012). PCDH19-related infantile epileptic encephalopathy: an unusual X-linked inheritance disorder. *Hum Mutat* **33**, 627-634.

Depienne, C., Moreno-De-Luca, D., Heron, D., Bouteiller, D., Gennetier, A., Delorme, R., Chaste, P., Siffroi, J. P., Chantot-Bastaraud, S., Benyahia, B., Trouillard, O., Nygren, G., Kopp, S., Johansson, M., Rastam, M., Burglen, L., Leguern, E., Verloes, A., Leboyer, M., Brice, A., Gillberg, C., and Betancur, C. (2009). Screening for genomic rearrangements and methylation abnormalities of the 15q11-q13 region in autism spectrum disorders. *Biol Psychiatry* **66**, 349-359.

Descheemaeker, M. J., Govers, V., Vermeulen, P., and Fryns, J. P. (2006). Pervasive developmental disorders in Prader-Willi syndrome: the Leuven experience in 59 subjects and controls. *Am J Med Genet A* **140**, 1136-1142.

Deveault, C., Billingsley, G., Duncan, J. L., Bin, J., Theal, R., Vincent, A., Fieggen, K. J., Gerth, C., Noordeh, N., Traboulsi, E. I., Fishman, G. A., Chitayat, D., Knueppel, T., Millan, J. M., Munier, F. L., Kennedy, D., Jacobson, S. G., Innes, A. M., Mitchell, G. A., Boycott, K., and Heon, E. (2011). BBS genotype-phenotype assessment of a multiethnic patient cohort calls for a revision of the disease definition. *Hum Mutat* **32**, 610-619.

Devillard, F., Guinchat, V., Moreno-De-Luca, D., Tabet, A. C., Gruchy, N., Guillem, P., Nguyen Morel, M. A., Leporrier, N., Leboyer, M., Jouk, P. S., Lespinasse, J., and Betancur, C. (2010). Paracentric inversion of chromosome 2 associated with cryptic duplication of 2q14 and deletion of 2q37 in a patient with autism. *Am J Med Genet A* **152A**, 2346-2354.

Dibbens, L. M., Tarpey, P. S., Hynes, K., Bayly, M. A., Scheffer, I. E., Smith, R., Bomar, J., Sutton, E., Vandeleur, L., Shoubridge, C., Edkins, S., Turner, S. J., Stevens, C., O'Meara, S., Tofts, C., Barthorpe, S., Buck, G., Cole, J., Halliday, K., Jones, D., Lee, R., Madison, M., Mironenko, T., Varian, J., West, S., Widaa, S., Wray, P., Teague, J., Dicks, E., Butler, A., Menzies, A., Jenkinson, A., Shepherd, R., Gusella, J. F., Afawi, Z., Mazarib, A., Neufeld, M. Y., Kivity, S., Lev, D., Lerman-Sagie, T., Korczyn, A. D., Derry, C. P., Sutherland, G. R., Friend, K., Shaw, M., Corbett, M., Kim, H. G., Geschwind, D. H., Thomas, P., Haan, E., Ryan, S., McKee, S., Berkovic, S. F., Futreal, P. A., Stratton, M. R., Mulley, J. C., and Gecz, J. (2008). X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet* **40**, 776-781.

Doherty, D., Parisi, M. A., Finn, L. S., Gunay-Aygun, M., Al-Mateen, M., Bates, D., Clericuzio, C., Demir, H., Dorschner, M., van Essen, A. J., Gahl, W. A., Gentile, M., Gorden, N. T., Hikida, A., Knutzen, D., Ozyurek, H., Phelps, I., Rosenthal, P., Verloes, A., Weigand, H., Chance, P. F., Dobyns, W. B., and Glass, I. A. (2010). Mutations in 3 genes (MKS3, CC2D2A and RPGRIP1L) cause COACH syndrome (Joubert syndrome with congenital hepatic fibrosis). *J Med Genet* **47**, 8-21.

Durand, C. M., Betancur, C., Boeckers, T. M., Bockmann, J., Chaste, P., Fauchereau, F., Nygren, G., Rastam, M., Gillberg, I. C., Anckarsater, H., Sponheim, E., Goubran-Botros, H., Delorme, R., Chabane, N., Mouren-Simeoni, M. C., de Mas, P., Bieth, E., Roge, B., Heron, D., Burglen, L., Gillberg, C., Leboyer, M., and Bourgeron, T. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* **39**, 25-27.

Ekstrom, A. B., Hakenas-Plate, L., Samuelsson, L., Tulinius, M., and Wentz, E. (2008). Autism spectrum conditions in myotonic dystrophy type 1: a study on 57 individuals with congenital and childhood forms. *Am J Med Genet B Neuropsychiatr Genet* **147B**, 918-926.

Endele, S., Rosenberger, G., Geider, K., Popp, B., Tamer, C., Stefanova, I., Milh, M., Kortum, F., Fritsch, A., Pientka, F. K., Hellenbroich, Y., Kalscheuer, V. M., Kohlhase, J., Moog, U., Rappold, G., Rauch, A., Ropers, H. H., von Spiczak, S., Tonnies, H., Villeneuve, N., Villard, L., Zabel, B., Zenker, M., Laube, B., Reis, A., Wieczorek, D., Van Maldergem, L., and Kutsche, K. (2010). Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. *Nat Genet* **42**, 1021-1026.

Falk, R. E., and Casas, K. A. (2007). Chromosome 2q37 deletion: clinical and molecular aspects. *Am J Med Genet C Semin Med Genet* **145C**, 357-371.

Fassio, A., Patry, L., Congia, S., Onofri, F., Piton, A., Gauthier, J., Pozzi, D., Messa, M., Defranchi, E., Fadda, M., Corradi, A., Baldelli, P., Lapointe, L., St-Onge, J., Meloche, C., Mottron, L., Valtorta, F., Khoa Nguyen, D., Rouleau, G. A., Benfenati, F., and Cossette, P. (2011). SYN1 loss-of-function mutations in autism and partial epilepsy cause impaired synaptic function. *Hum Mol Genet* **20**, 2297-2307.

Fine, S. E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E. H., McDonald-McGinn, D. M., and Emanuel, B. S. (2005). Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *J Autism Dev Disord* **35**, 461-470.

Fisch, G. S., Grossfeld, P., Falk, R., Battaglia, A., Youngblom, J., and Simensen, R. (2010). Cognitive-behavioral features of Wolf-Hirschhorn syndrome and other subtelomeric microdeletions. *Am J Med Genet C Semin Med Genet* **154C**, 417-426.

Flanagan, S. E., Patch, A. M., Mackay, D. J., Edghill, E. L., Gloyn, A. L., Robinson, D., Shield, J. P., Temple, K., Ellard, S., and Hattersley, A. T. (2007). Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. *Diabetes* **56**, 1930-1937.

Fombonne, E., Du Mazaubrun, C., Cans, C., and Grandjean, H. (1997). Autism and associated medical disorders in a French epidemiological survey. *J Am Acad Child Adolesc Psychiatry* **36**, 1561-1569.

Fontenelle, L. F., Mendlowicz, M. V., Bezerra de Menezes, G., dos Santos Martins, R. R., and Versiani, M. (2004). Asperger Syndrome, obsessive-compulsive disorder, and major depression in a patient with 45,X/46,XY mosaicism. *Psychopathology* **37**, 105-109.

Froyen, G., Bauters, M., Boyle, J., Van Esch, H., Govaerts, K., van Bokhoven, H., Ropers, H. H., Moraine, C., Chelly, J., Fryns, J. P., Marynen, P., Gecz, J., and Turner, G. (2007). Loss of SLC38A5 and FTSJ1 at Xp11.23 in three brothers with non-syndromic mental retardation due to a microdeletion in an unstable genomic region. *Hum Genet* **121**, 539-547.

Garbern, J. Y., Neumann, M., Trojanowski, J. Q., Lee, V. M., Feldman, G., Norris, J. W., Friez, M. J., Schwartz, C. E., Stevenson, R., and Sima, A. A. (2010). A mutation affecting the sodium/proton exchanger, SLC9A6, causes mental retardation with tau deposition. *Brain* **133**, 1391-1402.

Garcia, C. C., Blair, H. J., Seager, M., Coulthard, A., Tennant, S., Buddles, M., Curtis, A., and Goodship, J. A. (2004). Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. *J Med Genet* **41**, 183-186.

Gecz, J., Shoubridge, C., and Corbett, M. (2009). The genetic landscape of intellectual disability arising from chromosome X. *Trends Genet* **25**, 308-316.

Giannandrea, M., Bianchi, V., Mignogna, M. L., Sirri, A., Carrabino, S., D'Elia, E., Vecellio, M., Russo, S., Cogliati, F., Larizza, L., Ropers, H. H., Tzschach, A., Kalscheuer, V., Oehl-Jaschkowitz, B., Skinner, C., Schwartz, C. E., Gecz, J., Van Esch, H., Raynaud, M., Chelly, J., de Brouwer, A. P., Toniolo, D., and D'Adamo, P. (2010). Mutations in the small GTPase gene RAB39B are responsible for X-linked mental retardation associated with autism, epilepsy, and macrocephaly. *Am J Hum Genet* **86**, 185-195.

Gillberg, C. (1989). Asperger syndrome in 23 Swedish children. *Dev Med Child Neurol* **31**, 520-531.

Gorker, I., and Tuzun, U. (2005). Autistic-like findings associated with a urea cycle disorder in a 4-year-old girl. *J Psychiatry Neurosci* **30**, 133-135.

Gothelf, D., Presburger, G., Zohar, A. H., Burg, M., Nahmani, A., Frydman, M., Shohat, M., Inbar, D., Aviram-Goldring, A., Yeshaya, J., Steinberg, T., Finkelstein, Y., Frisch, A., Weizman, A., and Apter, A. (2004). Obsessive-compulsive disorder in patients with velocardiofacial (22q11 deletion) syndrome. *Am J Med Genet B Neuropsychiatr Genet* **126B**, 99-105.

Grisart, B., Willatt, L., Destree, A., Fryns, J. P., Rack, K., de Ravel, T., Rosenfeld, J., Vermeesch, J. R., Verellen-Dumoulin, C., and Sandford, R. (2009). 17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction. *J Med Genet* **46**, 524-530.

Hackett, A., Tarpey, P. S., Licata, A., Cox, J., Whibley, A., Boyle, J., Rogers, C., Grigg, J., Partington, M., Stevenson, R. E., Tolmie, J., Yates, J. R., Turner, G., Wilson, M., Futreal, A. P., Corbett, M., Shaw, M., Gecz, J., Raymond, F. L., Stratton, M. R., Schwartz, C. E., and Abidi, F. E. (2010). CASK mutations are frequent in males and cause X-linked nystagmus and variable XLMR phenotypes. *Eur J Hum Genet* **18**, 544-552.

Hagerman, R., Hoem, G., and Hagerman, P. (2010). Fragile X and autism: Intertwined at the molecular level leading to targeted treatments. *Mol Autism* **1**, 12.

Hagerman, R. J., Hull, C. E., Safanda, J. F., Carpenter, I., Staley, L. W., O'Connor, R. A., Seydel, C., Mazzocco, M. M., Snow, K., Thibodeau, S. N., Kuhl, D., Nelson, D. L., Caskey, C. T., and Taylor, A. K. (1994). High functioning fragile X males: demonstration of an unmethylated fully expanded FMR-1 mutation associated with protein expression. *Am J Med Genet* **51**, 298-308.

Halgren, C., Kjaergaard, S., Bak, M., Hansen, C., El-Schich, Z., Anderson, C., Henriksen, K., Hjalgrim, H., Kirchhoff, M., Bijlsma, E., Nielsen, M., den Hollander, N., Ruivenkamp, C., Isidor, B., Le Caignec, C., Zannolli, R., Mucciolo, M., Renieri, A., Mari, F., Anderlid, B. M., Andrieux, J., Dieux, A., Tommerup, N., and Bache, I. (2011). Corpus callosum abnormalities, intellectual disability, speech impairment, and autism in patients with haploinsufficiency of ARID1B. *Clin Genet* **(Epub ahead of print)**.

Haliloglu, G., Gross, C., Senbil, N., Talim, B., Hehr, U., Uyanik, G., Winkler, J., and Topaloglu, H. (2004). Clinical spectrum of muscle-eye-brain disease: from the typical presentation to severe autistic features. *Acta Myol* **23**, 137-139.

Hamdan, F. F., Daoud, H., Piton, A., Gauthier, J., Dobrzeniecka, S., Krebs, M. O., Joober, R., Lacaille, J. C., Nadeau, A., Milunsky, J. M., Wang, Z., Carmant, L., Mottron, L., Beauchamp, M. H., Rouleau, G. A., and Michaud, J. L. (2011). De novo SYNGAP1 mutations in nonsyndromic intellectual disability and autism. *Biol Psychiatry* **69**, 898-901.

Hamdan, F. F., Daoud, H., Rochefort, D., Piton, A., Gauthier, J., Langlois, M., Foomani, G., Dobrzeniecka, S., Krebs, M. O., Joober, R., Lafreniere, R. G., Lacaille, J. C., Mottron, L., Drapeau, P., Beauchamp, M. H., Phillips, M. S., Fombonne, E., Rouleau, G. A., and Michaud, J. L. (2010). De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment. *Am J Hum Genet* **87**, 671-678.

Hanson, E., Nasir, R. H., Fong, A., Lian, A., Hundley, R., Shen, Y., Wu, B. L., Holm, I. A., and Miller, D. T. (2010). Cognitive and behavioral characterization of 16p11.2 deletion syndrome. *J Dev Behav Pediatr* **31**, 649-657.

Hehr, U., Uyanik, G., Gross, C., Walter, M. C., Bohring, A., Cohen, M., Oehl-Jaschkowitz, B., Bird, L. M., Shamdeen, G. M., Bogdahn, U., Schuierer, G., Topaloglu, H., Aigner, L., Lochmuller, H., and Winkler, J. (2007). Novel POMGnT1 mutations define broader phenotypic spectrum of muscle-eye-brain disease. *Neurogenetics* **8**, 279-288.

Hemara-Wahanui, A., Berjukow, S., Hope, C. I., Dearden, P. K., Wu, S. B., Wilson-Wheeler, J., Sharp, D. M., Lundon-Treweek, P., Clover, G. M., Hoda, J. C., Striessnig, J., Marksteiner, R., Hering, S., and Maw, M. A. (2005). A CACNA1F mutation identified in an X-linked retinal disorder shifts the voltage dependence of Cav1.4 channel activation. *Proc Natl Acad Sci U S A* **102**, 7553-7558.

Heron, B., Mikaeloff, Y., Froissart, R., Caridade, G., Maire, I., Caillaud, C., Levade, T., Chabrol, B., Feillet, F., Ogier, H., Valayannopoulos, V., Michelakakis, H., Zafeiriou, D., Lavery, L., Wraith, E., Danos, O., Heard, J. M., and Tardieu, M. (2011). Incidence and natural history of mucopolysaccharidosis type III in France and comparison with United Kingdom and Greece. *Am J Med Genet A* **155A**, 58-68.

Hinton, V. J., Cyrulnik, S. E., Fee, R. J., Batchelder, A., Kiefel, J. M., Goldstein, E. M., Kaufmann, P., and De Vivo, D. C. (2009). Association of autistic spectrum disorders with dystrophinopathies. *Pediatr Neurol* **41**, 339-346.

Hogart, A., Wu, D., LaSalle, J. M., and Schanen, N. C. (2010). The comorbidity of autism with the genomic disorders of chromosome 15q11.2-q13. *Neurobiol Dis* **38**, 181-191.

Hood, R. L., Lines, M. A., Nikkel, S. M., Schwartzentruber, J., Beaulieu, C., Nowaczyk, M. J., Allanson, J., Kim, C. A., Wieczorek, D., Moilanen, J. S., Lacombe, D., Gillessen-Kaesbach, G., Whiteford, M. L., Quaio, C. R., Gomy, I., Bertola, D. R., Albrecht, B., Platzer, K., McGillivray, G., Zou, R., McLeod, D. R., Chudley, A. E., Chodirker, B. N., Marcadier, J., Majewski, J., Bulman, D. E., White, S. M., and Boycott, K. M. (2012). Mutations in SRCAP, encoding SNF2-related CREBBP activator protein, cause Floating-Harbor syndrome. *Am J Hum Genet* **90**, 308-313.

Howlin, P., Karpf, J., and Turk, J. (2005). Behavioural characteristics and autistic features in individuals with Cohen Syndrome. *Eur Child Adolesc Psychiatry* **14**, 57-64.

Hynes, K., Tarpey, P., Dibbens, L. M., Bayly, M. A., Berkovic, S. F., Smith, R., Raisi, Z. A., Turner, S. J., Brown, N. J., Desai, T. D., Haan, E., Turner, G., Christodoulou, J., Leonard, H., Gill, D., Stratton, M. R., Gecz, J., and Scheffer, I. E. (2010). Epilepsy and mental retardation limited to females with PCDH19 mutations can present de novo or in single generation families. *J Med Genet* **47**, 211-216.

Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I. C., Soderstrom, H., Giros, B., Leboyer, M., Gillberg, C., and Bourgeron, T. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* **34**, 27-29.

Jeffries, A. R., Curran, S., Elmslie, F., Sharma, A., Wenger, S., Hummel, M., and Powell, J. (2005). Molecular and phenotypic characterization of ring chromosome 22. *Am J Med Genet A* **137**, 139-147.

Johansson, M., Rastam, M., Billstedt, E., Danielsson, S., Stromland, K., Miller, M., and Gillberg, C. (2006). Autism spectrum disorders and underlying brain pathology in CHARGE association. *Dev Med Child Neurol* **48**, 40-50.

Kayser, M. A. (2008). Inherited metabolic diseases in neurodevelopmental and neurobehavioral disorders. *Semin Pediatr Neurol* **15**, 127-131.

Kerr, B., Delrue, M. A., Sigaudy, S., Perveen, R., Marche, M., Burgelin, I., Stef, M., Tang, B., Eden, O. B., O'Sullivan, J., De Sandre-Giovannoli, A., Reardon, W., Brewer, C., Bennett, C., Quarell, O., M'Cann, E., Donnai, D., Stewart, F., Hennekam, R., Cave, H., Verloes, A., Philip, N., Lacombe, D., Levy, N., Arveiler, B., and Black, G. (2006). Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. *J Med Genet* **43**, 401-405.

Kielinen, M., Rantala, H., Timonen, E., Linna, S. L., and Moilanen, I. (2004). Associated medical disorders and disabilities in children with autistic disorder: a population-based study. *Autism* **8**, 49-60.

Kilincaslan, A., Tanidir, C., Tutkunkardas, M. D., and Mukaddes, N. M. (2011). Asperger's disorder and Williams syndrome: a case report. *Turk J Pediatr* **53**, 352-355.

Kleefstra, T., van Zelst-Stams, W. A., Nillesen, W. M., Cormier-Daire, V., Houge, G., Foulds, N., van Dooren, M., Willemsen, M. H., Pfundt, R., Turner, A., Wilson, M., McGaughran, J., Rauch, A., Zenker, M., Adam, M. P., Innes, M., Davies, C., Lopez, A. G., Casalone, R., Weber, A., Brueton, L. A., Navarro, A. D., Bralo, M. P., Venselaar, H., Stegmann, S. P., Yntema, H. G., van Bokhoven, H., and Brunner, H. G. (2009). Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. *J Med Genet* **46**, 598-606.

Kleefstra, T., Yntema, H. G., Oudakker, A. R., Banning, M. J., Kalscheuer, V. M., Chelly, J., Moraine, C., Ropers, H. H., Fryns, J. P., Janssen, I. M., Sistermans, E. A., Nillesen, W. N., de Vries, L. B., Hamel, B. C., and van Bokhoven, H. (2004). Zinc finger 81 (ZNF81) mutations associated with X-linked mental retardation. *J Med Genet* **41**, 394-399.

Klein-Tasman, B. P., Phillips, K. D., Lord, C., Mervis, C. B., and Gallo, F. J. (2009). Overlap with the autism spectrum in young children with Williams syndrome. *J Dev Behav Pediatr* **30**, 289-299.

Knerr, I., Gibson, K. M., Jakobs, C., and Pearl, P. L. (2008). Neuropsychiatric morbidity in adolescent and adult succinic semialdehyde dehydrogenase deficiency patients. *CNS Spectr* **13**, 598-605.

Kumagai, T., Miura, K., Ohki, T., Matsumoto, A., Miyazaki, S., Nakamura, M., Ochi, N., and Takahashi, O. (2001). [Central nervous system involvements in Duchenne/Becker muscular dystrophy]. *No To Hattatsu* **33**, 480-486.

Kutsche, K., Yntema, H., Brandt, A., Jantke, I., Nothwang, H. G., Orth, U., Boavida, M. G., David, D., Chelly, J., Fryns, J. P., Moraine, C., Ropers, H. H., Hamel, B. C., van Bokhoven, H., and Gal, A. (2000). Mutations in ARHGEF6, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. *Nat Genet* **26**, 247-250.

Laje, G., Morse, R., Richter, W., Ball, J., Pao, M., and Smith, A. C. (2010). Autism spectrum features in Smith-Magenis syndrome. *Am J Med Genet C Semin Med Genet* **154C**, 456-462.

Laumonnier, F., Bonnet-Brilhault, F., Gomot, M., Blanc, R., David, A., Moizard, M. P., Raynaud, M., Ronce, N., Lemonnier, E., Calvas, P., Laudier, B., Chelly, J., Fryns, J. P., Ropers, H. H., Hamel, B. C., Andres, C., Barthelemy, C., Moraine, C., and Briault, S. (2004). X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. *Am J Hum Genet* **74**, 552-557.

Laumonnier, F., Shoubridge, C., Antar, C., Nguyen, L. S., Van Esch, H., Kleefstra, T., Briault, S., Fryns, J. P., Hamel, B., Chelly, J., Ropers, H. H., Ronce, N., Blesson, S., Moraine, C., Gecz, J., and Raynaud, M. (2010). Mutations of the UPF3B gene, which encodes a protein widely expressed in neurons, are associated with nonspecific mental retardation with or without autism. *Mol Psychiatry* **15**, 767-776.

Laycock-van Spyk, S., Jim, H. P., Thomas, L., Spurlock, G., Fares, L., Palmer-Smith, S., Kini, U., Saggar, A., Patton, M., Mautner, V., Pilz, D. T., and Upadhyaya, M. (2011). Identification of five novel SPRED1 germline mutations in Legius syndrome. *Clin Genet* **80**, 93-96.

Lee, J. E., and Gleeson, J. G. (2011). Cilia in the nervous system: linking cilia function and neurodevelopmental disorders. *Curr Opin Neurol* **24**, 98-105.

Leger, P. L., Souville, I., Boddaert, N., Elie, C., Pinard, J. M., Plouin, P., Moutard, M. L., des Portes, V., Van Esch, H., Joriot, S., Renard, J. L., Chelly, J., Francis, F., Beldjord, C., and Bahi-Buisson, N. (2008). The location of DCX mutations predicts malformation severity in X-linked lissencephaly. *Neurogenetics* **9**, 277-285.

Lerma-Carrillo, I., Molina, J. D., Cuevas-Duran, T., Julve-Correcher, C., Espejo-Saavedra, J. M., Andrade-Rosa, C., and Lopez-Munoz, F. (2006). Psychopathology in the Lujan-Fryns syndrome: report of two patients and review. *Am J Med Genet A* **140**, 2807-2811.

Liang, J. S., Shimojima, K., Ohno, K., Sugiura, C., Une, Y., Ohno, K., and Yamamoto, T. (2009). A newly recognised microdeletion syndrome of 2p15-16.1 manifesting moderate developmental delay, autistic behaviour, short stature, microcephaly, and dysmorphic features: a new patient with 3.2 Mb deletion. *J Med Genet* **46**, 645-647.

Longo, I., Frints, S. G., Fryns, J. P., Meloni, I., Pescucci, C., Ariani, F., Borghgraef, M., Raynaud, M., Marynen, P., Schwartz, C., Renieri, A., and Froyen, G. (2003). A third MRX family (MRX68) is the result of mutation in the long chain fatty acid-CoA ligase 4 (FACL4) gene: proposal of a rapid enzymatic assay for screening mentally retarded patients. *J Med Genet* **40**, 11-17.

Longo, N., Ardon, O., Vanzo, R., Schwartz, E., and Pasquali, M. (2011). Disorders of creatine transport and metabolism. *Am J Med Genet C Semin Med Genet* **157**, 72-78.

Lopez-Hernandez, T., Ridder, M. C., Montolio, M., Capdevila-Nortes, X., Polder, E., Sirisi, S., Duarri, A., Schulte, U., Fakler, B., Nunes, V., Scheper, G. C., Martinez, A., Estevez, R., and van der Knaap, M. S. (2011). Mutant GlialCAM causes megalencephalic leukoencephalopathy with subcortical cysts, benign familial macrocephaly, and macrocephaly with retardation and autism. *Am J Hum Genet* **88**, 422-432.

Lowenthal, R., Paula, C. S., Schwartzman, J. S., Brunoni, D., and Mercadante, M. T. (2007). Prevalence of pervasive developmental disorder in Down's syndrome. *J Autism Dev Disord* **37**, 1394-1395.

Lugtenberg, D., Yntema, H. G., Banning, M. J., Oudakker, A. R., Firth, H. V., Willatt, L., Raynaud, M., Kleefstra, T., Fryns, J. P., Ropers, H. H., Chelly, J., Moraine, C., Gecz, J., van Reeuwijk, J., Nabuurs, S. B., de Vries, B. B., Hamel, B. C., de Brouwer, A. P., and van Bokhoven, H. (2006). ZNF674: a new kruppel-associated box-containing zinc-finger gene involved in nonsyndromic X-linked mental retardation. *Am J Hum Genet* **78**, 265-278.

Lynch, N. E., Lynch, S. A., McMenamin, J., and Webb, D. (2009). Bannayan-Riley-Ruvalcaba syndrome: a cause of extreme macrocephaly and neurodevelopmental delay. *Arch Dis Child* **94**, 553-554.

Manning, M. A., Cassidy, S. B., Clericuzio, C., Cherry, A. M., Schwartz, S., Hudgins, L., Enns, G. M., and Hoyme, H. E. (2004). Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. *Pediatrics* **114**, 451-457.

Marini, C., Mei, D., Parmeggiani, L., Norci, V., Calado, E., Ferrari, A., Moreira, A., Pisano, T., Specchio, N., Vigevano, F., Battaglia, D., and Guerrini, R. (2010). Protocadherin 19 mutations in girls with infantile-onset epilepsy. *Neurology* **75**, 646-653.

Marini, C., Scheffer, I. E., Nabbout, R., Mei, D., Cox, K., Dibbens, L. M., McMahon, J. M., Iona, X., Carpintero, R. S., Elia, M., Cilio, M. R., Specchio, N., Giordano, L., Striano, P., Gennaro, E., Cross, J. H., Kivity, S., Neufeld, M. Y., Afawi, Z., Andermann, E., Keene, D., Dulac, O., Zara, F., Berkovic, S. F., Guerrini, R., and Mulley, J. C. (2009). SCN1A duplications and deletions detected in Dravet syndrome: Implications for molecular diagnosis. *Epilepsia* **50**, 1670-1678.

Marshall, C. R., Noor, A., Vincent, J. B., Lionel, A. C., Feuk, L., Skaug, J., Shago, M., Moessner, R., Pinto, D., Ren, Y., Thiruvahindrapduram, B., Fiebig, A., Schreiber, S., Friedman, J., Ketelaars, C. E., Vos, Y. J., Ficicioglu, C., Kirkpatrick, S., Nicolson, R., Sloman, L., Summers, A., Gibbons, C. A., Teebi, A., Chitayat, D., Weksberg, R., Thompson, A., Vardy, C., Crosbie, V., Luscombe, S., Baatjes, R., Zwaigenbaum, L., Roberts, W., Fernandez, B.,

Szatmari, P., and Scherer, S. W. (2008). Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet* **82**, 477-488.

Mastrangelo, M., and Leuzzi, V. (2012). Genes of early-onset epileptic encephalopathies: from genotype to phenotype. *Pediatr Neurol* **46**, 24-31.

McBride, K. L., Varga, E. A., Pastore, M. T., Prior, T. W., Manickam, K., Atkin, J. F., and Herman, G. E. (2010). Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Res* **3**, 137-141.

McInnes, L. A., Nakamine, A., Pilorge, M., Brandt, T., Jimenez Gonzalez, P., Fallas, M., Manghi, E. R., Edelmann, L., Glessner, J., Hakonarson, H., Betancur, C., and Buxbaum, J. D. (2010). A large-scale survey of the novel 15q24 microdeletion syndrome in autism spectrum disorders identifies an atypical deletion that narrows the critical region. *Mol Autism* **1**, 5.

Mefford, H. C., Rosenfeld, J. A., Shur, N., Slavotinek, A. M., Cox, V. A., Hennekam, R. C., Firth, H. V., Willatt, L., Wheeler, P., Morrow, E. M., Cook, J., Sullivan, R., Oh, A., McDonald, M. T., Zonana, J., Keller, K., Hannibal, M. C., Ball, S., Kussmann, J., Gorski, J., Zelewski, S., Banks, V., Smith, W., Smith, R., Paull, L., Rosenbaum, K. N., Amor, D. J., Silva, J., Lamb, A., and Eichler, E. E. (2012). Further clinical and molecular delineation of the 15q24 microdeletion syndrome. *J Med Genet* **49**, 110-118.

Mefford, H. C., Sharp, A. J., Baker, C., Itsara, A., Jiang, Z., Buysse, K., Huang, S., Maloney, V. K., Crolla, J. A., Baralle, D., Collins, A., Mercer, C., Norga, K., de Ravel, T., Devriendt, K., Bongers, E. M., de Leeuw, N., Reardon, W., Gimelli, S., Bena, F., Hennekam, R. C., Male, A., Gaunt, L., Clayton-Smith, J., Simonic, I., Park, S. M., Mehta, S. G., Nik-Zainal, S., Woods, C. G., Firth, H. V., Parkin, G., Fichera, M., Reitano, S., Lo Giudice, M., Li, K. E., Casuga, I., Broomer, A., Conrad, B., Schwerzmann, M., Raber, L., Gallati, S., Striano, P., Coppola, A., Tolmie, J. L., Tobias, E. S., Lilley, C., Armengol, L., Spysschaert, Y., Verloo, P., De Coene, A., Goossens, L., Mortier, G., Speleman, F., van Binsbergen, E., Nelen, M. R., Hochstenbach, R., Poot, M., Gallagher, L., Gill, M., McClellan, J., King, M. C., Regan, R., Skinner, C., Stevenson, R. E., Antonarakis, S. E., Chen, C., Estivill, X., Menten, B., Gimelli, G., Gribble, S., Schwartz, S., Sutcliffe, J. S., Walsh, T., Knight, S. J., Sebat, J., Romano, C., Schwartz, C. E., Veltman, J. A., de Vries, B. B., Vermeesch, J. R., Barber, J. C., Willatt, L., Tassabehji, M., and Eichler, E. E. (2008). Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. *N Engl J Med* **359**, 1685-1699.

Meloni, I., Muscettola, M., Raynaud, M., Longo, I., Bruttini, M., Moizard, M. P., Gomot, M., Chelly, J., des Portes, V., Fryns, J. P., Ropers, H. H., Magi, B., Bellan, C., Volpi, N., Yntema, H. G., Lewis, S. E., Schaffer, J. E., and Renieri, A. (2002). FACL4, encoding fatty acid-CoA ligase 4, is mutated in nonspecific X-linked mental retardation. *Nat Genet* **30**, 436-440.

Michelson, D. J., Shevell, M. I., Sherr, E. H., Moeschler, J. B., Gropman, A. L., and Ashwal, S. (2011). Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* **77**, 1629-1635.

Milh, M., Villeneuve, N., Chouchane, M., Kaminska, A., Laroche, C., Barthez, M. A., Gitiaux, C., Bartoli, C., Borges-Correia, A., Cacciagli, P., Mignon-Ravix, C., Cuberos, H., Chabrol, B., and Villard, L. (2011). Epileptic and nonepileptic features in patients with early onset epileptic encephalopathy and STXBP1 mutations. *Epilepsia* **52**, 1828-1834.

Miller, D. T., Shen, Y., Weiss, L. A., Korn, J., Anselm, I., Bridgemohan, C., Cox, G. F., Dickinson, H., Gentile, J., Harris, D. J., Hegde, V., Hundley, R., Khwaja, O., Kothare, S., Luedke, C., Nasir, R., Poduri, A., Prasad, K., Raffalli, P., Reinhard, A., Smith, S. E., Sobeih, M. M., Soul, J. S., Stoler, J., Takeoka, M., Tan, W. H., Thakuria, J., Wolff, R., Yusupov, R., Gusella, J. F., Daly, M. J., and Wu, B. L. (2009). Microdeletion/duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. *J Med Genet* **46**, 242-248.

Mills, P. B., Footitt, E. J., Mills, K. A., Tuschl, K., Aylett, S., Varadkar, S., Hemingway, C., Marlow, N., Rennie, J., Baxter, P., Dulac, O., Nabbout, R., Craigen, W. J., Schmitt, B., Feillet, F., Christensen, E., De Lonlay, P., Pike, M. G., Hughes, M. I., Struys, E. A., Jakobs, C., Zuberi, S. M., and Clayton, P. T. (2010). Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). *Brain* **133**, 2148-2159.

Moessner, R., Marshall, C. R., Sutcliffe, J. S., Skaug, J., Pinto, D., Vincent, J., Zwaigenbaum, L., Fernandez, B., Roberts, W., Szatmari, P., and Scherer, S. W. (2007). Contribution of SHANK3 mutations to autism spectrum disorder. *Am J Hum Genet* **81**, 1289-1297.

Moore, S. J., Green, J. S., Fan, Y., Bhogal, A. K., Dicks, E., Fernandez, B. A., Stefanelli, M., Murphy, C., Cramer, B. C., Dean, J. C., Beales, P. L., Katsanis, N., Bassett, A. S., Davidson, W. S., and Parfrey, P. S. (2005). Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. *Am J Med Genet A* **132**, 352-360.

Moreno-De-Luca, D., Mulle, J. G., Kaminsky, E. B., Sanders, S. J., Myers, S. M., Adam, M. P., Pakula, A. T., Eisenhauer, N. J., Uhas, K., Weik, L., Guy, L., Care, M. E., Morel, C. F., Boni, C., Salbert, B. A., Chandrareddy, A., Demmer, L. A., Chow, E. W., Surti, U., Aradhya, S., Pickering, D. L., Golden, D. M., Sanger, W. G., Aston, E., Brothman, A. R., Gliem, T. J., Thorland, E. C., Ackley, T., Iyer, R., Huang, S., Barber, J. C., Crolla, J. A., Warren, S. T., Martin, C. L., and Ledbetter, D. H. (2010). Deletion 17q12 Is a recurrent copy number variant that confers high risk of autism and schizophrenia. *Am J Hum Genet* **87**, 618-630.

Moss, J. F., Oliver, C., Berg, K., Kaur, G., Jephcott, L., and Cornish, K. (2008). Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. *Am J Ment Retard* **113**, 278-291.

Mulley, J. C., and Mefford, H. C. (2011). Epilepsy and the new cytogenetics. *Epilepsia* **52**, 423-432.

Nava, C., Hanna, N., Michot, C., Pereira, S., Pouvreau, N., Niihori, T., Aoki, Y., Matsubara, Y., Arveiler, B., Lacombe, D., Pasmant, E., Parfait, B., Baumann, C., Heron, D., Sigaudy, S., Toutain, A., Rio, M., Goldenberg, A., Leheup, B., Verloes, A., and Cave, H. (2007). Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. *J Med Genet* **44**, 763-771.

Neale, B. M., Kou, Y., Liu, L., Ma'ayan, A., Samocha, K. E., Sabo, A., Lin, C. F., Stevens, C., Wang, L. S., Makarov, V., Polak, P., Yoon, S., Maguire, J., Crawford, E. L., Campbell, N. G., Geller, E. T., Valladares, O., Schafer, C., Liu, H., Zhao, T., Cai, G., Lihm, J., Dannenfelser, R., Jabado, O., Peralta, Z., Nagaswamy, U., Muzny, D., Reid, J. G., Newsham, I., Wu, Y., Lewis, L., Han, Y., Voight, B. F., Lim, E., Rossin, E., Kirby, A., Flannick, J., Fromer, M., Shakir, K., Fennell, T., Garimella, K., Banks, E., Poplin, R., Gabriel, S., Depristo, M., Wimbish, J. R., Boone, B. E., Levy, S. E., Betancur, C., Sunyaev, S., Boerwinkle, E., Buxbaum, J. D., Cook, E. H., Devlin, B., Gibbs, R. A., Roeder, K., Schellenberg, G. D., Sutcliffe, J. S., and Daly, M. J. (2012). Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature* **485**, 242-245.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., and Gillberg, C. (2009). Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. *Res Dev Disabil* **30**, 763-773.

Noor, A., Whibley, A., Marshall, C. R., Gianakopoulos, P. J., Piton, A., Carson, A. R., Orlic-Milacic, M., Lionel, A. C., Sato, D., Pinto, D., Drmic, I., Noakes, C., Senman, L., Zhang, X., Mo, R., Gauthier, J., Crosbie, J., Pagnamenta, A. T., Munson, J., Estes, A. M., Fiebig, A., Franke, A., Schreiber, S., Stewart, A. F., Roberts, R., McPherson, R., Guter, S. J., Cook, E. H., Jr., Dawson, G., Schellenberg, G. D., Battaglia, A., Maestrini, E., Jeng, L., Hutchison, T., Rajcan-Separovic, E., Chudley, A. E., Lewis, S. M., Liu, X., Holden, J. J., Fernandez, B., Zwaigenbaum, L., Bryson, S. E., Roberts, W., Szatmari, P., Gallagher, L., Stratton, M. R., Gecz, J., Brady, A. F., Schwartz, C. E., Schachar, R. J., Monaco, A. P., Rouleau, G. A., Hui, C. C., Lucy Raymond, F., Scherer, S. W., and Vincent, J. B. (2010). Disruption at the PTCHD1 Locus on Xp22.11 in Autism Spectrum Disorder and Intellectual Disability. *Sci Transl Med* **2**, 49ra68.

Novara, F., Beri, S., Giorda, R., Ortibus, E., Nageshappa, S., Darra, F., Bernardina, B. D., Zuffardi, O., and Van Esch, H. (2010). Refining the phenotype associated with MEF2C haploinsufficiency. *Clin Genet* **78**, 471-477.

Numis, A. L., Major, P., Montenegro, M. A., Muzykewicz, D. A., Pulsifer, M. B., and Thiele, E. A. (2011). Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. *Neurology* **76**, 981-987.

Nystrom, A. M., Ekvall, S., Berglund, E., Bjorkqvist, M., Braathen, G., Duchen, K., Enell, H., Holmberg, E., Holmlund, U., Olsson-Engman, M., Anneren, G., and Bondeson, M. L. (2008). Noonan and cardio-facio-cutaneous syndromes: two clinically and genetically overlapping disorders. *J Med Genet* **45**, 500-506.

O'Roak, B. J., Deriziotis, P., Lee, C., Vives, L., Schwartz, J. J., Girirajan, S., Karakoc, E., Mackenzie, A. P., Ng, S. B., Baker, C., Rieder, M. J., Nickerson, D. A., Bernier, R., Fisher, S. E., Shendure, J., and Eichler, E. E. (2011). Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nat Genet* **43**, 585-589.

O'Roak, B. J., Vives, L., Girirajan, S., Karakoc, E., Krumm, N., Coe, B. P., Levy, R., Ko, A., Lee, C., Smith, J. D., Turner, E. H., Stanaway, I. B., Vernot, B., Malig, M., Baker, C., Reilly, B., Akey, J. M., Borenstein, E., Rieder, M. J., Nickerson, D. A., Bernier, R., Shendure, J., and Eichler, E. E. (2012). Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. *Nature* **485**, 246-250.

Oliveira, G., Ataide, A., Marques, C., Miguel, T. S., Coutinho, A. M., Mota-Vieira, L., Goncalves, E., Lopes, N. M., Rodrigues, V., Carmona da Mota, H., and Vicente, A. M. (2007). Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. *Dev Med Child Neurol* **49**, 726-733.

Oliver, C., Arron, K., Sloneem, J., and Hall, S. (2008). Behavioural phenotype of Cornelia de Lange syndrome: case-control study. *Br J Psychiatry* **193**, 466-470.

Ozonoff, S., Williams, B. J., Gale, S., and Miller, J. N. (1999). Autism and autistic behavior in Joubert syndrome. *J Child Neurol* **14**, 636-641.

Ozonoff, S., Young, G. S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., Bryson, S., Carver, L. J., Constantino, J. N., Dobkins, K., Hutman, T., Iverson, J. M., Landa, R., Rogers, S. J., Sigman, M., and Stone, W. L. (2011). Recurrence risk for autism spectrum disorders: a baby siblings research consortium study. *Pediatrics* **128**, e488-495.

Paciorkowski, A. R., Thio, L. L., and Dobyns, W. B. (2011). Genetic and biologic classification of infantile spasms. *Pediatr Neurol* **45**, 355-367.

Pagnamenta, A. T., Holt, R., Yusuf, M., Pinto, D., Wing, K., Betancur, C., Scherer, S. W., Volpi, E. V., and Monaco, A. P. (2011). A family with autism and rare copy number variants disrupting the Duchenne/Becker muscular dystrophy gene DMD and TRPM3. *J Neurodev Disord* **3**, 124-131.

Partington, M. W., Turner, G., Boyle, J., and Gecz, J. (2004). Three new families with X-linked mental retardation caused by the 428-451dup(24bp) mutation in ARX. *Clin Genet* **66**, 39-45.

Paul, M., and Allington-Smith, P. (1997). Asperger syndrome associated with Steinert's myotonic dystrophy. *Dev Med Child Neurol* **39**, 280-281.

Paylor, R., Glaser, B., Mupo, A., Ataliotis, P., Spencer, C., Sobotka, A., Sparks, C., Choi, C. H., Oghalai, J., Curran, S., Murphy, K. C., Monks, S., Williams, N., O'Donovan, M. C., Owen, M. J., Scambler, P. J., and Lindsay, E. (2006). Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proc Natl Acad Sci U S A* **103**, 7729-7734.

Pearl, P. L., Gibson, K. M., Acosta, M. T., Vezina, L. G., Theodore, W. H., Rogawski, M. A., Novotny, E. J., Gropman, A., Conry, J. A., Berry, G. T., and Tuchman, M. (2003). Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. *Neurology* **60**, 1413-1417.

Perrault, I., Delphin, N., Hanein, S., Gerber, S., Dufier, J. L., Roche, O., Defoort-Dhellemmes, S., Dollfus, H., Fazzi, E., Munnich, A., Kaplan, J., and Rozet, J. M. (2007). Spectrum of NPHP6/CEP290 mutations in Leber congenital amaurosis and delineation of the associated phenotype. *Hum Mutat* **28**, 416.

Petit, E., Herault, J., Raynaud, M., Cherpi, C., Perrot, A., Barthelemy, C., Lelord, G., and Muh, J. P. (1996). X chromosome and infantile autism. *Biol Psychiatry* **40**, 457-464.

Philippe, C., Amsallem, D., Francannet, C., Lambert, L., Saunier, A., Verneau, F., and Jonveaux, P. (2010). Phenotypic variability in Rett syndrome associated with FOXG1 mutations in females. *J Med Genet* **47**, 59-65.

Pierpont, E. I., Pierpont, M. E., Mendelsohn, N. J., Roberts, A. E., Tworog-Dube, E., and Seidenberg, M. S. (2009). Genotype differences in cognitive functioning in Noonan syndrome. *Genes Brain Behav* **8**, 275-282.

Pinto, D., Pagnamenta, A. T., Klei, L., Anney, R., Merico, D., Regan, R., Conroy, J., Magalhaes, T. R., Correia, C., Abrahams, B. S., Almeida, J., Bacchelli, E., Bader, G. D., Bailey, A. J., Baird, G., Battaglia, A., Berney, T., Bolshakova, N., Bolte, S., Bolton, P. F., Bourgeron, T., Brennan, S., Brian, J., Bryson, S. E., Carson, A. R., Casallo, G., Casey, J., Chung, B. H., Cochrane, L., Corsello, C., Crawford, E. L., Crossett, A., Cytrynbaum, C., Dawson, G., de Jonge, M., Delorme, R., Drmic, I., Duketis, E., Duque, F., Estes, A., Farrar, P., Fernandez, B. A., Folstein, S. E., Fombonne, E., Freitag, C. M., Gilbert, J., Gillberg, C., Glessner, J. T., Goldberg, J., Green, A., Green, J., Guter, S. J., Hakonarson, H., Heron, E. A., Hill, M., Holt, R., Howe, J. L., Hughes, G., Hus, V., Igliozzi, R., Kim, C., Klauck, S. M., Kolevzon, A., Korvatska, O., Kustanovich, V., Lajonchere, C. M., Lamb, J. A., Laskawiec, M., Leboyer, M., Le Couteur, A., Leventhal, B. L., Lionel, A. C., Liu, X. Q., Lord, C., Lotspeich, L., Lund, S. C., Maestrini, E., Mahoney, W., Mantoulan, C., Marshall, C. R., McConachie, H., McDougle, C. J., McGrath, J., McMahon, W. M., Merikangas, A., Migita, O., Minshew, N. J., Mirza, G. K., Munson, J., Nelson, S. F., Noakes, C., Noor, A., Nygren, G., Oliveira, G., Papanikolaou, K., Parr, J. R., Parrini, B., Paton, T., Pickles, A., Pilorge, M., Piven, J., Ponting, C. P., Posey, D. J., Poustka, A., Poustka, F., Prasad, A., Ragoussis, J., Renshaw, K., Rickaby, J., Roberts, W., Roeder, K., Roge, B., Rutter, M. L., Bierut, L. J., Rice, J. P., Salt, J., Sansom, K., Sato, D., Segurado, R., Sequeira, A. F., Senman, L., Shah, N., Sheffield, V. C., Soorya, L., Sousa, I., Stein, O., Sykes, N., Stoppioni, V., Strawbridge, C., Tancredi, R., Tansey, K., Thiruvahindrapduram, B., Thompson, A. P., Thomson, S., Tryfon, A., Tsiantis, J., Van Engeland, H., Vincent, J. B., Volkmar, F., Wallace, S., Wang, K., Wang, Z., Wassink, T. H., Webber, C., Weksberg, R., Wing, K., Wittemeyer, K., Wood, S., Wu, J., Yaspan, B. L., Zurawiecki, D., Zwaigenbaum, L., Buxbaum, J. D., Cantor, R. M., Cook, E. H., Coon, H., Cuccaro, M. L., Devlin, B., Ennis, S., Gallagher, L., Geschwind, D. H., Gill, M., Haines, J. L., Hallmayer, J., Miller, J., Monaco, A. P., Nurnberger, J. I., Jr., Paterson, A. D., Pericak-Vance, M. A., Schellenberg, G. D., Szatmari, P., Vicente, A. M., Vieland, V. J., Wijsman, E. M., Scherer, S. W., Sutcliffe, J. S., and Betancur, C. (2010). Functional impact of global rare copy number variation in autism spectrum disorders. *Nature* **466**, 368-372.

Piton, A., Michaud, J. L., Peng, H., Aradhya, S., Gauthier, J., Mottron, L., Champagne, N., Lafreniere, R. G., Hamdan, F. F., Joober, R., Fombonne, E., Marineau, C., Cossette, P., Dube, M. P., Haghighi, P., Drapeau, P., Barker, P. A., Carbonetto, S., and Rouleau, G. A. (2008). Mutations in the calcium-related gene IL1RAPL1 are associated with autism. *Hum Mol Genet* **17**, 3965-3974.

Pons, R., Andreu, A. L., Checcarelli, N., Vila, M. R., Engelstad, K., Sue, C. M., Shungu, D., Haggerty, R., de Vivo, D. C., and DiMauro, S. (2004). Mitochondrial DNA abnormalities and autistic spectrum disorders. *J Pediatr* **144**, 81-85.

Poo-Arguelles, P., Arias, A., Vilaseca, M. A., Ribes, A., Artuch, R., Sans-Fito, A., Moreno, A., Jakobs, C., and Salomons, G. (2006). X-Linked creatine transporter deficiency in two patients with severe mental retardation and autism. *J Inherit Metab Dis* **29**, 220-223.

Qiao, Y., Liu, X., Harvard, C., Hildebrand, M. J., Rajcan-Separovic, E., Holden, J. J., and Lewis, M. E. (2008). Autism-associated familial microdeletion of Xp11.22. *Clin Genet* **74**, 134-144.

Quintero-Rivera, F., Sharifi-Hannauer, P., and Martinez-Agosto, J. A. (2010). Autistic and psychiatric findings associated with the 3q29 microdeletion syndrome: case report and review. *Am J Med Genet A* **152A**, 2459-2467.

Rajcan-Separovic, E., Harvard, C., Liu, X., McGillivray, B., Hall, J. G., Qiao, Y., Hurlburt, J., Hildebrand, J., Mickelson, E. C., Holden, J. J., and Lewis, M. E. (2007). Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. *J Med Genet* **44**, 269-276.

Ramocki, M. B., Tavyev, Y. J., and Peters, S. U. (2010). The MECP2 duplication syndrome. *Am J Med Genet A* **152A**, 1079-1088.

Ropers, H. H. (2010). Genetics of early onset cognitive impairment. *Annu Rev Genomics Hum Genet* **11**, 161-187.

Rosenfeld, J. A., Coppinger, J., Bejjani, B. A., Girirajan, S., Eichler, E. E., Shaffer, L. G., and Ballif, B. C. (2010). Speech delays and behavioral problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications. *J Neurodev Disord* **2**, 26-38.

Russo, S., Marchi, M., Cogliati, F., Bonati, M. T., Pintaudi, M., Veneselli, E., Saletti, V., Balestrini, M., Ben-Zeev, B., and Larizza, L. (2009). Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. *Neurogenetics* **10**, 241-250.

Sahoo, T., Peters, S. U., Madduri, N. S., Glaze, D. G., German, J. R., Bird, L. M., Barbieri-Welge, R., Bichell, T. J., Beaudet, A. L., and Bacino, C. A. (2006). Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. *J Med Genet* **43**, 512-516.

Saillour, Y., Carion, N., Quelin, C., Leger, P. L., Boddaert, N., Elie, C., Toutain, A., Mercier, S., Barthez, M. A., Milh, M., Joriot, S., des Portes, V., Philip, N., Broglin, D., Roubertie, A., Pitelet, G., Moutard, M. L., Pinard, J. M., Cances, C., Kaminska, A., Chelly, J., Beldjord, C., and Bahi-Buisson, N. (2009). LIS1-related isolated lissencephaly: spectrum of mutations and relationships with malformation severity. *Arch Neurol* **66**, 1007-1015.

Samuels, I. S., Saitta, S. C., and Landreth, G. E. (2009). MAP'ing CNS development and cognition: an ERKsome process. *Neuron* **61**, 160-167.

Sanders, S. J., Ercan-Sencicek, A. G., Hus, V., Luo, R., Murtha, M. T., Moreno-De-Luca, D., Chu, S. H., Moreau, M. P., Gupta, A. R., Thomson, S. A., Mason, C. E., Bilguvar, K., Celestino-Soper, P. B., Choi, M., Crawford, E. L., Davis, L., Wright, N. R., Dhodapkar, R. M., DiCola, M., DiLullo, N. M., Fernandez, T. V., Fielding-Singh, V., Fishman, D. O., Frahm, S., Garagaloyan, R., Goh, G. S., Kammela, S., Klei, L., Lowe, J. K., Lund, S. C., McGrew, A. D., Meyer, K. A., Moffat, W. J., Murdoch, J. D., O'Roak, B. J., Ober, G. T., Pottenger, R. S., Raubeson, M. J., Song, Y., Wang, Q., Yaspan, B. L., Yu, T. W., Yurkiewicz, I. R., Beaudet, A. L., Cantor, R. M., Curland, M., Grice, D. E., Gunel, M., Lifton, R. P., Mane, S. M., Martin, D. M., Shaw, C. A., Sheldon, M., Tischfield, J. A., Walsh, C. A., Morrow, E. M., Ledbetter, D. H., Fombonne, E., Lord, C., Martin, C. L., Brooks, A. I., Sutcliffe, J. S., Cook, E. H., Jr., Geschwind, D., Roeder, K., Devlin, B., and State, M. W. (2011). Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. *Neuron* **70**, 863-885.

Sanders, S. J., Murtha, M. T., Gupta, A. R., Murdoch, J. D., Raubeson, M. J., Willsey, A. J., Ercan-Sencicek, A. G., Dilullo, N. M., Parikshak, N. N., Stein, J. L., Walker, M. F., Ober, G. T., Teran, N. A., Song, Y., El-Fishawy, P., Murtha, R. C., Choi, M., Overton, J. D., Bjornson, R. D., Carriero, N. J., Meyer, K. A., Bilguvar, K., Mane, S. M., Sestan, N., Lifton, R. P., Gunel, M., Roeder, K., Geschwind, D. H., Devlin, B., and State, M. W. (2012). De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* **485**, 237-241.

Santen, G. W., Aten, E., Sun, Y., Almomani, R., Gilissen, C., Nielsen, M., Kant, S. G., Snoeck, I. N., Peeters, E. A., Hilhorst-Hofstee, Y., Wessels, M. W., den Hollander, N. S., Ruivenkamp, C. A., van Ommen, G. J., Breuning, M. H., den Dunnen, J. T., van Haeringen, A., and Kriek, M. (2012). Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. *Nat Genet* **44**, 379-380.

Schaefer, G. B., and Lutz, R. E. (2006). Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. *Genet Med* **8**, 549-556.

Scheffer, I. E., Turner, S. J., Dibbens, L. M., Bayly, M. A., Friend, K., Hodgson, B., Burrows, L., Shaw, M., Wei, C., Ullmann, R., Ropers, H. H., Szepetowski, P., Haan, E., Mazarib, A., Afawi, Z., Neufeld, M. Y., Andrews, P. I., Wallace, G., Kivity, S., Lev, D., Lerman-Sagie, T., Derry, C. P., Korczyn, A. D., Gecz, J., Mulley, J. C., and Berkovic, S. F. (2008). Epilepsy and mental retardation limited to females: an under-recognized disorder. *Brain* **131**, 918-927.

Schorry, E. K., Keddache, M., Lanphear, N., Rubinstein, J. H., Srodulski, S., Fletcher, D., Blough-Pfau, R. I., and Grabowski, G. A. (2008). Genotype-phenotype correlations in Rubinstein-Taybi syndrome. *Am J Med Genet A* **146A**, 2512-2519.

Schwartz, C. E., Tarpey, P. S., Lubs, H. A., Verloes, A., May, M. M., Risheg, H., Friez, M. J., Futreal, P. A., Edkins, S., Teague, J., Briault, S., Skinner, C., Bauer-Carlin, A., Simensen, R. J., Joseph, S. M., Jones, J. R., Gecz, J., Stratton, M. R., Raymond, F. L., and Stevenson, R. E. (2007). The original Lujan syndrome family has a novel missense mutation (p.N1007S) in the MED12 gene. *J Med Genet* **44**, 472-477.

Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., Yamrom, B., Yoon, S., Krasnitz, A., Kendall, J., Leotta, A., Pai, D., Zhang, R., Lee, Y. H., Hicks, J., Spence, S. J., Lee, A. T., Puura, K., Lehtimaki, T., Ledbetter, D., Gregersen, P. K., Bregman, J., Sutcliffe, J. S., Jobanputra, V., Chung, W., Warburton, D., King, M. C., Skuse, D., Geschwind, D. H., Gilliam, T. C., Ye, K., and Wigler, M. (2007). Strong association of de novo copy number mutations with autism. *Science* **316**, 445-449.

Sempere, A., Fons, C., Arias, A., Rodriguez-Pombo, P., Colomer, R., Merinero, B., Alcaide, P., Capdevila, A., Ribes, A., Artuch, R., and Campistol, J. (2009a). Creatine transporter deficiency in two adult patients with static encephalopathy. *J Inherit Metab Dis* **Short report #158 Online**.

Sempere, A., Fons, C., Arias, A., Rodriguez-Pombo, P., Merinero, B., Alcaide, P., Capdevila, A., Ribes, A., Duque, R., Eiris, J., Poo, P., Fernandez-Alvarez, E., Campistol, J., and Artuch, R. (2009b). [Cerebral creatine deficiency: first Spanish patients harbouring mutations in GAMT gene]. *Med Clin (Barc)* **133**, 745-749.

Sharp, A. J., Mefford, H. C., Li, K., Baker, C., Skinner, C., Stevenson, R. E., Schroer, R. J., Novara, F., De Gregori, M., Ciccone, R., Broomer, A., Casuga, I., Wang, Y., Xiao, C., Barbacioru, C., Gimelli, G., Bernardina, B. D., Torniero, C., Giorda, R., Regan, R., Murday, V., Mansour, S., Fichera, M., Castiglia, L., Failla, P., Ventura, M., Jiang, Z., Cooper, G. M., Knight, S. J., Romano, C., Zuffardi, O., Chen, C., Schwartz, C. E., and Eichler, E. E. (2008). A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. *Nat Genet* **40**, 322-328.

Shinawi, M., Liu, P., Kang, S. H., Shen, J., Belmont, J. W., Scott, D. A., Probst, F. J., Craigen, W. J., Graham, B. H., Pursley, A., Clark, G., Lee, J., Proud, M., Stocco, A., Rodriguez, D. L., Kozel, B. A., Sparagana, S., Roeder, E. R., McGrew, S. G., Kurczynski, T. W., Allison, L. J., Amato, S., Savage, S., Patel, A., Stankiewicz, P., Beaudet, A. L., Cheung, S. W., and Lupski, J. R. (2010). Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. *J Med Genet* **47**, 332-341.

Shoubridge, C., Tarpey, P. S., Abidi, F., Ramsden, S. L., Rujirabanjerd, S., Murphy, J. A., Boyle, J., Shaw, M., Gardner, A., Proos, A., Puusepp, H., Raymond, F. L., Schwartz, C. E., Stevenson, R. E., Turner, G., Field, M., Walikonis, R. S., Harvey, R. J., Hackett, A., Futreal, P. A., Stratton, M. R., and Gecz, J. (2010). Mutations in the guanine nucleotide exchange factor gene IQSEC2 cause nonsyndromic intellectual disability. *Nat Genet* **42**, 486-488.

Sikora, D. M., Pettit-Kekel, K., Penfield, J., Merkens, L. S., and Steiner, R. D. (2006). The near universal presence of autism spectrum disorders in children with Smith-Lemli-Opitz syndrome. *Am J Med Genet A* **140**, 1511-1518.

Simonati, A., Boaretto, F., Vettori, A., Dabrilli, P., Criscuolo, L., Rizzuto, N., and Mostacciuolo, M. L. (2006). A novel missense mutation in the L1CAM gene in a boy with L1 disease. *Neurol Sci* **27**, 114-117.

Sousa, S. B., Abdul-Rahman, O. A., Bottani, A., Cormier-Daire, V., Fryer, A., Gillessen-Kaesbach, G., Horn, D., Josifova, D., Kuechler, A., Lees, M., MacDermot, K., Magee, A., Morice-Picard, F., Rosser, E., Sarkar, A., Shannon, N., Stolte-Dijkstra, I., Verloes, A., Wakeling, E., Wilson, L., and Hennekam, R. C. (2009). Nicolaides-Baraitser syndrome: Delineation of the phenotype. *Am J Med Genet A* **149A**, 1628-1640.

Spiegel, E. K., Colman, R. F., and Patterson, D. (2006). Adenylosuccinate lyase deficiency. *Mol Genet Metab* **89**, 19-31.

Splawski, I., Timothy, K. W., Sharpe, L. M., Decher, N., Kumar, P., Bloise, R., Napolitano, C., Schwartz, P. J., Joseph, R. M., Condouris, K., Tager-Flusberg, H., Priori, S. G., Sanguinetti, M. C., and Keating, M. T. (2004). Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* **119**, 19-31.

State, M. W. (2010). The genetics of child psychiatric disorders: focus on autism and Tourette syndrome. *Neuron* **68**, 254-269.

Steiner, C. E., Acosta, A. X., Guerreiro, M. M., and Marques-de-Faria, A. P. (2007). Genotype and natural history in unrelated individuals with phenylketonuria and autistic behavior. *Arq Neuropsiquiatr* **65**, 202-205.

Stettner, G. M., Shoukier, M., Hoger, C., Brockmann, K., and Auber, B. (2011). Familial intellectual disability and autistic behavior caused by a small FMR2 gene deletion. *Am J Med Genet A* **155A**, 2003-2007.

Stevenson, R. E., Bennett, C. W., Abidi, F., Kleefstra, T., Porteous, M., Simensen, R. J., Lubs, H. A., Hamel, B. C., and Schwartz, C. E. (2005). Renpenning syndrome comes into focus. *Am J Med Genet A* **134**, 415-421.

Strauss, K. A., Puffenberger, E. G., Huentelman, M. J., Gottlieb, S., Dobrin, S. E., Parod, J. M., Stephan, D. A., and Morton, D. H. (2006). Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med* **354**, 1370-1377.

Szatmari, P., Paterson, A. D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X. Q., Vincent, J. B., Skaug, J. L., Thompson, A. P., Senman, L., Feuk, L., Qian, C., Bryson, S. E., Jones, M. B., Marshall, C. R., Scherer, S. W., Vieland, V. J., Bartlett, C., Mangin, L. V., Goedken, R., Segre, A., Pericak-Vance, M. A., Cuccaro, M. L., Gilbert, J. R., Wright, H. H., Abramson, R. K., Betancur, C., Bourgeron, T., Gillberg, C., Leboyer, M., Buxbaum, J. D., Davis, K. L., Hollander, E., Silverman, J. M., Hallmayer, J., Lotspeich, L., Sutcliffe, J. S., Haines, J. L., Folstein, S. E., Piven, J., Wassink, T. H., Sheffield, V., Geschwind, D. H., Bucan, M., Brown, W. T., Cantor, R. M., Constantino, J. N., Gilliam, T. C., Herbert, M., Lajonchere, C., Ledbetter, D. H., Lese-Martin, C., Miller, J., Nelson, S., Samango-Sprouse, C. A., Spence, S., State, M., Tanzi, R. E., Coon, H., Dawson, G., Devlin, B., Estes, A., Flodman, P., Klei, L., McMahon, W. M., Minshew, N., Munson, J., Korvatska, E., Rodier, P. M., Schellenberg, G. D., Smith, M., Spence, M. A., Stodgell, C., Tepper, P. G., Wijsman, E. M., Yu, C. E., Roge, B., Mantoulan, C., Wittemeyer, K., Poustka, A., Felder, B., Klauck, S. M., Schuster, C., Poustka, F., Bolte, S., Feineis-Matthews, S., Herbrecht, E., Schmotzer, G., Tsiantis, J., Papanikolaou, K., Maestrini, E., Bacchelli, E., Blasi, F., Carone, S., Toma, C., Van Engeland, H., de Jonge, M., Kemner, C., Koop, F., Langemeijer, M., Hijmans, C., Staal, W. G., Baird, G., Bolton, P. F., Rutter, M. L., Weisblatt, E., Green, J., Aldred, C., Wilkinson, J. A., Pickles, A., Le Couteur, A., Berney, T., McConachie, H., Bailey, A. J., Francis, K., Honeyman, G., Hutchinson, A., Parr, J. R., Wallace, S., Monaco, A. P., Barnby, G., Kobayashi, K., Lamb, J. A., Sousa, I., Sykes, N., Cook, E. H., Guter, S. J., Leventhal, B. L., Salt, J., Lord, C., Corsello, C., Hus, V., Weeks, D. E., Volkmar, F., Tauber, M., Fombonne, E., Shih, A., and Meyer, K. J. (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet* **39**, 319-328.

Tabet, A. C., Pilorge, M., Delorme, R., Amsellem, F., Pinard, J. M., Leboyer, M., Verloes, A., Benzacken, B., and Betancur, C. (2012). Autism multiplex family with 16p11.2p12.2 microduplication syndrome in monozygotic twins and distal 16p11.2 deletion in their brother. *Eur J Hum Genet* **20**, 540-546.

Takahashi, T. N., Farmer, J. E., Deidrick, K. K., Hsu, B. S., Miles, J. H., and Maria, B. L. (2005). Joubert syndrome is not a cause of classical autism. *Am J Med Genet A* **132**, 347-351.

Talkowski, M. E., Mullegama, S. V., Rosenfeld, J. A., van Bon, B. W., Shen, Y., Repnikova, E. A., Gastier-Foster, J., Thrush, D. L., Kathiresan, S., Ruderfer, D. M., Chiang, C., Hanscom, C., Ernst, C., Lindgren, A. M., Morton, C. C., An, Y., Astbury, C., Brueton, L. A., Lichtenbelt, K. D., Ades, L. C., Fichera, M., Romano, C., Innis, J. W., Williams, C. A., Bartholomew, D., Van Allen, M. I., Parikh, A., Zhang, L., Wu, B. L., Pyatt, R. E., Schwartz, S., Shaffer, L. G., de Vries, B. B., Gusella, J. F., and Elsea, S. H. (2011). Assessment of 2q23.1 microdeletion syndrome implicates MBD5 as a single causal locus of intellectual disability, epilepsy, and autism spectrum disorder. *Am J Hum Genet* **89**, 551-563.

Tan, W. H., Baris, H. N., Burrows, P. E., Robson, C. D., Alomari, A. I., Mulliken, J. B., Fishman, S. J., and Irons, M. B. (2007). The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. *J Med Genet* **44**, 594-602.

Tartaglia, N., Davis, S., Hench, A., Nimishakavi, S., Beauregard, R., Reynolds, A., Fenton, L., Albrecht, L., Ross, J., Visootsak, J., Hansen, R., and Hagerman, R. (2008). A new look at XXYY syndrome: medical and psychological features. *Am J Med Genet A* **146A**, 1509-1522.

Tierney, E., Bukelis, I., Thompson, R. E., Ahmed, K., Aneja, A., Kratz, L., and Kelley, R. I. (2006). Abnormalities of cholesterol metabolism in autism spectrum disorders. *Am J Med Genet B Neuropsychiatr Genet* **141B**, 666-668.

Tonini, G., Bizzarri, C., Bonfanti, R., Vanelli, M., Cerutti, F., Faleschini, E., Meschi, F., Prisco, F., Ciacco, E., Cappa, M., Torelli, C., Cauvin, V., Tumini, S., Iafusco, D., and Barbetti, F. (2006). Sulfonylurea treatment outweighs insulin therapy in short-term metabolic control of patients with permanent neonatal diabetes mellitus due to activating mutations of the KCNJ11 (KIR6.2) gene. *Diabetologia* **49**, 2210-2213.

Tordjman, S., Anderson, G. M., Botbol, M., Toutain, A., Sarda, P., Carlier, M., Saugier-Veber, P., Baumann, C., Cohen, D., Lagneaux, C., Tabet, A. C., and Verloes, A. (2012). Autistic disorder in patients with Williams-Beuren syndrome: a reconsideration of the Williams-Beuren syndrome phenotype. *PLoS One* **7**, e30778.

Tory, K., Lacoste, T., Burglen, L., Moriniere, V., Boddaert, N., Macher, M. A., Llanas, B., Nivet, H., Bensman, A., Niaudet, P., Antignac, C., Salomon, R., and Saunier, S. (2007). High NPHP1 and NPHP6 mutation rate in patients with Joubert syndrome and nephronophthisis: potential epistatic effect of NPHP6 and AHI1 mutations in patients with NPHP1 mutations. *J Am Soc Nephrol* **18**, 1566-1575.

Treadwell-Deering, D. E., Powell, M. P., and Potocki, L. (2010). Cognitive and behavioral characterization of the Potocki-Lupski syndrome (duplication 17p11.2). *J Dev Behav Pediatr* **31**, 137-143.

Trillingsgaard, A., and Østergaard, J. (2004). Autism in Angelman syndrome: an exploration of comorbidity. *Autism* **8**, 163-174.

Turner, G., Partington, M., Kerr, B., Mangelsdorf, M., and Gecz, J. (2002). Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARX gene mutation. *Am J Med Genet* **112**, 405-411.

Ullmann, R., Turner, G., Kirchhoff, M., Chen, W., Tonge, B., Rosenberg, C., Field, M., Vianna-Morgante, A. M., Christie, L., Krepischi-Santos, A. C., Banna, L., Brereton, A. V., Hill, A., Bisgaard, A. M., Muller, I., Hultschig, C., Erdogan, F., Wieczorek, G., and Ropers, H. H. (2007). Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation. *Hum Mutat* **28**, 674-682.

van Bokhoven, H. (2011). Genetic and epigenetic networks in intellectual disabilities. *Annu Rev Genet* **45**, 81-104.

van Bokhoven, H., and Kramer, J. M. (2010). Disruption of the epigenetic code: an emerging mechanism in mental retardation. *Neurobiol Dis* **39**, 3-12.

van Bon, B. W., Mefford, H. C., Menten, B., Koolen, D. A., Sharp, A. J., Nillesen, W. M., Innis, J. W., de Ravel, T. J., Mercer, C. L., Fichera, M., Stewart, H., Connell, L. E., Ounap, K., Lachlan, K., Castle, B., Van der Aa, N., van Ravenswaaij, C., Nobrega, M. A., Serra-Juhe, C., Simonic, I., de Leeuw, N., Pfundt, R., Bongers, E. M., Baker, C., Finnemore, P., Huang, S., Maloney, V. K., Crolla, J. A., van Kalmthout, M., Elia, M., Vandeweyer, G., Fryns, J. P., Janssens, S., Foulds, N., Reitano, S., Smith, K., Parkel, S., Loeys, B., Woods, C. G., Oostra, A., Speleman, F., Pereira, A. C., Kurg, A., Willatt, L., Knight, S. J., Vermeesch, J. R., Romano, C., Barber, J. C., Mortier, G., Perez-Jurado, L. A., Kooy, F., Brunner, H. G., Eichler, E. E., Kleefstra, T., and de Vries, B. B. (2009). Further delineation of the 15q13 microdeletion and duplication syndromes: a clinical spectrum varying from non-pathogenic to a severe outcome. *J Med Genet* **46**, 511-523.

Van der Aa, N., Rooms, L., Vandeweyer, G., van den Ende, J., Reyniers, E., Fichera, M., Romano, C., Delle Chiaie, B., Mortier, G., Menten, B., Destree, A., Maystadt, I., Mannik, K., Kurg, A., Reimand, T., McMullan, D., Oley, C., Brueton, L., Bongers, E. M., van Bon, B. W., Pfund, R., Jacquemont, S., Ferrarini, A., Martinet, D., Schrander-Stumpel, C., Stegmann, A. P., Frints, S. G., de Vries, B. B., Ceulemans, B., and Kooy, R. F. (2009). Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. *Eur J Med Genet* **52**, 94-100.

Van Houdt, J. K., Nowakowska, B. A., Sousa, S. B., van Schaik, B. D., Seuntjens, E., Avonce, N., Sifrim, A., Abdul-Rahman, O. A., van den Boogaard, M. J., Bottani, A., Castori, M., Cormier-Daire, V., Deardorff, M. A., Filges, I., Fryer, A., Fryns, J. P., Gana, S., Garavelli, L., Gillessen-Kaesbach, G., Hall, B. D., Horn, D., Huylebroeck, D., Klapecki, J., Krajewska-Walasek, M., Kuechler, A., Lines, M. A., Maas, S., Macdermot, K. D., McKee, S., Magee, A., de Man, S. A., Moreau, Y., Morice-Picard, F., Obersztyn, E., Pilch, J., Rosser, E., Shannon, N., Stolte-Dijkstra, I., Van Dijck, P., Vilain, C., Vogels, A., Wakeling, E., Wieczorek, D., Wilson, L., Zuffardi, O., van Kampen, A. H., Devriendt, K., Hennekam, R., and Vermeesch, J. R. (2012). Heterozygous missense mutations in SMARCA2 cause Nicolaides-Baraitser syndrome. *Nat Genet* **44**, 445-449.

van Kuilenburg, A. B., Meijer, J., Mul, A. N., Hennekam, R. C., Hoovers, J. M., de Die-Smulders, C. E., Weber, P., Mori, A. C., Bierau, J., Fowler, B., Macke, K., Sass, J. O., Meinsma, R., Hennermann, J. B., Miny, P., Zoetekouw, L., Vijzelaar, R., Nicolai, J., Ylstra, B., and Rubio-Gozalbo, M. E. (2009). Analysis of severely affected patients with dihydropyrimidine dehydrogenase deficiency reveals large intragenic rearrangements of DPYD and a de novo interstitial deletion del(1)(p13.3p21.3). *Hum Genet* **125**, 581-590.

Van Kuilenburg, A. B., Vreken, P., Abeling, N. G., Bakker, H. D., Meinsma, R., Van Lenthe, H., De Abreu, R. A., Smeitink, J. A., Kayserili, H., Apak, M. Y., Christensen, E., Holopainen, I., Pulkki, K., Riva, D., Botteon, G., Holme, E., Tulinius, M., Kleijer, W. J., Beemer, F. A., Duran, M., Niezen-Koning, K. E., Smit, G. P., Jakobs, C., Smit, L. M., Moog, U., Spaapen, L. J., and Van Gennip, A. H. (1999). Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. *Hum Genet* **104**, 1-9.

van Rijn, S., Swaab, H., Aleman, A., and Kahn, R. S. (2008). Social behavior and autism traits in a sex chromosomal disorder: Klinefelter (47XXY) syndrome. *J Autism Dev Disord* **38**, 1634-1641.

Veltman, M. W., Craig, E. E., and Bolton, P. F. (2005). Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review. *Psychiatr Genet* **15**, 243-254.

Ververi, A., Vargiami, E., Papadopoulou, V., Tryfonas, D., and Zafeiriou, D. I. (2012). Clinical and laboratory data in a sample of Greek children with autism spectrum disorders. *J Autism Dev Disord* **42**, 1470-1476.

Vervoort, V. S., Beachem, M. A., Edwards, P. S., Ladd, S., Miller, K. E., de Mollerat, X., Clarkson, K., DuPont, B., Schwartz, C. E., Stevenson, R. E., Boyd, E., and Srivastava, A. K. (2002). AGTR2 mutations in X-linked mental retardation. *Science* **296**, 2401-2403.

Vorstman, J. A., Morcus, M. E., Duijff, S. N., Klaassen, P. W., Heineman-de Boer, J. A., Beemer, F. A., Swaab, H., Kahn, R. S., and van Engeland, H. (2006). The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. *J Am Acad Child Adolesc Psychiatry* **45**, 1104-1113.

Wada, T., and Gibbons, R. J. (2003). ATR-X syndrome. *In* "Genetics and Genomics of Neurobehavioral Disorders". Fisch G. S., Ed., p 309-334. Humana Press, Totowa, NJ.

Watanabe, Y., Yano, S., Niihori, T., Aoki, Y., Matsubara, Y., Yoshino, M., and Matsuishi, T. (2011). A familial case of LEOPARD syndrome associated with a high-functioning autism spectrum disorder. *Brain Dev* **33**, 576-579.

Weiss, L. A., Shen, Y., Korn, J. M., Arking, D. E., Miller, D. T., Fossdal, R., Saemundsen, E., Stefansson, H., Ferreira, M. A., Green, T., Platt, O. S., Ruderfer, D. M., Walsh, C. A., Altshuler, D., Chakravarti, A., Tanzi, R. E., Stefansson, K., Santangelo, S. L., Gusella, J. F., Sklar, P., Wu, B. L., and Daly, M. J. (2008). Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med* **358**, 667-675.

White, S. M., Morgan, A., Da Costa, A., Lacombe, D., Knight, S. J., Houlston, R., Whiteford, M. L., Newbury-Ecob, R. A., and Hurst, J. A. (2010). The phenotype of Floating-Harbor syndrome in 10 patients. *Am J Med Genet A* **152A**, 821-829.

Willatt, L., Cox, J., Barber, J., Cabanas, E. D., Collins, A., Donnai, D., FitzPatrick, D. R., Maher, E., Martin, H., Parnau, J., Pindar, L., Ramsay, J., Shaw-Smith, C., Sistermans, E. A., Tettenborn, M., Trump, D., de Vries, B. B., Walker, K., and Raymond, F. L. (2005). 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. *Am J Hum Genet* **77**, 154-160.

Williams, P. G., and Hersh, J. H. (1998). Brief report: the association of neurofibromatosis type 1 and autism. *J Autism Dev Disord* **28**, 567-571.

Wisniowiecka-Kowalnik, B., Nesteruk, M., Peters, S. U., Xia, Z., Cooper, M. L., Savage, S., Amato, R. S., Bader, P., Browning, M. F., Haun, C. L., Duda, A. W., 3rd, Cheung, S. W., and Stankiewicz, P. (2010). Intragenic rearrangements in NRXN1 in three families with autism spectrum disorder, developmental delay, and speech delay. *Am J Med Genet B Neuropsychiatr Genet* **153B**, 983-993.

Wolanczyk, T., Banaszkiewicz, A., Mierzewska, H., Czartoryska, B., and Zdziennicka, E. (2000). [Hyperactivity and behavioral disorders in Sanfilippo A (mucopolysaccharidosis type IIIA)--case report and review of the literature]. *Psychiatr Pol* **34**, 831-837.

Wu, J. Y., Kuban, K. C., Allred, E., Shapiro, F., and Darras, B. T. (2005). Association of Duchenne muscular dystrophy with autism spectrum disorder. *J Child Neurol* **20**, 790-795.

Wu, Y., Arai, A. C., Rumbaugh, G., Srivastava, A. K., Turner, G., Hayashi, T., Suzuki, E., Jiang, Y., Zhang, L., Rodriguez, J., Boyle, J., Tarpey, P., Raymond, F. L., Nevelsteen, J., Froyen, G., Stratton, M., Futreal, A., Gecz, J., Stevenson, R., Schwartz, C. E., Valle, D., Huganir, R. L., and Wang, T. (2007). Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. *Proc Natl Acad Sci U S A* **104**, 18163-18168.

Xu, S., Han, J. C., Morales, A., Menzie, C. M., Williams, K., and Fan, Y. S. (2008). Characterization of 11p14-p12 deletion in WAGR syndrome by array CGH for identifying genes contributing to mental retardation and autism. *Cytogenet Genome Res* **122**, 181-187.

Young, H. K., Barton, B. A., Waisbren, S., Portales Dale, L., Ryan, M. M., Webster, R. I., and North, K. N. (2008). Cognitive and psychological profile of males with Becker muscular dystrophy. *J Child Neurol* **23**, 155-162.

Yzer, S., van den Born, L. I., Schuil, J., Kroes, H. Y., van Genderen, M. M., Boonstra, F. N., van den Helm, B., Brunner, H. G., Koenekoop, R. K., and Cremers, F. P. (2003). A Tyr368His RPE65 founder mutation is associated with variable expression and progression of early onset retinal dystrophy in 10 families of a genetically isolated population. *J Med Genet* **40**, 709-713.

Zaffanello, M., Zamboni, G., Fontana, E., Zoccante, L., and Tato, L. (2003). A case of partial biotinidase deficiency associated with autism. *Child Neuropsychol* **9**, 184-188.

Zweier, C., de Jong, E. K., Zweier, M., Orrico, A., Ousager, L. B., Collins, A. L., Bijlsma, E. K., Oortveld, M. A., Ekici, A. B., Reis, A., Schenck, A., and Rauch, A. (2009). CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. *Am J Hum Genet* **85**, 655-666.

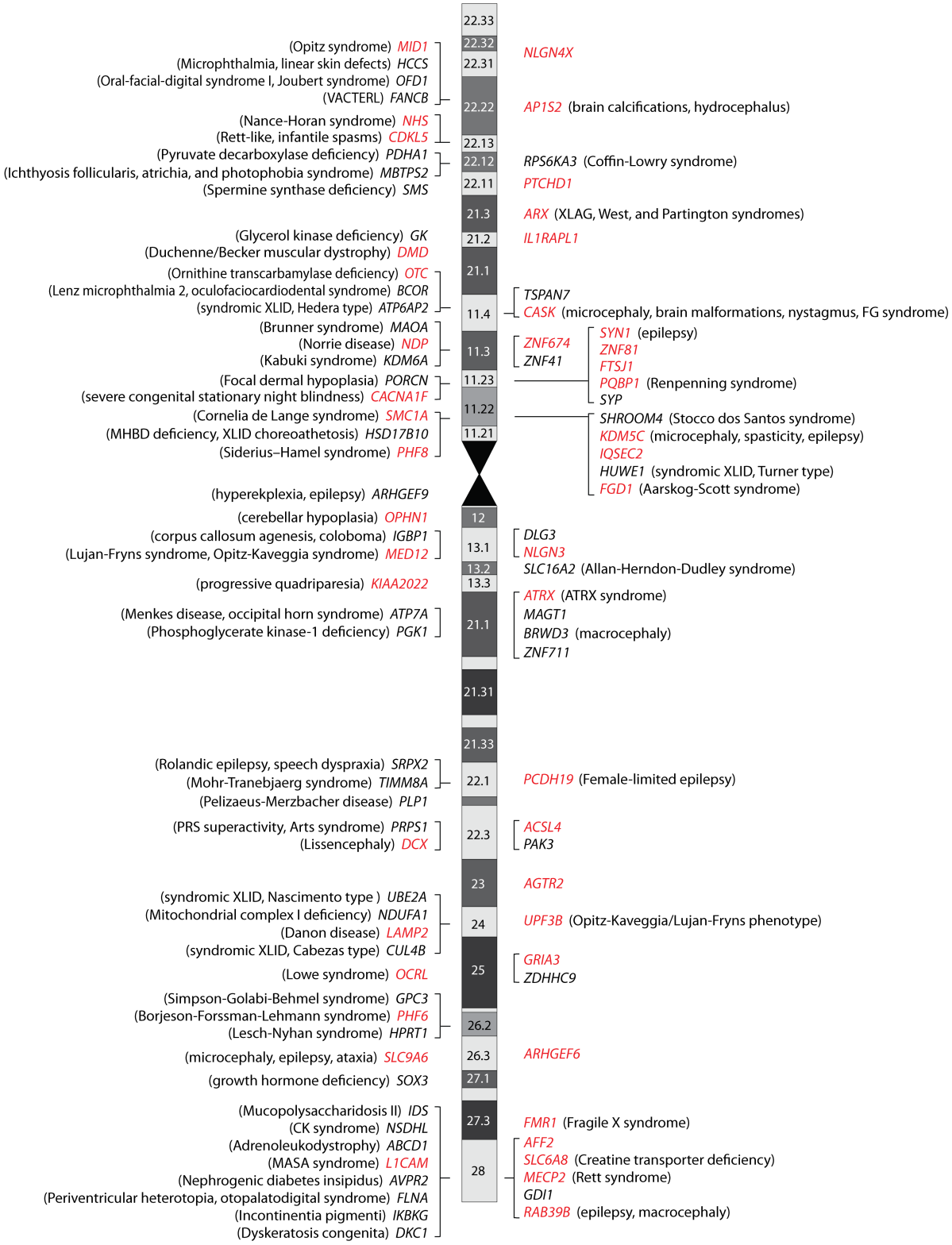


Figure 1. Genes implicated in syndromic and/or nonsyndromic forms of X-linked intellectual disability (XLID) and their localization on the X chromosome. Genes reported to be mutated in ASD are highlighted in red. Genes that cause syndromic forms of XLID are shown on the left; those that can cause nonsyndromic forms are on the right. The distinction between syndromic and nonsyndromic genes is not always clear-cut, and several genes on the right have been involved in syndromic as well as nonsyndromic XLID; the syndromic presentation is indicated in parentheses. Abbreviations: ATRX (alpha thalassemia, mental retardation syndrome, X-linked) syndrome; MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome; MHBD (2-methyl-3-hydroxybutyryl-CoA dehydrogenase) deficiency; PRS (phosphoribosylpyrophosphate synthetase) superactivity; VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies); XLAG (X-linked lissencephaly and abnormal genitalia) syndrome. *This figure is an updated version of the one originally published in Betancur (2011), Copyright 2011, with permission from Elsevier.*

Table 1. Genetic disorders strongly associated with ASD

Disorder (prevalence)[a]	Gene (locus); inheritance	Mutations	Prevalence in ASD	Proportion with ASD	Clinical features	Selected references[b]
Fragile X syndrome (1:4,000 males; 1:6,000 females)	*FMR1* (Xq27.3); X-linked	Trinucleotide repeat expansion	~2%	~60% males and ~20% females with the full mutation have ASD. Among premutation carriers, 15% males and 5% females have ASD	ID, ASD, ADHD, characteristic facial appearance, macroorchidism. Females are generally less affected than males.	(Clifford *et al.*, 2007; Hagerman *et al.*, 2010; Kielinen *et al.*, 2004)
22q13 deletion syndrome/Phelan-McDermid syndrome (>800 cases diagnosed)	*SHANK3* (22q13.33); dominant	22q13 deletion, mutation	~0.5%	55% (6/11) individuals with 22q13 deletions had autistic behavior; among subjects with ring chromosome 22 including a 22q13 deletion, 44% (12/27) had a clinical diagnosis of ASD and 85% (23/27) had autistic traits	ID, absent or severely delayed speech, autistic behavior, seizures, hypotonia, decreased sensitivity to pain, mouthing/chewing, dysplastic toenails	(Durand *et al.*, 2007; Jeffries *et al.*, 2005; Manning *et al.*, 2004)
Rett syndrome (1:8,500 females); *MECP2* duplication syndrome (~1% in males with ID)	*MECP2* (Xq28); X-linked	Mutation, deletion, duplication	~1% in females, rare in males	ASD/autistic features are frequent in girls with Rett syndrome; 76% (13/17) males with *MECP2* duplication have autism/autistic features	*MECP2* mutations or deletions cause Rett syndrome in females (severe ID and speech impairment, loss of purposeful hand use, ataxia, hyperventilation), and are often fatal in males; *MECP2* duplication syndrome occurs mostly in males	(Carney *et al.*, 2003; Ramocki *et al.*, 2010)
15q11-q13 duplication syndrome (1:20,000-30,000)	*UBE3A* (15q11.2); dominant; imprinted	Interstitial duplication or isodicentric chromosome 15, usually of maternal origin	~1%	81% (44/54) with isodicentric chromosome 15 met criteria for autism and 92% (50/54) for ASD	ID, language impairment, seizures, mild dysmorphism, infantile hypotonia. Maternally derived duplications confer a high risk of ASD, whereas duplications of paternal origin usually remain phenotypically silent but can lead to ASD/ID	(Depienne *et al.*, 2009; Hogart *et al.*, 2010)
Angelman syndrome (1:12,000-20,000)	*UBE3A* (15q11.2); dominant; imprinted	Maternal 15q11-q13 deletion, paternal uniparental disomy, mutation, imprinting defect	Rare	63% (38/60) ASD (range 50%-81%)	ID, lack of speech, inappropriate laughter, seizures, microcephaly, ataxia	(Sahoo *et al.*, 2006; Trillingsgaard and Østergaard, 2004)
Prader-Willi syndrome (1:10,000-25,000)	HBII-85 snoRNA cluster (15q11.2); dominant; imprinted	Paternal 15q11-q13 deletion, maternal uniparental disomy, imprinting defect	Rare	23% (49/209) ASD (range 19%-25%)	ID, obsessive compulsive behavior, skin picking, psychosis, hypotonia, obesity, hypogonadism, short stature	(Descheemaeker *et al.*, 2006; Veltman *et al.*, 2005)
Smith-Magenis syndrome (1:15,000)	*RAI1* (17p11.2); dominant	17p11.2 deletion, mutation	Rare	90% (18/20) ASD	ID, hyperactivity, sleep disorder, seizures, self-mutilation, hoarse voice, brachydactyly, hypotonia	(Laje *et al.*, 2010)
Potocki-Lupski syndrome (1:20,000)	*RAI1* (17p11.2); dominant	17p11.2 duplication	Rare	Autistic features are present in the majority; 67% (10/15) meet criteria for ASD	ID, ASD, ADHD, infantile hypotonia, failure to thrive, sleep apnea, cardiovascular abnormalities	(Treadwell-Deering *et al.*, 2010)
Tuberous sclerosis (1:5,800)	*TSC1* (9q34.13), *TSC2* (16p13.3); dominant	Mutation, deletion	~1%	40% ASD (20%-60%)	ID, non-malignant tumors in the brain, kidneys, heart, eyes, lungs, and skin, seizures	(Numis *et al.*, 2011)
Adenylosuccinate lyase deficiency (<100 cases reported)	*ADSL* (22q13.1); recessive	Mutation	Extremely rare	~50% autism/autistic features	Disorder of purine metabolism characterized by ID, epilepsy and autistic features	(Spiegel *et al.*, 2006)
Smith-Lemli-Opitz syndrome (1:20,000-40,000)	*DHCR7* (11q13.4); recessive	Mutation	Rare	53% (9/17) autism, 71% (10/14) ASD	Inborn error of metabolism affecting cholesterol biosynthesis characterized by growth retardation, microcephaly, ID, and multiple malformations of variable severity	(Sikora *et al.*, 2006; Tierney *et al.*, 2006)
CHARGE syndrome (1:10,000)	*CHD7* (8q12.2); dominant	Mutation, deletion (rare)	Rare	68% (17/25) ASD/autistic traits (including 48% with ASD)	ID, coloboma, heart anomaly, choanal atresia, genital and ear anomalies	(Johansson *et al.*, 2006)
Timothy syndrome (<20 individuals reported)	*CACNA1C* (12p13.33); dominant	Mutation	Extremely rare	80% (4/5) ASD	ID, ASD, cardiac abnormalities (long QT syndrome, malformations), hand/foot syndactyly, facial dysmorphism, seizures	(Splawski *et al.*, 2004)
Cortical dysplasia-focal epilepsy syndrome (10 individuals reported)	*CNTNAP2* (7q35); recessive	Mutation	Extremely rare	67% (6/9) autism or ASD	Severe intractable seizures, ID, ASD, and focal brain malformations in Amish children	(Strauss *et al.*, 2006)
Brain creatine transporter deficiency syndrome (>150 individuals diagnosed; 45 families reported)	*SLC6A8* (Xq28); X-linked	Mutation	Very rare	Frequent ASD/autistic features	Inborn error of creatine metabolism characterized by ID, speech delay, autistic behavior and seizures	(Longo *et al.*, 2011)
2q23.1 microdeletion syndrome (65 individuals reported)	*MBD5 (*2q23.1); dominant	2q23.1 deletion	0.17% (7/4061)	100% (65/65) subjects with deletions or translocations involving *MBD5* had autistic features	Angelman-like phenotype including ID, severe speech impairment, seizures, behavioral problems, microcephaly, mild dysmorphism, short stature, ataxic gait	(Talkowski *et al.*, 2011)
8p23.1 deletion syndrome (1:10,000-30,000)	? (8p23.1); dominant	8p23.1 deletion	Rare	57% (4/7) autism	Congenital heart defects, congenital diaphragmatic hernia, mild facial dysmorphism, ID, hyperactivity	(Fisch *et al.*, 2010)
Cohen syndrome (500-1000 individuals diagnosed)	*VPS13B* (8q22.2); recessive	Mutation, deletion	Very rare	49% (22/45) autism	ID, typical facial dysmorphism, retinal dystrophy, neutropenia, obesity, microcephaly	(Howlin *et al.*, 2005)
Cornelia de Lange syndrome (1:50,000)	*NIPBL* (5p13.2), dominant; *SMC1A* (Xp11.22), X-linked	Mutation, deletion (rare)	Very rare	47%-67% autism	ID, facial dysmorphism, upper limb malformations, growth retardation	(Bhuiyan *et al.*, 2006; Moss *et al.*, 2008; Oliver *et al.*, 2008)

Disorder (prevalence)[a]	Gene (locus); inheritance	Mutations	Prevalence in ASD	Proportion with ASD	Clinical features	Selected references[b]
Myotonic dystrophy 1/Steinert disease (1:20,000)	*DMPK* (19q13.32); dominant	Trinucleotide repeat expansion	Unknown	49% (28/57) ASD (including 35% with autism)	Muscle weakness, myotonia (sustained muscle contraction), cataract, cardiac arrhythmia, variable degrees of ID	(Ekstrom *et al.*, 2008)
Williams-Beuren syndrome (1:7,500-20,000)	Contiguous gene syndrome (7q11.23); dominant	7q11.23 deletion	Rare	50% (15/30) ASD	ID, ADHD, characteristic neurobehavioral profile (poor visuospatial skills and strengths in selected language skills), aortic stenosis, distinctive facial features, connective tissue abnormalities, endocrine abnormalities	(Klein-Tasman *et al.*, 2009; Tordjman *et al.*, 2012)
7q11.23 duplication (unknown)	Contiguous gene syndrome (7q11.23); dominant	7q11.23 duplication	Rare	40% (11/27) autism	ID, speech delay, expressive language impairment, ASD, ADHD, seizures, mild dysmorphic features, congenital heart defects, brain MRI abnormalities	(Depienne *et al.*, 2007; Van der Aa *et al.*, 2009)
WAGR syndrome (1:100,000)	Contiguous gene syndrome (11p13); dominant	11p13 deletion	Very rare	52% (16/31) ASD (including 14 with autism)	ID, Wilms tumor, aniridia, genitourinary anomalies	(Xu *et al.*, 2008)
16p11.2 microdeletion (1:3,500-5,000)	Contiguous gene syndrome (16p11.2); dominant	16p11.2 deletion	~0.5%	33% (7/21) ASD; 19% (3/16) autism	ID, ASD, language impairment, behavioral problems, epilepsy, dysmorphism, macrocephaly, congenital abnormalities, obesity	(Hanson *et al.*, 2010; Shinawi *et al.*, 2010; Weiss *et al.*, 2008)
16p11.2 microduplication (1:3,500-5,000)	Contiguous gene syndrome (16p11.2); dominant	16p11.2 duplication	~0.5%	20% (2/10) autistic features; several cases reported with autism/ASD	ID, ASD, SCZ, ADHD, speech delay, epilepsy, dysmorphism, microcephaly, congenital abnormalities, underweight	(Shinawi *et al.*, 2010; Weiss *et al.*, 2008)
22q11 deletion syndrome/DiGeorge syndrome /velocardiofacial syndrome (1:4,000-6,000)	*TBX1* + other(s) (22q11.21); dominant	22q11.2 deletion, mutation	Rare	28% (84/299) ASD (range 14%-50%)	ID, ASD, OCD, ADHD, SCZ, speech delay, epilepsy, facial abnormalities, velopharyngeal insufficiency, cleft palate, heart defects, renal anomalies, immune deficiency, hypocalcemia	(Antshel *et al.*, 2007; Fine *et al.*, 2005; Niklasson *et al.*, 2009; Vorstman *et al.*, 2006)
Joubert syndrome (1:100,000)	*AHI1* (6q23.3), *NPHP1* (2q13), *CEP290* (12q21.32), *RPGRIP1L* (16q12.2); recessive	Mutation, deletion	Very rare	13%-36% ASD	ID, distinctive cerebellar and brainstem malformation (molar tooth sign on MRI), ataxia, breathing abnormalities, some times retinal dystrophy and renal disease. Only 4 of 16 genes implicated in Joubert syndrome so far have been reported to be mutated in subjects with ASD	(Ozonoff *et al.*, 1999; Takahashi *et al.*, 2005)
Female-limited epilepsy and ID (unknown)	*PCDH19* (Xq22.1); X-linked	Mutation, deletion	Rare	30% (12/40) autistic features/ASD	Unique pattern of X-linked inheritance with male sparing; early infantile epileptic encephalopathy, variable ID	(Dibbens *et al.*, 2008; Marini *et al.*, 2010; Scheffer *et al.*, 2008)
2q37 deletion syndrome (estimated at 1:12,000)	*HDAC4* + other(s) (2q37); dominant	2q37 deletion	Rare	24% (16/66) autistic behavior; in a smaller study, 63% (5/8) had autism	Mild-moderate ID, brachydactyly, characteristic facial appearance, short stature, obesity, hypotonia, ASD, and seizures. Haploinsufficiency of *HDAC4* causes the core manifestations, including brachydactyly and ID, but other genes yet to be identified contribute to the phenotype in individuals with terminal deletions distal to *HDAC4*	(Devillard *et al.*, 2010; Falk and Casas, 2007; Fisch *et al.*, 2010)
Cri du Chat syndrome/5p deletion syndrome (1:15,000-50,000)	? (candidates *SEMAF*, *CTNND2*) (5p15.2-p15.33); dominant	5p deletion	Rare	39% (9/23) ASD	ID, high-pitched cat-like cry, microcephaly, dysmorphic facial features	(Moss *et al.*, 2008)
9q subtelomeric deletion syndrome/Kleefstra syndrome (unknown)	*EHMT1* (9q34.3); dominant	9q deletion, mutation	Rare	23% (5/22) ASD/autistic features	ID, childhood hypotonia, distinctive facial features, severe speech impairment, seizures, congenital defects	(Kleefstra *et al.*, 2009)
PTEN related syndromes (unknown, likely underdiagnosed)	*PTEN* (10q23.31); dominant	Mutation, deletion	7% among 99 individuals with ASD and macrocephaly tested clinically for *PTEN* mutations	15% (4/26) ASD	Marked macrocephaly, ASD, ID. The penetrance of other manifestations of *PTEN* hamartoma-tumor syndrome (Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome) increases with age and includes benign and malignant tumors and mucocutaneous lesions	(McBride *et al.*, 2010; Tan *et al.*, 2007)
Klinefelter syndrome (XXY) (1:500-1,000 males)	Many	Extra X chromosome	~0.5%	48% (15/31) had significant autism traits; in 2 studies, 11% (2/19) and 27% (14/51) met criteria for ASD	Tall stature, hypogonadism, infertility, ID, speech impairments	(Bishop *et al.*, 2011; Bruining *et al.*, 2009; Kielinen *et al.*, 2004; van Rijn *et al.*, 2008)
XYY syndrome (1:1,000 males)	Many	Extra Y chromosome	~0.5%	19% (11/58) ASD	Tall stature, hypogonadism, infertility, language impairment	(Bishop *et al.*, 2011; Kielinen *et al.*, 2004)
XXYY syndrome (1:18,000-40,000 males)	Many	Extra X and Y chromosomes	Rare	28% (26/92) ASD (6 autism, 20 PDD-NOS)	Tall stature, hypogonadism, infertility, learning disabilities, ID, ADHD	(Tartaglia *et al.*, 2008)
Down syndrome (1:800)	Many	Trisomy 21	3% (1.7-3.7%) in epidemiological studies; considerably less (<0.5%) in clinical or research samples	15% ASD (5% autism and 10% PDD-NOS)	ID, facial dysmorphism, hypotonia, joint laxity, short stature, heart defects	(Fombonne *et al.*, 1997; Kielinen *et al.*, 2004; Lowenthal *et al.*, 2007; Oliveira *et al.*, 2007)

[a] The prevalence of many of these disorders is likely underestimated, due to lack of systematic surveillance and because individuals with atypical, milder features are not diagnosed. [b] Additional references implicating these disorders in ASD can be found in (Betancur, 2011). Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ID, intellectual disability; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PDD-NOS, pervasive developmental disorder not otherwise specified; SCZ, schizophrenia.

Table 2. Novel microdeletion and microduplication syndromes reported in individuals with ASD and other neurodevelopmental disorders

Disorder	Cytoband	Position (Mb)[a]	Comment	References reporting ASD
1q21.1 microdeletion/ microduplication syndrome	1q21.1	146.5-147.7	Neurodevelopmental disorders (ID, learning disability, ASD, schizophrenia, ADHD, epilepsy), dysmorphic features, congenital abnormalities, microcephaly (deletions) or macrocephaly (duplications). Both deletions and duplications exhibit incomplete penetrance (reported in unaffected parents and controls)	(Brunetti-Pierri *et al.*, 2008; Mefford *et al.*, 2008; Pinto *et al.*, 2010; Szatmari *et al.*, 2007)
2p15-p16.1 microdeletion syndrome	2p15-p16.1	57.7-61.7	ID, growth retardation, microcephaly, dysmorphic features, congenital abnormalities; 4 of 6 subjects reported with the microdeletion have ASD/autistic behavior	(Liang *et al.*, 2009; Rajcan-Separovic *et al.*, 2007)
3q29 microdeletion/ microduplication syndrome	3q29	195.7-197.5	3q29 deletions are associated with reduced head size, mild dysmorphic features, multiple congenital anomalies and have been reported in patients with ID, ASD (including one with Asperger syndrome and another one with autism and normal IQ) and schizophrenia. No microduplications have been described thus far in ASD	(Ballif *et al.*, 2008; Quintero-Rivera *et al.*, 2010; Willatt *et al.*, 2005)
10q22-q23 deletion	10q22.3-q23.2	81.7-88.9	Recurrent 10q22-q23 deletions of varying sizes have been associated with cognitive and behavioral abnormalities including ASD and hyperactivity	(Alliman *et al.*, 2010; Balciuniene *et al.*, 2007)
15q13.3 microdeletion syndrome/15q13.3 microduplication	15q13.2-q13.3	30.8-32.7	Microdeletion syndrome associated with highly variable phenotype and incomplete penetrance, including ID, seizures, subtle facial dysmorphism and neuropsychiatric disorders; 44% (15/34) have ASD. Males are more likely to be symptomatic. Reciprocal duplications have been reported in association with ID, ASD and ADHD, as well as in controls and unaffected parents, and their clinical significance is uncertain at present. The CNVs span *CHRNA7*, a candidate gene for epilepsy.	(Ben-Shachar *et al.*, 2009; Miller *et al.*, 2009; Pinto *et al.*, 2010; Sharp *et al.*, 2008; van Bon *et al.*, 2009)
15q24 microdeletion syndrome	15q24.1-q24.2	74.4-76.2	Microdeletion syndrome characterized by ID, typical facial characteristics, and mild hand and genital anomalies. 23% (8/35) of reported cases have ASD	(Marshall *et al.*, 2008; McInnes *et al.*, 2010; Mefford *et al.*, 2012)
16p13.11 microdeletion/ microduplication	16p13.11	15.5-16.3	Recurrent 16p13.11 microdeletions are associated with a variable phenotype and incomplete penetrance, and have been reported in subjects with ID, ASD, congenital anomalies, epilepsy and schizophrenia, sometimes inherited from unaffected parents. Duplications have been reported in ID, autism, schizophrenia and in controls, and their clinical significance is unclear at present	(Pinto *et al.*, 2010; Ullmann *et al.*, 2007)
16p11.2-p12.2 microdeletion/ microduplication syndrome	16p11.2-p12.2	21.6-29.0	Newly recognized microdeletion syndrome; 6 deletions reported in subjects with ID, severe language impairment and distinct dysmorphic features (without ASD); 5 reciprocal duplications described, the only feature shared by all patients is ASD	(Tabet *et al.*, 2012)
16p11.2 microdeletion/ microduplication syndrome	16p11.2	29.5-30.2	16p11.2 microdeletions/microduplications have been reported in ASD, ID, schizophrenia, epilepsy, ADHD and in healthy subjects; both types are associated with incomplete penetrance and variable expressivity, particularly in the case of duplications. Deletions are associated with obesity and duplications with being underweight	(Hanson *et al.*, 2010; Rosenfeld *et al.*, 2010; Shinawi *et al.*, 2010; Weiss *et al.*, 2008)
17p13.3 microdeletion (Miller-Dieker syndrome, isolated lissencephaly), 17p13.3 microduplication	17p13.3	1-2.5	17p13.3 deletions encompassing *PAFAH1B1* cause isolated lissencephaly; larger deletions including *YWHAE* cause Miller-Dieker syndrome, characterized by severe lissencephaly and additional dysmorphic features and malformations. Microduplications of the Miller-Dieker region as well as smaller duplications affecting *PAFAH1B1* or *YWHAE* have been described recently, including in ASD	(Bi *et al.*, 2009; Bruno *et al.*, 2010)
17q12 deletion/duplication syndrome	17q12	34.8-36.2	17q12 deletions encompassing the *HNF1B* gene cause renal cysts and diabetes syndrome, with ID, ASD, schizophrenia, seizures, and brain abnormalities; the reciprocal duplications are associated with ID and epilepsy, and are less penetrant than deletions. The gene responsible for the neuropsychiatric phenotypes is unknown	(Moreno-De-Luca *et al.*, 2010)
17q21.31 microdeletion/ microduplication syndrome	17q21.31	43.6-44.2	The 17q21.3 microdeletion syndrome is characterized by ID, hypotonia and facial dysmorphism; only 2 cases with ASD have been identified. 17q21.31 microduplications have been reported in several ASD cases. *KANSL1* was recently identified as the causative gene	(Cooper *et al.*, 2011; Grisart *et al.*, 2009)
Xq28 duplication syndrome (*MECP2* duplication syndrome)	Xq28	152.7-153.4	The Xq28 duplication syndrome is caused by the duplication of *MECP2*; it is mostly reported in males (females are protected by X inactivation) and is often associated with ASD or autistic features	(Ramocki *et al.*, 2010)

[a] Human reference genome hg19, NCBI 37 (February 2009).

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ID, intellectual disability.

Table 3. Disease genes and genetic disorders reported in individuals with ASD: examples of clinical and etiological subgroups

Gene	Gene name	Cytoband	Disorder	Inheritance pattern	References reporting ASD
Early-onset epilepsy					
SCN1A	sodium channel, voltage-gated, type I, alpha subunit	2q24.3	Severe myoclonic epilepsy of infancy (Dravet syndrome)	Dominant	(Marini *et al.*, 2009; O'Roak *et al.*, 2011)
SCN2A	sodium channel, voltage-gated, type II, alpha subunit	2q24.3	Early infantile epileptic encephalopathy; benign familial infantile seizures	Dominant	(Neale *et al.*, 2012; Sanders *et al.*, 2012)
MEF2C	myocyte enhancer factor 2C	5q14.3	5q14.3 microdeletion syndrome	Dominant	(Novara *et al.*, 2010)
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	5q23.2	Pyridoxine-dependent epilepsy	Recessive	(Burd *et al.*, 2000; Mills *et al.*, 2010)
CNTNAP2	contactin associated protein-like 2	7q35-q36.1	Cortical dysplasia-focal epilepsy syndrome; Pitt-Hopkins-like syndrome-1	Recessive	(Strauss *et al.*, 2006; Zweier *et al.*, 2009)
STXBP1	syntaxin binding protein 1	9q34.11	Early infantile epileptic encephalopathy	Dominant	(Milh *et al.*, 2011; Neale *et al.*, 2012)
FOXG1	forkhead box G1	14q12	Congenital variant of Rett syndrome	Dominant	(Brunetti-Pierri *et al.*, 2011; Philippe *et al.*, 2010)
PAFAH1B1	platelet-activating factor acetylhydrolase 1b, regulatory subunit 1	17p13.3	Isolated lissencephaly	Dominant	(Saillour *et al.*, 2009)
CDKL5	cyclin-dependent kinase-like 5	Xp22.13	Early infantile epileptic encephalopathy	X linked	(Archer *et al.*, 2006; Russo *et al.*, 2009)
ARX	aristaless related homeobox	Xp21.3	Early infantile epileptic encephalopathy; brain malformations with abnormal genitalia; nonsyndromic ID	X linked	(Partington *et al.*, 2004; Turner *et al.*, 2002)
SYN1	synapsin I	Xp11.23	X-linked epilepsy with variable learning disabilities and behavior disorders	X linked	(Fassio *et al.*, 2011; Garcia *et al.*, 2004)
PCDH19	protocadherin 19	Xq22.1	X-linked female-limited epilepsy and cognitive impairment; early infantile epileptic encephalopathy	X linked	(Hynes *et al.*, 2010; Marini *et al.*, 2010)
DCX	doublecortin	Xq22.3	X-linked lissencephaly	X linked	(Leger *et al.*, 2008)
SLC9A6	solute carrier family 9 (sodium/hydrogen exchanger), member 6	Xq26.3	Syndromic X-linked ID, Christianson type (ID, microcephaly, epilepsy, and ataxia)	X linked	(Garbern *et al.*, 2010)
RAB39B	RAB39B, member RAS oncogene family	Xq28	X-linked ID associated with autism, epilepsy, and macrocephaly	X linked	(Giannandrea *et al.*, 2010)
Metabolic disorders					
Disorders of purine and pyrimidine metabolism					
ADSL	adenylosuccinate lyase	22q13.1	Adenylosuccinate lyase deficiency (purine synthesis disorder)	Recessive	(Spiegel *et al.*, 2006)
DPYD	dihydropyrimidine dehydrogenase	1p21.3	Dihydropyrimidine dehydrogenase deficiency (disorder of the pyrimidine degradation pathway)	Recessive	(van Kuilenburg *et al.*, 2009; Van Kuilenburg *et al.*, 1999)
Creatine deficiency syndromes					
SLC6A8	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Xq28	Brain creatine deficiency can be caused by mutation in the creatine transporter gene *SLC6A8*, or by defects in the biosynthesis of creatine (*GAMT* and *GATM* genes)	X linked	(Poo-Arguelles *et al.*, 2006; Sempere *et al.*, 2009a)
GATM	glycine amidinotransferase	15q21.1	Arginine:glycine amidinotransferase (AGAT) deficiency	Recessive	(Battini *et al.*, 2002)
GAMT	guanidinoacetate N-methyltransferase	19p13.3	Guanidinoacetate methyltransferase (GAMT) deficiency	Recessive	(Sempere *et al.*, 2009b)
Disorder of cholesterol synthesis					
DHCR7	7-dehydrocholesterol reductase	11q13.4	Smith-Lemli-Opitz syndrome	Recessive	(Sikora *et al.*, 2006; Tierney *et al.*, 2006)
Defect of phenylalanine metabolism					
PAH	phenylalanine hydroxylase	12q23.2	Phenylketonuria	Recessive	(Baieli *et al.*, 2003; Steiner *et al.*, 2007)
Disorders of vitamin metabolism					
BTD	biotinidase	3p24.3	Biotinidase deficiency (defect in the recycling of the vitamin biotin)	Recessive	(Zaffanello et al., 2003)
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	5q23.2	Pyridoxine-dependent epilepsy (vitamin B6)	Recessive	(Burd *et al.*, 2000; Mills *et al.*, 2010)
Defect of GABA catabolism					
ALDH5A1	aldehyde dehydrogenase 5 family, member A1	6p22.2	Succinic semialdehyde dehydrogenase deficiency (gamma-hydroxybutyric aciduria)	Recessive	(Knerr *et al.*, 2008; Pearl *et al.*, 2003)
Lysosomal storage disorders					
SGSH	N-sulfoglucosamine sulfohydrolase	17q25.3	Mucopolysaccharidosis IIIA (Sanfilippo syndrome A)	Recessive	(Petit *et al.*, 1996; Wolanczyk *et al.*, 2000)
NAGLU	N-acetylglucosaminidase, alpha	17q21.31	Mucopolysaccharidosis IIIB (Sanfilippo syndrome B)	Recessive	(Heron *et al.*, 2011)
HGSNAT	heparan-alpha-glucosaminide N-acetyltransferase	8p11.21	Mucopolysaccharidosis IIIC (Sanfilippo syndrome C)	Recessive	(Heron *et al.*, 2011)
GNS	glucosamine (N-acetyl)-6-sulfatase	12q14.3	Mucopolysaccharidosis IIID (Sanfilippo syndrome D)	Recessive	(Heron *et al.*, 2011)
Folate deficiency syndrome					
FOLR1	folate receptor 1	11q13.4	Cerebral folate transport deficiency	Recessive	(Cario *et al.*, 2009)
Urea cycle disorder					
OTC	ornithine carbamoyltransferase	Xp11.4	Ornithine transcarbamylase deficiency	X linked	(Gorker and Tuzun, 2005)
Defect of amino acid metabolism					
MUT	methylmalonyl CoA mutase	6p12.3	Methylmalonic aciduria	Recessive	(de Baulny *et al.*, 2005)
Joubert syndrome and related ciliopathies					
AHI1	Abelson helper integration site 1	6q23.3	Joubert syndrome 3	Recessive	(Ozonoff *et al.*, 1999; Takahashi *et al.*, 2005)
NPHP1	nephronophthisis 1	2q13	Joubert syndrome 4; nephronophthisis 1, juvenile	Recessive	(Tory *et al.*, 2007)
CEP290	centrosomal protein 290kDa	12q21.32	Joubert syndrome 5; Leber congenital amaurosis 10; Bardet-Biedl syndrome 14	Recessive	(Coppieters *et al.*, 2010; Perrault *et al.*, 2007; Tory *et al.*, 2007)
RPGRIP1L	RPGRIP1-like (retinitis pigmentosa GTPase regulator-like)	16q12.2	Joubert syndrome 7	Recessive	(Doherty *et al.*, 2010)
GUCY2D	guanylate cyclase 2D, membrane	17p13.1	Leber congenital amaurosis 1	Recessive	(Coppieters *et al.*, 2010)
RPE65	retinal pigment epithelium-specific protein 65kDa	1p31.3	Leber congenital amaurosis 2	Recessive	(Coppieters *et al.*, 2010; Yzer *et al.*, 2003)
MKKS	McKusick-Kaufman syndrome	20p12.2	Bardet-Biedl syndrome 6; McKusick-Kaufman syndrome	Recessive	(Barnett *et al.*, 2002; Moore *et al.*, 2005)
BBS10	Bardet-Biedl syndrome 10	12q21.2	Bardet-Biedl syndrome 10	Recessive	(Deveault *et al.*, 2011)
Muscular dystrophies					
DMD	dystrophin	Xp21.2-p21.1	Muscular dystrophy, Duchenne and Becker types	X linked	(Hinton *et al.*, 2009; Young *et al.*, 2008)
DMPK	dystrophia myotonica-protein kinase	19q13.32	Myotonic dystrophy 1 (Steinert disease)	Dominant	(Ekstrom *et al.*, 2008)
POMGNT1	protein O-linked mannose beta1,2-N-acetylglucosaminyltransferase	1p34.1	Muscle-eye-brain disease (congenital muscular dystrophy, structural eye abnormalities and lissencephaly)	Recessive	(Haliloglu *et al.*, 2004; Hehr *et al.*, 2007)
POMT1	protein-O-mannosyltransferase 1	9q34.13	Limb-girdle muscular dystrophy with ID; Walker-Warburg syndrome	Recessive	(D'Amico *et al.*, 2006)

Abbreviations: ID, intellectual disability

Table 4. Disease genes and genetic disorders reported in individuals with ASD: examples of functional pathways

Gene	Gene name	Cytoband	Disorder	Inheritance pattern	References reporting ASD
RAS/MAPK signaling pathway [a]					
BRAF	v-raf murine sarcoma viral oncogene homolog B1 (BRAF, serine/threonine kinase)	7q34	Cardio-facio-cutaneous syndrome, Noonan syndrome, LEOPARD syndrome	Dominant	(Nava *et al.*, 2007; Nystrom *et al.*, 2008)
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS, small G-protein)	12p12.1	Cardio-facio-cutaneous syndrome, Noonan syndrome	Dominant	(Nava *et al.*, 2007; Nystrom *et al.*, 2008)
MAP2K1	mitogen-activated protein kinase kinase 1 (MEK1, tyrosine/serine/threonine kinase)	15q22.31	Cardio-facio-cutaneous syndrome	Dominant	(Nava *et al.*, 2007)
PTPN11	protein tyrosine phosphatase, non-receptor type 11 (SHP2, tyrosine phosphatase)	12q24.13	Noonan syndrome, LEOPARD syndrome	Dominant	(Pierpont *et al.*, 2009; Watanabe *et al.*, 2011)
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS, small G-protein)	11p15.5	Costello syndrome	Dominant	(Kerr *et al.*, 2006)
NF1	neurofibromin 1 (neurofibromin, RAS-GTPase activator protein)	17q11.2	Neurofibromatosis type 1	Dominant	(Williams and Hersh, 1998)
SPRED1	sprouty-related, EVH1 domain containing 1 (SPRED1, inhibitor of Raf activation by Ras)	15q14	Neurofibromatosis type 1-like syndrome (Legius syndrome)	Dominant	(Laycock-van Spyk *et al.*, 2011)
SYNGAP1	synaptic Ras GTPase activating protein 1 (SYNGAP1, RAS-GTPase activator protein)	6p21.32	Nonsyndromic ID	Dominant	(Hamdan *et al.*, 2011; Pinto *et al.*, 2010)
Channelopathies					
SCN1A	sodium channel, voltage-gated, type I, alpha	2q24.3	Severe myoclonic epilepsy of infancy (Dravet syndrome)	Dominant	(Marini *et al.*, 2009; O'Roak *et al.*, 2011)
SCN2A	sodium channel, voltage-gated, type II, alpha	2q24.3	Early infantile epileptic encephalopathy; benign familial infantile seizures	Dominant	(Neale *et al.*, 2012; Sanders *et al.*, 2012)
CACNA1C	calcium channel, voltage-dependent, L type, alpha 1C subunit	12p13.33	Timothy syndrome (long QT syndrome with syndactyly)	Dominant	(Splawski *et al.*, 2004)
CACNA1F	calcium channel, voltage-dependent, L type, alpha 1F subunit	Xp11.23	X-linked incomplete congenital stationary night blindness, severe form	X linked	(Hemara-Wahanui *et al.*, 2005)
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	11p15.1	DEND syndrome (developmental delay, epilepsy, and neonatal diabetes)	Dominant	(Flanagan *et al.*, 2007; Tonini *et al.*, 2006)
Cell-adhesion molecules					
NRXN1	neurexin 1	2p16.3	Disrupted in ASD, ID, and other neurodevelopmental and psychiatric disorders (dominant?); Pitt-Hopkins-like syndrome-2 (recessive)	Dominant?/ Recessive	(Ching *et al.*, 2010; Pinto *et al.*, 2010; Szatmari *et al.*, 2007; Zweier *et al.*, 2009)
CNTNAP2	contactin associated protein-like 2	7q35-q36.1	Cortical dysplasia-focal epilepsy syndrome and Pitt-Hopkins-like syndrome-1 (recessive). Deletions or chromosomal rearrangements disrupting a *single* copy of *CNTNAP2* have been reported in patients with ASD, ID, epilepsy, schizophrenia and bipolar disorder as well as in healthy subjects; their clinical significance is unknown	Recessive	(Strauss *et al.*, 2006; Zweier *et al.*, 2009)
HEPACAM	hepatic and glial cell adhesion molecule	11q24.2	Megalencephalic leukoencephalopathy with subcortical cysts	Recessive	(Lopez-Hernandez *et al.*, 2011)
NLGN4X	neuroligin 4, X-linked	Xp22.31-p22.32	Nonsyndromic X-linked ASD and/or ID	X linked	(Jamain *et al.*, 2003; Laumonnier *et al.*, 2004)
NLGN3	neuroligin 3	Xq13.1	Nonsyndromic X-linked ASD and/or ID	X linked	(Jamain *et al.*, 2003)
PCDH19	protocadherin 19	Xq22.1	X-linked female-limited epilepsy and cognitive impairment	X linked	(Hynes *et al.*, 2010; Marini *et al.*, 2010)
L1CAM	L1 cell adhesion molecule	Xq28	Syndromic X-linked ID with hydrocephalus, MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome	X linked	(Simonati *et al.*, 2006)
mTOR signaling pathway [b]					
PTEN	phosphatase and tensin homolog (tyrosine phosphatase)	10q23.31	PTEN hamartoma-tumor syndrome (including Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome); macrocephaly/autism syndrome	Dominant	(Butler *et al.*, 2005; Buxbaum *et al.*, 2007; McBride *et al.*, 2010)
TSC1	tuberous sclerosis 1 (tumor suppressor protein)	9q34.13	Tuberous sclerosis complex	Dominant	(Numis *et al.*, 2011)
TSC2	tuberous sclerosis 2 (tumor suppressor protein)	16p13.3	Tuberous sclerosis complex	Dominant	(Numis *et al.*, 2011)
Epigenetic regulation [c]					
MBD5	methyl-CpG binding domain protein 5 (methyl DNA binding)	2q23.1	2q23.1 microdeletion syndrome (ID, severe speech impairment, seizures, short stature, microcephaly and mild dysmorphic features)	Dominant	(Talkowski *et al.*, 2011)
NSD1	nuclear receptor binding SET domain protein 1 (histone methyltransferase)	5q35.2-q35.3	Sotos syndrome (overgrowth syndrome characterized by macrocephaly, advanced bone age, characteristic facial features and learning disabilities)	Dominant	{Schaefer *et al.*, 2006; Ververi *et al.*, 2012}
ARID1B	AT rich interactive domain 1B, SWI1-like (chromatin remodeling)	6q25.3	ID, speech impairment, autism, corpus callosum abnormalities, Coffin-Siris syndrome	Dominant	(Halgren *et al.*, 2011; Santen *et al.*, 2012)
CHD7	chromodomain helicase DNA binding protein 7 (ATPase/helicase)	8q12.2	CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies)	Dominant	(Johansson *et al.*, 2006)
SMARCA2	SWI/SNF-related matrix-associated (ATPase/helicase)	9p24.3	Nicolaides-Baraitser syndrome, Coffin-Siris syndrome	Dominant	(Sousa *et al.*, 2009; Van Houdt *et al.*, 2012)
EHMT1	euchromatic histone-lysine N-methyltransferase 1 (histone methyltransferase)	9q34.3	Kleefstra syndrome/9q subtelomeric deletion syndrome (ID, distinctive facial features, microcephaly, and hypotonia)	Dominant	(Kleefstra *et al.*, 2009)
FOXG1	forkhead box G1 (transcription regulation)	14q12	Congenital variant of Rett syndrome	Dominant	(Brunetti-Pierri *et al.*, 2011; Philippe *et al.*, 2010)
CREBBP	CREB binding protein (histone acetyltransferase)	16p13.3	Rubinstein-Taybi syndrome (ID, characteristic facial features, broad thumbs and great toes)	Dominant	(Schorry *et al.*, 2008)
SRCAP	Snf2-related CREBBP activator protein (chromatin remodeling)	16p11.2	Floating-Harbor syndrome	Dominant	(Hood *et al.*, 2012; White *et al.*, 2010)
CDKL5	cyclin-dependent kinase-like 5 (kinase)	Xp22.13	Early infantile epileptic encephalopathy	X linked	(Archer *et al.*, 2006; Russo *et al.*, 2009)
ZNF674	zinc finger family member 674 (DNA binding)	Xp11.3	Nonsyndromic X-linked ID	X linked	(Lugtenberg *et al.*, 2006)
KDM5C (JARID1C)	lysine (K)-specific demethylase 5C (histone demethylase)	Xp11.22	Large spectrum of phenotypes including ID with microcephaly, spasticity, short stature, epilepsy, and facial anomalies, as well as nonsyndromic ID	X linked	(Adegbola *et al.*, 2008)
PHF8	PHD finger protein 8 (histone demethylase)	Xp11.22	Siderius–Hamel syndrome (ID with cleft lip or cleft palate)	X linked	(Qiao *et al.*, 2008)
MED12	mediator complex subunit 12 (transcription regulation)	Xq13.1	Lujan-Fryns syndrome (X-linked ID with marfanoid habitus)	X linked	(Lerma-Carrillo *et al.*, 2006; Schwartz *et al.*, 2007)
ATRX	transcriptional regulator ATRX (ATPase/helicase)	Xq21.1	Large spectrum of phenotypes including ATRX syndrome (alpha thalassemia/mental retardation syndrome X-linked) and nonsyndromic ID	X linked	(Wada and Gibbons, 2003)
PHF6	PHD finger protein 6 (histone binding)	Xq26.2	Borjeson-Forssman-Lehmann syndrome (ID, epilepsy, and hypogonadism)	X linked	(de Winter *et al.*, 2009)
MECP2	methyl CpG binding protein 2 (methyl DNA binding)	Xq28	Rett syndrome in females; congenital encephalopathy or nonsyndromic ID in males; *MECP2* duplication syndrome, mostly in males	X linked	(Carney *et al.*, 2003; Ramocki *et al.*, 2010)

[a] The protein name and its function are indicated after the gene name. [b] The protein function is indicated after the gene name. [c] The epigenetic function is indicated after the gene name. Abbreviations: ASD, autism spectrum disorder; ID, intellectual disability

Box 1. Genetic disorders reported in Asperger syndrome

Although all the genetic disorders identified thus far in subjects with ASD are also established causes of intellectual disability (ID), this does not mean that they are invariably associated with ID. For instance, tuberous sclerosis is associated with ID in only 30% of patients, and Williams syndrome (7q11.23 deletion) in 75%, although almost all affected subjects have neuropsychiatric problems. Thus, it is not surprising that genetic and genomic mutations are found in higher functioning patients, and not exclusively in patients with autism and ID. Several disorders have been identified in individuals without ID, including subjects with Asperger syndrome (see table below).

Genetic disorder	References
NRXN1 deletion (2p16.3)	(Wisniowiecka-Kowalnik *et al.*, 2010)
3q29 microdeletion	(Baynam *et al.*, 2006)
Williams syndrome (7q11.23 deletion)	(Kilincaslan *et al.*, 2011)
Bannayan-Riley-Ruvalcaba syndrome (*PTEN* mutation, 10q23.31)	(Lynch *et al.*, 2009)
LEOPARD syndrome (*PTPN11* mutation, 12q24.13)	(Watanabe *et al.*, 2011)
15q13.3 microdeletion	(Ben-Shachar *et al.*, 2009)
16p11.2 microdeletion	(Rosenfeld *et al.*, 2010; Sebat *et al.*, 2007)
Myotonic dystrophy 1 (*DMPK* mutation, 19q13.32)	(Blondis *et al.*, 1996; Paul and Allington-Smith, 1997)
22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome)	(Gothelf *et al.*, 2004; Pinto *et al.*, 2010)
Velocardiofacial syndrome (*TBX1* mutation, 22q11.21)	(Paylor *et al.*, 2006)
22q13.33 duplication including *SHANK3*	(Durand *et al.*, 2007)
NLGN4X mutation (Xp22.31-p22.32)	(Jamain *et al.*, 2003)
Nance-Horan syndrome (*NHS* deletion, Xp22.13)	(PARIS study, unpublished)
IL1RAPL1 mutation (Xp21.2-p21.3)	(Piton *et al.*, 2008)
Lujan-Fryns syndrome (*MED12* mutation, Xq13.1)	(Schwartz *et al.*, 2007)
NLGN3 mutation (Xq13.1)	(Jamain *et al.*, 2003)
Female-limited epilepsy and ID (*PCDH19* mutation, Xq22.1)	(Hynes *et al.*, 2010)
Fragile X syndrome (*FMR1* mutation, Xq27.3)	(Hagerman *et al.*, 1994)
Fragile X premutation (*FMR1* premutation, Xq27.3)	(Aziz *et al.*, 2003)
Klinefelter syndrome (XXY)	(van Rijn *et al.*, 2008)
XYY syndrome	(Gillberg, 1989)
45,X/46,XY mosaicism	(Fontenelle *et al.*, 2004)
Mitochondrial disorder (A3243G mutation)	(Pons *et al.*, 2004)

Box 2. Genes involved in nonsyndromic ASD

There is a widely spread misconception that genetic disorders are only identified in individuals with ASD that have a syndromic presentation, i.e., that exhibit facial dysmorphism, congenital malformations, and/or neurologic abnormalities such as microcephaly or structural brain malformations. However, the evidence is clear that many genetic defects can be observed in children that present only with ASD, with no apparent physical abnormalities. For example, many genes involved in X-linked or autosomal nonsyndromic ID have also been implicated in nonsyndromic ASD (see table below and Figure 1). In addition, many other genes have been implicated in both syndromic as well as nonsyndromic forms of ASD/ID. The table below summarizes examples of genes for which nonsyndromic cases have been reported. For genes for which both nonsyndromic and syndromic cases have been reported, this is noted.

Gene	Gene name	Cytoband	Presentation	References
Autosomal dominant				
FOXP1	forkhead box P1	3p14.1	Nonsyndromic	(Hamdan *et al.*, 2010; O'Roak *et al.*, 2011)
SYNGAP1	synaptic Ras GTPase activating protein 1	6p21.32	Nonsyndromic	(Hamdan *et al.*, 2011; Pinto *et al.*, 2010)
SHANK2	SH3 and multiple ankyrin repeat domains 2	11q13.3	Nonsyndromic	(Berkel *et al.*, 2010; Pinto *et al.*, 2010)
GRIN2B	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	12p13.1	Nonsyndromic/syndromic	(Endele *et al.*, 2010; O'Roak *et al.*, 2011)
SHANK3	SH3 and multiple ankyrin repeat domains 3	22q13.33	Nonsyndromic/syndromic	(Durand *et al.*, 2007; Moessner *et al.*, 2007)
Autosomal recessive				
PRSS12	protease, serine, 12 (neurotrypsin)	4q26	Nonsyndromic	(PARIS study, unpublished)
X-linked				
NLGN4X	neuroligin 4, X-linked	Xp22.31-p22.32	Nonsyndromic	(Jamain *et al.*, 2003; Laumonnier *et al.*, 2004)
AP1S2	adaptor-related protein complex 1, sigma 2 subunit	Xp22.2	Nonsyndromic/syndromic	(Borck *et al.*, 2008)
PTCHD1	patched domain containing 1	Xp22.11	Nonsyndromic	(Noor *et al.*, 2010; Pinto *et al.*, 2010)
ARX	aristaless related homeobox	Xp21.3	Nonsyndromic/syndromic	(Partington *et al.*, 2004; Turner *et al.*, 2002)
IL1RAPL1	interleukin 1 receptor accessory protein-like 1	Xp21.2-p21.3	Nonsyndromic	(Pinto *et al.*, 2010; Piton *et al.*, 2008)
CASK	calcium/calmodulin-dependent serine protein kinase	Xp11.4	Nonsyndromic/syndromic	(Hackett *et al.*, 2010)
ZNF674	zinc finger protein 674	Xp11.3	Nonsyndromic	(Lugtenberg *et al.*, 2006)
SYN1	synapsin I	Xp11.23	Nonsyndromic/syndromic	(Fassio *et al.*, 2011)
ZNF81	zinc finger protein 81	Xp11.23	Nonsyndromic	(Kleefstra *et al.*, 2004)
FTSJ1	FtsJ homolog 1	Xp11.23	Nonsyndromic	(Froyen *et al.*, 2007)
PQBP1	polyglutamine binding protein 1	Xq11.23	Nonsyndromic/syndromic	(Cossee *et al.*, 2006; Stevenson *et al.*, 2005)
KDM5C	lysine (K)-specific demethylase 5C	Xp11.22	Nonsyndromic/syndromic	(Adegbola *et al.*, 2008)
IQSEC2	IQ motif and Sec7 domain 2	Xp11.22	Nonsyndromic	(Shoubridge *et al.*, 2010)
FGD1	FYVE, RhoGEF and PH domain containing 1	Xp11.22	Nonsyndromic/syndromic	(Assumpcao *et al.*, 1999)
NLGN3	neuroligin 3	Xq13.1	Nonsyndromic	(Jamain *et al.*, 2003)
ATRX	alpha thalassemia/mental retardation syndrome X-linked	Xq21.1	Nonsyndromic/syndromic	(Wada and Gibbons, 2003)
PCDH19	protocadherin 19	Xq22.1	Nonsyndromic/syndromic	(Hynes *et al.*, 2010; Marini *et al.*, 2010)
ACSL4	acyl-CoA synthetase long-chain family member 4	Xq22.3	Nonsyndromic	(Longo *et al.*, 2003; Meloni *et al.*, 2002)
AGTR2	angiotensin II receptor, type 2	Xq23	Nonsyndromic	(Vervoort *et al.*, 2002)
UPF3B	UPF3 regulator of nonsense transcripts homolog B	Xq24	Nonsyndromic	(Addington *et al.*, 2011; Laumonnier *et al.*, 2010)
GRIA3	glutamate receptor, ionotrophic, AMPA 3	Xq25	Nonsyndromic	(Chiyonobu *et al.*, 2007; Wu *et al.*, 2007)
ARHGEF6	Rac/Cdc42 guanine nucleotide exchange factor 6	Xq26.3	Nonsyndromic	(Kutsche *et al.*, 2000)
FMR1	fragile X mental retardation 1	Xq27.3	Nonsyndromic/syndromic	(Hagerman *et al.*, 2010)
AFF2	AF4/FMR2 family, member 2	Xq28	Nonsyndromic	(Stettner *et al.*, 2011)
SLC6A8	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Xq28	Nonsyndromic/syndromic	(Poo-Arguelles *et al.*, 2006; Sempere *et al.*, 2009a)
MECP2	methyl CpG binding protein 2	Xq28	Nonsyndromic/syndromic	(Carney *et al.*, 2003)
RAB39B	RAB39B, member RAS oncogene family	Xq28	Nonsyndromic/syndromic	(Giannandrea *et al.*, 2010)