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# **Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting**

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## **Abstract**

There is increasing evidence that autism spectrum disorders (ASDs) can arise from rare highly penetrant mutations and genomic imbalances. The rare nature of these variants, and the often differing orbits of clinical and research geneticists, can make it difficult to fully appreciate the extent to which we have made progress in understanding the genetic etiology of autism. In fact, there is a persistent view in the autism research community that there are only a modest number of autism loci known. We carried out an exhaustive review of the clinical genetics and research genetics literature in an attempt to collate all genes and recurrent genomic imbalances that have been implicated in the etiology of ASD. We provide data on 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior. These genes and loci have all been causally implicated in intellectual disability, indicating that these two neurodevelopmental disorders share common genetic bases. A genetic overlap between ASD and epilepsy is also apparent in many cases. Taken together, these findings clearly show that autism is not a single clinical entity but a behavioral manifestation of tens or perhaps hundreds of genetic and genomic disorders. Increased recognition of the etiological heterogeneity of ASD will greatly expand the number of target genes for neurobiological investigations and thereby provide additional avenues for the development of pathway-based pharmacotherapy. Finally, the data provide strong support for high-resolution DNA microarrays as well as whole-exome and whole-genome sequencing as critical approaches for identifying the genetic causes of ASDs.

**Keywords:** autism; intellectual disability; mutation; copy number variation; deletion; duplication

### **Abbreviations:**

ASDs: autism spectrum disorders

CNV: copy number variation

ID: intellectual disability

PDD-NOS: pervasive developmental disorder not otherwise specified

## 1. Introduction

Autism is the most severe manifestation of a group of neurodevelopmental disabilities known as autism spectrum disorders (ASDs), which also include Asperger syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS). ASDs are characterized by impaired social interaction and communication and by restricted interests and repetitive behaviors. Over 70% of individuals with autism have intellectual disability (ID), while epilepsy occurs in ~25% (Baird et al., 2006; Tuchman and Rapin, 2002). ASDs are identified in about 1% of children (Baird et al., 2006) and are four times more common in males than in females. There is a strong genetic basis to ASDs, as indicated by the recurrence risk in families, twin studies, and the co-occurrence with chromosomal disorders and rare genetic syndromes. The genetic architecture of ASDs is highly heterogeneous (Abrahams and Geschwind, 2008). About 10–20% of individuals with an ASD have an identified genetic etiology. Microscopically visible chromosomal alterations have been reported in ~5% of cases; the most frequent abnormalities are 15q11-q13 duplications, and 2q37, 22q11.2 and 22q13.3 deletions. ASDs can also be due to mutations of single genes involved in autosomal dominant, autosomal recessive and X-linked disorders. The most common single gene mutation in ASDs is fragile X syndrome (*FMR1*), present in ~2% of cases. Other monogenic disorders described in ASD include tuberous sclerosis (*TSC1*, *TSC2*), neurofibromatosis (*NF1*), Angelman syndrome (*UBE3A*), Rett syndrome (*MECP2*) and *PTEN* mutations in patients with macrocephaly and autism. Rare mutations have been identified in synaptic genes, including *NLGN3*, *NLGN4X* (Jamain et al., 2003), *SHANK3* (Durand et al., 2007), and *SHANK2* (Berkel et al., 2010). Recent whole-genome microarray studies have revealed submicroscopic deletions and duplications, called copy number variation (CNV), affecting many loci and including *de novo* events in 5%–10% of ASD cases (Christian et al., 2008; Glessner et al., 2009; Marshall et al., 2008; Pinto et al., 2010; Sebat et al., 2007; Szatmari et al., 2007).

The accumulating number of distinct, individually rare genetic causes in ASD suggests that the genetic architecture of autism resembles that of ID, with many genetic and genomic disorders involved, each accounting for a small fraction of cases. In fact, all the known genetic causes of ASDs are also causes of ID, indicating that these two neurodevelopmental disorders share common genetic bases. An illustrative example is that of the X-linked neuroligin 4 (*NLGN4X*) gene, encoding a synaptic cell-adhesion protein. The first *NLGN4X* mutation was reported in a family with two brothers affected with ASD, one with autism and ID and the other with Asperger syndrome and normal intelligence (Jamain et al., 2003). Subsequently, a truncating mutation in *NLGN4X* was identified in a multi-generational pedigree with 13 affected males having either non-syndromic ID (10 individuals), ID with ASD (2 individuals) or ASD without ID (1 individual) (Laumonnier et al., 2004). This indicates that exploring ID genes in individuals with ASD can greatly expand the number of genes playing a causal role and identify additional molecular pathways.

Like ASDs, ID is a common and highly heterogeneous neurodevelopmental disorder, affecting 2%–3% of the population. About 25%–50% of ID is believed to be caused by genetic defects, and the

large number of X-linked forms account in part for the 30% higher prevalence of ID in males compared to females (for recent reviews, see (Ropers, 2010) and (Gecz et al., 2009)). Like in ASD, chromosomal abnormalities detected with conventional karyotyping account for about 5% of cases of ID, while novel molecular karyotyping methods have a diagnostic yield of 10%-15%. Again like in ASD, fragile X syndrome is the most common monogenic cause of ID. At least 50 genes have been identified that are associated with syndromic, or clinically distinctive, X-linked ID, and over 40 genes have been found to be associated with non-syndromic X-linked ID (Figure 1). In addition, numerous autosomal genes, both dominant and recessive, have been linked to non-syndromic and syndromic ID. The distinction between syndromic and non-syndromic ID is not precise, and several genes, initially identified in syndromic conditions, were later reported in subjects with non-syndromic forms (e.g., *ARX*, *CASK*, *JARID1C*, *FGD1* and *ATRX*).

Here, we review the different genetic and genomic disorders in which ASDs have been described as one of the possible manifestations. The findings indicate that, in contrast to a persisting claim that we know very little about the etiology of autism, there are more than 100, already identified, recurrent genetic defects than can cause ASD. All the genes and chromosomal rearrangements identified are well-known causes of ID, either syndromic or non-syndromic. Several have been involved in epilepsy, with or without ID, suggesting that this is another neurodevelopmental disorder that shares genetic risk factors with ASD. It is also of interest to see that the genes implicated in ASD go beyond those involved in synaptic function and affect a wide range of cellular processes.

## 2. Method

An extensive literature search was conducted looking for articles describing genetic disorders in patients with autism, ASD, pervasive developmental disorder, Asperger syndrome, PDD-NOS, or autistic/autistic-like traits/features/behavior, using PubMed and Google Scholar, as well as follow-up of references cited in the papers thus identified. The genetic disorders considered all can have neurological manifestations, most commonly ID and/or epilepsy.

For disorders for which the association with ASD is well known and for which many cases have been reported in the literature, representative references were selected. For rare or novel disorders, without a well-documented association with ASD, all the references identified were cited.

All the genetic evidence presented in this review is based on rare variant approaches, i.e., studies searching for sequence variants, chromosomal rearrangements, and CNV that are associated with high odds ratios and are hence subject to purifying selection. Results from common variant studies (as typically examined with candidate gene or genome-wide association analyses) were not included because of the absence of accepted, replicated findings with such approaches in ASD.

Mitochondrial disorders were not included in the literature review, although they are among the genetic disorders that can manifest with ASD.

### 3. Results

Table 1 presents a list of 103 known disease genes that have been reported to be mutated, deleted, duplicated, or disrupted by a translocation breakpoint in individuals with ASD or autistic features. Table 2 shows 44 recurrent genomic disorders and chromosomal aneuploidies reported in subjects with ASD/autistic traits. Only recurrent rearrangements were included. Fifteen genes from Table 1 are responsible for the phenotypic characteristics of microdeletion/microduplication syndromes listed in Table 2, for example *SHANK3* is involved in the 22q13 deletion syndrome (Phelan-McDermid syndrome), *EHMT1* in the 9q34.3 subtelomeric deletion syndrome (Kleefstra syndrome), and *MEF2C* in the 5q14.3 microdeletion syndrome.

Note that Table 2 includes several recently identified microdeletions and microduplications characterized by variable expressivity and/or incomplete penetrance, which have been reported in subjects with neurodevelopmental disorders as well as in unaffected parents and controls. These include CNVs at 1q21.1, 15q13.3, 16p13.11, 16p11.2 and 22q11.2. Some of these CNVs have been studied in very large samples of subjects with various neuropsychiatric disorders, including ID, epilepsy, ASD, and schizophrenia, and there appears to be a clear increased frequency in affecteds versus controls, suggesting that they might act as risk factors; for others, the clinical significance is less well established (see Table 2).

For some of the genes in Table 1, only a single case with ASD/autistic features (n=21) or a single family with 2-3 males with ASD/autistic features (n=6) were identified through the literature search. We can assume that in many instances other cases likely exist, which either escaped my attention or were not reported. These genes were included in this review on the assumption that what we are seeing reported in the literature is just the tip of the iceberg, given that the majority of individuals with ASD are not routinely screened for the presence of genetic disorders. Conversely, most geneticists and cytogeneticists do not evaluate their patients for the presence of ASD. Furthermore, it should be noted that some of the genetic disorders in Table 1 are very rare or newly described and hence only a handful of patients have been reported in the literature; therefore, the fact that there is only one case or family with ASD among the few reported might actually support a strong association with ASD (e.g., *KIAA2022* and *ARHGEF6*, two X-linked ID genes found to be mutated in single extended pedigrees, and *PRSS12* and *GATM*, two autosomal recessive genes reported in only 3 families each) (see Table 1 for references). In other cases, support for the implication of a given gene in ASD comes from the description of other subjects with the same genetic syndrome and mutations in related genes. For instance, although only one case with autism and *NPHP1* mutations was identified in the literature, the comorbidity of Joubert syndrome with ASD is well recognized and other Joubert syndrome genes associated with ciliary dysfunction have been reported in ASD (*AH11*, *CEP290*, *RPGRIP1L*). The role of *GUCY2D*, involved in Leber congenital amaurosis, another ciliopathy, is supported by the Joubert syndrome genes and by *RPE65*, another cause of Leber congenital amaurosis reported in subjects with ASD. Similarly, the Costello syndrome gene *HRAS* garners support from other mutations in the RAS/MAPK signaling pathway involved in cardio-facio-cutaneous

syndrome and Noonan syndrome, which overlap with Costello syndrome, and described in ASD (*PTPN11*, *KRAS*, *BRAF*, *MEK1*). *POMT1*, involved in limb-girdle muscular dystrophy, is supported by other dystroglycan-related muscular dystrophies reported in ASD, such as muscle-eye-brain disease (*POMGnT1*) and Duchenne and Becker muscular dystrophies (*DMD*). Finally, *SMC1A*, responsible for 5% of cases of Cornelia de Lange syndrome, has been reported to be mutated in a single case with autistic behavior, but numerous *NIPBL* mutations (responsible for 60% of cases of Cornelia de Lange syndrome) have been reported in ASD.

#### **4. Discussion**

Our exhaustive review of the current literature identified more than 100 loci for which there is evidence for a causal role in ASDs. The majority have not been explored in ASD. Sequencing would be required to identify many of these mutations but to date only very targeted sequencing approaches have been performed in ASD research. There is every reason to believe that with whole-exome and whole-genome sequencing approaches mutations in these genes will be identified in additional cases, and many more ASD loci will be discovered.

##### *4.1. Limitations*

Several limitations of this review should be taken into account when interpreting these gene/loci lists. First, the diagnostic information concerning ASD was not always comprehensive. The diagnostic methods employed in the studies examined are very variable, and in many instances no standardized diagnostic assessments were used. Many cases were reported in genetics journals where the main emphasis is on describing the mutation and the physical findings, while the behavioral presentation is described with great brevity. “Autistic features” or “autistic behavior” are often reported, with no indication of whether a formal diagnostic evaluation was performed. Moving forward, patients with genetically determined syndromes should be assessed by clinicians with expertise in ASD, using reliable diagnostic assessment tools, to carefully characterize the behavioral phenotypes.

Second, the degree of ID of the individual clearly impacts the development and presentation of ASD-like characteristics, and caution should be taken when assessing ASD manifestations in genetic syndromes associated with severe ID. Nevertheless, the degree of cognitive impairment cannot entirely account for the increased prevalence of ASD in some of these syndromes.

Third, for most genetic disorders, no reliable estimates of either the prevalence of ASD among affected individuals or the prevalence of the disorder among patients with ASD are available. Even in medical conditions for which prevalence studies have been conducted, the rates vary, due in part to differing diagnostic criteria and assessment techniques, as well as the populations surveyed (e.g., rates vary depending on the proportion of individuals with ID, epilepsy, syndromic vs. non-syndromic forms, sporadic vs. multiplex families). Moreover, the vast majority of studies exploring the frequency of a particular genetic disorder among patients with ASD or the frequency of ASD in particular syndrome groups are not population-based (and hence are subject to referral biases,

which might contribute to overestimation of severely affected subjects) and the study samples are usually quite small. 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 disorders.

Fourth, in a few reports, especially in the older studies, some of the syndromes were diagnosed clinically, when the gene/microdeletion had not yet been identified (e.g., Sotos syndrome, Lujan-Fryns syndrome, Aarskog-Scott syndrome).

Finally, in several instances where only one or very few cases with ASD have been reported, it is not possible to determine whether the genetic abnormalities are etiologically causative of ASD or comorbid conditions. Although it is possible that the patients' ASD is unrelated to the genetic disorders, parsimony suggests a causative relationship. Indeed, it would be difficult to assume that a genetic defect plays a causative role in the cognitive impairment of the patients but not in the ASD manifestations.

Notwithstanding these caveats, the evidence provided here indicates that careful study of the overlap of ASD with genetic syndromes involved in ID and epilepsy is warranted. Large-scale studies of well-characterized samples to evaluate the frequency of these genetic defects in autism as well as the frequency of autism in specific genetic disorders need to be performed. Detailed investigation of ASD phenomenology within individual genetically determined syndromes, taking into account the intellectual functioning and looking also for the presence of other neuropsychiatric disorders such as obsessive compulsive disorder, attention deficit-hyperactivity disorder, schizophrenia and bipolar disorder, would contribute to strengthen the emerging notion of shared genetic bases among some or all of these conditions.

#### 4.2. Findings

Even from the results to date, several important dimensions emerge. First, in some disorders, ASD is among the clinical hallmarks. Disorders known for their high comorbidity with ASD include 22q13 deletion syndrome/*SHANK3* mutations, maternal 15q11-q13 duplications, Rett syndrome (*MECP2*), fragile X syndrome (*FMR1*), tuberous sclerosis (*TSC1*, *TSC2*), adenylosuccinate lyase deficiency (*ADSL*), Timothy syndrome (*CACNA1C*), cortical dysplasia-focal epilepsy syndrome (*CNTNAP2*), and Smith-Lemli-Opitz syndrome (*DHCR7*) (see Tables 1 and 2 for references). Other disorders with common ASD manifestations are brain creatine deficiency (*SLC6A8*, *GAMT*, *GATM*), Cornelia de Lange syndrome (*NIPBL*, *SMC1A*, *SMC3*), CHARGE syndrome (*CHD7*), Cohen syndrome (*VPS13B*), Joubert syndrome and related syndromes (*INPP5E*, *TMEM216*, *AHI1*, *NPHP1*, *CEP290*, *TMEM67*, *RPGRIP1L*, *ARL13B*, *CC2D2A*, *OFD1*), myotonic dystrophy type 1 (*DMPK*), X-linked female-limited epilepsy and ID (*PCDH19*), Cri du Chat syndrome (5p deletion), Williams syndrome (7q11.23 deletion), 7q11.23 duplication syndrome, WAGR syndrome (11p13 deletion), Angelman and Prader-Willi syndromes (15q11-q13 deletion), 16p11.2 microdeletion and microduplication, Smith-Magenis syndrome (17p11.2 deletion), Potocki-Lupski syndrome (17p11.2 duplication), 22q11 deletion syndrome



(velocardiofacial/DiGeorge syndrome), 22q11 duplication syndrome, and Xq28 duplication syndrome (*MECP2*). In other disorders, ASDs appear to be a less frequent but repeatedly reported manifestation, such as in Duchenne and Becker muscular dystrophies (*DMD*), *PTEN* related syndromes, cardio-facio-cutaneous syndrome (*KRAS*, *BRAF*, *MAP2K1*, *MAP2K2*), Noonan syndrome (*PTPN11*), 2q37 deletion syndrome, 9q subtelomeric deletion syndrome/*EHMT1* mutations (Kleefstra syndrome), and 15q24 microdeletion syndrome. Finally, certain chromosomal aneuploidies carry an increased risk for autism/ASD, including Down syndrome, Turner syndrome, Klinefelter syndrome (XXY), XYY syndrome, XXYY syndrome and 45,X/46,XY mosaicism.

Second, the results challenge a common misconception that genetic disorders are only identified in individuals with syndromic ASD, i.e., that present with dysmorphic features and other malformations. This is not the case. Some of these disorders can be observed in children that present only with ASD and ID, with no associated dysmorphic features, including 15q11-q13 duplications, 2q37 deletions, 22q13 deletions, and 16p11.2 microdeletion/microduplication, to name but a few. Many genes involved in non-syndromic ID have also been implicated in non-syndromic ASD (see Table 1 and Figure 1). This underscores the need for genetic explorations in individuals with ASD, regardless of whether they have other abnormal phenotypic findings.

Third, genetic defects are not exclusively found in patients with autism and ID, some are present in patients without ID, including individuals with Asperger syndrome. Genetic disorders reported in Asperger syndrome include Steinert myotonic dystrophy 1 (Blondis et al., 1996; Paul and Allington-Smith, 1997), 3q29 microdeletion (Baynam et al., 2006), 15q13.3 microdeletion (Ben-Shachar et al., 2009), 22q13 duplication including *SHANK3* (Durand et al., 2007), *NRXN1* deletion (Wisniewiecka-Kowalnik et al., 2010), *PTEN* mutation, Bannayan-Riley-Ruvalcaba syndrome (Lynch et al., 2009), *MED12* mutation, Lujan-Fryns syndrome (Schwartz et al., 2007), 22q11 deletion syndrome/DiGeorge syndrome (Gothelf et al., 2004; Pinto et al., 2010), *TBX1* mutation, 22q11 deletion syndrome phenotype (Paylor et al., 2006), *NLGN3* mutation (Jamain et al., 2003), *NLGN4X* mutation (Jamain et al., 2003), *PCDH19* mutation, X-linked female-limited epilepsy and cognitive impairment (Hynes et al., 2010), *IL1RAPL1* mutation (Piton et al., 2008), *NHS* mutation, Nance-Horan syndrome (unpublished), fragile X syndrome (Hagerman et al., 1994), fragile X premutation (Aziz et al., 2003), Klinefelter syndrome (van Rijn et al., 2008), XYY syndrome (Gillberg, 1989), and 45,X/46,XY mosaicism (Fontenelle et al., 2004).

## 5. Conclusion

The data presented in this review makes it abundantly clear that autism represents the final common pathway for numerous genetic brain disorders. Many well-recognized "ID genes" (which in fact do not cause ID in all affected individuals) can also cause ASD, with or without ID. Similarly, several genes initially identified in epilepsy samples can also result in ASD and ID. These findings indicate that these genes cause a continuum of neurodevelopmental disorders that manifest in different ways depending on other genetic, environmental or stochastic factors.

The literature review indicates that more data is needed on the estimates of prevalence of specific genetic disorders in ASD, and of ASD in genetic disorders, as the existing data are limited and not accurate. Many practitioners are reluctant to give an additional ASD diagnosis in the presence of a genetic disorder. However, this practice is not helpful to the families as the autistic behavior is sometimes the most disruptive facet of the child's problems, and the ASD diagnosis is crucial in ensuring that children receive appropriate behavioral management and educational placement, not otherwise available for individuals with genetic syndromes.

Thanks to novel methods for high-throughput whole-exome and whole-genome sequencing, together with rapidly decreasing costs, it will soon be possible to screen large ASD cohorts for mutations in all these genes and to identify additional ASD genes and loci. These results will have important implications for the patients and their families, in terms of etiological diagnosis, genetic counseling and patient care. The increase in the number of disease genes available for neurobiological investigations will provide additional targets for the development of pathway pharmacotherapy.

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**Table 1. Disease genes and genetic disorders reported in individuals with ASD/autistic traits**

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
<i>POMGNT1</i>	O-linked mannose	1p34.1	Muscle-eye-brain disease (congenital muscular dystrophy, structural eye abnormalities and lissencephaly)	AR	(Haliloglu et al., 2004; Hehr et al., 2007)
<i>RPE65</i>	retinal pigment epithelium-specific protein	1p31.3	Leber congenital amaurosis	AR	(Coppieters et al., 2010; Yzer et al., 2003)
<i>NRXN1</i>	neurexin 1	2p16.3	Disrupted in ASD, ID, and other neurodevelopmental and psychiatric disorders (autosomal dominant?); Pitt-Hopkins-like syndrome-2 (autosomal recessive)	AD?/AR (Pitt-Hopkins-like)	(Ching et al., 2010; Glessner et al., 2009; Guilmatre et al., 2009; Kim et al., 2008; Pinto et al., 2010; Szatmari et al., 2007; Wisniowiecka-Kowalnik et al., 2010; Zweier et al., 2009)
<i>NPHP1</i>	nephrocystin-1	2q13	Joubert syndrome 4 and nephronophthisis (see <i>AHI1</i> below, 6q23.3)	AR	(Tory et al., 2007)†
<i>MBD5*</i>	methyl-CpG binding domain protein 5	2q23.1	<i>MBD5</i> is the only gene deleted in all subjects with the 2q23.1 microdeletion syndrome	AD	(Jaillard et al., 2009; van Bon et al., 2010)
<i>SCN1A</i>	sodium channel, voltage-gated, type I, alpha	2q24.3	Severe myoclonic epilepsy of infancy (Dravet syndrome); ASD or autistic features have been reported repeatedly	AD	(Caraballo and Fejerman, 2006; Cassé-Perrot et al., 2001; Kimura et al., 2005; Livingston et al., 2009; Madia et al., 2006; Marini et al., 2009; Riva et al., 2009)
<i>SATB2*</i>	SATB homeobox 2	2q33.1	Haploinsufficiency of <i>SATB2</i> causes some of the clinical features of the 2q33.1 microdeletion syndrome, including severe ID, cleft palate and tooth anomalies. <i>SATB2</i> was disrupted in an individual with ASD carrying a balanced translocation	AD	(Marshall et al., 2008; Van Buggenhout et al., 2005)
<i>FOXP1</i>	forkhead box P1 isoform 1	3p14.1	Autosomal dominant non-syndromic ID and ASD; disrupted in two patients with ID and autism/ASD	AD	(Hamdan et al., 2010)
<i>BTD</i>	biotinidase	3p24.3	Biotinidase deficiency	AR	(Zaffanello et al., 2003)†
<i>PRSS12</i>	neurotrypsin precursor (protease, serine, 12)	4q26	Autosomal recessive non-syndromic ID; mutated in 3 consanguineous families from North Africa, including one with two brothers with autism and ID	AR	(Betancur et al., 2004)†
<i>NIPBL</i>	delangin (Drosophila Nipped-B homolog)	5p13.2	Cornelia de Lange syndrome (facial dysmorphism, upper limb malformations, growth and cognitive retardation) is caused by mutations in <i>NIPBL</i> (60%), <i>SMC1A</i> (5%), and <i>SMC3</i> (1 patient). ASD has been reported in subjects with <i>NIPBL</i> and <i>SMC1A</i> mutations. 47-67% of individuals with de Lange syndrome have autism/ASD	AD	(Basile et al., 2007; Berney et al., 1999; Bhuiyan et al., 2006; Moss et al., 2008; Oliver et al., 2008)
<i>MEF2C*</i>	myocyte enhancer factor 2C	5q14.3	<i>MEF2C</i> is responsible for the 5q14.3 microdeletion syndrome; both mutations and deletions have been described in individuals with ASD or autistic behavior	AD	(Berland and Houge, 2010; Novara et al., 2010; Nowakowska et al., 2010; Zweier et al., 2010)
<i>ALDH7A1</i>	aldehyde dehydrogenase 7 family, member A1	5q23.2	Pyridoxine-dependent epilepsy (antiquitin deficiency) is a rare disorder characterized by early onset seizures that are controlled by pyridoxine (vitamin B6). Among 64 published <i>ALDH7A1</i> mutations, at least 3 have been reported with autism or autistic features	AR	(Bennett et al., 2009; Burd et al., 2000; Mills et al., 2010)

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
<i>NSD1*</i>	nuclear receptor binding SET domain protein 1	5q35.2-q35.3	Sotos syndrome (overgrowth syndrome characterized by macrocephaly, advanced bone age, characteristic facial features and learning disabilities). The proportion of subjects with Sotos that have ASD is unknown, as only isolated cases have been reported	AD	(Battaglia and Carey, 2006; Bolton et al., 2004; Kielinen et al., 2004; Miles and Hillman, 2000; Morrow et al., 1990; Mouridsen and Hansen, 2002; Schaefer and Lutz, 2006; Trad et al., 1991)
<i>ALDH5A1</i>	aldehyde dehydrogenase 5 family, member A1	6p22.2	Succinic semialdehyde dehydrogenase deficiency (gamma-hydroxybutyric aciduria); 12% (4/33) have autistic features	AR	(Knerr et al., 2008; Pearl et al., 2003)
<i>AHI1</i>	Abelson helper integration site 1	6q23.3	Joubert syndrome 3. Joubert syndrome is a clinically and genetically heterogeneous group of ciliopathies characterized by cerebellar ataxia, ID and breathing abnormalities, sometimes including retinal dystrophy and renal disease. ASD is a relatively frequent finding in patients with Joubert syndrome, present in 13-36% of patients. Ten genes have been implicated in Joubert syndrome, but so far, only 4 have been reported to be mutated in subjects with ASD/autistic traits	AR	(Ozonoff et al., 1999; Takahashi et al., 2005)
<i>SYNGAP1</i>	synaptic Ras GTPase activating protein 1	6p21.32	Non-syndromic ID	AD	(Pinto et al., 2010)†
<i>HOXA1</i>	homeobox A1	7p15.2	<i>HOXA1</i> syndrome, Bosley-Salih-Alorainy variant (horizontal gaze abnormalities, deafness, facial weakness, hypoventilation, cardiovascular malformations, ID and ASD); 2/9 patients meet criteria for autism	AR	(Bosley et al., 2007)
<i>BRAF</i>	B-Raf	7q34	Cardio-facio-cutaneous syndrome is caused by gain of function mutations in <i>KRAS</i> , <i>BRAF</i> , <i>MEK1</i> , or <i>MEK2</i> . CFC syndrome shows phenotypic overlap with Noonan syndrome and Costello syndrome. Among patients with CFC syndrome, 23% (5/22) have autism/autistic features	AD	(Denayer et al., 2010; Nava et al., 2007; Nystrom et al., 2008; Yoon et al., 2007)
<i>CNTNAP2</i>	contactin associated protein-like 2	7q35-q36.1	Cortical dysplasia-focal epilepsy syndrome and Pitt-Hopkins-like syndrome-1 are autosomal recessive disorders. Deletions or chromosomal rearrangements disrupting a single copy of <i>CNTNAP2</i> have been reported in patients with ASD, ID, epilepsy, schizophrenia and bipolar disorder as well as in healthy subjects; however, the clinical significance of the disruption of only one allele is unknown	AR (AD too?)	(Strauss et al., 2006; Zweier et al., 2009)
<i>CHD7</i>	chromodomain helicase DNA binding protein 7	8q12.2	CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies); 68% (17/25) have ASD/autistic traits	AD	(Hartshorne et al., 2005; Johansson et al., 2006; Smith et al., 2005)
<i>VPS13B</i>	vacuolar protein sorting 13 homolog B	8q22.2	Cohen syndrome (ID, microcephaly, facial dysmorphism, obesity, retinal dystrophy, and neutropenia); 49% (22/45) meet criteria for autism	AR	(Howlin et al., 2005)
<i>POMT1</i>	protein-O-mannosyltransferase 1	9q34.13	Limb-girdle muscular dystrophy with ID; Walker-Warburg syndrome	AR	(D'Amico et al., 2006)†

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<i>TSC1</i>	tuberous sclerosis 1	9q34.13	Tuberous sclerosis is caused by mutations in the <i>TSC1</i> or <i>TSC2</i> genes. The frequency of tuberous sclerosis among patients with ASD in epidemiological samples is ~1%; the frequency of ASD in subjects with tuberous sclerosis varies between 16-60%	AD	(Fombonne et al., 1997; Gillberg et al., 1994; Lewis et al., 2004; Muzykewicz et al., 2007; Wong, 2006)
<i>EHMT1*</i>	euchromatic histone-lysine N-methyltransferase 1	9q34.3	<i>EHMT1</i> is responsible for the core phenotype of the 9q subtelomeric deletion syndrome (Kleefstra syndrome). 23% (5/22) of subjects with Kleefstra syndrome due to deletions or mutations have ASD/autistic features	AD	(Anderlid et al., 2002; Dawson et al., 2002; Iwakoshi et al., 2004; Kleefstra et al., 2005; Kleefstra et al., 2009; Sahoo et al., 2006b)(Autism Genome Project, unpublished)
<i>PTEN</i>	phosphatase and tensin homolog	10q23.31	<i>PTEN</i> hamartoma-tumor syndrome (including Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome); ID and ASD with macrocephaly. The frequency of <i>PTEN</i> mutations in children with ASD and macrocephaly is unknown; in one study, 15% (4/26) of children with <i>PTEN</i> mutations had ASD	AD	(Butler et al., 2005; Buxbaum et al., 2007; Delatycki et al., 2003; Goffin et al., 2001; Keller et al., 2003; Lynch et al., 2009; McBride et al., 2010; Orrico et al., 2009; Stein et al., 2010; Tan et al., 2007; Varga et al., 2009)
<i>FGFR2</i>	fibroblast growth factor receptor 2	10q26.13	Apert syndrome	AD	(Morey-Canellas et al., 2003)†
<i>HRAS</i>	v-Ha-ras Harvey rat sarcoma viral oncogene	11p15.5	Costello syndrome	AD	(Kerr et al., 2006)†
<i>IGF2*</i>	insulin-like growth factor 2	11p15.5	Aberrant imprinting of <i>IGF2</i> is associated with Beckwith-Wiedemann syndrome and Silver-Russell syndrome, characterized by growth abnormalities. Both disorders have been reported in ASD; 7% (6/87) of children with Beckwith-Wiedemann syndrome have ASD	AD	(Kent et al., 2008a)
<i>DHCR7</i>	7-dehydrocholesterol reductase	11q13.4	Smith-Lemli-Opitz syndrome is an inborn error of metabolism affecting cholesterol biosynthesis. The rate of ASD in this syndrome is high: 53% (9/17) meet criteria for autism and 71% (10/14) have ASD, according to two studies	AR	(Sikora et al., 2006; Tierney et al., 2006)
<i>SHANK2</i>	SH3 and multiple ankyrin repeat domains 2	11q13.3	3 <i>de novo</i> deletions and 1 stop mutation were reported recently in patients with non-syndromic ASD and ID	AD	(Berkel et al., 2010; Pinto et al., 2010)
<i>CACNA1C</i>	calcium channel, voltage-dependent, L type, alpha 1C subunit	12p13.33	Timothy syndrome (long QT syndrome with syndactyly). Among 5 children with Timothy syndrome, 3 had autism, one had ASD, and one had severe language delay	AD	(Splawski et al., 2004)
<i>KRAS</i>	c-K-ras2	12p12.1	Cardio-facio-cutaneous syndrome	AD	(Nava et al., 2007; Nystrom et al., 2008)
<i>CEP290 (NPHP6)</i>	centrosomal protein 290kDa	12q21.32	Joubert syndrome 5; Leber congenital amaurosis (see <i>AHI1</i> above, 6q23.3)	AR	(Coppieters et al., 2010; Perrault et al., 2007; Tory et al., 2007)
<i>PAH</i>	phenylalanine hydroxylase	12q23.2	Phenylketonuria was identified as a cause of ASD in older studies, but it is no longer observed where neonatal testing exists	AR	(Baieli et al., 2003; Steiner et al., 2007; van Karnebeek et al., 2002)
<i>PTPN11</i>	protein tyrosine phosphatase, non-receptor type 11	12q24.13	Noonan syndrome (craniofacial anomalies, short stature, heart defects). In a sample of 65 children with Noonan syndrome, 8% had a diagnosis of ASD	AD	(Ghaziuddin et al., 1994; Paul et al., 1983; Pierpont et al., 2009; Swillen et al., 1996)
<i>FOXP1</i>	forkhead box G1	14q12	Deletions and mutations cause a congenital variant of Rett syndrome, duplications are associated with ID, severe speech delay, and epilepsy	AD	(Brunetti-Pierri et al., 2010; Philippe et al., 2010)
<i>L2HGDH</i>	L-2-hydroxyglutarate dehydrogenase	14q22.1	L-2-hydroxyglutaric aciduria	AR	(Zafeiriou et al., 2008)†

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<i>UBE3A</i> *	ubiquitin protein ligase E3A	15q11.2	Angelman syndrome is an imprinting disorder caused by maternal deletion of chromosome 15, paternal uniparental disomy, imprinting defect, or <i>UBE3A</i> mutation. Over one-half of the patients with Angelman syndrome have ASD	AD	(Bonati et al., 2007; Sahoo et al., 2006a; Trillingsgaard and Østergaard, 2004)
<i>GATM</i> ( <i>AGAT</i> )	glycine amidinotransferase	15q21.1	Arginine:glycine amidinotransferase (AGAT) deficiency (brain creatine deficiency, synthesis defect) has been described in only three families with 6 affected; autistic features were reported in one	AR	(Battini et al., 2002)†
<i>MAP2K1</i> ( <i>MEK1</i> )	mitogen-activated protein kinase kinase 1	15q22.31	Cardio-facio-cutaneous syndrome	AD	(Nava et al., 2007)
<i>TSC2</i>	tuberous sclerosis 2	16p13.3	Tuberous sclerosis is caused by mutations in the <i>TSC1</i> or <i>TSC2</i> genes (see <i>TSC1</i> above, 9q34.13)	AD	(Fombonne et al., 1997; Gillberg et al., 1994; Lewis et al., 2004; Muzykewicz et al., 2007; Wong, 2006)
<i>CREBBP</i> *	CREB binding protein	16p13.3	Rubinstein-Taybi syndrome (ID, characteristic facial features, broad thumbs and great toes). Mutations in <i>EP300</i> can also cause Rubinstein-Taybi syndrome (in 3%) but have not been reported in ASD	AD	(Schorry et al., 2008)
<i>RPGRIP1L</i>	RPGRIP1-like (retinitis pigmentosa GTPase regulator-like)	16q12.2	Joubert syndrome 7, Meckel syndrome, COACH syndrome (Joubert syndrome with congenital hepatic fibrosis)	AR	(Doherty et al., 2010)
<i>PAFAH1B1</i> *	platelet-activating factor acetylhydrolase, isoform lb, subunit 1	17p13.3	Deletions or point mutations of <i>PAFAH1B1</i> ( <i>LIS1</i> ) result in isolated lissencephaly; extended deletions including <i>YWHAE</i> cause Miller-Dieker syndrome; microduplications of <i>PAFAH1B1</i> cause ID and subtle brain abnormalities. 30% (12/40) of patients with <i>PAFAH1B1</i> point mutations or intragenic deletions have moderate to severe autistic features	AD	(Bi et al., 2009; Bruno et al., 2010; Saillour et al., 2009)
<i>YWHAE</i> *	tyrosine 3/tryptophan 5 - monooxygenase	17p13.3	Deletions including <i>YWHAE</i> are associated with Miller-Dieker syndrome, a contiguous gene syndrome; <i>YWHAE</i> is thought to be responsible for the more severe brain phenotype compared to deletions affecting only <i>PAFAH1B1</i> ; 17p13.3 microduplications mapping to the Miller-Dieker critical region have also been identified. Only microduplications have been reported in ASD	AD	(Bi et al., 2009; Bruno et al., 2010)
<i>GUCY2D</i>	guanylate cyclase 2D, membrane	17p13.1	Leber congenital amaurosis	AR	(Coppieters et al., 2010)†
<i>RAI1</i> *	retinoic acid induced 1	17p11.2	Deletions or mutations of <i>RAI1</i> cause Smith-Magenis syndrome; duplications result in Potocki-Lupski syndrome. ASDs are observed frequently in both syndromes	AD	(Hicks et al., 2008; Nakamine et al., 2008; Park et al., 1998; Potocki et al., 2007; Schaefer and Lutz, 2006; Smith et al., 1986; Stratton et al., 1986; Treadwell-Deering et al., 2010; Udwin, 2002; Vostanis et al., 1994)
<i>RNF135</i>	ring finger protein 135 isoform 1	17q11.2	Mutations in <i>RNF135</i> , which is within the <i>NF1</i> microdeletion region, cause overgrowth, ID, and dysmorphic features, demonstrating that haploinsufficiency of <i>RNF135</i> contributes to the phenotype of <i>NF1</i> microdeletion cases	AD	(Douglas et al., 2007)



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<i>NF1*</i>	neurofibromin 1	17q11.2	Neurofibromatosis type 1. The frequency of neurofibromatosis among patients with ASD is ~0.5%; the frequency of ASD in subjects with neurofibromatosis is 4% (3/74)	AD	(Fombonne et al., 1997; Schaefer and Lutz, 2006; Vazna et al., 2008; Williams and Hersh, 1998)
<i>SGSH</i>	N-sulfoglucosamine sulfohydrolase	17q25.3	Sanfilippo syndrome A (mucopolysaccharidosis III A)	AR	(Petit et al., 1996; Ritvo et al., 1990; Wolanczyk et al., 2000)
<i>NFIX</i>	nuclear factor I/X	19p13.13	Sotos-like overgrowth syndrome with advanced bone age, macrocephaly, ID, scoliosis, and unusual facial features	AD	(Malan et al., 2010)
<i>GAMT</i>	guanidinoacetate N-methyltransferase	19p13.3	Guanidine acetate methyltransferase (GAMT) deficiency (brain creatine deficiency, synthesis defect)	AR	(Sempere et al., 2009b)
<i>DMPK</i>	myotonic dystrophy protein kinase	19q13.32	Myotonic dystrophy 1 (Steinert disease). In a study of 57 children and adolescents with myotonic dystrophy 1, 49% had ASD (including 35% with autism). Several individuals with Asperger syndrome have been reported	AD	(Blondis et al., 1996; Ekstrom et al., 2008; Paul and Allington-Smith, 1997; Yoshimura et al., 1989)
<i>MKKS</i>	McKusick-Kaufman syndrome	20p12.2	Bardet-Biedl syndrome is a ciliopathy, like Joubert syndrome	AR	(Barnett et al., 2002; Moore et al., 2005)
<i>TBX1*</i>	T-box 1	22q11.21	22q11 deletion syndrome phenotype (velocardiofacial/DiGeorge syndrome); mutated in a male with velocardiofacial syndrome and Asperger syndrome	AD	(Paylor et al., 2006)†
<i>ADSL</i>	adenylosuccinate lyase	22q13.1	Adenylosuccinate lyase deficiency; ~50% present autism/autistic features	AR	(Jaeken and Van den Berghe, 1984; Spiegel et al., 2006)
<i>SHANK3*</i>	SH3 and multiple ankyrin repeat domains 3	22q13.33	22q13 deletion syndrome (Phelan-McDermid syndrome) is caused by deletions of <i>SHANK3</i> ; ASD or autistic features are frequent. <i>SHANK3</i> mutations have also been reported in individuals with ASD	AD	(Dhar et al., 2010; Durand et al., 2007; Gauthier et al., 2009; Guilmatre et al., 2009; Manning et al., 2004; Moessner et al., 2007; Prasad et al., 2000)
<i>NLGN4X</i>	neuroligin 4, X-linked	Xp22.31-p22.32	Non-syndromic X-linked ID and/or ASD; both mutations and deletions have been reported	XL	(Baris et al., 2007; Jamain et al., 2003; Kent et al., 2008b; Laumonnier et al., 2004; Lawson-Yuen et al., 2008; Marshall et al., 2008)
<i>MID1</i>	midline 1	Xp22.2	Opitz syndrome (Opitz/BBB syndrome)	XL	(Cox et al., 2000; Hsieh et al., 2008)
<i>AP1S2</i>	adaptor-related protein complex 1, sigma 2 subunit	Xp22.2	X-linked ID and autism syndrome characterized by hypotonia, speech delay, aggressive behavior, and brain calcifications	XL	(Borck et al., 2008)‡
<i>NHS</i>	Nance-Horan syndrome	Xp22.13	Nance-Horan syndrome (congenital cataracts and dental anomalies)	XL	(Toutain et al., 1997)(PARIS study, unpublished)
<i>CDKL5</i>	cyclin-dependent kinase-like 5	Xp22.13	Rett-like syndrome with infantile spasms and severe ID in female patients	XL	(Archer et al., 2006; Russo et al., 2009; Weaving et al., 2004)
<i>PTCHD1</i>	patched domain containing 1	Xp22.11	X-linked ID and ASD; deletions and mutations reported recently	XL	(Marshall et al., 2008; Noor et al., 2010; Pinto et al., 2010)
<i>ARX</i>	aristaless related homeobox	Xp21.3	Large spectrum of ID phenotypes, including X-linked lissencephaly and abnormal genitalia, West syndrome, Partington syndrome, and non-syndromic ID	XL	(Nawara et al., 2006; Partington et al., 2004; Romero-Rubio et al., 2008; Turner et al., 2002)
<i>IL1RAPL1</i>	interleukin 1 receptor accessory protein-like 1	Xp21.2-p21.3	Non-syndromic X-linked ID and/or ASD	XL	(Bhat et al., 2008; Pinto et al., 2010; Piton et al., 2008)

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<i>DMD</i>	dystrophin	Xp21.1-21.2	Muscular dystrophy, Duchenne and Becker types; in one study, 19% (16/85) met criteria for ASD	XL	(Erturk et al., 2010; Hendriksen and Vles, 2008; Hinton et al., 2009; Komoto et al., 1984; Kumagai et al., 2001; Wu et al., 2005; Young et al., 2008; Zwaigenbaum and Tarnopolsky, 2003)
<i>OTC</i>	ornithine carbamoyltransferase	Xp11.4	Ornithine transcarbamylase deficiency	XL	(Gorker and Tuzun, 2005)†
<i>CASK</i>	calcium/calmodulin-dependent serine protein kinase	Xp11.4	Variable phenotypes, ranging from non-syndromic mild ID to severe ID with microcephaly, brain malformations, congenital nystagmus and dysmorphic facial features	XL	(Hackett et al., 2010)†
<i>NDP</i>	norrin	Xp11.3	Norrie Disease (oculoacousticocerebral dysplasia)	XL	(Halpin and Sims, 2008; Schuback et al., 1995)
<i>ZNF674</i>	zinc finger family member 674	Xp11.3	Non-syndromic X-linked ID	XL	(Lugtenberg et al., 2006)†
<i>PQBP1</i>	polyglutamine binding protein 1	Xp11.23	Large spectrum of ID phenotypes, including Renpenning syndrome (microcephaly, short stature, small testes and dysmorphic features) and non-syndromic ID	XL	(Cossee et al., 2006; Stevenson et al., 2005)
<i>SYN1</i>	synapsin I	Xp11.23	X-linked epilepsy with variable learning disabilities and behavior disorders	XL	(Garcia et al., 2004)†
<i>ZNF81</i>	zinc finger protein 81	Xp11.23	Non-syndromic X-linked ID	XL	(Kleefstra et al., 2004)†
<i>FTSJ1</i>	FtsJ homolog 1	Xp11.23	Non-syndromic X-linked ID	XL	(Froyen et al., 2007a)‡
<i>CACNA1F</i>	calcium channel, voltage-dependent, L type, alpha 1F subunit	Xp11.23	X-linked incomplete congenital stationary night blindness, severe form	XL	(Hemara-Wahanui et al., 2005)
<i>JARID1C</i>	jumonji, AT rich interactive domain 1C	Xp11.22	Large spectrum of phenotypes including ID with microcephaly, spasticity, short stature, epilepsy, and facial anomalies, as well as non-syndromic ID	XL	(Adegbola et al., 2008)†
<i>IQSEC2</i>	IQ motif and Sec7 domain 2	Xp11.22	Non-syndromic X-linked ID; mutations in 4 large pedigrees, 2 of which include individuals with ASD/autistic traits	XL	(Shoubridge et al., 2010)
<i>SMC1A</i>	structural maintenance of chromosomes 1A	Xp11.22	Cornelia de Lange syndrome (see <i>NIPBL</i> above, 5p13.2)	XL	(Deardorff et al., 2007)†
<i>PHF8</i>	PHD finger protein 8	Xp11.22	Siderius–Hamel syndrome (ID with cleft lip or cleft palate)	XL	(Qiao et al., 2008)‡
<i>FGD1</i>	faciogenital dysplasia protein	Xp11.22	Aarskog–Scott syndrome (faciogenital dysplasia); non-syndromic X-linked ID. Four cases with a clinical diagnosis of Aarskog–Scott syndrome and ASD/autistic features have been described (not confirmed molecularly)	XL	(Assumpcao et al., 1999; Taub and Stanton, 2008)
<i>OPHN1</i>	oligophrenin 1	Xq12	ID with cerebellar and vermis hypoplasia	XL	(Al-Owain et al., 2010; Froyen et al., 2007b)
<i>MED12</i>	mediator complex subunit 12	Xq13.1	Lujan-Fryns syndrome (X-linked ID with marfanoid habitus); 62.5% (20/32) of subjects with Lujan-Fryns syndrome have an autistic-like disorder	XL	(Lerma-Carrillo et al., 2006; Schwartz et al., 2007; Swillen et al., 1996)
<i>NLGN3</i>	neuroligin 3	Xq13.1	Mutations in <i>NLGN3</i> have been reported only in one family with two brothers with non-syndromic ASD, one with Asperger syndrome and the second with autism and ID	XL	(Jamain et al., 2003)‡
<i>KIAA2022</i>	hypothetical protein LOC340533	Xq13.3	X-linked ID, progressive quadriparesia, and autism	XL	(Cantagrel et al., 2004)‡

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
<i>ATRX</i>	transcriptional regulator ATRX	Xq21.1	Large spectrum of phenotypes including ATRX syndrome (alpha thalassemia/mental retardation syndrome X-linked) and non-syndromic X-linked ID	XL	(Gibbons, 2006; Pavone et al., 2010; Wada and Gibbons, 2003)
<i>PCDH19</i>	protocadherin 19	Xq22.1	X-linked female-limited epilepsy and cognitive impairment; ASD/autistic features are common: 22% (6/27) and 38% (5/13) in two studies	XL	(Depienne et al., 2009a; Dibbens et al., 2008; Hynes et al., 2010; Jamal et al., 2010; Marini et al., 2010; Scheffer et al., 2008)
<i>ACSL4 (FACL4)</i>	acyl-CoA synthetase long-chain family member 4	Xq22.3	Non-syndromic X-linked ID	XL	(Longo et al., 2003; Meloni et al., 2002)
<i>DCX</i>	doublecortin	Xq22.3	Type 1 lissencephaly	XL	(Leger et al., 2008)
<i>AGTR2</i>	angiotensin II receptor, type 2	Xq23	Non-syndromic X-linked ID	XL	(Vervoort et al., 2002)
<i>UPF3B</i>	UPF3 regulator of nonsense transcripts homolog B	Xq24	Non-syndromic X-linked ID with or without autism	XL	(Addington et al., 2010; Laumonnier et al., 2010)
<i>LAMP2</i>	lysosomal-associated membrane protein 2	Xq24	Danon disease (X-linked vacuolar cardiomyopathy and myopathy) is a lysosomal glycogen storage disorder	XL	(Burusnukul et al., 2008)†
<i>GRIA3</i>	glutamate receptor, ionotropic, AMPA 3	Xq25	Non-syndromic X-linked ID; mutations as well as 3 cases of partial duplication of <i>GRIA3</i> have been reported in patients with autism or autistic behavior	XL	(Chiyonobu et al., 2007; Guilmatre et al., 2009; Jacquemont et al., 2006; Wu et al., 2007)
<i>OCRL</i>	phosphatidylinositol polyphosphate 5-phosphatase	Xq25	Low syndrome or oculo-cerebro-renal syndrome (ID, bilateral cataract and renal Fanconi syndrome)	XL	(Fisher, 2005; Steffenburg et al., 2003)
<i>SLC9A6</i>	solute carrier family 9 (sodium/hydrogen exchanger), member 6	Xq26.3	Syndromic X-linked ID, Christianson type (ID, microcephaly, epilepsy, and ataxia)	XL	(Garbern et al., 2010)
<i>PHF6</i>	PHD finger protein 6	Xq26.2	Borjeson-Forssman-Lehmann syndrome (ID, epilepsy, and hypogonadism)	XL	(de Winter et al., 2009)†
<i>ARHGEF6</i>	Rac/Cdc42 guanine nucleotide exchange factor 6	Xq26.3	Non-syndromic X-linked ID	XL	(Kutsche et al., 2000; Yntema et al., 1998)
<i>FMR1</i>	fragile X mental retardation 1	Xq27.3	Fragile X syndrome is found in ~2% of individuals with ASD. ~60% of males with the full mutation have ASD, ~20% in females. The premutation is also associated with an increased risk of ASD: 10-15% in males, 5% in females	XL	(Clifford et al., 2007; Kielinen et al., 2004; Wang et al., 2010)
<i>AFF2</i>	fragile X mental retardation 2	Xq28	Fragile X mental retardation 2 (FRAXE)	XL	(Abrams et al., 1997; Barnicoat et al., 1997; Mazzocco et al., 1998)
<i>SLC6A8</i>	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Xq28	Creatine deficiency syndrome; non-syndromic ID. Brain creatine deficiency can be caused by mutation in the creatine transporter gene <i>SLC6A8</i> , or by defects in the biosynthesis of creatine ( <i>GAMT</i> and <i>GATM</i> genes); mutations in all three genes have been reported in ASD; ASD/autistic features appear to be frequent in creatine deficiency syndromes	XL	(Bizzi et al., 2002; Lion-Francois et al., 2006; Poo-Arguelles et al., 2006; Puusepp et al., 2009; Sempere et al., 2009a)

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
<i>L1CAM</i>	L1 cell adhesion molecule	Xq28	Syndromic X-linked ID, MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome	XL	(Simonati et al., 2006)†
<i>MECP2</i> *	methyl CpG binding protein 2	Xq28	<i>MECP2</i> mutations or deletions cause Rett syndrome in females, and congenital encephalopathy or non-syndromic ID in males; <i>MECP2</i> duplication syndrome, mostly in males	XL	(Abdul-Rahman and Hudgins, 2006; Carney et al., 2003; Herman et al., 2007; Mount et al., 2003; Schaefer and Lutz, 2006; Zappella et al., 2003)
<i>RAB39B</i>	RAB39B, member RAS oncogene family	Xq28	X-linked ID associated with autism, epilepsy, and macrocephaly in two large pedigrees	XL	(Giannandrea et al., 2010)

\* These genes are responsible for the core phenotypic features of microdeletion/microduplication syndromes listed in Table 2 (e.g., the *SHANK3* gene appears in Table 1 and the 22q13 deletion syndrome in Table 2).

† To my knowledge, these genes have only been reported in single cases with ASD/autistic features; ‡ genes reported in a single family with 2-3 males with ASD/autistic features. For both of these categories, additional patients with ASD need to be identified to definitely implicate these genes in ASD.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ASD, autism spectrum disorder; ID, intellectual disability; XL, X linked

**Table 2. Recurrent genomic disorders and chromosomal abnormalities reported in individuals with ASD/autistic traits**

Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
1p36 microdeletion syndrome	1p36.32-p36.33	1-5,308,621	1p36 microdeletion is a contiguous gene syndrome, considered the most common subtelomeric microdeletion syndrome; few cases have been reported in association with ASD/autistic features	(Blennow et al., 1996; Bruno et al., 2009; D'Angelo et al., 2010; Jacquemont et al., 2006; Knight-Jones et al., 2000; Redon et al., 2005)	
1q21.1 microdeletion/microduplication syndrome	1q21.1	144,979,000-146,204,000	Novel microdeletion/microduplication syndrome associated with neurodevelopmental disorders, microcephaly or macrocephaly. 7% (3/42) with deletion and 30% (7/23) with duplication have ASD/autistic features. Both 1q21.1 deletions and duplications have been reported in unaffected parents and controls	(Brunetti-Pierri et al., 2008; Mefford et al., 2008)	(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	57,595,300-61,591,838	Recently delineated microdeletion; 4 of 6 subjects reported have ASD/autistic behavior	(Liang et al., 2009; Rajcan-Separovic et al., 2007; Unique, 2008)	
2q23.1 microdeletion syndrome	2q23.1	148,932,508-148,987,514	Size of deletion varies, but the minimal region of overlap includes only one gene, <i>MBD5</i> . The 2q23.1 microdeletion syndrome is characterized by ID, severe speech impairment, seizures, short stature, microcephaly and mild dysmorphic features. Stereotypic repetitive behavior is present in the majority of patients; only 2 have been reported with "autistic features", although several exhibit social deficits and rigid routines	(Jaillard et al., 2009; van Bon et al., 2010)	
2q33.1 deletion syndrome (2q32q33 microdeletion syndrome)	2q32.3-q33.2	196,633,334-204,915,185	Novel microdeletion syndrome associated with severe ID, growth retardation, dysmorphic features, and cleft or high palate. Haploinsufficiency of <i>SATB2</i> causes some of the clinical features associated with the 2q33.1 microdeletion syndrome, including palate abnormalities and ID (Rosenfeld et al., 2009)	(Van Buggenhout et al., 2005)	
2q37 monosomy	2q37.3	239,619,630-242,951,149	Numerous 2q37 deletions have been reported in subjects with ASD. Autistic behavior was reported in 24% (16/66) patients with 2q37 deletions; in a smaller study, 63% (5/8) had autism. Haploinsufficiency of <i>HDAC4</i> was recently shown to cause the core manifestations of this syndrome, including brachydactyly and ID (Williams et al., 2010). However, other genes yet to be identified contribute to the phenotype in individuals with terminal deletions distal to <i>HDAC4</i>	(Casas et al., 2004; Devillard et al., 2010; Fisch et al., 2010; Galasso et al., 2008; Ghaziuddin and Burmeister, 1999; Lukusa et al., 2005; Sebat et al., 2007; Smith et al., 2001; Wolff et al., 2002)	
3q29 microdeletion/microduplication syndrome	3q29	197,156,626-198,982,266	19 3q29 deletions reported, 5 with ASD (26%), including 3 patients with autism and one with Asperger syndrome. No microduplications have been described thus far in ASD	(Ballif et al., 2008; Baynam et al., 2006; Quintero-Rivera et al., 2010; Willatt et al., 2005)	—
Wolf-Hirschhorn syndrome	4p16.3	1-2,043,468	The Wolf-Hirschhorn syndrome (4p16.3 deletion syndrome) is a contiguous gene syndrome characterized by pre- and postnatal growth deficiency, characteristic facial appearance, ID and seizures. Autism was reported in 1/19 (5%)	(Fisch et al., 2008; Fisch et al., 2010; Sogaard et al., 2005)(PARIS study, unpublished)	

Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
4q21 microdeletion syndrome	4q21.21-q21.22	82,228,875-83,182,488	Novel microdeletion syndrome, size of deletion varies (minimal region of overlap based on 13 deletions reviewed by Bonnet et al., 2010)	(Bonnet et al., 2010)	
Cri du Chat syndrome	5p15.2-p15.33	1-11,776,854	Among individuals with Cri du Chat syndrome (5p deletion syndrome), ASD was reported in 39% (9/23)	(Cantu et al., 1990; Dykens and Clarke, 1997; Marshall et al., 2008; Moss et al., 2008)	
5q14.3 microdeletion syndrome	5q14.3	88,051,922-88,214,780	Novel microdeletion syndrome characterized by severe ID, ASD, absent speech, hand stereotypies, epilepsy and cerebral malformations. The causal gene is <i>MEF2C</i> . One reciprocal duplication reported thus far in ID, not in ASD	(Berland and Houge, 2010; Novara et al., 2010; Nowakowska et al., 2010; Zweier et al., 2010)	—
Sotos syndrome (5q35 deletion), 5q35.2q35.3 duplication	5q35.2-q35.3	175,063,008-177,389,151	Sotos syndrome is due to mutations or deletions of <i>NSD1</i> . Several cases of Sotos syndrome and ASD have been reported, some diagnosed clinically before the genetic defect was identified and others confirmed molecularly, but it was not specified whether they had deletions or mutations of <i>NSD1</i> . A few reciprocal 5q35.2q35.3 duplications have been described in ID, not in ASD	(Battaglia and Carey, 2006; Bolton et al., 2004; Kielinen et al., 2004; Miles and Hillman, 2000; Morrow et al., 1990; Mouridsen and Hansen, 2002; Schaefer and Lutz, 2006; Trad et al., 1991)	—
Williams syndrome (7q11.23 deletion), 7q11.23 duplication syndrome	7q11.23	71,970,679-74,254,837	Williams syndrome (Williams-Beuren syndrome) is a contiguous gene syndrome resulting from a 7q11.23 deletion. Reciprocal duplications have been reported in individuals with severe language delay and ASD. 50% (15/30) of patients with Williams syndrome meet criteria for ASD; 11/27 (40%) subjects with 7q11.23 duplication have autism	(Challman et al., 2003; Gillberg and Rasmussen, 1994; Gosch and Pankau, 1994; Herguner and Mukaddes, 2006; Klein-Tasman et al., 2009; Lincoln et al., 2007; Reiss et al., 1985)	(Berg et al., 2007; Depienne et al., 2007; Kirchhoff et al., 2007; Qiao et al., 2009; Van der Aa et al., 2009)
8p23.1 deletion/duplication syndrome	8p23.1	8,156,705-11,803,128	Microdeletion syndrome characterized by ID, hyperactivity, congenital heart disease (due to haploinsufficiency of <i>GATA4</i> ) and diaphragmatic hernia. The reciprocal duplications are associated with a less severe and more variable phenotype including ID, speech delay, mild dysmorphism, and congenital heart disease. 7 deletions and 3 duplications reported in ASD; in one study, 57% (4/7) patients with 8p23 deletion had autism	(Fisch et al., 2008; Fisch et al., 2010; Ozgen et al., 2009)	(Glancy et al., 2009; Ozgen et al., 2009)
9q subtelomeric deletion syndrome (Kleefstra syndrome)	9q34.3	139,523,184-140,273,252	Deletions vary in size but all include the <i>EHMT1</i> gene, shown to be responsible for the distinctive facial features, microcephaly, hypotonia and ID. Several patients have been reported with autistic traits or, in 4 cases, ASD	(Anderlid et al., 2002; Dawson et al., 2002; Iwakoshi et al., 2004; Kleefstra et al., 2005; Kleefstra et al., 2009; McMullan et al., 2009; Sahoo et al., 2006b; Unique, 2009b)(Autism Genome Project, unpublished)	
10p14p15 deletion	10p14-p15.1	4,700,001-10,600,000	Chromosome 10p terminal deletions have been associated with DiGeorge-like phenotype (DGS2 syndrome), and within the same region, haploinsufficiency of <i>GATA3</i> causes the HDR syndrome (hypoparathyroidism, deafness, renal disease)	(Lindstrand et al., 2010; Verri et al., 2004)	

Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
10q22-q23 deletion	10q22.3-q23.2	81,682,644-88,931,994	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)	
Distal 10q deletion syndrome	10q26.2-q26.3	128,000,000-135,374,737	Deletions vary in size and the critical region has not been defined. Over 100 cases of distal 10q deletion syndrome have been described in the literature but only 4 cases were reported with ASD/autistic features	(Colleaux et al., 2001; Ravnan et al., 2006; Yatsenko et al., 2009)	
11p15.5 duplication/ Beckwith-Wiedemann syndrome/Silver-Russell syndrome	11p15.4-p15.5	1,970,000-2,870,000	Defective expression of imprinted genes on chromosome 11p15.5 cause Beckwith-Wiedemann syndrome (BWS), an overgrowth disorder, or Silver-Russell syndrome (SRS), characterized by pre- and post-natal growth retardation. Uniparental disomy, copy number changes, and epigenetic mutations have been involved in both syndromes; mutations in <i>CDKN1C</i> have been reported in BWS. Paternal 11p15.5 duplications of the <i>H19</i> and <i>IGF2</i> genes cause BWS, whereas maternal duplications cause SRS. Both disorders have been reported in ASD. In a survey of 87 children with BWS, 6 (7%) had an ASD diagnosis	(Kent et al., 2008a)	
WAGR syndrome (11p13 deletion syndrome)	11p13	31,760,085-32,467,564	The WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome is a contiguous gene syndrome due to deletion of the 11p13 region. It is strongly associated with ASD: among 31 subjects, 16 (52%) had ASD (14 autism and 2 PDD-NOS)	(Xu et al., 2008)	
Potocki-Shaffer syndrome (11p11.2 deletion syndrome)	11p11.2	43,941,853-46,021,136	Potocki-Shaffer syndrome is a contiguous gene syndrome due to haploinsufficiency of the 11p11.2 region, characterized by ID, craniofacial abnormalities, biparietal foramina and multiple exostoses. The genes <i>EXT2</i> and <i>ALX4</i> are responsible for the multiple exostoses and skull defects, but do not account for other cardinal features such as ID. Among 31 individuals described to date, autistic features have been reported in 4	(Swarr et al., 2010; Wuyts et al., 2004)	
Jacobsen syndrome (11q deletion syndrome)	11q23.3-qter	115,400,001-134,452,384	Jacobsen syndrome is a contiguous gene syndrome involving distal 11q; deletions vary in size from 4 to 30 Mb, the breakpoints usually occur within or distal to 11q23.3 and usually extend to the telomere. Typical features include ID, macrocephaly, facial dysmorphism and thrombocytopenia. Over 200 cases have been reported, but very few cases described in association with ASD/autistic features; however, in a recent study, 33% (3/9) patients with Jacobsen syndrome had autism	(Bernaciak et al., 2008; Fisch et al., 2010; Lucchese et al., 2003; Pinto et al., 2010)	

Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
Angelman syndrome, Prader-Willi syndrome, 15q11-q13 duplication syndrome	15q11.2-q13.1	type 1: 20,428,073-26,230,781; type 2: 21,309,483-26,230,781	Angelman syndrome is due to maternal deletions or mutations of <i>UBE3A</i> ; Prader-Willi syndrome is due to paternal deletions; the 15q11-q13 duplication syndrome is caused by supernumerary chromosome 15 (isodicentric chromosome) or interstitial duplications, most commonly of maternal origin. 15q11-q13 duplications are the most frequently reported chromosomal abnormalities in ASD; rearrangements in this region account for ~1% of cases. ASD is present in 63% (38/60) patients with Angelman, 23% (49/209) with Prader-Willi syndrome, and 92% (50/54) with isodicentric chromosome 15	(Bonati et al., 2007; Depienne et al., 2009b; Descheemaeker et al., 2006; Hogart et al., 2010; Sahoo et al., 2006a; Schroer et al., 1998; Steffenburg et al., 1996; Trillingsgaard and Østergaard, 2004; Veltman et al., 2005)	(Bolton et al., 2004; Cook et al., 1997; Depienne et al., 2009b; Hogart et al., 2010; Pinto et al., 2010; Schroer et al., 1998; Szatmari et al., 2007)
15q13.3 microdeletion/microduplication syndrome	15q13.2-q13.3	28,557,287-30,488,774	Novel microdeletion syndrome with highly variable phenotype and incomplete penetrance, including ID, seizures, subtle facial dysmorphism and neuropsychiatric disorders. 44% (15/34) children with 15q13.3 microdeletion syndrome have ASD. Males are more likely to be symptomatic. Reciprocal duplications have also been reported in association with ASD/autistic features, but their clinical significance is uncertain at present. The deletion and duplication span <i>CHRNA7</i> , a candidate gene for epilepsy	(Ben-Shachar et al., 2009; Masurel-Paulet et al., 2010; Miller et al., 2009; Pagnamenta et al., 2009; Pinto et al., 2010; Sharp et al., 2008; Unique, 2009a; van Bon et al., 2009)	(Guilmatre et al., 2009; Miller et al., 2009; Szafranski et al., 2010; van Bon et al., 2009)
15q24 microdeletion syndrome	15q24.1-q24.2	72,164,227-73,949,332	Recently defined microdeletion syndrome characterized by ID, typical facial characteristics, and mild hand and genital anomalies. 22% (4/18) of reported cases have ASD/autistic traits (3 ASD, 1 autistic traits)	(Marshall et al., 2008; McInnes et al., 2010; Sharp et al., 2007; Smith et al., 2000) <sup>b</sup>	
15q26 overgrowth syndrome	15q26.3	97,175,493-100,338,915	15q26 duplications cause an overgrowth syndrome; the causal gene is <i>IGF1R</i>		(Bonati et al., 2007)
Rubinstein-Taybi syndrome, 16p13.3 duplication syndrome	16p13.3	3,721,465-3,801,247	16p13.3 deletions including <i>CREBBP</i> cause Rubinstein-Taybi syndrome; 16p13.3 duplications cause a novel recognizable syndrome; both have been reported in individuals with ASD	(Hellings et al., 2002; Schorry et al., 2008)	(Thienpont et al., 2010)
16p13.11 microdeletion/microduplication	16p13.11	15,411,955-16,191,749	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, so their clinical significance is unclear at present	(Pinto et al., 2010)	(Pinto et al., 2010; Ullmann et al., 2007)
16p11.2-p12.2 microdeletion/microduplication syndrome	16p11.2-p12.2	21,521,457-28,949,693	Newly recognized microdeletion syndrome; 6 deletions reported in subjects with ID (not in ASD); 3 reciprocal duplications described with ASD	—	(Engelen et al., 2002; Finelli et al., 2004)



Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
16p11.2 microdeletion/microduplication syndrome	16p11.2	29,408,699-30,110,070	Initially reported as an autism susceptibility locus, 16p11.2 microdeletions/microduplications have also been reported in ID, schizophrenia, epilepsy and in healthy subjects; both types are associated with incomplete penetrance and variable expressivity, particularly in the case of duplications	(Bijlsma et al., 2009; Fernandez et al., 2010; Hanson et al., 2010; Marshall et al., 2008; Pinto et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010; Weiss et al., 2008)	(Fernandez et al., 2010; Marshall et al., 2008; Pinto 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	1-2,492,179	17p13.3 deletions encompassing the <i>PAFAH1B1</i> gene cause isolated lissencephaly; larger deletions including <i>YWHAE</i> cause Miller-Dieker syndrome, a contiguous gene syndrome characterized by severe lissencephaly and additional dysmorphic features and malformations. Microduplications of the Miller-Dieker region as well as smaller duplications affecting <i>PAFAH1B1</i> or <i>YWHAE</i> have also been described. To date, only microduplications have been reported in ASD	—	(Bi et al., 2009; Bruno et al., 2010)
Smith-Magenis syndrome (17p11.2 microdeletion), Potocki-Lupski syndrome (17p11.2 microduplication)	17p11.2	16,646,746-20,422,653	Smith-Magenis-syndrome (17p11.2 microdeletion) and Potocki-Lupski syndrome (17p11.2 microduplication) are due to copy number changes or mutations in <i>RAI1</i> ; both are frequently associated with ASD. In one study, 90% (18/20) individuals with Smith-Magenis-syndrome had ASD	(Hicks et al., 2008; Laje et al., 2010; Park et al., 1998; Shaffer et al., 2006; Smith et al., 1986; Stratton et al., 1986; Udwin, 2002; Vostanis et al., 1994)	(Moog et al., 2004; Nakamine et al., 2008; Potocki et al., 2007; Treadwell-Deering et al., 2010)
NF1 microdeletion/microduplication syndrome	17q11.2	26,186,948-27,242,780	5%-10% of patients with neurofibromatosis 1 have a 17q11 deletion involving <i>NF1</i> and other genes. The NF1 microdeletion syndrome is characterized by a more severe phenotype than that observed in patients with intragenic <i>NF1</i> mutations; haploinsufficiency of <i>RNF135</i> contributes to the overgrowth, facial dysmorphism and ID present in individuals with NF1 microdeletions. A 17q11 microduplication was reported in a single large family with mild ID and mild dysmorphic features	(Tonsgard et al., 1997)	—
17q12 deletion/duplication syndrome	17q12	31,981,479-33,150,916	17q12 deletions encompassing the <i>HNF1B</i> gene cause renal cysts and diabetes syndrome, with ID, seizures, and brain abnormalities; the reciprocal duplications are associated with ID and epilepsy, and are less penetrant than deletions. At least 8 cases with 17q12 deletions and autism or ASD have been reported; in one study, 44% (4/9) had autism and 22% (2/9) had autistic features	(Loirat et al., 2010; Moreno-De-Luca et al., 2010)	(Joseph Buxbaum, personal communication)
17q21.31 microdeletion/microduplication syndrome	17q21.31	40,988,249-41,565,982	The 17q21.3 microdeletion syndrome is characterized by ID, hypotonia and facial dysmorphism; only 1 case with ASD has been identified. 17q21.31 microduplications have been reported in several ASD cases	(Betancur et al., 2008)	(Grisart et al., 2009)

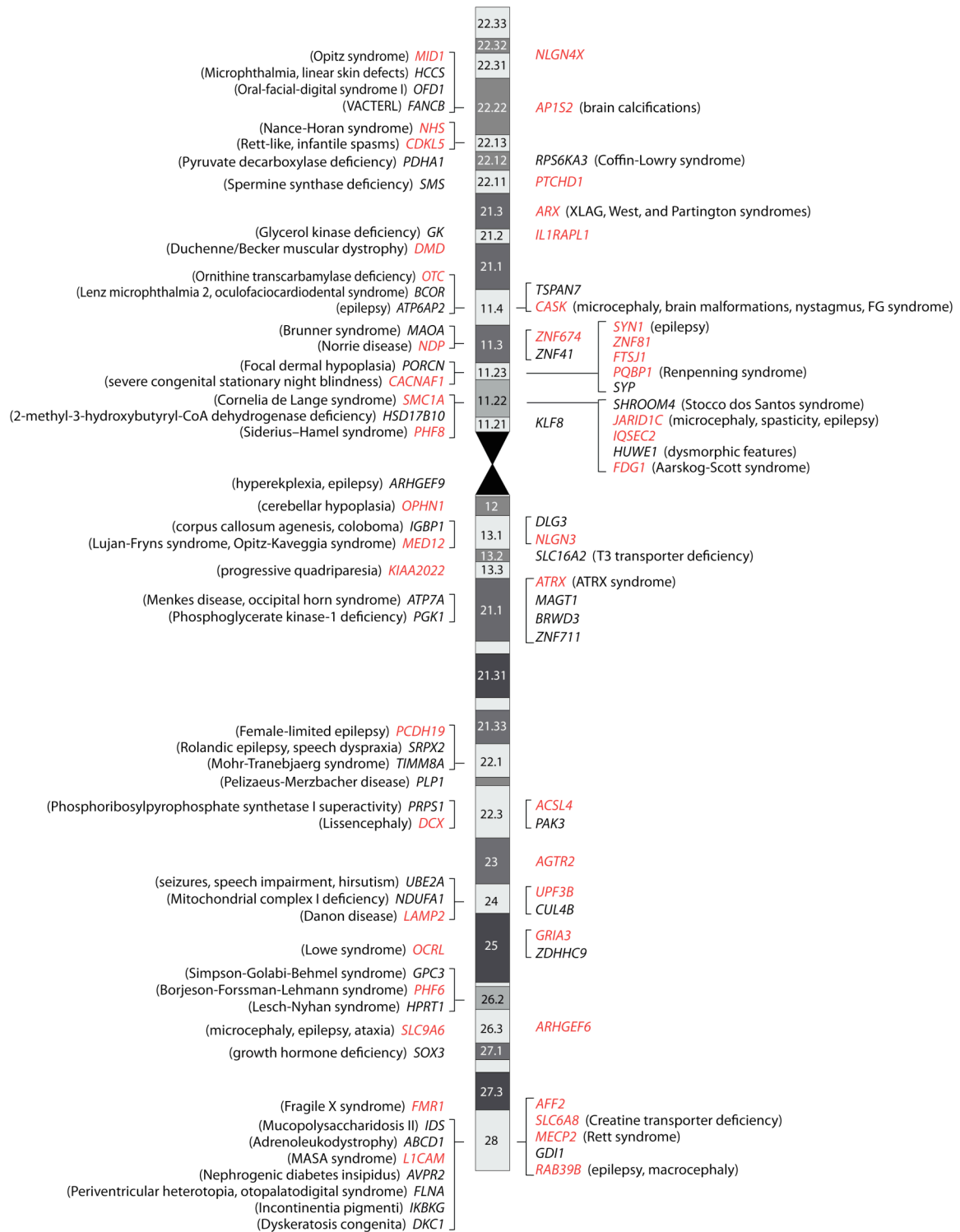
Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
Down syndrome	21	1-46,944,323	Down syndrome (trisomy 21) is consistently identified in epidemiological, clinical and research samples of ASD. The proportion of patients with Down syndrome meeting autism/ASD criteria varies between 5% and 15%		(Carter et al., 2007; Fombonne et al., 1997; Kent et al., 1999; Kielinen et al., 2004; Li et al., 1993; Lowenthal et al., 2007; Molloy et al., 2009; Oliveira et al., 2007; Pinto et al., 2010; Rasmussen et al., 2001; Steiner et al., 2003)
22q11 deletion syndrome (Velocardiofacial/DiGeorge syndrome), 22q11 duplication syndrome	22q11.21-q11.22	16,926,349-20,666,469	28% (84/299, range 14%-50%) of individuals with the 22q11 deletion syndrome (velocardiofacial/DiGeorge syndrome) meet criteria for ASD. The recently recognized 22q11 duplication syndrome has been reported in several subjects with ASD. Both deletions and duplications exhibit extensive phenotypic heterogeneity	(Antshel et al., 2007; Fine et al., 2005; Niklasson et al., 2009; Pinto et al., 2010; Vorstman et al., 2006)	(Bucan et al., 2009; Lo-Castro et al., 2009; Marshall et al., 2008; Mukaddes and Herguner, 2007; Pinto et al., 2010; Ramelli et al., 2008; Szatmari et al., 2007)
22q13 deletion syndrome (Phelan-McDermid syndrome), 22q13 duplication	22q13.33	49,392,382-49,534,710	Phelan-McDermid syndrome is due to 22q13 deletions or mutations of <i>SHANK3</i> . Autism or autistic traits are common: in one study, 55% (6/11) individuals with 22q13 deletions had autistic behavior; among subjects with ring chromosome 22 including a 22q13 deletion, 12/27 (44%) had a clinical diagnosis of ASD and 23/27 (85%) had autistic traits. A few cases with 22q13 duplications including <i>SHANK3</i> have also been reported, including one with Asperger syndrome and another with ASD and ID	(Dhar et al., 2010; Durand et al., 2007; Goizet et al., 2000; Guilmatre et al., 2009; Jeffries et al., 2005; Manning et al., 2004; Moessner et al., 2007; Prasad et al., 2000; Sebat et al., 2007)	(Durand et al., 2007; Peeters et al., 2008)
Xq28 duplication syndrome ( <i>MECP2</i> duplication syndrome)	Xq28,	152,403,094-153,044,193	The Xq28 duplication syndrome is caused by the duplication of <i>MECP2</i> ; it is mostly reported in males (females are protected by X inactivation) and is often associated with ASD or autistic features		(Ramocki et al., 2009; Ramocki et al., 2010)
Turner syndrome (monosomy X)	X	1-154,913,754	5/150 (3.3%) females with Turner syndrome have autism	(Creswell and Skuse, 1999; Donnelly et al., 2000; El Abd et al., 1999; Skuse et al., 1997; Wassink et al., 2001)	
Klinefelter syndrome (XXY)	X	1-154,913,754	Subjects with Klinefelter syndrome (XXY) have been identified repeatedly in epidemiological, clinical and research samples of ASD. Significant autism traits were reported in 48% (15/31); in 2 studies, 11% (2/19) and 27% (14/51) met criteria for ASD		(Bishop et al.; Bruining et al., 2009; Jha et al., 2007; Kielinen et al., 2004; Konstantareas and Homatidis, 1999; Merhar and Manning-Courtney, 2007; Miles et al., 2005; van Rijn et al., 2008)

Disorder	Cytoband	Genomic coordinates <sup>a</sup>	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
YYY syndrome	Y	1-57,772,954	Males with XYY syndrome have been identified in epidemiological, clinical and research samples of ASD. ASD was present in 19% (11/58) cases of XYY.		(Bishop et al., 2010; Challman et al., 2003; Geerts et al., 2003; Gillberg et al., 1984; Gillberg, 1989; Kielinen et al., 2004; Nicolson et al., 1998; Petit et al., 1996; Pinto et al., 2010; Weidmer-Mikhail et al., 1998)
XXYY syndrome	X-Y		The XXYY syndrome also carries an increased risk for ASD: in a sample of 92 males with XXYY syndrome, 26 (28%) had ASD (6 autism, 20 PDD-NOS)		(Tartaglia et al., 2008)
45,X/46,XY mosaicism	X	1-154,913,754	In a series of 27 males with 45,X/46,XY mosaicism, 2 had ASD (7%)	(Fontenelle et al., 2004; Telvi et al., 1999; van Karnebeek et al., 2002)	

<sup>a</sup> Human reference genome hg18, NCBI 36 (March 2006). Genomic coordinates of microdeletion/microduplication syndromes were taken from Decipher (<https://decipher.sanger.ac.uk>) when available.

<sup>b</sup> The deletion reported by Smith et al. (2000) was originally mapped by FISH to 15q22-q23, but subsequent microarray mapping revealed a 15q24 deletion (Moyra Smith, personal communication)

Abbreviations: ASD, autism spectrum disorder; ID, intellectual disability; PDD-NOS, pervasive developmental disorder not otherwise specified; —, microdeletion/microduplication syndrome not reported in individuals with ASD/autistic traits



**Figure 1. Genes implicated in syndromic and/or non-syndromic forms of X-linked mental retardation (XLMR) and their localization on the X chromosome.** Genes that have been reported to be mutated in ASD are highlighted in red. Genes that cause syndromic forms of XLMR are shown on the left; those that can cause non-syndromic forms are on the right. The distinction between syndromic and non-syndromic genes is not precise, and for several genes on the right, mutations have been reported in families with syndromic as well as non-syndromic XLMR; 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; VACTERL (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula, renal anomalies, and limb anomalies); XLAG (X-linked lissencephaly and abnormal genitalia) syndrome.