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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 (Gecez et al., 2009).

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 (Kiellinen 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

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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 \textit{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/\textit{SHANK3} mutations), maternal 15q11-q13 duplications, Rett syndrome (\textit{MECP2}) and \textit{MECP2} duplication syndrome, fragile X syndrome (\textit{FMR1}), tuberous sclerosis (\textit{TSC1}, \textit{TSC2}), adenyllosuccinate lyase deficiency (\textit{ADSL}), Timothy syndrome (\textit{CACNA1C}), cortical dysplasia-focal epilepsy syndrome (\textit{CNTNAP2}), Smith-Lemli-Opitz syndrome (\textit{DHC8R7}), Smith-Magenis syndrome (17p11.2 deletion, \textit{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 (\textit{MBD5}) gene. An analysis of 65 individuals with deletions or translocations involving \textit{MBD5} reported that all had "autistic-like" behaviors (Talkowski \textit{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 (\textit{SLC6A8}, \textit{GAMT}, \textit{GATM}), Cornelia de Lange syndrome (\textit{NIPBL}, \textit{SMC1A}), CHARGE syndrome (\textit{CHD7}), Cohen syndrome (\textit{VPS13B}), Joubert syndrome and related syndromes (\textit{AHI1}, \textit{NPHP1}, \textit{CEP290}, \textit{RPGRIPI1L}), myotonic dystrophy type 1 (\textit{DMPK}), X-linked female-limited epilepsy and ID (\textit{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 \textit{PTEN} related syndromes, Kleefstra syndrome (9q subtelomeric deletion syndrome/\textit{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) (Geç, 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 1 and neurofibromatosis type 1-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 syndrome), *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


Fragile X and autism: Intertwined at the molecular level


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) 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

<table>
<thead>
<tr>
<th>Disorder (prevalence)*</th>
<th>Gene [locus]; inheritance</th>
<th>Mutations</th>
<th>Prevalence in ASD</th>
<th>Proportion with ASD</th>
<th>Clinical features</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X syndrome (1:4,000 males; 1:6,000 females)</td>
<td>FMR1 (Xq27.3); X-linked</td>
<td>Trinucleotide repeat expansion</td>
<td>~2%</td>
<td>~60% males and ~20% females with the full mutation have ASD. Among premutation carriers, 15% males and 5% females have ASD</td>
<td>ID, ASD, ADHD, characteristic facial appearance, macroorchidism. Females are generally less affected than males.</td>
<td>[Clifford et al., 2007; Haageman et al., 2010; Kielinen et al., 2004]</td>
</tr>
<tr>
<td>22q11 deletion syndrome/Phelan-McDermid syndrome (&gt;400 cases diagnosed)</td>
<td>SHANK3 (22q13.3); dominant</td>
<td>22q13 deletion, mutation</td>
<td>~0.5%</td>
<td>55% (6/11) individuals with 22q11 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</td>
<td>ID, absent or severely delayed speech, autistic behavior, seizures, hypotonia, decreased sensitivity to pain, mouthing/chewing, dysplastic toenails</td>
<td>[Durand et al., 2007; Jeffries et al., 2005; Manning et al., 2004]</td>
</tr>
<tr>
<td>Rett syndrome (1:8,500 females); MECP2 duplication syndrome (~1% in males with ID)</td>
<td>MECP2 (Xq28); X-linked</td>
<td>Mutation, deletion, duplication</td>
<td>~1% in females, rare in males</td>
<td>ASD/autistic features are frequent in girls with Rett syndrome; 76% (13/17) males with MECP2 duplication have autism/autistic features 81% (44/54) with isodicentric chromosome 15 met criteria for autism and 92% (50/54) for ASD</td>
<td>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 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</td>
<td>[Carney et al., 2003; Ramocki et al., 2010]</td>
</tr>
<tr>
<td>15q11-q13 duplication syndrome (1:20,000-30,000)</td>
<td>UBE3A (15q11.2); dominant; imprinted</td>
<td>Intersitial duplication or isodicentric isodicentric chromosome 15, usually of maternal origin</td>
<td>~1%</td>
<td>Maternal 15q11-q13 deletion, paternal uniparental disomy, mutation, imprinting defect</td>
<td>ID, lack of speech, inappropriate laughter, seizures, microcephaly, ataxia</td>
<td>[Sahoo et al., 2006; Trillinggaard and Østergaard, 2004]</td>
</tr>
<tr>
<td>Angelman syndrome (1:12,000-20,000)</td>
<td>UBE3A (15q11.2); dominant; imprinted</td>
<td>Paternal 15q11-q13 deletion, maternal uniparental disomy, mutation, imprinting defect</td>
<td>Rare</td>
<td>63% (38/60) ASD (range 50%-81%)</td>
<td>ID, hypersomnia, compulsive behavior, skin picking, psychomotor retardation, autism, obesity, developmental delay</td>
<td>[Descheemaeker et al., 2006; Veitman et al., 2005]</td>
</tr>
<tr>
<td>Prader-Willi syndrome (1:10,000-25,000)</td>
<td>H111-85 snoRNA cluster (15q11.2); dominant; imprinted</td>
<td>Paternal 15q11-q13 deletion, maternal uniparental disomy, mutation, imprinting defect</td>
<td>Rare</td>
<td>23% (49/209) ASD (range 19%-25%)</td>
<td>ID, obsessive compulsive behavior, skin picking, hypospadias, hypotonia, self-injury, seizures, microcephaly, ataxia, autistic features</td>
<td>[Treadwell-Deering et al., 2010]</td>
</tr>
<tr>
<td>Smith-Magenis syndrome (1:15,000)</td>
<td>RAI1 (17p11.2); dominant</td>
<td>17p11.2 deletion, mutation</td>
<td>Rare</td>
<td>90% (18/20) ASD</td>
<td>ID, hypervigilance, sleep disturbance, seizures, self-mutilation, hoarse voice, brachydactyly, hypotonia</td>
<td>[Laje et al., 2010]</td>
</tr>
<tr>
<td>Pottoki-Lupski syndrome (1:20,000)</td>
<td>RAI1 (17p11.2); dominant</td>
<td>17p11.2 duplication</td>
<td>Rare</td>
<td>Autistic features are present in the majority; 67% (10/15) meet criteria for ASD</td>
<td>ID, ASD, ADHD hormone imbalance, infantile hypotonia, failure to thrive, sleep apnea, cardiovascular abnormalities</td>
<td>[Treadwell-Deering et al., 2010]</td>
</tr>
<tr>
<td>Tuberous sclerosis (1:5,800)</td>
<td>TSC2 (9q34.13); TSC2 (16p13.3); dominant</td>
<td>Mutation, deletion, duplication</td>
<td>~1%</td>
<td>40% ASD (20%-60%)</td>
<td>ID, non-malignant tumors in the brain, kidneys, heart, eyes, lungs, and skin, seizures</td>
<td>[Numis et al., 2011]</td>
</tr>
<tr>
<td>Adenylsuccinate lyase deficiency (&lt;100 cases reported)</td>
<td>ADSL (22q13.1); recessive</td>
<td>Mutation</td>
<td>Extremely rare</td>
<td>~50% autism/autistic features</td>
<td>Disorder of purine metabolism characterized by ID, epilepsy and autistic features</td>
<td>[Spiegel et al., 2006]</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome (1:12,000-40,000)</td>
<td>DMCR7 (11q13.4); recessive</td>
<td>Mutation</td>
<td>Rare</td>
<td>53% (9/17) autism, 71% (10/14) ASD</td>
<td>Inborn error of metabolism affecting cholesterol biosynthesis characterized by growth retardation, macrocephaly, ID, and multiple malformations of variable severity</td>
<td>[Sikora et al., 2006; Tierney et al., 2006]</td>
</tr>
<tr>
<td>CHARGE syndrome (1:10,000)</td>
<td>CHD7 (8q12.2); dominant</td>
<td>Mutation, deletion (rare)</td>
<td>Rare</td>
<td>68% (17/25) ASD/autistic traits (including 48% with ASD)</td>
<td>ID, coloboma, heart anomaly, choanal atresia, cataracts, genital and ear anomalies</td>
<td>[Johansson et al., 2006]</td>
</tr>
<tr>
<td>Timothy syndrome (&lt;20 individuals reported)</td>
<td>CACNA1C (12p13.33); dominant</td>
<td>Mutation</td>
<td>Extremely rare</td>
<td>80% (4/5) ASD</td>
<td>ID, ASD, cardiac abnormalities (long QT syndrome, malformations), hand/foot dysmorphism, facial dysmorphism, seizures</td>
<td>[Splatowski et al., 2004]</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome (10 individuals reported)</td>
<td>CNTNAP2 (7q35); recessive</td>
<td>Mutation</td>
<td>Extremely rare</td>
<td>67% (6/9) autism or ASD</td>
<td>Severe intractable seizures, ID, ASD, and focal brain malformations in Amish children</td>
<td>[Strauss et al., 2006]</td>
</tr>
<tr>
<td>Brain creatine transporter deficiency syndrome (&gt;150 individuals diagnosed, 45 families reported)</td>
<td>ScC6A4 (Xq28); X-linked</td>
<td>Mutation</td>
<td>Very rare</td>
<td>Frequent ASD/autistic features</td>
<td>Inborn error of creatine metabolism characterized by ID, speech delay, autistic behavior and seizures</td>
<td>[Longo et al., 2011]</td>
</tr>
<tr>
<td>2q23.1 microdeletion syndrome (65 individuals reported)</td>
<td>MBDS (2q23.1); dominant</td>
<td>2q23.1 deletion</td>
<td>0.17% (7/4061)</td>
<td>100% (65/65) subjects with deletions or translocations involving MBDS had autistic features</td>
<td>Angelman-like phenotype including ID, severe speech impairment, seizures, behavioral problems, microcephaly, mild dysmorphism, short stature, ataxic gait</td>
<td>[Talukdar et al., 2011]</td>
</tr>
<tr>
<td>8p23.1 deletion syndrome (1:10,000-30,000)</td>
<td>? (8p23.1); dominant</td>
<td>8p23.1 deletion</td>
<td>Rare</td>
<td>57% (4/7) autism</td>
<td>Congenital heart defects, congenital diaphragmatic hernia, mild facial dysmorphism, ID, hyperactivity</td>
<td>[Fisch et al., 2010]</td>
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<tr>
<td>Cohen syndrome (500-1000 individuals diagnosed)</td>
<td>VPS13B (8q22.1); recessive</td>
<td>Mutation, deletion</td>
<td>Very rare</td>
<td>49% (22/45) autism</td>
<td>ID, typical facial dysmorphism, renal dysplasia, neutropenia, obesity, microcephaly</td>
<td>[Howlin et al., 2005]</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome (1:50,000)</td>
<td>NIPBL (5p13.2); dominant; SMC2A (Xp11.22); X-linked</td>
<td>Mutation, deletion (rare)</td>
<td>Very rare</td>
<td>47%-67% autism</td>
<td>ID, facial dysmorphism, upper limb malformations, growth retardation</td>
<td>[Bhuiyan et al., 2006; Moss et al., 2008; Oliver et al., 2008]</td>
</tr>
</tbody>
</table>
| Disorder (prevalence)* | Gene (focus); inheritance | Mutations | Prevalence in ASD | Proportion with ASD | Clinical features | Selected references
|------------------------|--------------------------|-----------|------------------|-------------------|-----------------|-------------------|
| Trisomy 21 (1:800)     | DMPK (2q13.2); 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, ID, speech delay, expressive language impairment, ASD, ADHD, seizures, mild dysorphic features, congenital heart defects, brain MRI abnormalities | (Klein-Tasman et al., 2009; Toddman et al., 2012)
| 9q11.23 duplication (unknown) | Contiguous gene syndrome (7q11.23); dominant | 7q11.23 duplication | Rare | 40% (11/27) autism | ID, language impairment, behavioral problems, epilepsy, dysmorphism, macrocephaly, congenital abnormalities, obesity | (Depienne et al., 2007; Van der Aa et al., 2009)
| Cri du Chat syndrome/5p (1:15,000) | 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 syndrome (1:500-5,000) | 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 | (Hansson et al., 2010; Shinawi et al., 2010; Weiss et al., 2008)
| 16p11.2 microduplication syndrome (1:500-5,000) | 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, macrocephaly, congenital abnormalities, underweight | (Shinawi et al., 2010; Weiss et al., 2008)
| Williams syndrome (1:4,000) | 22q11 deletion syndrome/DiGeorge syndrome/cardiocerebrofacial 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, velociphenalgal 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% (3-36) 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 (9q22.1); 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; Marin et al., 2010; Scheffer et al., 2008; Devillard et al., 2010; Falk and Casas, 2007; Fisch et al., 2010)
| 2q37 deletion syndrome (estimated at 1:22,000) | HDAC4 + other(s) (2q17); dominant | 2q37 deletion | Rare | 24% (16/66) autistic behavior; in a smaller study, 63% (5/8) had autism | Mild-moderate ID, brachycephaly, characteristic facial appearance, short stature, obesity, hypotonia, ASD, and seizures. Haplosufficiency of HDAC4 causes the core manifestations, including brachycephaly and ID, but other genes yet to be identified contribute to the phenotype in individuals with terminal deletions distal to HDAC4 | (D'Arcangelo et al., 2004; Leblanc et al., 2008)
| Cri du Chat syndrome/Sp deletion syndrome (1:15,000-50,000) | ? (candidates SEMAPI, CTNND2) (5p15.2-p15.33); dominant | Sp 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) | EHMT2 (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 | (Mbfie 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)
| XXY 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) (Tartaglia et al., 2008)
| XXY 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 | (Bishop et al., 2011; Kielinen et al., 2004) (Tartaglia et al., 2008)
| Down syndrome (1:800) | Many | Trisomy 21 | ~3% (1.7-2.7%) 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)

* 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. Additional references implicating these disorders in ASD can be found in (Betancur, 2011). Abbreviations: ASD, attention deficit hyperactivity 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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cytoband</th>
<th>Position (Mb)</th>
<th>Comment</th>
<th>References reporting ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21.1 microdeletion/microduplication syndrome</td>
<td>1q21.1</td>
<td>146.5-147.7</td>
<td>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)</td>
<td>(Brunetti-Pierri et al., 2008; Mefford et al., 2008; Pinto et al., 2010; Szatmari et al., 2007)</td>
</tr>
<tr>
<td>2p15-p16.1 microdeletion syndrome</td>
<td>2p15-p16.1</td>
<td>57.7-61.7</td>
<td>ID, growth retardation, microcephaly, dysmorphic features, congenital abnormalities; 4 of 6 subjects reported with the microdeletion have ASD/autistic behavior</td>
<td>(Liang et al., 2009; Rajcan-Separovic et al., 2007)</td>
</tr>
<tr>
<td>3q29 microdeletion/microduplication syndrome</td>
<td>3q29</td>
<td>195.7-197.5</td>
<td>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</td>
<td>(Baliff et al., 2008; Quintero-Rivera et al., 2010; Willatt et al., 2005)</td>
</tr>
<tr>
<td>10q22-q23 deletion</td>
<td>10q22.3-q23.2</td>
<td>81.7-88.9</td>
<td>Recurrent 10q22-q23 deletions of varying sizes have been associated with cognitive and behavioral abnormalities including ASD and hyperactivity</td>
<td>(Allman et al., 2010; Ballioni et al., 2007)</td>
</tr>
<tr>
<td>15q13.3 microdeletion syndrome/15q13.3 microduplication</td>
<td>15q13.2-q13.3</td>
<td>30.8-32.7</td>
<td>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.</td>
<td>(Ben-Shachar et al., 2009; Miller et al., 2009; Pinto et al., 2010; Sharp et al., 2008; van Bon et al., 2009)</td>
</tr>
<tr>
<td>15q24 microdeletion syndrome</td>
<td>15q24.1-q24.2</td>
<td>74.4-76.2</td>
<td>Microdeletion syndrome characterized by ID, typical facial characteristics, and mild hand and genital anomalies. 23% (8/35) of reported cases have ASD</td>
<td>(Marshall et al., 2008; McInnes et al., 2010; Mefford et al., 2012)</td>
</tr>
<tr>
<td>16p13.11 microdeletion/microduplication</td>
<td>16p13.11</td>
<td>15.5-16.3</td>
<td>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</td>
<td>(Pinto et al., 2010; Ullmann et al., 2007)</td>
</tr>
<tr>
<td>16p11.2-p12.2 microdeletion/microduplication syndrome</td>
<td>16p11.2-p12.2</td>
<td>21.6-29.0</td>
<td>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</td>
<td>(Tabet et al., 2012)</td>
</tr>
<tr>
<td>16p11.2 microdeletion/microduplication</td>
<td>16p11.2</td>
<td>29.5-30.2</td>
<td>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</td>
<td>(Hanson et al., 2010; Rosenfeld et al., 2010; Weiss et al., 2008)</td>
</tr>
<tr>
<td>17p13.3 microdeletion (Miller-Dieker syndrome, isolated lissencephaly), 17p13.3 microduplication</td>
<td>17p13.3</td>
<td>1-2.5</td>
<td>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</td>
<td>(Bi et al., 2009; Bruno et al., 2010)</td>
</tr>
<tr>
<td>17q12 deletion/duplication syndrome</td>
<td>17q12</td>
<td>34.8-36.2</td>
<td>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</td>
<td>(Moreno-De-Luca et al., 2010)</td>
</tr>
<tr>
<td>17q21.31 microdeletion/microduplication</td>
<td>17q21.31</td>
<td>43.6-44.2</td>
<td>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. KANK5L1 was recently identified as the causative gene</td>
<td>(Cooper et al., 2011; Grisart et al., 2009)</td>
</tr>
<tr>
<td>Xq28 duplication syndrome (MECP2 duplication syndrome)</td>
<td>Xq28</td>
<td>152.7-153.4</td>
<td>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</td>
<td>(Ramocki et al., 2010)</td>
</tr>
</tbody>
</table>

Footnotes:

* Human reference genome hg19, NCBI 37 (February 2009).
Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ID, intellectual disability.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease genes and genetic disorders reported in individuals with ASD: examples of clinical and etiological subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASDL</td>
<td>Adenosylcystic acid lyase (ADSL) deficiency (ADSL)</td>
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<td>DF/HY</td>
<td>Dihydroyipridine dehydrogenase (DF/HY) deficiency (DF/HY)</td>
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<tr>
<td>CREAT</td>
<td>Creatine deficiency syndrome (CREAT) deficiency (CREAT)</td>
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<tr>
<td>SLC6A8</td>
<td>Solute carrier family 6, member A8 (SLC6A8) deficiency (SLC6A8)</td>
</tr>
<tr>
<td>GATM</td>
<td>Gastric acid transferase (GATM) deficiency (GATM)</td>
</tr>
<tr>
<td>DHCR7</td>
<td>7-dehydrocholesterol reductase (DHCR7) deficiency (DHCR7)</td>
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<tr>
<td>PAH</td>
<td>Phenylalanine hydroxylase (PAH) deficiency (PAH)</td>
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<td>BICD2</td>
<td>Bicoid domain (BICD2) deficiency (BICD2)</td>
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<tr>
<td>GAB1</td>
<td>Glutamyltransferase (GAB1) deficiency (GAB1)</td>
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<td>SGSH</td>
<td>Sulfoglucosamine sulfohydrolase (SGSH) deficiency (SGSH)</td>
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<td>NAGLU</td>
<td>N-acetylglucosaminidase (NAGLU) deficiency (NAGLU)</td>
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<td>GNS</td>
<td>Glucose-6-phosphatase (GNS) deficiency (GNS)</td>
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<td>FOLR1</td>
<td>Folate receptor 1 (FOLR1) deficiency (FOLR1)</td>
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<td>UTRD2</td>
<td>Uridine transporter (UTRD2) deficiency (UTRD2)</td>
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<td>Ornithine carbamoyltransferase (OTC) deficiency (OTC)</td>
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<td>Methylmalonyl-CoA mutase (MAF) deficiency (MAF)</td>
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<td>AHI1</td>
<td>Abelson helper integration site 1 (AHI1) deficiency (AHI1)</td>
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<td>NPH1</td>
<td>Neognathus physis (NPH1) deficiency (NPH1)</td>
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<td>Centrosomal protein 290KDa (CEP290) deficiency (CEP290)</td>
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<td>RGGRP1-like (RGGRP1L) deficiency (RGGRP1L)</td>
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<td>GUCY2D</td>
<td>Guanylate cyclase 2D, membrane (GUCY2D) deficiency (GUCY2D)</td>
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<td>RPE65</td>
<td>Retinal pigment epithelium-specific protein 65kDa (RPE65) deficiency (RPE65)</td>
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<td>MKS</td>
<td>McKusick-Kaufman syndrome (MKS) deficiency (MKS)</td>
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<td>BBS10</td>
<td>Bardet-Biedl syndrome 10 (BBS10) deficiency (BBS10)</td>
</tr>
<tr>
<td>DMD</td>
<td>Dystrophin (DMD) deficiency (DMD)</td>
</tr>
<tr>
<td>DMPK</td>
<td>Dystrophia myotonica-protein kinase (DMPK) deficiency (DMPK)</td>
</tr>
<tr>
<td>POMGNT1</td>
<td>Protein O-linked mannose beta1,2-N-acetylglucosaminyltransferase (POMGNT1) deficiency (POMGNT1)</td>
</tr>
<tr>
<td>POMT1</td>
<td>Protein O-mannosyltransferase 1 (POMT1) deficiency (POMT1)</td>
</tr>
</tbody>
</table>

Abbreviations: ID, intellectual disability
<table>
<thead>
<tr>
<th>Gene name</th>
<th>Cytoband</th>
<th>Disorder</th>
<th>Inheritance pattern</th>
<th>References reporting ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS/MAPK signaling pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>7q34</td>
<td>Cardiac-facio-cutaneous syndrome, Noonan syndrome, LEOPARD syndrome</td>
<td>Dominant</td>
<td>[Nava et al., 2007; Nystrom et al., 2008]</td>
</tr>
<tr>
<td>KRAS</td>
<td>12p12.1</td>
<td>Cardiac-facio-cutaneous syndrome, Noonan syndrome</td>
<td>Dominant</td>
<td>[Nava et al., 2007; Nystrom et al., 2008]</td>
</tr>
<tr>
<td>MAP2K1</td>
<td>15q22.31</td>
<td>Cardiac-facio-cutaneous syndrome</td>
<td>Dominant</td>
<td>[Nava et al., 2007]</td>
</tr>
<tr>
<td>PTPN11</td>
<td>12q24.13</td>
<td>Noonan syndrome, LEOPARD syndrome</td>
<td>Dominant</td>
<td>[Pierpont et al., 2009; Watanabe et al., 2011]</td>
</tr>
<tr>
<td>HRAS</td>
<td>11p15.5</td>
<td>Costello syndrome</td>
<td></td>
<td>[Kerr et al., 2006]</td>
</tr>
<tr>
<td>NF1</td>
<td>17q11.2</td>
<td>Neurofibromatosis type 1</td>
<td></td>
<td>[Williams and Hersh, 1998]</td>
</tr>
<tr>
<td>SPORET1</td>
<td>15e14</td>
<td>Neurofibromatosis type 1-like syndrome (Legius syndrome)</td>
<td></td>
<td>[Laycock-van Spyk et al., 2011]</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>6p21.32</td>
<td>Nonsyndromic ID</td>
<td></td>
<td>[Hamdan et al., 2011; Pinto et al., 2010]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Channelopathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A</td>
<td>2q24.3</td>
<td>Severe myoclonic epilepsy of infancy (Dravet syndrome)</td>
<td>Dominant</td>
<td>[Marini et al., 2009; D’Roak et al., 2011]</td>
</tr>
<tr>
<td>SCN2A</td>
<td>2q24.3</td>
<td>Early infantile epileptic encephalopathy; benign familial infantile seizures</td>
<td>Dominant</td>
<td>[Néalet al., 2012; Sanders et al., 2012]</td>
</tr>
<tr>
<td>CACNA1C</td>
<td>12p13.33</td>
<td>Timothy syndrome (long QT syndrome with syndactyly)</td>
<td>Dominant</td>
<td>[Spiliakos et al., 2004]</td>
</tr>
<tr>
<td>CACNA1F</td>
<td>1p11.23</td>
<td>X-linked incomplete congenital stationary night blindness, severe form</td>
<td></td>
<td>[Hemara-Wahanui et al., 2005]</td>
</tr>
<tr>
<td>KCN11</td>
<td>11p15.5</td>
<td>DEND syndrome (developmental delay, epilepsy, and neonatal diabetes)</td>
<td></td>
<td>[Flanagan et al., 2007; Tonini et al., 2006]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cell-adhesion molecules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCKX1</td>
<td>2p16.3</td>
<td>Disrupted in ASD, ID, and other neurodevelopmental and psychiatric disorders (dominant?); Pitt-Hopkins-like syndrome-2 (recessive)</td>
<td>Dominant/?</td>
<td>[Ching et al., 2010; Pinto et al., 2010; Sztatman et al., 2007; Zweier et al., 2009]</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>7q35- q36.1</td>
<td>Cortical dysplasia-focal epilepsy syndrome and Pitt-Hopkins-like syndrome-1 (recessive). Deletions or chromosomal rearrangements disrupting a simple copy of CNNTAP2 have been reported in patients with ASD, ID, epilepsy, schizophrenia and bipolar disorder as well as in healthy subjects; [Strauss et al., 2006; Zweier et al., 2009]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPACAM</td>
<td>11q24.2</td>
<td>Megalencephalic leuкоencephalopathy with subcortical cysts</td>
<td>Recessive</td>
<td>[Lopez-Hernandez et al., 2011]</td>
</tr>
<tr>
<td>NLGN4X</td>
<td>2p21.31- p22.32</td>
<td>Nonsyndromic X-linked ASD and/or ID</td>
<td>X linked</td>
<td>[Jamaï et al., 2003; Laumonier et al., 2004]</td>
</tr>
<tr>
<td>NLGN3</td>
<td>1p13.1</td>
<td>Nonsyndromic X-linked ASD and/or ID</td>
<td>X linked</td>
<td>[Jamaï et al., 2003]</td>
</tr>
<tr>
<td>PCDH19</td>
<td>Xq22.1</td>
<td>X-linked female-limited epilepsy and cognitive impairment</td>
<td>X linked</td>
<td>[Hynes et al., 2010; Marino et al., 2011]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR-signaling pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>10q23.31</td>
<td>PTEN hamartoma-tumor syndrome (including Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome); macrocephaly/autism syndrome</td>
<td>Dominant</td>
<td>[Butler et al., 2005; Busbaum et al., 2007; McBride et al., 2010]</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Epigenetic regulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBD5</td>
<td>2p23.3</td>
<td>2p23.1 microdeletion syndrome (ID, severe speech impairment, seizures, short stature, microcephaly and mild dysmorphic features)</td>
<td>Dominant</td>
<td>[Takowksi et al., 2011]</td>
</tr>
<tr>
<td>NSD1</td>
<td>3q25.2- q35.3</td>
<td>Sotos syndrome (overgrowth syndrome characterized by macrocephaly, advanced bone age, characteristic facial features and learning disabilities)</td>
<td>Dominant</td>
<td>[Schafer et al., 2006; Ververi et al., 2012]</td>
</tr>
<tr>
<td>ARD18</td>
<td>6q25.3</td>
<td>ID, speech impairment, autism, corpus callosum abnormalities, Coffin-Siris syndrome</td>
<td></td>
<td>[Halgren et al., 2011; Santen et al., 2012]</td>
</tr>
<tr>
<td>CHD7</td>
<td>8q12.2</td>
<td>CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies)</td>
<td>Dominant</td>
<td>[Johansson et al., 2006]</td>
</tr>
<tr>
<td>SMCARCA2</td>
<td>9p24.3</td>
<td>Nieolaides-Barisat syndrome, Coffin-Siris syndrome</td>
<td></td>
<td>[OUSa et al., 2009; Van Houdt et al., 2012]</td>
</tr>
<tr>
<td>EHMT1</td>
<td>9q34.3</td>
<td>Euchromatin-lysine-N-methyltransferase 1 (histone methyltransferase)</td>
<td></td>
<td>[Kleefstra et al., 2009]</td>
</tr>
<tr>
<td>FOXG1</td>
<td>Xp11.3</td>
<td>Congenital variant of Rett syndrome</td>
<td>Dominant</td>
<td>[Brunetti-Pierri et al., 2011; Philippe et al., 2010]</td>
</tr>
<tr>
<td>CREBBP</td>
<td>16p13.33</td>
<td>Rubinstein-Taybi syndrome (ID, characteristic facial features, broad thumbs and great toes)</td>
<td>Dominant</td>
<td>[Schorry et al., 2008]</td>
</tr>
<tr>
<td>SRCAP</td>
<td>16p11.12</td>
<td>Floating-Harbor syndrome</td>
<td></td>
<td>[Hood et al., 2012; White et al., 2010]</td>
</tr>
<tr>
<td>CDKL5</td>
<td>Xp22.13</td>
<td>Early infantile epileptic encephalopathy</td>
<td>X linked</td>
<td>[Archer et al., 2006; Russo et al., 2009]</td>
</tr>
<tr>
<td>ZNF674</td>
<td>Xp11.3</td>
<td>Nonsyndromic X-linked ID</td>
<td>X linked</td>
<td>[Lugtenberg et al., 2006]</td>
</tr>
<tr>
<td>KDM3C (JARID1C)</td>
<td>Xp11.22</td>
<td>Large spectrum of phenotypes including ID with microcephaly, spasticity, short stature, epilepsy, and facial anomalies, as well as nonsyndromic ID</td>
<td></td>
<td>[Adgebola et al., 2008]</td>
</tr>
<tr>
<td>PHF8</td>
<td>Xp11.22</td>
<td>Siderius–Hamel syndrome (ID with cleft lip or cleft palate)</td>
<td>X linked</td>
<td>[Qiao et al., 2008]</td>
</tr>
<tr>
<td>MED12</td>
<td>Xq13.11</td>
<td>Lujan-Fryns syndrome (X-linked with marfanoid habitus)</td>
<td>X linked</td>
<td>[Lemara-Carrillo et al., 2006; Schwartz et al., 2007]</td>
</tr>
<tr>
<td>ATRX</td>
<td>Xq21.11</td>
<td>Large spectrum of phenotypes including ATRX syndrome (alpha thalassemia/mental retardation syndrome X-linked) and nonsyndromic ID</td>
<td>X linked</td>
<td>[Wada and Gibbons, 2003]</td>
</tr>
<tr>
<td>PHF6</td>
<td>Xq26.2</td>
<td>Borjeson-Forssman-Lehmann syndrome (ID, epilepsy, and hypogonadism)</td>
<td>X linked</td>
<td>[de Winter et al., 2009]</td>
</tr>
<tr>
<td>MECP2</td>
<td>Xq28</td>
<td>Rett syndrome in females; congenital encephalopathy or nonsyndromic ID in males; MECP2 duplication syndrome, mostly in males</td>
<td>X linked</td>
<td>[Carney et al., 2003; Ramocki et al., 2010]</td>
</tr>
</tbody>
</table>

1 The protein name and its function are indicated after the gene name. 2 The protein function is indicated after the gene name. 3 The epigenetic function is indicated after the gene name. Abbreviations: ASD, autism spectrum disorder; ID, intellectual disability
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).

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

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Cytoband</th>
<th>Presentation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXP2</td>
<td>3p14.1</td>
<td>Nonsyndromic</td>
<td>(Hamdan et al., 2010; O’Roak et al., 2011)</td>
</tr>
<tr>
<td>SYNGAP1</td>
<td>6p21.32</td>
<td>Nonsyndromic</td>
<td>(Hamdan et al., 2011; Pinto et al., 2010)</td>
</tr>
<tr>
<td>SHANK2</td>
<td>11q13.3</td>
<td>Nonsyndromic</td>
<td>(Berkel et al., 2010; Pinto et al., 2010)</td>
</tr>
<tr>
<td>GRIN2B</td>
<td>12p13.1</td>
<td>Nonsyndromic/syndromic</td>
<td>(Endele et al., 2010; O’Roak et al., 2011)</td>
</tr>
<tr>
<td>SHANK3</td>
<td>22q13.33</td>
<td>Nonsyndromic/syndromic</td>
<td>(Durand et al., 2007; Moessner et al., 2007)</td>
</tr>
</tbody>
</table>

**Autosomal dominant**

- RAB39B: member RAS oncogene family
- MECP2: methyl CpG binding protein 2

**Autosomal recessive**

- PRR5L2: protease, serine, 12 (neuromedin)
- NLGN4X: neurexin 4, X-linked
- AP1S2: adaptor-related protein complex 1, sigma 2 subunit
- PTCHD1: patched domain containing 1
- ARX: aristless related homeobox
- IGLAP1: interleukin 1 receptor accessory protein-like 1
- CASK: calcium/calmodulin-dependent serine protein kinase
- ZNF674: zinc finger protein 674
- SYN2: synapse protein 1
- ZNF81: zinc finger protein 81
- FTSJ1: FtsJ homolog 1
- PRKABP1: polypeptide binding protein 1
- KDM5C: lysine (K)-specific demethylase 5C
- IQSEC2: IQ motif and Sec7 domain 2
- FGD1: FYVE, RhOGEF and PH domain containing 1
- NLGN3: neurexin 3
- ATRX: alpha thalassemia/mental retardation syndrome X-linked
- PCDH19: protocadherin 19
- ACSL4: acyl-CoA synthetase long-chain family member 4
- AGTR2: angiotensin II receptor, type 2
- UPF3B: UPF3 regulator of nonsense transcripts homolog 8
- GRIA3: glutamate receptor, ionotrophic, AMPA 3
- ARHGEF6: Rac/Cdc42 guanine nucleotide exchange factor 6
- FMR1: fragile X mental retardation 1
- AFF2: AF4/FMR2 family, member 2
- SLC6A8: solute carrier family 6 (neurotransmitter transporter, creatine), member 8

**References**

- Hamdan et al., 2010; O’Roak et al., 2011
- Hamdan et al., 2011; Pinto et al., 2010
- Berkel et al., 2010; Pinto et al., 2010
- Endele et al., 2010; O’Roak et al., 2011
- Durand et al., 2007; Moessner et al., 2007
- Jamain et al., 2003; Laumann et al., 2004
- Bork et al., 2008
- Noor et al., 2010; Pinto et al., 2010
- Partington et al., 2004; Turner et al., 2002
- Pinto et al., 2010; Piton et al., 2008
- Hackett et al., 2010
- Lugtenberg et al., 2006
- Fassio et al., 2011
- Kleeftstra et al., 2004
- frozen et al., 2007
- Cosea et al., 2006; Stevenson et al., 2005
- Adegbola et al., 2008
- Shohrbridge et al., 2010
- Assumpcao et al., 1999
- Jamain et al., 2003
- Wada and Gibbons, 2003
- Hynes et al., 2010; Marin et al., 2010
- Longo et al., 2003; Meloni et al., 2002
- Vervoort et al., 2002
- Addington et al., 2011; Laumann et al., 2010
- Chiyonobu et al., 2007; Wu et al., 2007
- Kutsche et al., 2000
- Hagerman et al., 2010
- Stettner et al., 2011
- Poo–Arguelles et al., 2006; Sempere et al., 2009a
- Carney et al., 2003
- Giannandrea et al., 2010