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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, a 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 than 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 (*AHI1, CEP290, RPGRIP1L*). The role of *GUCY2D*, involved in Leber congenital amaurosis, another ciliopathy, is supported by the Joubert syndrome genes and by *RPE6*5, 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 (reponsible 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 (Wisniowiecka-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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References

Abdul-Rahman, O.A., Hudgins, L., 2006. The diagnostic utility of a genetics evaluation in children with pervasive developmental disorders. Genet Med. 8**,** 50-4.

Abrahams, B.S., Geschwind, D.H., 2008. Advances in autism genetics: on the threshold of a new neurobiology. Nat Rev Genet. 9**,** 341-55.

Abrams, M.T., Doheny, K.F., Mazzocco, M.M., Knight, S.J., Baumgardner, T.L., Freund, L.S., Davies, K.E., Reiss, A.L., 1997. Cognitive, behavioral, and neuroanatomical assessment of two unrelated male children expressing FRAXE. Am J Med Genet. 74**,** 73-81.

Addington, A.M., Gauthier, J., Piton, A., Hamdan, F.F., Raymond, A., Gogtay, N., Miller, R., Tossell, J., Bakalar, J., Inoff-Germain, G., Gochman, P., Long, R., Rapoport, J.L., Rouleau, G.A., 2010. A novel frameshift mutation in UPF3B identified in brothers affected with childhood onset schizophrenia and autism spectrum disorders. Mol Psychiatry. (Epub ahead of print).

Adegbola, A., Gao, H., Sommer, S., Browning, M., 2008. A novel mutation in JARID1C/SMCX in a patient with autism spectrum disorder (ASD). Am J Med Genet A. 146A**,** 505-11.

Al-Owain, M., Kaya, N., Al-Zaidan, H., Al-Hashmi, N., Al-Bakheet, A., Al-Muhaizea, M., Chedrawi, A., Basran, R., Milunsky, A., 2010. Novel intragenic deletion in OPHN1 in a family causing XLMR with cerebellar hypoplasia and distinctive facial appearance. Clin Genet. (Epub ahead of print).

Alliman, S., Coppinger, J., Marcadier, J., Thiese, H., Brock, P., Shafer, S., Weaver, C., Asamoah, A., Leppig, K., Dyack, S., Morash, B., Schultz, R., Torchia, B.S., Lamb, A.N., Bejjani, B.A., 2010. Clinical and molecular characterization of individuals with recurrent genomic disorder at 10q22.3q23.2. Clin Genet. 78**,** 162-8.

Anderlid, B.M., Schoumans, J., Anneren, G., Sahlen, S., Kyllerman, M., Vujic, M., Hagberg, B., Blennow, E., Nordenskjold, M., 2002. Subtelomeric rearrangements detected in patients with idiopathic mental retardation. Am J Med Genet. 107**,** 275-84.

Antshel, K.M., Aneja, A., Strunge, L., Peebles, J., Fremont, W.P., Stallone, K., Abdulsabur, N., Higgins, A.M., Shprintzen, R.J., Kates, W.R., 2007. Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). J Autism Dev Disord. 37**,** 1776-86.

Archer, H.L., Evans, J., Edwards, S., Colley, J., Newbury-Ecob, R., O'Callaghan, F., Huyton, M., O'Regan, M., Tolmie, J., Sampson, J., Clarke, A., Osborne, J., 2006. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. J Med Genet. 43**,** 729-34.

Assumpcao, F., Santos, R.C., Rosario, M., Mercadante, M., 1999. Brief report: autism and Aarskog syndrome. J Autism Dev Disord. 29**,** 179-81.

Aziz, M., Stathopulu, E., Callias, M., Taylor, C., Turk, J., Oostra, B., Willemsen, R., Patton, M., 2003. Clinical features of boys with fragile X premutations and intermediate alleles. Am J Med Genet B Neuropsychiatr Genet. 121B**,** 119-27.

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

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., Charman, T., 2006. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet. 368**,** 210-5.

Balciuniene, J., Feng, N., Iyadurai, K., Hirsch, B., Charnas, L., Bill, B.R., Easterday, M.C., Staaf, J., Oseth, L., Czapansky-Beilman, D., Avramopoulos, D., Thomas, G.H., Borg, A., Valle, D., Schimmenti, L.A., Selleck, S.B., 2007. Recurrent 10q22-q23 deletions: a genomic disorder on 10q associated with cognitive and behavioral abnormalities. Am J Hum Genet. 80**,** 938-47.

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

Baris, H.N., Tan, W.H., Kimonis, V.E., Irons, M.B., 2007. Diagnostic utility of array-based comparative genomic hybridization in a clinical setting. Am J Med Genet A. 143A**,** 2523-33.

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

Barnicoat, A.J., Wang, Q., Turk, J., Green, E., Mathew, C.G., Flynn, G., Buckle, V., Hirst, M., Davies, K., Bobrow, M., 1997. Clinical, cytogenetic, and molecular analysis of three families with FRAXE. J Med Genet. 34**,** 13-7.

Basile, E., Villa, L., Selicorni, A., Molteni, M., 2007. The behavioural phenotype of Cornelia de Lange Syndrome: a study of 56 individuals. J Intellect Disabil Res. 51**,** 671-81.

Battaglia, A., Carey, J.C., 2006. Etiologic yield of autistic spectrum disorders: a prospective study. Am J Med Genet C Semin Med Genet. 142**,** 3-7.

Battini, R., Leuzzi, V., Carducci, C., Tosetti, M., Bianchi, M.C., Item, C.B., Stockler-Ipsiroglu, S., Cioni, G., 2002. Creatine depletion in a new case with AGAT deficiency: clinical and genetic study in a large pedigree. Mol Genet Metab. 77**,** 326-31.

Baynam, G., Goldblatt, J., Townshend, S., 2006. A case of 3q29 microdeletion with novel features and a review of cytogenetically visible terminal 3q deletions. Clin Dysmorphol. 15**,** 145-8.

Ben-Shachar, S., Lanpher, B., German, J.R., Qasaymeh, M., Potocki, L., Nagamani, S.C., Franco, L.M., Malphrus, A., Bottenfield, G.W., Spence, J.E., Amato, S., Rousseau, J.A., Moghaddam, B., Skinner, C., Skinner, S.A., Bernes, S., Armstrong, N., Shinawi, M., Stankiewicz, P., Patel, A., Cheung, S.W., Lupski, J.R., Beaudet, A.L., Sahoo, T., 2009. Microdeletion 15q13.3: a locus with incomplete penetrance for autism, mental retardation, and psychiatric disorders. J Med Genet. 46**,** 382-8.

Bennett, C.L., Chen, Y., Hahn, S., Glass, I.A., Gospe, S.M., Jr., 2009. Prevalence of ALDH7A1 mutations in 18 North American pyridoxine-dependent seizure (PDS) patients. Epilepsia. 50**,** 1167-75.

Berg, J.S., Brunetti-Pierri, N., Peters, S.U., Kang, S.H., Fong, C.T., Salamone, J., Freedenberg, D., Hannig, V.L., Prock, L.A., Miller, D.T., Raffalli, P., Harris, D.J., Erickson, R.P., Cunniff, C., Clark, G.D., Blazo, M.A., Peiffer, D.A., Gunderson, K.L., Sahoo, T., Patel, A., Lupski, J.R., Beaudet, A.L., Cheung, S.W., 2007. Speech delay and autism spectrum behaviors are frequently associated with duplication of the 7q11.23 Williams-Beuren syndrome region. Genet Med. 9**,** 427-41.

Berkel, S., Marshall, C.R., Weiss, B., Howe, J., Roeth, R., Moog, U., Endris, V., Roberts, W., Szatmari, P., Pinto, D., Bonin, M., Riess, A., Engels, H., Sprengel, R., Scherer, S.W., Rappold, G.A., 2010. Mutations in the SHANK2 synaptic scaffolding gene in autism spectrum disorder and mental retardation. Nat Genet. 42**,** 489-91.

Berland, S., Houge, G., 2010. Late-onset gain of skills and peculiar jugular pit in an 11-year-old girl with 5q14.3 microdeletion including MEF2C. Clin Dysmorphol. 19**,** 222-4.

Bernaciak, J., Szczaluba, K., Derwinska, K., Wisniowiecka-Kowalnik, B., Bocian, E., Sasiadek, M.M., Makowska, I., Stankiewicz, P., Smigiel, R., 2008. Clinical and molecular-cytogenetic evaluation of a family with partial Jacobsen syndrome without thrombocytopenia caused by an approximately 5 Mb deletion del(11)(q24.3). Am J Med Genet A. 146A**,** 2449-54.

Berney, T.P., Ireland, M., Burn, J., 1999. Behavioural phenotype of Cornelia de Lange syndrome. Arch Dis Child. 81**,** 333-6.

Betancur, C., Héron, D., Verloes, A., Philippe, A., Munnich, A., Depienne, C., Brice, A., Leboyer, M., 2004. Etiological heterogeneity in autism: implications for linkage and association studies. Abstract presented at the XIIth World Congress on Psychiatric Genetics. October 9-13, Dublin, Ireland.

Betancur, C., Moreno De Luca, D., Gennetier, A., Devillard, F., Ginchat, V., Assouline, B., Gillberg, C., Leboyer, M., 2008. Chromosome 17q21.31 microdeletion in a patient with autism. Abstract (program number 449) presented at the annual meeting of The American Society of Human Genetics. November 11-15, Philadelphia, PA.

Bhat, S.S., Ladd, S., Grass, F., Spence, J.E., Brasington, C.K., Simensen, R.J., Schwartz, C.E., Dupont, B.R., Stevenson, R.E., Srivastava, A.K., 2008. Disruption of the IL1RAPL1 gene associated with a pericentromeric inversion of the X chromosome in a patient with mental retardation and autism. Clin Genet. 73**,** 94-6.

Bhuiyan, Z.A., Klein, M., Hammond, P., van Haeringen, A., Mannens, M.M., Van Berckelaer-Onnes, I., Hennekam, R.C., 2006. Genotype-phenotype correlations of 39 patients with Cornelia De Lange syndrome: the Dutch experience. J Med Genet. 43**,** 568-75.

Bi, W., Sapir, T., Shchelochkov, O.A., Zhang, F., Withers, M.A., Hunter, J.V., Levy, T., Shinder, V., Peiffer, D.A., Gunderson, K.L., Nezarati, M.M., Shotts, V.A., Amato, S.S., Savage, S.K., Harris, D.J., Day-Salvatore, D.L., Horner, M., Lu, X.Y., Sahoo, T., Yanagawa, Y., Beaudet, A.L., Cheung, S.W., Martinez, S., Lupski, J.R., Reiner, O., 2009. Increased LIS1 expression affects human and mouse brain development. Nat Genet. 41**,** 168-77.

Bijlsma, E.K., Gijsbers, A.C., Schuurs-Hoeijmakers, J.H., van Haeringen, A., Fransen van de Putte, D.E., Anderlid, B.M., Lundin, J., Lapunzina, P., Perez Jurado, L.A., Delle Chiaie, B., Loeys, B., Menten, B., Oostra, A., Verhelst, H., Amor, D.J., Bruno, D.L., van Essen, A.J., Hordijk, R., Sikkema-Raddatz, B., Verbruggen, K.T., Jongmans, M.C., Pfundt, R., Reeser, H.M., Breuning, M.H., Ruivenkamp, C.A., 2009. Extending the phenotype of recurrent rearrangements of 16p11.2: deletions in mentally retarded patients without autism and in normal individuals. Eur J Med Genet. 52**,** 77-87.

Bishop, D.V., Jacobs, P.A., Lachlan, K., Wellesley, D., Barnicoat, A., Boyd, P.A., Fryer, A., Middlemiss, P., Smithson, S., Metcalfe, K., Shears, D., Leggett, V., Nation, K., Scerif, G., 2010. Autism, language and communication in children with sex chromosome trisomies. Arch Dis Child. (Epub ahead of print).

Bizzi, A., Bugiani, M., Salomons, G.S., Hunneman, D.H., Moroni, I., Estienne, M., Danesi, U., Jakobs, C., Uziel, G., 2002. X-linked creatine deficiency syndrome: a novel mutation in creatine transporter gene SLC6A8. Ann Neurol. 52**,** 227-31.

Blennow, E., Bui, T.H., Wallin, A., Kogner, P., 1996. Monosomy 1p36.31-33-->pter due to a paternal reciprocal translocation: prognostic significance of FISH analysis. Am J Med Genet. 65**,** 60-7.

Blondis, T.A., Cook, E., Jr., Koza-Taylor, P., Finn, T., 1996. Asperger syndrome associated with Steinert's myotonic dystrophy. Dev Med Child Neurol. 38**,** 840-7.

Bolton, P.F., Veltman, M.W., Weisblatt, E., Holmes, J.R., Thomas, N.S., Youings, S.A., Thompson, R.J., Roberts, S.E., Dennis, N.R., Browne, C.E., Goodson, S., Moore, V., Brown, J., 2004. Chromosome 15q11-13 abnormalities and other medical conditions in individuals with autism spectrum disorders. Psychiatr Genet. 14**,** 131-7.

Bonati, M.T., Russo, S., Finelli, P., Valsecchi, M.R., Cogliati, F., Cavalleri, F., Roberts, W., Elia, M., Larizza, L., 2007. Evaluation of autism traits in Angelman syndrome: a resource to unfold autism genes. Neurogenetics. 8**,** 169-78.

Bonnet, C., Andrieux, J., Beri-Dexheimer, M., Leheup, B., Boute, O., Manouvrier, S., Delobel, B., Copin, H., Receveur, A., Mathieu, M., Thiriez, G., Le Caignec, C., David, A., de Blois, M.C., Malan, V., Philippe, A., Cormier-Daire, V., Colleaux, L., Flori, E., Dollfus, H., Pelletier, V., Thauvin-Robinet, C., Masurel-Paulet, A., Faivre, L., Tardieu, M., Bahi-Buisson, N., Callier, P., Mugneret, F., Edery, P., Jonveaux, P., Sanlaville, D., 2010. Microdeletion at chromosome 4q21 defines a new emerging syndrome with marked growth restriction, mental retardation and absent or severely delayed speech. J Med Genet. 47**,** 377-84.

Borck, G., Molla-Herman, A., Boddaert, N., Encha-Razavi, F., Philippe, A., Robel, L., Desguerre, I., Brunelle, F., Benmerah, A., Munnich, A., Colleaux, L., 2008. Clinical, cellular, and neuropathological consequences of AP1S2 mutations: further delineation of a recognizable X-linked mental retardation syndrome. Hum Mutat. 29**,** 966-74.

Bosley, T.M., Salih, M.A., Alorainy, I.A., Oystreck, D.T., Nester, M., Abu-Amero, K.K., Tischfield, M.A., Engle, E.C., 2007. Clinical characterization of the HOXA1 syndrome BSAS variant. Neurology. 69**,** 1245-53.

Bruining, H., Swaab, H., Kas, M., van Engeland, H., 2009. Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. Pediatrics. 123**,** e865-70.

Brunetti-Pierri, N., Berg, J.S., Scaglia, F., Belmont, J., Bacino, C.A., Sahoo, T., Lalani, S.R., Graham, B., Lee, B., Shinawi, M., Shen, J., Kang, S.H., Pursley, A., Lotze, T., Kennedy, G., Lansky-Shafer, S., Weaver, C., Roeder, E.R., Grebe, T.A., Arnold, G.L., Hutchison, T., Reimschisel, T., Amato, S., Geragthy, M.T., Innis, J.W., Obersztyn, E., Nowakowska, B., Rosengren, S.S., Bader, P.I., Grange,

D.K., Naqvi, S., Garnica, A.D., Bernes, S.M., Fong, C.T., Summers, A., Walters, W.D., Lupski, J.R., Stankiewicz, P., Cheung, S.W., Patel, A., 2008. Recurrent reciprocal 1q21.1 deletions and duplications associated with microcephaly or macrocephaly and developmental and behavioral abnormalities. Nat Genet. 40**,** 1466-71.

Brunetti-Pierri, N., Paciorkowski, A.R., Ciccone, R., Mina, E.D., Bonaglia, M.C., Borgatti, R., Schaaf, C.P., Sutton, V.R., Xia, Z., Jelluma, N., Ruivenkamp, C., Bertrand, M., de Ravel, T.J., Jayakar, P., Belli, S., Rocchetti, K., Pantaleoni, C., D'Arrigo, S., Hughes, J., Cheung, S.W., Zuffardi, O., Stankiewicz, P., 2010. Duplications of FOXG1 in 14q12 are associated with developmental epilepsy, mental retardation, and severe speech impairment. Eur J Hum Genet. (Epub ahead of print).

Bruno, D.L., Ganesamoorthy, D., Schoumans, J., Bankier, A., Coman, D., Delatycki, M., Gardner, R.J., Hunter, M., James, P.A., Kannu, P., McGillivray, G., Pachter, N., Peters, H., Rieubland, C., Savarirayan, R., Scheffer, I.E., Sheffield, L., Tan, T., White, S.M., Yeung, A., Bowman, Z., Ngo, C., Choy, K.W., Cacheux, V., Wong, L., Amor, D.J., Slater, H.R., 2009. Detection of cryptic pathogenic copy number variations and constitutional loss of heterozygosity using high resolution SNP microarray analysis in 117 patients referred for cytogenetic analysis and impact on clinical practice. J Med Genet. 46**,** 123-31.

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

Bucan, M., Abrahams, B.S., Wang, K., Glessner, J.T., Herman, E.I., Sonnenblick, L.I., Alvarez Retuerto, A.I., Imielinski, M., Hadley, D., Bradfield, J.P., Kim, C., Gidaya, N.B., Lindquist, I., Hutman, T., Sigman, M., Kustanovich, V., Lajonchere, C.M., Singleton, A., Kim, J., Wassink, T.H., McMahon, W.M., Owley, T., Sweeney, J.A., Coon, H., Nurnberger, J.I., Li, M., Cantor, R.M., Minshew, N.J., Sutcliffe, J.S., Cook, E.H., Dawson, G., Buxbaum, J.D., Grant, S.F., Schellenberg, G.D., Geschwind, D.H., Hakonarson, H., 2009. Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes. PLoS Genet. 5**,** e1000536.

Burd, L., Stenehjem, A., Franceschini, L.A., Kerbeshian, J., 2000. A 15-year follow-up of a boy with pyridoxine (vitamin B6)-dependent seizures with autism, breath holding, and severe mental retardation. J Child Neurol. 15**,** 763-5.

Burusnukul, P., de Los Reyes, E.C., Yinger, J., Boue, D.R., 2008. Danon disease: an unusual presentation of autism. Pediatr Neurol. 39**,** 52-4.

Butler, M.G., Dasouki, M.J., Zhou, X.P., Talebizadeh, Z., Brown, M., Takahashi, T.N., Miles, J.H., Wang, C.H., Stratton, R., Pilarski, R., Eng, C., 2005. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. J Med Genet. 42**,** 318-21.

Buxbaum, J.D., Cai, G., Chaste, P., Nygren, G., Goldsmith, J., Reichert, J., Anckarsater, H., Rastam, M., Smith, C.J., Silverman, J.M., Hollander, E., Leboyer, M., Gillberg, C., Verloes, A., Betancur, C., 2007. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. Am J Med Genet B Neuropsychiatr Genet. 144B**,** 484-91.

Cantagrel, V., Lossi, A.M., Boulanger, S., Depetris, D., Mattei, M.G., Gecz, J., Schwartz, C.E., Van Maldergem, L., Villard, L., 2004. Disruption of a new X linked gene highly expressed in brain in a family with two mentally retarded males. J Med Genet. 41**,** 736-42.

Cantu, E.S., Stone, J.W., Wing, A.A., Langee, H.R., Williams, C.A., 1990. Cytogenetic survey for autistic fragile X carriers in a mental retardation center. Am J Ment Retard. 94**,** 442-7.

Caraballo, R.H., Fejerman, N., 2006. Dravet syndrome: a study of 53 patients. Epilepsy Res. 70 Suppl 1**,** S231-8.

Carney, R.M., Wolpert, C.M., Ravan, S.A., Shahbazian, M., Ashley-Koch, A., Cuccaro, M.L., Vance, J.M., Pericak-Vance, M.A., 2003. Identification of MeCP2 mutations in a series of females with autistic disorder. Pediatr Neurol. 28**,** 205-11.

Carter, J.C., Capone, G.T., Gray, R.M., Cox, C.S., Kaufmann, W.E., 2007. Autistic-spectrum disorders in Down syndrome: further delineation and distinction from other behavioral abnormalities. Am J Med Genet B Neuropsychiatr Genet. 144B**,** 87-94.

Casas, K.A., Mononen, T.K., Mikail, C.N., Hassed, S.J., Li, S., Mulvihill, J.J., Lin, H.J., Falk, R.E., 2004. Chromosome 2q terminal deletion: report of 6 new patients and review of phenotype-breakpoint correlations in 66 individuals. Am J Med Genet A. 130**,** 331-9.

Cassé-Perrot, C., Wolf, M., Dravet, C., 2001. Neuropsychological aspects of severe myoclonic epilepsy in infancy. In Neuropsychology of childhood epilepsy, I. Jambaqué, M. Lassonde, O. Dulac, eds. Kluwer Academic/Plenum Publishers, New York, pp. 131-140.

Challman, T.D., Barbaresi, W.J., Katusic, S.K., Weaver, A., 2003. The yield of the medical evaluation of children with pervasive developmental disorders. J Autism Dev Disord. 33**,** 187-92.

Ching, M.S., Shen, Y., Tan, W.H., Jeste, S.S., Morrow, E.M., Chen, X., Mukaddes, N.M., Yoo, S.Y., Hanson, E., Hundley, R., Austin, C., Becker, R.E., Berry, G.T., Driscoll, K., Engle, E.C., Friedman, S., Gusella, J.F., Hisama, F.M., Irons, M.B., Lafiosca, T., LeClair, E., Miller, D.T., Neessen, M., Picker, J.D., Rappaport, L., Rooney, C.M., Sarco, D.P., Stoler, J.M., Walsh, C.A., Wolff, R.R., Zhang, T., Nasir, R.H., Wu, B.L., 2010. Deletions of NRXN1 (neurexin-1) predispose to a wide spectrum of developmental disorders. Am J Med Genet B Neuropsychiatr Genet. 153B**,** 937-47.

Chiyonobu, T., Hayashi, S., Kobayashi, K., Morimoto, M., Miyanomae, Y., Nishimura, A., Nishimoto, A., Ito, C., Imoto, I., Sugimoto, T., Jia, Z., Inazawa, J., Toda, T., 2007. Partial tandem duplication of GRIA3 in a male with mental retardation. Am J Med Genet A. 143A**,** 1448-55.

Christian, S.L., Brune, C.W., Sudi, J., Kumar, R.A., Liu, S., Karamohamed, S., Badner, J.A., Matsui, S., Conroy, J., McQuaid, D., Gergel, J., Hatchwell, E., Gilliam, T.C., Gershon, E.S., Nowak, N.J., Dobyns, W.B., Cook, E.H., Jr., 2008. Novel submicroscopic chromosomal abnormalities detected in autism spectrum disorder. Biol Psychiatry. 63**,** 1111-7.

Clifford, S., Dissanayake, C., Bui, Q.M., Huggins, R., Taylor, A.K., Loesch, D.Z., 2007. Autism spectrum phenotype in males and females with fragile X full mutation and premutation. J Autism Dev Disord. 37**,** 738-47.

Colleaux, L., Rio, M., Heuertz, S., Moindrault, S., Turleau, C., Ozilou, C., Gosset, P., Raoult, O., Lyonnet, S., Cormier-Daire, V., Amiel, J., Le Merrer, M., Picq, M., de Blois, M.C., Prieur, M., Romana, S., Cornelis, F., Vekemans, M., Munnich, A., 2001. A novel automated strategy for screening cryptic telomeric rearrangements in children with idiopathic mental retardation. Eur J Hum Genet. 9**,** 319-27.

Cook, E.H., Jr., Lindgren, V., Leventhal, B.L., Courchesne, R., Lincoln, A., Shulman, C., Lord, C., Courchesne, E., 1997. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. Am J Hum Genet. 60**,** 928-34.

Coppieters, F., Casteels, I., Meire, F., De Jaegere, S., Hooghe, S., van Regemorter, N., Van Esch, H., Matuleviciene, A., Nunes, L., Meersschaut, V., Walraedt, S., Standaert, L., Coucke, P., Hoeben, H., Kroes, H.Y., Vande Walle, J., de Ravel, T., Leroy, B.P., De Baere, E., 2010. Genetic screening of LCA in Belgium: predominance of CEP290 and identification of potential modifier alleles in AHI1 of CEP290-related phenotypes. Hum Mutat. 31**,** E1709-66.

Cossee, M., Demeer, B., Blanchet, P., Echenne, B., Singh, D., Hagens, O., Antin, M., Finck, S., Vallee, L., Dollfus, H., Hegde, S., Springell, K., Thelma, B.K., Woods, G., Kalscheuer, V., Mandel, J.L., 2006. Exonic microdeletions in the X-linked PQBP1 gene in mentally retarded patients: a pathogenic mutation and in-frame deletions of uncertain effect. Eur J Hum Genet. 14**,** 418-25.

Cox, T.C., Allen, L.R., Cox, L.L., Hopwood, B., Goodwin, B., Haan, E., Suthers, G.K., 2000. New mutations in MID1 provide support for loss of function as the cause of X-linked Opitz syndrome. Hum Mol Genet. 9**,** 2553-62.

Creswell, C.S., Skuse, D.H., 1999. Autism in association with Turner syndrome: genetic implications for male vulnerability to pervasive developmental disorders. Neurocase. 5**,** 511-518.

D'Amico, A., Tessa, A., Bruno, C., Petrini, S., Biancheri, R., Pane, M., Pedemonte, M., Ricci, E., Falace, A., Rossi, A., Mercuri, E., Santorelli, F.M., Bertini, E., 2006. Expanding the clinical spectrum of POMT1 phenotype. Neurology. 66**,** 1564-7.

D'Angelo, C.S., Kohl, I., Varela, M.C., de Castro, C.I., Kim, C.A., Bertola, D.R., Lourenco, C.M., Koiffmann, C.P., 2010. Extending the phenotype of monosomy 1p36 syndrome and mapping of a critical region for obesity and hyperphagia. Am J Med Genet A. 152A**,** 102-10.

Dawson, A.J., Putnam, S., Schultz, J., Riordan, D., Prasad, C., Greenberg, C.R., Chodirker, B.N., Mhanni, A.A., Chudley, A.E., 2002. Cryptic chromosome rearrangements detected by subtelomere assay in patients with mental retardation and dysmorphic features. Clin Genet. 62**,** 488-94.

de Winter, C.F., van Dijk, F., Stolker, J.J., Hennekam, R.C., 2009. Behavioural phenotype in Borjeson-Forssman-Lehmann syndrome. J Intellect Disabil Res. 53**,** 319-28.

Deardorff, M.A., Kaur, M., Yaeger, D., Rampuria, A., Korolev, S., Pie, J., Gil-Rodriguez, C., Arnedo, M., Loeys, B., Kline, A.D., Wilson, M., Lillquist, K., Siu, V., Ramos, F.J., Musio, A., Jackson, L.S., Dorsett, D., Krantz, I.D., 2007. Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. Am J Hum Genet. 80**,** 485-94.

Delatycki, M.B., Danks, A., Churchyard, A., Zhou, X.P., Eng, C., 2003. De novo germline PTEN mutation in a man with Lhermitte-Duclos disease which arose on the paternal chromosome and was transmitted to his child with polydactyly and Wormian bones. J Med Genet. 40**,** e92.

Denayer, E., Devriendt, K., de Ravel, T., Van Buggenhout, G., Smeets, E., Francois, I., Sznajer, Y., Craen, M., Leventopoulos, G., Mutesa, L., Vandecasseye, W., Massa, G., Kayserili, H., Sciot, R., Fryns, J.P., Legius, E., 2010. Tumor spectrum in children with Noonan syndrome and SOS1 or RAF1 mutations. Genes Chromosomes Cancer. 49**,** 242-52.

Depienne, C., Heron, D., Betancur, C., Benyahia, B., Trouillard, O., Bouteiller, D., Verloes, A., LeGuern, E., Leboyer, M., Brice, A., 2007. Autism, language delay and mental retardation in a patient with 7q11 duplication. J Med Genet. 44**,** 452-8.

Depienne, C., Bouteiller, D., Keren, B., Cheuret, E., Poirier, K., Trouillard, O., Benyahia, B., Quelin, C., Carpentier, W., Julia, S., Afenjar, A., Gautier, A., Rivier, F., Meyer, S., Berquin, P., Helias, M., Py, I., Rivera, S., Bahi-Buisson, N., Gourfinkel-An, I., Cazeneuve, C., Ruberg, M., Brice, A., Nabbout, R., Leguern, E., 2009a. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. PLoS Genet. 5**,** e1000381.

Depienne, C., Moreno-De-Luca, D., Heron, D., Bouteiller, D., Gennetier, A., Delorme, R., Chaste, P., Siffroi, J.P., Chantot-Bastaraud, S., Benyahia, B., Trouillard, O., Nygren, G., Kopp, S., Johansson, M., Rastam, M., Burglen, L., Leguern, E., Verloes, A., Leboyer, M., Brice, A., Gillberg, C., Betancur, C., 2009b. Screening for genomic rearrangements and methylation abnormalities of the 15q11-q13 region in autism spectrum disorders. Biol Psychiatry. 66**,** 349-59.

Descheemaeker, M.J., Govers, V., Vermeulen, P., Fryns, J.P., 2006. Pervasive developmental disorders in Prader-Willi syndrome: the Leuven experience in 59 subjects and controls. Am J Med Genet A. 140**,** 1136-42.

Devillard, F., Guinchat, V., Moreno-De-Luca, D., Tabet, A.C., Gruchy, N., Guillem, P., Nguyen Morel, M.A., Leporrier, N., Leboyer, M., Jouk, P.S., Lespinasse, J., Betancur, C., 2010. Paracentric inversion of chromosome 2 associated with cryptic duplication of 2q14 and deletion of 2q37 in a patient with autism. Am J Med Genet A. 152A**,** 2346-54.

Dhar, S.U., del Gaudio, D., German, J.R., Peters, S.U., Ou, Z., Bader, P.I., Berg, J.S., Blazo, M., Brown, C.W., Graham, B.H., Grebe, T.A., Lalani, S., Irons, M., Sparagana, S., Williams, M., Phillips, J.A., 3rd, Beaudet, A.L., Stankiewicz, P., Patel, A., Cheung, S.W., Sahoo, T., 2010. 22q13.3 deletion syndrome: clinical and molecular analysis using array CGH. Am J Med Genet A. 152A**,** 573-81.

Dibbens, L.M., Tarpey, P.S., Hynes, K., Bayly, M.A., Scheffer, I.E., Smith, R., Bomar, J., Sutton, E., Vandeleur, L., Shoubridge, C., Edkins, S., Turner, S.J., Stevens, C., O'Meara, S., Tofts, C., Barthorpe, S., Buck, G., Cole, J., Halliday, K., Jones, D., Lee, R., Madison, M., Mironenko, T., Varian, J., West, S., Widaa, S., Wray, P., Teague, J., Dicks, E., Butler, A., Menzies, A., Jenkinson, A., Shepherd, R., Gusella, J.F., Afawi, Z., Mazarib, A., Neufeld, M.Y., Kivity, S., Lev, D., Lerman-Sagie, T., Korczyn,

A.D., Derry, C.P., Sutherland, G.R., Friend, K., Shaw, M., Corbett, M., Kim, H.G., Geschwind, D.H., Thomas, P., Haan, E., Ryan, S., McKee, S., Berkovic, S.F., Futreal, P.A., Stratton, M.R., Mulley, J.C., Gecz, J., 2008. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. Nat Genet. 40**,** 776-81.

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

Donnelly, S.L., Wolpert, C.M., Menold, M.M., Bass, M.P., Gilbert, J.R., Cuccaro, M.L., Delong, G.R., Pericak-Vance, M.A., 2000. Female with autistic disorder and monosomy X (Turner syndrome): parent-of-origin effect of the X chromosome. Am J Med Genet. 96**,** 312-6.

Douglas, J., Cilliers, D., Coleman, K., Tatton-Brown, K., Barker, K., Bernhard, B., Burn, J., Huson, S., Josifova, D., Lacombe, D., Malik, M., Mansour, S., Reid, E., Cormier-Daire, V., Cole, T., Rahman, N., 2007. Mutations in RNF135, a gene within the NF1 microdeletion region, cause phenotypic abnormalities including overgrowth. Nat Genet. 39**,** 963-5.

Durand, C.M., Betancur, C., Boeckers, T.M., Bockmann, J., Chaste, P., Fauchereau, F., Nygren, G., Rastam, M., Gillberg, I.C., Anckarsater, H., Sponheim, E., Goubran-Botros, H., Delorme, R., Chabane, N., Mouren-Simeoni, M.C., de Mas, P., Bieth, E., Roge, B., Heron, D., Burglen, L., Gillberg, C., Leboyer, M., Bourgeron, T., 2007. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet. 39**,** 25-7.

Dykens, E.M., Clarke, D.J., 1997. Correlates of maladaptive behavior in individuals with 5p- (cri du chat) syndrome. Dev Med Child Neurol. 39**,** 752-6.

Ekstrom, A.B., Hakenas-Plate, L., Samuelsson, L., Tulinius, M., Wentz, E., 2008. Autism spectrum conditions in myotonic dystrophy type 1: a study on 57 individuals with congenital and childhood forms. Am J Med Genet B Neuropsychiatr Genet. 147B**,** 918-26.

El Abd, S., Patton, M.A., Turk, J., Hoey, H., Howlin, P., 1999. Social, communicational, and behavioral deficits associated with ring X Turner syndrome. Am J Med Genet. 88**,** 510-6.

Engelen, J.J., de Die-Smulders, C.E., Dirckx, R., Verhoeven, W.M., Tuinier, S., Curfs, L.M., Hamers, A.J., 2002. Duplication of chromosome region (16)(p11.2 --> p12.1) in a mother and daughter with mild mental retardation. Am J Med Genet. 109**,** 149-53.

Erturk, O., Bilguvar, K., Korkmaz, B., Bayri, Y., Bayrakli, F., Arlier, Z., Ozturk, A.K., Yalcinkaya, C., Tuysuz, B., State, M.W., Gunel, M., 2010. A patient with Duchenne muscular dystrophy and autism demonstrates a hemizygous deletion affecting Dystrophin. Am J Med Genet A. 152A**,** 1039-42.

Fernandez, B.A., Roberts, W., Chung, B., Weksberg, R., Meyn, S., Szatmari, P., Joseph-George, A.M., Mackay, S., Whitten, K., Noble, B., Vardy, C., Crosbie, V., Luscombe, S., Tucker, E., Turner, L., Marshall, C.R., Scherer, S.W., 2010. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. J Med Genet. 47**,** 195-203.

Fine, S.E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E.H., McDonald-McGinn, D.M., Emanuel, B.S., 2005. Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. J Autism Dev Disord. 35**,** 461-70.

Finelli, P., Natacci, F., Bonati, M.T., Gottardi, G., Engelen, J.J., de Die-Smulders, C.E., Sala, M., Giardino, D., Larizza, L., 2004. FISH characterisation of an identical (16)(p11.2p12.2) tandem duplication in two unrelated patients with autistic behaviour. J Med Genet. 41**,** e90.

Fisch, G.S., Battaglia, A., Parrini, B., Youngblom, J., Simensen, R., 2008. Cognitive-behavioral features of children with Wolf-Hirschhorn syndrome: preliminary report of 12 cases. Am J Med Genet C Semin Med Genet. 148C**,** 252-6.

Fisch, G.S., Grossfeld, P., Falk, R., Battaglia, A., Youngblom, J., Simensen, R., 2010. Cognitive-behavioral features of Wolf-Hirschhorn syndrome and other subtelomeric microdeletions. Am J Med Genet C Semin Med Genet. 154C**,** 417-26.

Fisher, F., 2005. Our life with Jonathan. Arch Dis Child. 90**,** 433.
Fombonne, E., Du Mazaubrun, C., Cans, C., Grandjean, H., 1997. Autism and associated medical disorders in a French epidemiological survey. J Am Acad Child Adolesc Psychiatry. 36**,** 1561-9.
Fontenelle, L.F., Mendlowicz, M.V., Bezerra de Menezes, G., dos Santos Martins, R.R., Versiani, M., 2004. Asperger Syndrome, obsessive-compulsive disorder, and major depression in a patient with 45,X/46,XY mosaicism. Psychopathology. 37**,** 105-9.
Froyen, G., Bauters, M., Boyle, J., Van Esch, H., Govaerts, K., van Bokhoven, H., Ropers, H.H., Moraine, C., Chelly, J., Fryns, J.P., Marynen, P., Gecz, J., Turner, G., 2007a. Loss of SLC38A5 and FTSJ1 at Xp11.23 in three brothers with non-syndromic mental retardation due to a microdeletion in an unstable genomic region. Hum Genet. 121**,** 539-47.
Froyen, G., Van Esch, H., Bauters, M., Hollanders, K., Frints, S.G., Vermeesch, J.R., Devriendt, K., Fryns, J.P., Marynen, P., 2007b. Detection of genomic copy number changes in patients with idiopathic mental retardation by high-resolution X-array-CGH: important role for increased gene dosage of XLMR genes. Hum Mutat. 28**,** 1034-42.
Galasso, C., Lo-Castro, A., Lalli, C., Nardone, A.M., Gullotta, F., Curatolo, P., 2008. Deletion 2q37: an identifiable clinical syndrome with mental retardation and autism. J Child Neurol. 23**,** 802-6.
Garbern, J.Y., Neumann, M., Trojanowski, J.Q., Lee, V.M., Feldman, G., Norris, J.W., Friez, M.J., Schwartz, C.E., Stevenson, R., Sima, A.A., 2010. A mutation affecting the sodium/proton exchanger, SLC9A6, causes mental retardation with tau deposition. Brain. 133**,** 1391-402.
Garcia, C.C., Blair, H.J., Seager, M., Coulthard, A., Tennant, S., Buddles, M., Curtis, A., Goodship, J.A., 2004. Identification of a mutation in synapsin I, a synaptic vesicle protein, in a family with epilepsy. J Med Genet. 41**,** 183-6.
Gauthier, J., Spiegelman, D., Piton, A., Lafreniere, R.G., Laurent, S., St-Onge, J., Lapointe, L., Hamdan, F.F., Cossette, P., Mottron, L., Fombonne, E., Joober, R., Marineau, C., Drapeau, P., Rouleau, G.A., 2009. Novel de novo SHANK3 mutation in autistic patients. Am J Med Genet B Neuropsychiatr Genet. 150B**,** 421-424.
Gecz, J., Shoubridge, C., Corbett, M., 2009. The genetic landscape of intellectual disability arising from chromosome X. Trends Genet. 25**,** 308-16.
Geerts, M., Steyaert, J., Fryns, J.P., 2003. The XYY syndrome: a follow-up study on 38 boys. Genet Couns. 14**,** 267-79.
Ghaziuddin, M., Bolyard, B., Alessi, N., 1994. Autistic disorder in Noonan syndrome. J Intellect Disabil Res. 38**,** 67-72.
Ghaziuddin, M., Burmeister, M., 1999. Deletion of chromosome 2q37 and autism: a distinct subtype? J Autism Dev Disord. 29**,** 259-63.
Giannandrea, M., Bianchi, V., Mignogna, M.L., Sirri, A., Carrabino, S., D'Elia, E., Vecellio, M., Russo, S., Cogliati, F., Larizza, L., Ropers, H.H., Tzschach, A., Kalscheuer, V., Oehl-Jaschkowitz, B., Skinner, C., Schwartz, C.E., Gecz, J., Van Esch, H., Raynaud, M., Chelly, J., de Brouwer, A.P., Toniolo, D., D'Adamo, P., 2010. Mutations in the small GTPase gene RAB39B are responsible for X-linked mental retardation associated with autism, epilepsy, and macrocephaly. Am J Hum Genet. 86**,** 185-95.
Gibbons, R., 2006. Alpha thalassaemia-mental retardation, X linked. Orphanet J Rare Dis. 1**,** 15.
Gillberg, C., Winnergard, I., Wahlstrom, J., 1984. The sex chromosomes--one key to autism? An XYY case of infantile autism. Appl Res Ment Retard. 5**,** 353-60.
Gillberg, C., 1989. Asperger syndrome in 23 Swedish children. Dev Med Child Neurol. 31**,** 520-31.
Gillberg, C., Rasmussen, P., 1994. Brief report: four case histories and a literature review of Williams syndrome and autistic behavior. J Autism Dev Disord. 24**,** 381-93.
Gillberg, I.C., Gillberg, C., Ahlsen, G., 1994. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. Dev Med Child Neurol. 36**,** 50-6.
Glancy, M., Barnicoat, A., Vijeratnam, R., de Souza, S., Gilmore, J., Huang, S., Maloney, V.K., Thomas, N.S., Bunyan, D.J., Jackson, A., Barber, J.C., 2009. Transmitted duplication of 8p23.1-8p23.2 associated with speech delay, autism and learning difficulties. Eur J Hum Genet. 17**,** 37-43.

Glessner, J.T., Wang, K., Cai, G., Korvatska, O., Kim, C.E., Wood, S., Zhang, H., Estes, A., Brune, C.W., Bradfield, J.P., Imielinski, M., Frackelton, E.C., Reichert, J., Crawford, E.L., Munson, J., Sleiman, P.M., Chiavacci, R., Annaiah, K., Thomas, K., Hou, C., Glaberson, W., Flory, J., Otieno, F., Garris, M., Soorya, L., Klei, L., Piven, J., Meyer, K.J., Anagnostou, E., Sakurai, T., Game, R.M., Rudd, D.S., Zurawiecki, D., McDougle, C.J., Davis, L.K., Miller, J., Posey, D.J., Michaels, S., Kolevzon, A., Silverman, J.M., Bernier, R., Levy, S.E., Schultz, R.T., Dawson, G., Owley, T., McMahon, W.M., Wassink, T.H., Sweeney, J.A., Nurnberger, J.I., Coon, H., Sutcliffe, J.S., Minshew, N.J., Grant, S.F., Bucan, M., Cook, E.H., Buxbaum, J.D., Devlin, B., Schellenberg, G.D., Hakonarson, H., 2009. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature. 459**,** 569-73.

Goffin, A., Hoefsloot, L.H., Bosgoed, E., Swillen, A., Fryns, J.P., 2001. PTEN mutation in a family with Cowden syndrome and autism. Am J Med Genet. 105**,** 521-4.

Goizet, C., Excoffier, E., Taine, L., Taupiac, E., El Moneim, A.A., Arveiler, B., Bouvard, M., Lacombe, D., 2000. Case with autistic syndrome and chromosome 22q13.3 deletion detected by FISH. Am J Med Genet. 96**,** 839-44.

Gorker, I., Tuzun, U., 2005. Autistic-like findings associated with a urea cycle disorder in a 4-year-old girl. J Psychiatry Neurosci. 30**,** 133-5.

Gosch, A., Pankau, R., 1994. "Autistic" behavior in two children with Williams-Beuren syndrome. Am J Med Genet. 53**,** 83-4.

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

Grisart, B., Willatt, L., Destree, A., Fryns, J.P., Rack, K., de Ravel, T., Rosenfeld, J., Vermeesch, J.R., Verellen-Dumoulin, C., Sandford, R., 2009. 17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction. J Med Genet. 46**,** 524-30.

Guilmatre, A., Dubourg, C., Mosca, A.L., Legallic, S., Goldenberg, A., Drouin-Garraud, V., Layet, V., Rosier, A., Briault, S., Bonnet-Brilhault, F., Laumonnier, F., Odent, S., Le Vacon, G., Joly-Helas, G., David, V., Bendavid, C., Pinoit, J.M., Henry, C., Impallomeni, C., Germano, E., Tortorella, G., Di Rosa, G., Barthelemy, C., Andres, C., Faivre, L., Frebourg, T., Saugier Veber, P., Campion, D., 2009. Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. Arch Gen Psychiatry. 66**,** 947-56.

Hackett, A., Tarpey, P.S., Licata, A., Cox, J., Whibley, A., Boyle, J., Rogers, C., Grigg, J., Partington, M., Stevenson, R.E., Tolmie, J., Yates, J.R., Turner, G., Wilson, M., Futreal, A.P., Corbett, M., Shaw, M., Gecz, J., Raymond, F.L., Stratton, M.R., Schwartz, C.E., Abidi, F.E., 2010. CASK mutations are frequent in males and cause X-linked nystagmus and variable XLMR phenotypes. Eur J Hum Genet. 18**,** 544-52.

Hagerman, R.J., Hull, C.E., Safanda, J.F., Carpenter, I., Staley, L.W., O'Connor, R.A., Seydel, C., Mazzocco, M.M., Snow, K., Thibodeau, S.N., et al., 1994. High functioning fragile X males: demonstration of an unmethylated fully expanded FMR-1 mutation associated with protein expression. Am J Med Genet. 51**,** 298-308.

Haliloglu, G., Gross, C., Senbil, N., Talim, B., Hehr, U., Uyanik, G., Winkler, J., Topaloglu, H., 2004. Clinical spectrum of muscle-eye-brain disease: from the typical presentation to severe autistic features. Acta Myol. 23**,** 137-9.

Halpin, C., Sims, K., 2008. Twenty years of audiology in a patient with Norrie disease. Int J Pediatr Otorhinolaryngol. 72**,** 1705-10.

Hamdan, F.F., Daoud, H., Rochefort, D., Piton, A., Gauthier, J., Langlois, M., Foomani, G., Dobrzeniecka, S., Krebs, M.O., Joober, R., Lafreniere, R.G., Lacaille, J.C., Mottron, L., Drapeau, P., Beauchamp, M.H., Phillips, M.S., Fombonne, E., Rouleau, G.A., Michaud, J.L., 2010. De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment. Am J Hum Genet. 87**,** 671-8.

Hanson, E., Nasir, R.H., Fong, A., Lian, A., Hundley, R., Shen, Y., Wu, B.L., Holm, I.A., Miller, D.T., 2010. Cognitive and behavioral characterization of 16p11.2 deletion syndrome. J Dev Behav Pediatr. 31**,** 649-57.

Hartshorne, T.S., Grialou, T.L., Parker, K.R., 2005. Autistic-like behavior in CHARGE syndrome. Am J Med Genet A. 133A**,** 257-61.

Hehr, U., Uyanik, G., Gross, C., Walter, M.C., Bohring, A., Cohen, M., Oehl-Jaschkowitz, B., Bird, L.M., Shamdeen, G.M., Bogdahn, U., Schuierer, G., Topaloglu, H., Aigner, L., Lochmuller, H., Winkler, J., 2007. Novel POMGnT1 mutations define broader phenotypic spectrum of muscle-eye-brain disease. Neurogenetics. 8**,** 279-88.

Hellings, J.A., Hossain, S., Martin, J.K., Baratang, R.R., 2002. Psychopathology, GABA, and the Rubinstein-Taybi syndrome: a review and case study. Am J Med Genet. 114**,** 190-5.

Hemara-Wahanui, A., Berjukow, S., Hope, C.I., Dearden, P.K., Wu, S.B., Wilson-Wheeler, J., Sharp, D.M., Lundon-Treweek, P., Clover, G.M., Hoda, J.C., Striessnig, J., Marksteiner, R., Hering, S., Maw, M.A., 2005. A CACNA1F mutation identified in an X-linked retinal disorder shifts the voltage dependence of Cav1.4 channel activation. Proc Natl Acad Sci U S A. 102**,** 7553-8.

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

Herguner, S., Mukaddes, N.M., 2006. Autism and Williams syndrome: a case report. World J Biol Psychiatry. 7**,** 186-8.

Herman, G.E., Butter, E., Enrile, B., Pastore, M., Prior, T.W., Sommer, A., 2007. Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly. Am J Med Genet A. 143**,** 589-93.

Hicks, M., Ferguson, S., Bernier, F., Lemay, J.F., 2008. A case report of monozygotic twins with Smith-Magenis syndrome. J Dev Behav Pediatr. 29**,** 42-6.

Hinton, V.J., Cyrulnik, S.E., Fee, R.J., Batchelder, A., Kiefel, J.M., Goldstein, E.M., Kaufmann, P., De Vivo, D.C., 2009. Association of autistic spectrum disorders with dystrophinopathies. Pediatr Neurol. 41**,** 339-46.

Hogart, A., Wu, D., LaSalle, J.M., Schanen, N.C., 2010. The comorbidity of autism with the genomic disorders of chromosome 15q11.2-q13. Neurobiol Dis. 38**,** 181-91.

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

Hsieh, E.W., Vargervik, K., Slavotinek, A.M., 2008. Clinical and molecular studies of patients with characteristics of Opitz G/BBB syndrome shows a novel MID1 mutation. Am J Med Genet A. 146A**,** 2337-45.

Hynes, K., Tarpey, P., Dibbens, L.M., Bayly, M.A., Berkovic, S.F., Smith, R., Raisi, Z.A., Turner, S.J., Brown, N.J., Desai, T.D., Haan, E., Turner, G., Christodoulou, J., Leonard, H., Gill, D., Stratton, M.R., Gecz, J., Scheffer, I.E., 2010. Epilepsy and mental retardation limited to females with PCDH19 mutations can present de novo or in single generation families. J Med Genet. 47**,** 211-6.

Iwakoshi, M., Okamoto, N., Harada, N., Nakamura, T., Yamamori, S., Fujita, H., Niikawa, N., Matsumoto, N., 2004. 9q34.3 deletion syndrome in three unrelated children. Am J Med Genet A. 126A**,** 278-83.

Jacquemont, M.L., Sanlaville, D., Redon, R., Raoul, O., Cormier-Daire, V., Lyonnet, S., Amiel, J., Le Merrer, M., Heron, D., de Blois, M.C., Prieur, M., Vekemans, M., Carter, N.P., Munnich, A., Colleaux, L., Philippe, A., 2006. Array-based comparative genomic hybridisation identifies high frequency of cryptic chromosomal rearrangements in patients with syndromic autism spectrum disorders. J Med Genet. 43**,** 843-9.

Jaeken, J., Van den Berghe, G., 1984. An infantile autistic syndrome characterised by the presence of succinylpurines in body fluids. Lancet. 2**,** 1058-61.

Jaillard, S., Dubourg, C., Gerard-Blanluet, M., Delahaye, A., Pasquier, L., Dupont, C., Henry, C., Tabet, A.C., Lucas, J., Aboura, A., David, V., Benzacken, B., Odent, S., Pipiras, E., 2009. 2q23.1

microdeletion identified by array comparative genomic hybridisation: an emerging phenotype with Angelman-like features? J Med Genet. 46**,** 847-55.
Jamain, S., Quach, H., Betancur, C., Rastam, M., Colineaux, C., Gillberg, I.C., Soderstrom, H., Giros, B., Leboyer, M., Gillberg, C., Bourgeron, T., 2003. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nat Genet. 34**,** 27-9.
Jamal, S.M., Basran, R.K., Newton, S., Wang, Z., Milunsky, J.M., 2010. Novel de novo PCDH19 mutations in three unrelated females with epilepsy female restricted mental retardation syndrome. Am J Med Genet A. 152A**,** 2475-81.
Jeffries, A.R., Curran, S., Elmslie, F., Sharma, A., Wenger, S., Hummel, M., Powell, J., 2005. Molecular and phenotypic characterization of ring chromosome 22. Am J Med Genet A. 137**,** 139-47.
Jha, P., Sheth, D., Ghaziuddin, M., 2007. Autism spectrum disorder and Klinefelter syndrome. Eur Child Adolesc Psychiatry. 16**,** 305-8.
Johansson, M., Rastam, M., Billstedt, E., Danielsson, S., Stromland, K., Miller, M., Gillberg, C., 2006. Autism spectrum disorders and underlying brain pathology in CHARGE association. Dev Med Child Neurol. 48**,** 40-50.
Keller, K., Williams, C., Wharton, P., Paulk, M., Bent-Williams, A., Gray, B., Ward, A., Stalker, H., Wallace, M., Carter, R., Zori, R., 2003. Routine cytogenetic and FISH studies for 17p11/15q11 duplications and subtelomeric rearrangement studies in children with autism spectrum disorders. Am J Med Genet A. 117**,** 105-11.
Kent, L., Evans, J., Paul, M., Sharp, M., 1999. Comorbidity of autistic spectrum disorders in children with Down syndrome. Dev Med Child Neurol. 41**,** 153-8.
Kent, L., Bowdin, S., Kirby, G.A., Cooper, W.N., Maher, E.R., 2008a. Beckwith Weidemann syndrome: a behavioral phenotype-genotype study. Am J Med Genet B Neuropsychiatr Genet. 147B**,** 1295-7.
Kent, L., Emerton, J., Bhadravathi, V., Weisblatt, E., Pasco, G., Willatt, L.R., McMahon, R., Yates, J.R., 2008b. X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. J Med Genet. 45**,** 519-24.
Kerr, B., Delrue, M.A., Sigaudy, S., Perveen, R., Marche, M., Burgelin, I., Stef, M., Tang, B., Eden, O.B., O'Sullivan, J., De Sandre-Giovannoli, A., Reardon, W., Brewer, C., Bennett, C., Quarell, O., M'Cann, E., Donnai, D., Stewart, F., Hennekam, R., Cave, H., Verloes, A., Philip, N., Lacombe, D., Levy, N., Arveiler, B., Black, G., 2006. Genotype-phenotype correlation in Costello syndrome: HRAS mutation analysis in 43 cases. J Med Genet. 43**,** 401-5.
Kielinen, M., Rantala, H., Timonen, E., Linna, S.L., Moilanen, I., 2004. Associated medical disorders and disabilities in children with autistic disorder: a population-based study. Autism. 8**,** 49-60.
Kim, H.G., Kishikawa, S., Higgins, A.W., Seong, I.S., Donovan, D.J., Shen, Y., Lally, E., Weiss, L.A., Najm, J., Kutsche, K., Descartes, M., Holt, L., Braddock, S., Troxell, R., Kaplan, L., Volkmar, F., Klin, A., Tsatsanis, K., Harris, D.J., Noens, I., Pauls, D.L., Daly, M.J., MacDonald, M.E., Morton, C.C., Quade, B.J., Gusella, J.F., 2008. Disruption of neurexin 1 associated with autism spectrum disorder. Am J Hum Genet. 82**,** 199-207.
Kimura, K., Sugawara, T., Mazaki-Miyazaki, E., Hoshino, K., Nomura, Y., Tateno, A., Hachimori, K., Yamakawa, K., Segawa, M., 2005. A missense mutation in SCN1A in brothers with severe myoclonic epilepsy in infancy (SMEI) inherited from a father with febrile seizures. Brain Dev. 27**,** 424-30.
Kirchhoff, M., Bisgaard, A.M., Bryndorf, T., Gerdes, T., 2007. MLPA analysis for a panel of syndromes with mental retardation reveals imbalances in 5.8% of patients with mental retardation and dysmorphic features, including duplications of the Sotos syndrome and Williams-Beuren syndrome regions. Eur J Med Genet. 50**,** 33-42.
Kleefstra, T., Yntema, H.G., Oudakker, A.R., Banning, M.J., Kalscheuer, V.M., Chelly, J., Moraine, C., Ropers, H.H., Fryns, J.P., Janssen, I.M., Sistermans, E.A., Nillesen, W.N., de Vries, L.B., Hamel, B.C., van Bokhoven, H., 2004. Zinc finger 81 (ZNF81) mutations associated with X-linked mental retardation. J Med Genet. 41**,** 394-9.

Kleefstra, T., Smidt, M., Banning, M.J., Oudakker, A.R., Van Esch, H., de Brouwer, A.P., Nillesen, W., Sistermans, E.A., Hamel, B.C., de Bruijn, D., Fryns, J.P., Yntema, H.G., Brunner, H.G., de Vries, B.B., van Bokhoven, H., 2005. Disruption of the gene Euchromatin Histone Methyl Transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomeric deletion syndrome. J Med Genet. 42**,** 299-306.

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

Klein-Tasman, B.P., Phillips, K.D., Lord, C., Mervis, C.B., Gallo, F.J., 2009. Overlap with the autism spectrum in young children with Williams syndrome. J Dev Behav Pediatr. 30**,** 289-99.

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

Knight-Jones, E., Knight, S., Heussler, H., Regan, R., Flint, J., Martin, K., 2000. Neurodevelopmental profile of a new dysmorphic syndrome associated with submicroscopic partial deletion of 1p36.3. Dev Med Child Neurol. 42**,** 201-6.

Komoto, J., Usui, S., Otsuki, S., Terao, A., 1984. Infantile autism and Duchenne muscular dystrophy. J Autism Dev Disord. 14**,** 191-5.

Konstantareas, M.M., Homatidis, S., 1999. Chromosomal abnormalities in a series of children with autistic disorder. J Autism Dev Disord. 29**,** 275-85.

Kumagai, T., Miura, K., Ohki, T., Matsumoto, A., Miyazaki, S., Nakamura, M., Ochi, N., Takahashi, O., 2001. [Central nervous system involvements in Duchenne/Becker muscular dystrophy]. No To Hattatsu. 33**,** 480-6.

Kutsche, K., Yntema, H., Brandt, A., Jantke, I., Nothwang, H.G., Orth, U., Boavida, M.G., David, D., Chelly, J., Fryns, J.P., Moraine, C., Ropers, H.H., Hamel, B.C., van Bokhoven, H., Gal, A., 2000. Mutations in ARHGEF6, encoding a guanine nucleotide exchange factor for Rho GTPases, in patients with X-linked mental retardation. Nat Genet. 26**,** 247-50.

Laje, G., Morse, R., Richter, W., Ball, J., Pao, M., Smith, A.C., 2010. Autism spectrum features in Smith-Magenis syndrome. Am J Med Genet C Semin Med Genet. 154C**,** 456-62.

Laumonnier, F., Bonnet-Brilhault, F., Gomot, M., Blanc, R., David, A., Moizard, M.P., Raynaud, M., Ronce, N., Lemonnier, E., Calvas, P., Laudier, B., Chelly, J., Fryns, J.P., Ropers, H.H., Hamel, B.C., Andres, C., Barthelemy, C., Moraine, C., Briault, S., 2004. X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. Am J Hum Genet. 74**,** 552-7.

Laumonnier, F., Shoubridge, C., Antar, C., Nguyen, L.S., Van Esch, H., Kleefstra, T., Briault, S., Fryns, J.P., Hamel, B., Chelly, J., Ropers, H.H., Ronce, N., Blesson, S., Moraine, C., Gecz, J., Raynaud, M., 2010. Mutations of the UPF3B gene, which encodes a protein widely expressed in neurons, are associated with nonspecific mental retardation with or without autism. Mol Psychiatry. 15**,** 767-76.

Lawson-Yuen, A., Saldivar, J.S., Sommer, S., Picker, J., 2008. Familial deletion within NLGN4 associated with autism and Tourette syndrome. Eur J Hum Genet. 16**,** 614-8.

Leger, P.L., Souville, I., Boddaert, N., Elie, C., Pinard, J.M., Plouin, P., Moutard, M.L., des Portes, V., Van Esch, H., Joriot, S., Renard, J.L., Chelly, J., Francis, F., Beldjord, C., Bahi-Buisson, N., 2008. The location of DCX mutations predicts malformation severity in X-linked lissencephaly. Neurogenetics. 9**,** 277-85.

Lerma-Carrillo, I., Molina, J.D., Cuevas-Duran, T., Julve-Correcher, C., Espejo-Saavedra, J.M., Andrade-Rosa, C., Lopez-Munoz, F., 2006. Psychopathology in the Lujan-Fryns syndrome: report of two patients and review. Am J Med Genet A. 140**,** 2807-11.

Lewis, J.C., Thomas, H.V., Murphy, K.C., Sampson, J.R., 2004. Genotype and psychological phenotype in tuberous sclerosis. J Med Genet. 41**,** 203-7.
Li, S.Y., Chen, Y.C., Lai, T.J., Hsu, C.Y., Wang, Y.C., 1993. Molecular and cytogenetic analyses of autism in Taiwan. Hum Genet. 92**,** 441-5.
Liang, J.S., Shimojima, K., Ohno, K., Sugiura, C., Une, Y., Ohno, K., Yamamoto, T., 2009. A newly recognised microdeletion syndrome of 2p15-16.1 manifesting moderate developmental delay, autistic behaviour, short stature, microcephaly, and dysmorphic features: a new patient with 3.2 Mb deletion. J Med Genet. 46**,** 645-7.
Lincoln, A.J., Searcy, Y.M., Jones, W., Lord, C., 2007. Social interaction behaviors discriminate young children with autism and Williams syndrome. J Am Acad Child Adolesc Psychiatry. 46**,** 323-31.
Lindstrand, A., Malmgren, H., Verri, A., Benetti, E., Eriksson, M., Nordgren, A., Anderlid, B.M., Golovleva, I., Schoumans, J., Blennow, E., 2010. Molecular and clinical characterization of patients with overlapping 10p deletions. Am J Med Genet A. 152A**,** 1233-43.
Lion-Francois, L., Cheillan, D., Pitelet, G., Acquaviva-Bourdain, C., Bussy, G., Cotton, F., Guibaud, L., Gerard, D., Rivier, C., Vianey-Saban, C., Jakobs, C., Salomons, G.S., des Portes, V., 2006. High frequency of creatine deficiency syndromes in patients with unexplained mental retardation. Neurology. 67**,** 1713-4.
Livingston, J.H., Cross, J.H., McLellan, A., Birch, R., Zuberi, S.M., 2009. A novel inherited mutation in the voltage sensor region of SCN1A is associated with Panayiotopoulos syndrome in siblings and generalized epilepsy with febrile seizures plus. J Child Neurol. 24**,** 503-8.
Lo-Castro, A., Galasso, C., Cerminara, C., El-Malhany, N., Benedetti, S., Nardone, A.M., Curatolo, P., 2009. Association of syndromic mental retardation and autism with 22q11.2 duplication. Neuropediatrics. 40**,** 137-40.
Loirat, C., Bellanne-Chantelot, C., Husson, I., Deschenes, G., Guigonis, V., Chabane, N., 2010. Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant. 25**,** 3430-3.
Longo, I., Frints, S.G., Fryns, J.P., Meloni, I., Pescucci, C., Ariani, F., Borghgraef, M., Raynaud, M., Marynen, P., Schwartz, C., Renieri, A., Froyen, G., 2003. A third MRX family (MRX68) is the result of mutation in the long chain fatty acid-CoA ligase 4 (FACL4) gene: proposal of a rapid enzymatic assay for screening mentally retarded patients. J Med Genet. 40**,** 11-7.
Lowenthal, R., Paula, C.S., Schwartzman, J.S., Brunoni, D., Mercadante, M.T., 2007. Prevalence of pervasive developmental disorder in Down's syndrome. J Autism Dev Disord. 37**,** 1394-5.
Lucchese, S., Takahashi, N., Miles, J., 2003. Is autism caused by numerous genetic and cytogenetic syndromes? Abstract (program number 589) presented at the annual meeting of The American Society of Human Genetics, November 4-8, Los Angeles, CA.
Lugtenberg, D., Yntema, H.G., Banning, M.J., Oudakker, A.R., Firth, H.V., Willatt, L., Raynaud, M., Kleefstra, T., Fryns, J.P., Ropers, H.H., Chelly, J., Moraine, C., Gecz, J., van Reeuwijk, J., Nabuurs, S.B., de Vries, B.B., Hamel, B.C., de Brouwer, A.P., van Bokhoven, H., 2006. ZNF674: a new kruppel-associated box-containing zinc-finger gene involved in nonsyndromic X-linked mental retardation. Am J Hum Genet. 78**,** 265-78.
Lukusa, T., Smeets, E., Vogels, A., Vermeesch, J.R., Fryns, J.P., 2005. Terminal 2q37 deletion and autistic behaviour. Genet Couns. 16**,** 179-80.
Lynch, N.E., Lynch, S.A., McMenamin, J., Webb, D., 2009. Bannayan-Riley-Ruvalcaba syndrome: a cause of extreme macrocephaly and neurodevelopmental delay. Arch Dis Child. 94**,** 553-4.
Madia, F., Striano, P., Gennaro, E., Malacarne, M., Paravidino, R., Biancheri, R., Budetta, M., Cilio, M.R., Gaggero, R., Pierluigi, M., Minetti, C., Zara, F., 2006. Cryptic chromosome deletions involving SCN1A in severe myoclonic epilepsy of infancy. Neurology. 67**,** 1230-5.
Malan, V., Rajan, D., Thomas, S., Shaw, A.C., Louis Dit Picard, H., Layet, V., Till, M., van Haeringen, A., Mortier, G., Nampoothiri, S., Puseljic, S., Legeai-Mallet, L., Carter, N.P., Vekemans, M., Munnich, A., Hennekam, R.C., Colleaux, L., Cormier-Daire, V., 2010. Distinct effects of allelic NFIX mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. Am J Hum Genet. 87**,** 189-98.

Manning, M.A., Cassidy, S.B., Clericuzio, C., Cherry, A.M., Schwartz, S., Hudgins, L., Enns, G.M., Hoyme, H.E., 2004. Terminal 22q deletion syndrome: a newly recognized cause of speech and language disability in the autism spectrum. Pediatrics. 114**,** 451-7.

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

Marini, C., Mei, D., Parmeggiani, L., Norci, V., Calado, E., Ferrari, A., Moreira, A., Pisano, T., Specchio, N., Vigevano, F., Battaglia, D., Guerrini, R., 2010. Protocadherin 19 mutations in girls with infantile-onset epilepsy. Neurology. 75**,** 646-53.

Marshall, C.R., Noor, A., Vincent, J.B., Lionel, A.C., Feuk, L., Skaug, J., Shago, M., Moessner, R., Pinto, D., Ren, Y., Thiruvahindrapduram, B., Fiebig, A., Schreiber, S., Friedman, J., Ketelaars, C.E., Vos, Y.J., Ficicioglu, C., Kirkpatrick, S., Nicolson, R., Sloman, L., Summers, A., Gibbons, C.A., Teebi, A., Chitayat, D., Weksberg, R., Thompson, A., Vardy, C., Crosbie, V., Luscombe, S., Baatjes, R., Zwaigenbaum, L., Roberts, W., Fernandez, B., Szatmari, P., Scherer, S.W., 2008. Structural variation of chromosomes in autism spectrum disorder. Am J Hum Genet. 82**,** 477-88.

Masurel-Paulet, A., Andrieux, J., Callier, P., Cuisset, J.M., Le Caignec, C., Holder, M., Thauvin-Robinet, C., Doray, B., Flori, E., Alex-Cordier, M.P., Beri, M., Boute, O., Delobel, B., Dieux, A., Vallee, L., Jaillard, S., Odent, S., Isidor, B., Beneteau, C., Vigneron, J., Bilan, F., Gilbert-Dussardier, B., Dubourg, C., Labalme, A., Bidon, C., Gautier, A., Pernes, P., Pinoit, J.M., Huet, F., Mugneret, F., Aral, B., Jonveaux, P., Sanlaville, D., Faivre, L., 2010. Delineation of 15q13.3 microdeletions. Clin Genet. 78**,** 149-61.

Mazzocco, M.M., Myers, G.F., Hamner, J.L., Panoscha, R., Shapiro, B.K., Reiss, A.L., 1998. The prevalence of the FMR1 and FMR2 mutations among preschool children with language delay. J Pediatr. 132**,** 795-801.

McBride, K.L., Varga, E.A., Pastore, M.T., Prior, T.W., Manickam, K., Atkin, J.F., Herman, G.E., 2010. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. Autism Res. 3**,** 137-41.

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

McMullan, D.J., Bonin, M., Hehir-Kwa, J.Y., de Vries, B.B., Dufke, A., Rattenberry, E., Steehouwer, M., Moruz, L., Pfundt, R., de Leeuw, N., Riess, A., Altug-Teber, O., Enders, H., Singer, S., Grasshoff, U., Walter, M., Walker, J.M., Lamb, C.V., Davison, E.V., Brueton, L., Riess, O., Veltman, J.A., 2009. Molecular karyotyping of patients with unexplained mental retardation by SNP arrays: a multicenter study. Hum Mutat. 30**,** 1082-92.

Mefford, H.C., Sharp, A.J., Baker, C., Itsara, A., Jiang, Z., Buysse, K., Huang, S., Maloney, V.K., Crolla, J.A., Baralle, D., Collins, A., Mercer, C., Norga, K., de Ravel, T., Devriendt, K., Bongers, E.M., de Leeuw, N., Reardon, W., Gimelli, S., Bena, F., Hennekam, R.C., Male, A., Gaunt, L., Clayton-Smith, J., Simonic, I., Park, S.M., Mehta, S.G., Nik-Zainal, S., Woods, C.G., Firth, H.V., Parkin, G., Fichera, M., Reitano, S., Lo Giudice, M., Li, K.E., Casuga, I., Broomer, A., Conrad, B., Schwerzmann, M., Raber, L., Gallati, S., Striano, P., Coppola, A., Tolmie, J.L., Tobias, E.S., Lilley, C., Armengol, L., Spysschaert, Y., Verloo, P., De Coene, A., Goossens, L., Mortier, G., Speleman, F., van Binsbergen, E., Nelen, M.R., Hochstenbach, R., Poot, M., Gallagher, L., Gill, M., McClellan, J., King, M.C., Regan, R., Skinner, C., Stevenson, R.E., Antonarakis, S.E., Chen, C., Estivill, X., Menten, B., Gimelli, G., Gribble, S., Schwartz, S., Sutcliffe, J.S., Walsh, T., Knight, S.J., Sebat, J., Romano, C., Schwartz, C.E., Veltman, J.A., de Vries, B.B., Vermeesch, J.R., Barber, J.C., Willatt, L., Tassabehji, M., Eichler, E.E., 2008. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. N Engl J Med. 359**,** 1685-99.

Meloni, I., Muscettola, M., Raynaud, M., Longo, I., Bruttini, M., Moizard, M.P., Gomot, M., Chelly, J., des Portes, V., Fryns, J.P., Ropers, H.H., Magi, B., Bellan, C., Volpi, N., Yntema, H.G., Lewis, S.E., Schaffer, J.E., Renieri, A., 2002. FACL4, encoding fatty acid-CoA ligase 4, is mutated in nonspecific X-linked mental retardation. Nat Genet. 30**,** 436-40.

Merhar, S.L., Manning-Courtney, P., 2007. Two boys with 47, XXY and autism. J Autism Dev Disord. 37**,** 840-6.

Miles, J.H., Hillman, R.E., 2000. Value of a clinical morphology examination in autism. Am J Med Genet. 91**,** 245-53.

Miles, J.H., Takahashi, T.N., Bagby, S., Sahota, P.K., Vaslow, D.F., Wang, C.H., Hillman, R.E., Farmer, J.E., 2005. Essential versus complex autism: definition of fundamental prognostic subtypes. Am J Med Genet A. 135**,** 171-80.

Miller, D.T., Shen, Y., Weiss, L.A., Korn, J., Anselm, I., Bridgemohan, C., Cox, G.F., Dickinson, H., Gentile, J., Harris, D.J., Hegde, V., Hundley, R., Khwaja, O., Kothare, S., Luedke, C., Nasir, R., Poduri, A., Prasad, K., Raffalli, P., Reinhard, A., Smith, S.E., Sobeih, M.M., Soul, J.S., Stoler, J., Takeoka, M., Tan, W.H., Thakuria, J., Wolff, R., Yusupov, R., Gusella, J.F., Daly, M.J., Wu, B.L., 2009. Microdeletion/duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. J Med Genet. 46**,** 242-8.

Mills, P.B., Footitt, E.J., Mills, K.A., Tuschl, K., Aylett, S., Varadkar, S., Hemingway, C., Marlow, N., Rennie, J., Baxter, P., Dulac, O., Nabbout, R., Craigen, W.J., Schmitt, B., Feillet, F., Christensen, E., De Lonlay, P., Pike, M.G., Hughes, M.I., Struys, E.A., Jakobs, C., Zuberi, S.M., Clayton, P.T., 2010. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain. 133**,** 2148-59.

Moessner, R., Marshall, C.R., Sutcliffe, J.S., Skaug, J., Pinto, D., Vincent, J., Zwaigenbaum, L., Fernandez, B., Roberts, W., Szatmari, P., Scherer, S.W., 2007. Contribution of SHANK3 mutations to autism spectrum disorder. Am J Hum Genet. 81**,** 1289-97.

Molloy, C.A., Murray, D.S., Kinsman, A., Castillo, H., Mitchell, T., Hickey, F.J., Patterson, B., 2009. Differences in the clinical presentation of Trisomy 21 with and without autism. J Intellect Disabil Res. 53**,** 143-51.

Moog, U., Engelen, J.J., Weber, B.W., Van Gelderen, M., Steyaert, J., Baas, F., Sijstermans, H.M., Fryns, J.P., 2004. Hereditary motor and sensory neuropathy (HMSN) IA, developmental delay and autism related disorder in a boy with duplication (17)(p11.2p12). Genet Couns. 15**,** 73-80.

Moore, S.J., Green, J.S., Fan, Y., Bhogal, A.K., Dicks, E., Fernandez, B.A., Stefanelli, M., Murphy, C., Cramer, B.C., Dean, J.C., Beales, P.L., Katsanis, N., Bassett, A.S., Davidson, W.S., Parfrey, P.S., 2005. Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. Am J Med Genet A. 132**,** 352-60.

Moreno-De-Luca, D., Mulle, J.G., Kaminsky, E.B., Sanders, S.J., Myers, S.M., Adam, M.P., Pakula, A.T., Eisenhauer, N.J., Uhas, K., Weik, L., Guy, L., Care, M.E., Morel, C.F., Boni, C., Salbert, B.A., Chandrareddy, A., Demmer, L.A., Chow, E.W., Surti, U., Aradhya, S., Pickering, D.L., Golden, D.M., Sanger, W.G., Aston, E., Brothman, A.R., Gliem, T.J., Thorland, E.C., Ackley, T., Iyer, R., Huang, S., Barber, J.C., Crolla, J.A., Warren, S.T., Martin, C.L., Ledbetter, D.H., 2010. Deletion 17q12 Is a recurrent copy number variant that confers high risk of autism and schizophrenia. Am J Hum Genet. 87**,** 618-30.

Morey-Canellas, J., Sivagamasundari, U., Barton, H., 2003. A case of autism in a child with Apert's syndrome. Eur Child Adolesc Psychiatry. 12**,** 100-2.

Morrow, J.D., Whitman, B.Y., Accardo, P.J., 1990. Autistic disorder in Sotos syndrome: a case report. Eur J Pediatr. 149**,** 567-9.

Moss, J.F., Oliver, C., Berg, K., Kaur, G., Jephcott, L., Cornish, K., 2008. Prevalence of autism spectrum phenomenology in Cornelia de Lange and Cri du Chat syndromes. Am J Ment Retard. 113**,** 278-91.

Mount, R.H., Charman, T., Hastings, R.P., Reilly, S., Cass, H., 2003. Features of autism in Rett syndrome and severe mental retardation. J Autism Dev Disord. 33**,** 435-42.

Mouridsen, S.E., Hansen, M.B., 2002. Neuropsychiatric aspects of Sotos syndrome. A review and two case illustrations. Eur Child Adolesc Psychiatry. 11**,** 43-8.

Mukaddes, N.M., Herguner, S., 2007. Autistic disorder and 22q11.2 duplication. World J Biol Psychiatry. 8**,** 127-30.

Muzykewicz, D.A., Newberry, P., Danforth, N., Halpern, E.F., Thiele, E.A., 2007. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. Epilepsy Behav. 11**,** 506-13.

Nakamine, A., Ouchanov, L., Jimenez, P., Manghi, E.R., Esquivel, M., Monge, S., Fallas, M., Burton, B.K., Szomju, B., Elsea, S.H., Marshall, C.R., Scherer, S.W., McInnes, L.A., 2008. Duplication of 17(p11.2p11.2) in a male child with autism and severe language delay. Am J Med Genet A. 146A**,** 636-43.

Nava, C., Hanna, N., Michot, C., Pereira, S., Pouvreau, N., Niihori, T., Aoki, Y., Matsubara, Y., Arveiler, B., Lacombe, D., Pasmant, E., Parfait, B., Baumann, C., Heron, D., Sigaudy, S., Toutain, A., Rio, M., Goldenberg, A., Leheup, B., Verloes, A., Cave, H., 2007. Cardio-facio-cutaneous and Noonan syndromes due to mutations in the RAS/MAPK signalling pathway: genotype-phenotype relationships and overlap with Costello syndrome. J Med Genet. 44**,** 763-71.

Nawara, M., Szczaluba, K., Poirier, K., Chrzanowska, K., Pilch, J., Bal, J., Chelly, J., Mazurczak, T., 2006. The ARX mutations: a frequent cause of X-linked mental retardation. Am J Med Genet A. 140**,** 727-32.

Nicolson, R., Bhalerao, S., Sloman, L., 1998. 47,XYY karyotypes and pervasive developmental disorders. Can J Psychiatry. 43**,** 619-22.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., Gillberg, C., 2009. Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. Res Dev Disabil. 30**,** 763-73.

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

Novara, F., Beri, S., Giorda, R., Ortibus, E., Nageshappa, S., Darra, F., Bernardina, B.D., Zuffardi, O., Van Esch, H., 2010. Refining the phenotype associated with MEF2C haploinsufficiency. Clin Genet. 78**,** 471-7.

Nowakowska, B.A., Obersztyn, E., Szymanska, K., Bekiesinska-Figatowska, M., Xia, Z., Ricks, C.B., Bocian, E., Stockton, D.W., Szczaluba, K., Nawara, M., Patel, A., Scott, D.A., Cheung, S.W., Bohan, T.P., Stankiewicz, P., 2010. Severe mental retardation, seizures, and hypotonia due to deletions of MEF2C. Am J Med Genet B Neuropsychiatr Genet. 153B**,** 1042-51.

Nystrom, A.M., Ekvall, S., Berglund, E., Bjorkqvist, M., Braathen, G., Duchen, K., Enell, H., Holmberg, E., Holmlund, U., Olsson-Engman, M., Anneren, G., Bondeson, M.L., 2008. Noonan and cardio-facio-cutaneous syndromes: two clinically and genetically overlapping disorders. J Med Genet. 45**,** 500-6.

Oliveira, G., Ataide, A., Marques, C., Miguel, T.S., Coutinho, A.M., Mota-Vieira, L., Goncalves, E., Lopes, N.M., Rodrigues, V., Carmona da Mota, H., Vicente, A.M., 2007. Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions. Dev Med Child Neurol. 49**,** 726-33.

Oliver, C., Arron, K., Sloneem, J., Hall, S., 2008. Behavioural phenotype of Cornelia de Lange syndrome: case-control study. Br J Psychiatry. 193**,** 466-70.

Orrico, A., Galli, L., Buoni, S., Orsi, A., Vonella, G., Sorrentino, V., 2009. Novel PTEN mutations in neurodevelopmental disorders and macrocephaly. Clin Genet. 75**,** 195-8.

Ozgen, H.M., van Daalen, E., Bolton, P.F., Maloney, V.K., Huang, S., Cresswell, L., van den Boogaard, M.J., Eleveld, M.J., van 't Slot, R., Hochstenbach, R., Beemer, F.A., Barrow, M., Barber, J.C., Poot, M., 2009. Copy number changes of the microcephalin 1 gene (MCPH1) in patients with autism spectrum disorders. Clin Genet. 76**,** 348-56.

Ozonoff, S., Williams, B.J., Gale, S., Miller, J.N., 1999. Autism and autistic behavior in Joubert syndrome. J Child Neurol. 14**,** 636-41.

Pagnamenta, A.T., Wing, K., Sadighi Akha, E., Knight, S.J., Bolte, S., Schmotzer, G., Duketis, E., Poustka, F., Klauck, S.M., Poustka, A., Ragoussis, J., Bailey, A.J., Monaco, A.P., 2009. A 15q13.3 microdeletion segregating with autism. Eur J Hum Genet. 17**,** 687-92.

Park, J.P., Moeschler, J.B., Davies, W.S., Patel, P.I., Mohandas, T.K., 1998. Smith-Magenis syndrome resulting from a de novo direct insertion of proximal 17q into 17p11.2. Am J Med Genet. 77**,** 23-7.

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

Paul, M., Allington-Smith, P., 1997. 'Asperger syndrome associated with Steinert's myotonic dystrophy'. Dev Med Child Neurol. 39**,** 280-1.

Paul, R., Cohen, D.J., Volkmar, F.R., 1983. Autistic behaviors in a boy with Noonan syndrome. J Autism Dev Disord. 13**,** 433-4.

Pavone, P., Taibi, R., Lionetti, E., Incorpora, G., Fisher, C.A., 2010. First case of dizygous twins with X-linked alpha-thalassemia/mental retardation syndrome showing wide clinical variability. Pediatr Int. 52**,** e72-5.

Paylor, R., Glaser, B., Mupo, A., Ataliotis, P., Spencer, C., Sobotka, A., Sparks, C., Choi, C.H., Oghalai, J., Curran, S., Murphy, K.C., Monks, S., Williams, N., O'Donovan, M.C., Owen, M.J., Scambler, P.J., Lindsay, E., 2006. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. Proc Natl Acad Sci U S A. 103**,** 7729-34.

Pearl, P.L., Gibson, K.M., Acosta, M.T., Vezina, L.G., Theodore, W.H., Rogawski, M.A., Novotny, E.J., Gropman, A., Conry, J.A., Berry, G.T., Tuchman, M., 2003. Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. Neurology. 60**,** 1413-7.

Peeters, H., Vermeesch, J., Fryns, J.P., 2008. A cryptic duplication 22q13.31 to qter leads to a distinct phenotype with mental retardation, microcephaly and mild facial dysmorphism. Genet Couns. 19**,** 365-71.

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

Petit, E., Herault, J., Raynaud, M., Cherpi, C., Perrot, A., Barthelemy, C., Lelord, G., Muh, J.P., 1996. X chromosome and infantile autism. Biol Psychiatry. 40**,** 457-64.

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

Pierpont, E.I., Pierpont, M.E., Mendelsohn, N.J., Roberts, A.E., Tworog-Dube, E., Seidenberg, M.S., 2009. Genotype differences in cognitive functioning in Noonan syndrome. Genes Brain Behav. 8**,** 275-82.

Pinto, D., Pagnamenta, A.T., Klei, L., Anney, R., Merico, D., Regan, R., Conroy, J., Magalhaes, T.R., Correia, C., Abrahams, B.S., Almeida, J., Bacchelli, E., Bader, G.D., Bailey, A.J., Baird, G., Battaglia, A., Berney, T., Bolshakova, N., Bolte, S., Bolton, P.F., Bourgeron, T., Brennan, S., Brian, J., Bryson, S.E., Carson, A.R., Casallo, G., Casey, J., Chung, B.H., Cochrane, L., Corsello, C., Crawford, E.L., Crossett, A., Cytrynbaum, C., Dawson, G., de Jonge, M., Delorme, R., Drmic, I., Duketis, E., Duque, F., Estes, A., Farrar, P., Fernandez, B.A., Folstein, S.E., Fombonne, E., Freitag, C.M., Gilbert, J., Gillberg, C., Glessner, J.T., Goldberg, J., Green, A., Green, J., Guter, S.J., Hakonarson, H., Heron, E.A., Hill, M., Holt, R., Howe, J.L., Hughes, G., Hus, V., Igliozzi, R., Kim, C., Klauck, S.M., Kolevzon, A., Korvatska, O., Kustanovich, V., Lajonchere, C.M., Lamb, J.A., Laskawiec, M., Leboyer, M., Le Couteur, A., Leventhal, B.L., Lionel, A.C., Liu, X.Q., Lord, C., Lotspeich, L., Lund, S.C., Maestrini, E., Mahoney, W., Mantoulan, C., Marshall, C.R., McConachie, H., McDougle, C.J., McGrath, J.,

McMahon, W.M., Merikangas, A., Migita, O., Minshew, N.J., Mirza, G.K., Munson, J., Nelson, S.F., Noakes, C., Noor, A., Nygren, G., Oliveira, G., Papanikolaou, K., Parr, J.R., Parrini, B., Paton, T., Pickles, A., Pilorge, M., Piven, J., Ponting, C.P., Posey, D.J., Poustka, A., Poustka, F., Prasad, A., Ragoussis, J., Renshaw, K., Rickaby, J., Roberts, W., Roeder, K., Roge, B., Rutter, M.L., Bierut, L.J., Rice, J.P., Salt, J., Sansom, K., Sato, D., Segurado, R., Sequeira, A.F., Senman, L., Shah, N., Sheffield, V.C., Soorya, L., Sousa, I., Stein, O., Sykes, N., Stoppioni, V., Strawbridge, C., Tancredi, R., Tansey, K., Thiruvahindrapduram, B., Thompson, A.P., Thomson, S., Tryfon, A., Tsiantis, J., Van Engeland, H., Vincent, J.B., Volkmar, F., Wallace, S., Wang, K., Wang, Z., Wassink, T.H., Webber, C., Weksberg, R., Wing, K., Wittemeyer, K., Wood, S., Wu, J., Yaspan, B.L., Zurawiecki, D., Zwaigenbaum, L., Buxbaum, J.D., Cantor, R.M., Cook, E.H., Coon, H., Cuccaro, M.L., Devlin, B., Ennis, S., Gallagher, L., Geschwind, D.H., Gill, M., Haines, J.L., Hallmayer, J., Miller, J., Monaco, A.P., Nurnberger, J.I., Jr., Paterson, A.D., Pericak-Vance, M.A., Schellenberg, G.D., Szatmari, P., Vicente, A.M., Vieland, V.J., Wijsman, E.M., Scherer, S.W., Sutcliffe, J.S., Betancur, C., 2010. Functional impact of global rare copy number variation in autism spectrum disorders. Nature. 466**,** 368-72.

Piton, A., Michaud, J.L., Peng, H., Aradhya, S., Gauthier, J., Mottron, L., Champagne, N., Lafreniere, R.G., Hamdan, F.F., Joober, R., Fombonne, E., Marineau, C., Cossette, P., Dube, M.P., Haghighi, P., Drapeau, P., Barker, P.A., Carbonetto, S., Rouleau, G.A., 2008. Mutations in the calcium-related gene IL1RAPL1 are associated with autism. Hum Mol Genet. 17**,** 3965-74.

Poo-Arguelles, P., Arias, A., Vilaseca, M.A., Ribes, A., Artuch, R., Sans-Fito, A., Moreno, A., Jakobs, C., Salomons, G., 2006. X-Linked creatine transporter deficiency in two patients with severe mental retardation and autism. J Inherit Metab Dis. 29**,** 220-3.

Potocki, L., Bi, W., Treadwell-Deering, D., Carvalho, C.M., Eifert, A., Friedman, E.M., Glaze, D., Krull, K., Lee, J.A., Lewis, R.A., Mendoza-Londono, R., Robbins-Furman, P., Shaw, C., Shi, X., Weissenberger, G., Withers, M., Yatsenko, S.A., Zackai, E.H., Stankiewicz, P., Lupski, J.R., 2007. Characterization of Potocki-Lupski syndrome (dup(17)(p11.2p11.2)) and delineation of a dosage-sensitive critical interval that can convey an autism phenotype. Am J Hum Genet. 80**,** 633-49.

Prasad, C., Prasad, A.N., Chodirker, B.N., Lee, C., Dawson, A.K., Jocelyn, L.J., Chudley, A.E., 2000. Genetic evaluation of pervasive developmental disorders: the terminal 22q13 deletion syndrome may represent a recognizable phenotype. Clin Genet. 57**,** 103-9.

Puusepp, H., Kall, K., Salomons, G.S., Talvik, I., Mannamaa, M., Rein, R., Jakobs, C., Ounap, K., 2009. The screening of SLC6A8 deficiency among Estonian families with X-linked mental retardation. J Inherit Metab Dis. Short report #147 Online.

Qiao, Y., Liu, X., Harvard, C., Hildebrand, M.J., Rajcan-Separovic, E., Holden, J.J., Lewis, M.E., 2008. Autism-associated familial microdeletion of Xp11.22. Clin Genet. 74**,** 134-44.

Qiao, Y., Riendeau, N., Koochek, M., Liu, X., Harvard, C., Hildebrand, M.J., Holden, J.J., Rajcan-Separovic, E., Lewis, M.E., 2009. Phenomic determinants of genomic variation in autism spectrum disorders. J Med Genet. 46**,** 680-8.

Quintero-Rivera, F., Sharifi-Hannauer, P., Martinez-Agosto, J.A., 2010. Autistic and psychiatric findings associated with the 3q29 microdeletion syndrome: case report and review. Am J Med Genet A. 152A**,** 2459-67.

Rajcan-Separovic, E., Harvard, C., Liu, X., McGillivray, B., Hall, J.G., Qiao, Y., Hurlburt, J., Hildebrand, J., Mickelson, E.C., Holden, J.J., Lewis, M.E., 2007. Clinical and molecular cytogenetic characterisation of a newly recognised microdeletion syndrome involving 2p15-16.1. J Med Genet. 44**,** 269-76.

Ramelli, G.P., Silacci, C., Ferrarini, A., Cattaneo, C., Visconti, P., Pescia, G., 2008. Microduplication 22q11.2 in a child with autism spectrum disorder: clinical and genetic study. Dev Med Child Neurol. 50**,** 953-5.

Ramocki, M.B., Peters, S.U., Tavyev, Y.J., Zhang, F., Carvalho, C.M., Schaaf, C.P., Richman, R., Fang, P., Glaze, D.G., Lupski, J.R., Zoghbi, H.Y., 2009. Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome. Ann Neurol. 66**,** 771-82.

Ramocki, M.B., Tavyev, Y.J., Peters, S.U., 2010. The MECP2 duplication syndrome. Am J Med Genet A. 152A**,** 1079-88.

Rasmussen, P., Borjesson, O., Wentz, E., Gillberg, C., 2001. Autistic disorders in Down syndrome: background factors and clinical correlates. Dev Med Child Neurol. 43**,** 750-4.

Ravnan, J.B., Tepperberg, J.H., Papenhausen, P., Lamb, A.N., Hedrick, J., Eash, D., Ledbetter, D.H., Martin, C.L., 2006. Subtelomere FISH analysis of 11 688 cases: an evaluation of the frequency and pattern of subtelomere rearrangements in individuals with developmental disabilities. J Med Genet. 43**,** 478-89.

Redon, R., Rio, M., Gregory, S.G., Cooper, R.A., Fiegler, H., Sanlaville, D., Banerjee, R., Scott, C., Carr, P., Langford, C., Cormier-Daire, V., Munnich, A., Carter, N.P., Colleaux, L., 2005. Tiling path resolution mapping of constitutional 1p36 deletions by array-CGH: contiguous gene deletion or "deletion with positional effect" syndrome? J Med Genet. 42**,** 166-71.

Reiss, A.L., Feinstein, C., Rosenbaum, K.N., Borengasser-Caruso, M.A., Goldsmith, B.M., 1985. Autism associated with Williams syndrome. J Pediatr. 106**,** 247-9.

Ritvo, E.R., Mason-Brothers, A., Freeman, B.J., Pingree, C., Jenson, W.R., McMahon, W.M., Petersen, P.B., Jorde, L.B., Mo, A., Ritvo, A., 1990. The UCLA-University of Utah epidemiologic survey of autism: the etiologic role of rare diseases. Am J Psychiatry. 147**,** 1614-21.

Riva, D., Vago, C., Pantaleoni, C., Bulgheroni, S., Mantegazza, M., Franceschetti, S., 2009. Progressive neurocognitive decline in two children with Dravet syndrome, de novo SCN1A truncations and different epileptic phenotypes. Am J Med Genet A. 149A**,** 2339-45.

Romero-Rubio, M.T., Andres-Celma, M., Castello-Pomares, M.L., Rosello, M., Ferrer-Bolufer, I., Martinez-Castellano, F., 2008. [ARX mutations and mental retardation of unknown etiology: three new cases in Spain]. Rev Neurol. 47**,** 634-7.

Ropers, H.H., 2010. Genetics of early onset cognitive impairment. Annu Rev Genomics Hum Genet. 11**,** 161-87.

Rosenfeld, J.A., Ballif, B.C., Lucas, A., Spence, E.J., Powell, C., Aylsworth, A.S., Torchia, B.A., Shaffer, L.G., 2009. Small deletions of SATB2 cause some of the clinical features of the 2q33.1 microdeletion syndrome. PLoS One. 4**,** e6568.

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

Russo, S., Marchi, M., Cogliati, F., Bonati, M.T., Pintaudi, M., Veneselli, E., Saletti, V., Balestrini, M., Ben-Zeev, B., Larizza, L., 2009. Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. Neurogenetics. 10**,** 241-50.

Sahoo, T., Peters, S.U., Madduri, N.S., Glaze, D.G., German, J.R., Bird, L.M., Barbieri-Welge, R., Bichell, T.J., Beaudet, A.L., Bacino, C.A., 2006a. Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. J Med Genet. 43**,** 512-6.

Sahoo, T., Wells, W., Cheung, S.W., Patel, A., Beaudet, A.L., 2006b. Use of array-CGH for analysis of patients with a laboratory referral diagnosis of autism spectrum disorder. Abstract (program number 822) presented at the annual meeting of The American Society of Human Genetics, October 9-13, New Orleans, LA.

Saillour, Y., Carion, N., Quelin, C., Leger, P.L., Boddaert, N., Elie, C., Toutain, A., Mercier, S., Barthez, M.A., Milh, M., Joriot, S., des Portes, V., Philip, N., Broglin, D., Roubertie, A., Pitelet, G., Moutard, M.L., Pinard, J.M., Cances, C., Kaminska, A., Chelly, J., Beldjord, C., Bahi-Buisson, N., 2009. LIS1-related isolated lissencephaly: spectrum of mutations and relationships with malformation severity. Arch Neurol. 66**,** 1007-15.

Schaefer, G.B., Lutz, R.E., 2006. Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. Genet Med. 8**,** 549-56.

Scheffer, I.E., Turner, S.J., Dibbens, L.M., Bayly, M.A., Friend, K., Hodgson, B., Burrows, L., Shaw, M., Wei, C., Ullmann, R., Ropers, H.H., Szepetowski, P., Haan, E., Mazarib, A., Afawi, Z., Neufeld, M.Y., Andrews, P.I., Wallace, G., Kivity, S., Lev, D., Lerman-Sagie, T., Derry, C.P., Korczyn, A.D., Gecz, J.,

Mulley, J.C., Berkovic, S.F., 2008. Epilepsy and mental retardation limited to females: an under-recognized disorder. Brain. 131**,** 918-27.

Schorry, E.K., Keddache, M., Lanphear, N., Rubinstein, J.H., Srodulski, S., Fletcher, D., Blough-Pfau, R.I., Grabowski, G.A., 2008. Genotype-phenotype correlations in Rubinstein-Taybi syndrome. Am J Med Genet A. 146A**,** 2512-9.

Schroer, R.J., Phelan, M.C., Michaelis, R.C., Crawford, E.C., Skinner, S.A., Cuccaro, M., Simensen, R.J., Bishop, J., Skinner, C., Fender, D., Stevenson, R.E., 1998. Autism and maternally derived aberrations of chromosome 15q. Am J Med Genet. 76**,** 327-36.

Schuback, D.E., Chen, Z.Y., Craig, I.W., Breakefield, X.O., Sims, K.B., 1995. Mutations in the Norrie disease gene. Hum Mutat. 5**,** 285-92.

Schwartz, C.E., Tarpey, P.S., Lubs, H.A., Verloes, A., May, M.M., Risheg, H., Friez, M.J., Futreal, P.A., Edkins, S., Teague, J., Briault, S., Skinner, C., Bauer-Carlin, A., Simensen, R.J., Joseph, S.M., Jones, J.R., Gecz, J., Stratton, M.R., Raymond, F.L., Stevenson, R.E., 2007. The original Lujan syndrome family has a novel missense mutation (p.N1007S) in the MED12 gene. J Med Genet. 44**,** 472-7.

Sebat, J., Lakshmi, B., Malhotra, D., Troge, J., Lese-Martin, C., Walsh, T., Yamrom, B., Yoon, S., Krasnitz, A., Kendall, J., Leotta, A., Pai, D., Zhang, R., Lee, Y.H., Hicks, J., Spence, S.J., Lee, A.T., Puura, K., Lehtimaki, T., Ledbetter, D., Gregersen, P.K., Bregman, J., Sutcliffe, J.S., Jobanputra, V., Chung, W., Warburton, D., King, M.C., Skuse, D., Geschwind, D.H., Gilliam, T.C., Ye, K., Wigler, M., 2007. Strong association of de novo copy number mutations with autism. Science. 316**,** 445-9.

Sempere, A., Fons, C., Arias, A., Rodriguez-Pombo, P., Colomer, R., Merinero, B., Alcaide, P., Capdevila, A., Ribes, A., Artuch, R., Campistol, J., 2009a. Creatine transporter deficiency in two adult patients with static encephalopathy. J Inherit Metab Dis. (Epub ahead of print).

Sempere, A., Fons, C., Arias, A., Rodriguez-Pombo, P., Merinero, B., Alcaide, P., Capdevila, A., Ribes, A., Duque, R., Eiris, J., Poo, P., Fernandez-Alvarez, E., Campistol, J., Artuch, R., 2009b. [Cerebral creatine deficiency: first Spanish patients harbouring mutations in GAMT gene]. Med Clin (Barc). 133**,** 745-9.

Shaffer, L.G., Kashork, C.D., Saleki, R., Rorem, E., Sundin, K., Ballif, B.C., Bejjani, B.A., 2006. Targeted genomic microarray analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. J Pediatr. 149**,** 98-102.

Sharp, A.J., Selzer, R.R., Veltman, J.A., Gimelli, S., Gimelli, G., Striano, P., Coppola, A., Regan, R., Price, S.M., Knoers, N.V., Eis, P.S., Brunner, H.G., Hennekam, R.C., Knight, S.J., de Vries, B.B., Zuffardi, O., Eichler, E.E., 2007. Characterization of a recurrent 15q24 microdeletion syndrome. Hum Mol Genet. 16**,** 567-72.

Sharp, A.J., Mefford, H.C., Li, K., Baker, C., Skinner, C., Stevenson, R.E., Schroer, R.J., Novara, F., De Gregori, M., Ciccone, R., Broomer, A., Casuga, I., Wang, Y., Xiao, C., Barbacioru, C., Gimelli, G., Bernardina, B.D., Torniero, C., Giorda, R., Regan, R., Murday, V., Mansour, S., Fichera, M., Castiglia, L., Failla, P., Ventura, M., Jiang, Z., Cooper, G.M., Knight, S.J., Romano, C., Zuffardi, O., Chen, C., Schwartz, C.E., Eichler, E.E., 2008. A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. Nat Genet. 40**,** 322-8.

Shinawi, M., Liu, P., Kang, S.H., Shen, J., Belmont, J.W., Scott, D.A., Probst, F.J., Craigen, W.J., Graham, B.H., Pursley, A., Clark, G., Lee, J., Proud, M., Stocco, A., Rodriguez, D.L., Kozel, B.A., Sparagana, S., Roeder, E.R., McGrew, S.G., Kurczynski, T.W., Allison, L.J., Amato, S., Savage, S., Patel, A., Stankiewicz, P., Beaudet, A.L., Cheung, S.W., Lupski, J.R., 2010. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J Med Genet. 47**,** 332-41.

Shoubridge, C., Tarpey, P.S., Abidi, F., Ramsden, S.L., Rujirabanjerd, S., Murphy, J.A., Boyle, J., Shaw, M., Gardner, A., Proos, A., Puusepp, H., Raymond, F.L., Schwartz, C.E., Stevenson, R.E., Turner, G., Field, M., Walikonis, R.S., Harvey, R.J., Hackett, A., Futreal, P.A., Stratton, M.R., Gecz, J., 2010. Mutations in the guanine nucleotide exchange factor gene IQSEC2 cause nonsyndromic intellectual disability. Nat Genet. 42**,** 486-8.

Sikora, D.M., Pettit-Kekel, K., Penfield, J., Merkens, L.S., Steiner, R.D., 2006. The near universal presence of autism spectrum disorders in children with Smith-Lemli-Opitz syndrome. Am J Med Genet A. 140**,** 1511-8.

Simonati, A., Boaretto, F., Vettori, A., Dabrilli, P., Criscuolo, L., Rizzuto, N., Mostacciuolo, M.L., 2006. A novel missense mutation in the L1CAM gene in a boy with L1 disease. Neurol Sci. 27**,** 114-7.

Skuse, D.H., James, R.S., Bishop, D.V., Coppin, B., Dalton, P., Aamodt-Leeper, G., Bacarese-Hamilton, M., Creswell, C., McGurk, R., Jacobs, P.A., 1997. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. Nature. 387**,** 705-8.

Smith, A.C., McGavran, L., Robinson, J., Waldstein, G., Macfarlane, J., Zonona, J., Reiss, J., Lahr, M., Allen, L., Magenis, E., 1986. Interstitial deletion of (17)(p11.2p11.2) in nine patients. Am J Med Genet. 24**,** 393-414.

Smith, I.M., Nichols, S.L., Issekutz, K., Blake, K., 2005. Behavioral profiles and symptoms of autism in CHARGE syndrome: preliminary Canadian epidemiological data. Am J Med Genet A. 133A**,** 248-56.

Smith, M., Filipek, P.A., Wu, C., Bocian, M., Hakim, S., Modahl, C., Spence, M.A., 2000. Analysis of a 1-megabase deletion in 15q22-q23 in an autistic patient: identification of candidate genes for autism and of homologous DNA segments in 15q22-q23 and 15q11-q13. Am J Med Genet. 96**,** 765-70.

Smith, M., Escamilla, J.R., Filipek, P., Bocian, M.E., Modahl, C., Flodman, P., Spence, M.A., 2001. Molecular genetic delineation of 2q37.3 deletion in autism and osteodystrophy: report of a case and of new markers for deletion screening by PCR. Cytogenet Cell Genet. 94**,** 15-22.

Sogaard, M., Tumer, Z., Hjalgrim, H., Hahnemann, J., Friis, B., Ledaal, P., Pedersen, V.F., Baekgaard, P., Tommerup, N., Cingoz, S., Duno, M., Brondum-Nielsen, K., 2005. Subtelomeric study of 132 patients with mental retardation reveals 9 chromosomal anomalies and contributes to the delineation of submicroscopic deletions of 1pter, 2qter, 4pter, 5qter and 9qter. BMC Med Genet. 6**,** 21.

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

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

Steffenburg, S., Gillberg, C.L., Steffenburg, U., Kyllerman, M., 1996. Autism in Angelman syndrome: a population-based study. Pediatr Neurol. 14**,** 131-6.

Steffenburg, S., Steffenburg, U., Gillberg, C., 2003. Autism spectrum disorders in children with active epilepsy and learning disability: comorbidity, pre- and perinatal background, and seizure characteristics. Dev Med Child Neurol. 45**,** 724-30.

Stein, M.T., Elias, E.R., Saenz, M., Pickler, L., Reynolds, A., 2010. Autistic spectrum disorder in a 9-year-old girl with macrocephaly. J Dev Behav Pediatr. 31**,** 632-4.

Steiner, C.E., Guerreiro, M.M., Marques-de-Faria, A.P., 2003. Genetic and neurological evaluation in a sample of individuals with pervasive developmental disorders. Arq Neuropsiquiatr. 61**,** 176-80.

Steiner, C.E., Acosta, A.X., Guerreiro, M.M., Marques-de-Faria, A.P., 2007. Genotype and natural history in unrelated individuals with phenylketonuria and autistic behavior. Arq Neuropsiquiatr. 65**,** 202-5.

Stevenson, R.E., Bennett, C.W., Abidi, F., Kleefstra, T., Porteous, M., Simensen, R.J., Lubs, H.A., Hamel, B.C., Schwartz, C.E., 2005. Renpenning syndrome comes into focus. Am J Med Genet A. 134**,** 415-21.

Stratton, R.F., Dobyns, W.B., Greenberg, F., DeSana, J.B., Moore, C., Fidone, G., Runge, G.H., Feldman, P., Sekhon, G.S., Pauli, R.M., et al., 1986. Interstitial deletion of (17)(p11.2p11.2): report of six additional patients with a new chromosome deletion syndrome. Am J Med Genet. 24**,** 421-32.

Strauss, K.A., Puffenberger, E.G., Huentelman, M.J., Gottlieb, S., Dobrin, S.E., Parod, J.M., Stephan, D.A., Morton, D.H., 2006. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med. 354**,** 1370-7.

Swarr, D.T., Bloom, D., Lewis, R.A., Elenberg, E., Friedman, E.M., Glotzbach, C., Wissman, S.D., Shaffer, L.G., Potocki, L., 2010. Potocki-Shaffer syndrome: comprehensive clinical assessment, review of the literature, and proposals for medical management. Am J Med Genet A. 152A**,** 565-72.

Swillen, A., Hellemans, H., Steyaert, J., Fryns, J.P., 1996. Autism and genetics: high incidence of specific genetic syndromes in 21 autistic adolescents and adults living in two residential homes in Belgium. Am J Med Genet. 67**,** 315-6.

Szafranski, P., Schaaf, C.P., Person, R.E., Gibson, I.B., Xia, Z., Mahadevan, S., Wiszniewska, J., Bacino, C.A., Lalani, S., Potocki, L., Kang, S.H., Patel, A., Cheung, S.W., Probst, F.J., Graham, B.H., Shinawi, M., Beaudet, A.L., Stankiewicz, P., 2010. Structures and molecular mechanisms for common 15q13.3 microduplications involving CHRNA7: benign or pathological? Hum Mutat. 31**,** 840-50.

Szatmari, P., Paterson, A.D., Zwaigenbaum, L., Roberts, W., Brian, J., Liu, X.Q., Vincent, J.B., Skaug, J.L., Thompson, A.P., Senman, L., Feuk, L., Qian, C., Bryson, S.E., Jones, M.B., Marshall, C.R., Scherer, S.W., Vieland, V.J., Bartlett, C., Mangin, L.V., Goedken, R., Segre, A., Pericak-Vance, M.A., Cuccaro, M.L., Gilbert, J.R., Wright, H.H., Abramson, R.K., Betancur, C., Bourgeron, T., Gillberg, C., Leboyer, M., Buxbaum, J.D., Davis, K.L., Hollander, E., Silverman, J.M., Hallmayer, J., Lotspeich, L., Sutcliffe, J.S., Haines, J.L., Folstein, S.E., Piven, J., Wassink, T.H., Sheffield, V., Geschwind, D.H., Bucan, M., Brown, W.T., Cantor, R.M., Constantino, J.N., Gilliam, T.C., Herbert, M., Lajonchere, C., Ledbetter, D.H., Lese-Martin, C., Miller, J., Nelson, S., Samango-Sprouse, C.A., Spence, S., State, M., Tanzi, R.E., Coon, H., Dawson, G., Devlin, B., Estes, A., Flodman, P., Klei, L., McMahon, W.M., Minshew, N., Munson, J., Korvatska, E., Rodier, P.M., Schellenberg, G.D., Smith, M., Spence, M.A., Stodgell, C., Tepper, P.G., Wijsman, E.M., Yu, C.E., Roge, B., Mantoulan, C., Wittemeyer, K., Poustka, A., Felder, B., Klauck, S.M., Schuster, C., Poustka, F., Bolte, S., Feineis-Matthews, S., Herbrecht, E., Schmotzer, G., Tsiantis, J., Papanikolaou, K., Maestrini, E., Bacchelli, E., Blasi, F., Carone, S., Toma, C., Van Engeland, H., de Jonge, M., Kemner, C., Koop, F., Langemeijer, M., Hijmans, C., Staal, W.G., Baird, G., Bolton, P.F., Rutter, M.L., Weisblatt, E., Green, J., Aldred, C., Wilkinson, J.A., Pickles, A., Le Couteur, A., Berney, T., McConachie, H., Bailey, A.J., Francis, K., Honeyman, G., Hutchinson, A., Parr, J.R., Wallace, S., Monaco, A.P., Barnby, G., Kobayashi, K., Lamb, J.A., Sousa, I., Sykes, N., Cook, E.H., Guter, S.J., Leventhal, B.L., Salt, J., Lord, C., Corsello, C., Hus, V., Weeks, D.E., Volkmar, F., Tauber, M., Fombonne, E., Shih, A., Meyer, K.J., 2007. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet. 39**,** 319-28.

Takahashi, T.N., Farmer, J.E., Deidrick, K.K., Hsu, B.S., Miles, J.H., Maria, B.L., 2005. Joubert syndrome is not a cause of classical autism. Am J Med Genet A. 132**,** 347-51.

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

Tartaglia, N., Davis, S., Hench, A., Nimishakavi, S., Beauregard, R., Reynolds, A., Fenton, L., Albrecht, L., Ross, J., Visootsak, J., Hansen, R., Hagerman, R., 2008. A new look at XXYY syndrome: medical and psychological features. Am J Med Genet A. 146A**,** 1509-22.

Taub, M.B., Stanton, A., 2008. Aarskog syndrome: a case report and literature review. Optometry. 79**,** 371-7.

Telvi, L., Lebbar, A., Del Pino, O., Barbet, J.P., Chaussain, J.L., 1999. 45,X/46,XY mosaicism: report of 27 cases. Pediatrics. 104**,** 304-8.

Thienpont, B., Bena, F., Breckpot, J., Philip, N., Menten, B., Van Esch, H., Scalais, E., Salamone, J.M., Fong, C.T., Kussmann, J.L., Grange, D.K., Gorski, J.L., Zahir, F., Yong, S.L., Morris, M.M., Gimelli, S., Fryns, J.P., Mortier, G., Friedman, J.M., Villard, L., Bottani, A., Vermeesch, J.R., Cheung, S.W., Devriendt, K., 2010. Duplications of the critical Rubinstein-Taybi deletion region on chromosome 16p13.3 cause a novel recognisable syndrome. J Med Genet. 47**,** 155-61.

Tierney, E., Bukelis, I., Thompson, R.E., Ahmed, K., Aneja, A., Kratz, L., Kelley, R.I., 2006. Abnormalities of cholesterol metabolism in autism spectrum disorders. Am J Med Genet B Neuropsychiatr Genet. 141B**,** 666-8.

Tonsgard, J.H., Yelavarthi, K.K., Cushner, S., Short, M.P., Lindgren, V., 1997. Do NF1 gene deletions result in a characteristic phenotype? Am J Med Genet. 73**,** 80-6.

Tory, K., Lacoste, T., Burglen, L., Moriniere, V., Boddaert, N., Macher, M.A., Llanas, B., Nivet, H., Bensman, A., Niaudet, P., Antignac, C., Salomon, R., Saunier, S., 2007. High NPHP1 and NPHP6 mutation rate in patients with Joubert syndrome and nephronophthisis: potential epistatic effect of NPHP6 and AHI1 mutations in patients with NPHP1 mutations. J Am Soc Nephrol. 18**,** 1566-75.

Toutain, A., Ayrault, A.D., Moraine, C., 1997. Mental retardation in Nance-Horan syndrome: clinical and neuropsychological assessment in four families. Am J Med Genet. 71**,** 305-14.

Trad, P.V., Schlefer, E., Hertzig, M., Kernberg, P.F., 1991. Treatment strategies for a case of concurrent pervasive developmental disorder and cerebral gigantism. J Am Acad Child Adolesc Psychiatry. 30**,** 499-506.

Treadwell-Deering, D.E., Powell, M.P., Potocki, L., 2010. Cognitive and behavioral characterization of the Potocki-Lupski syndrome (duplication 17p11.2). J Dev Behav Pediatr. 31**,** 137-43.

Trillingsgaard, A., Østergaard, J., 2004. Autism in Angelman syndrome: an exploration of comorbidity. Autism. 8**,** 163-74.

Tuchman, R., Rapin, I., 2002. Epilepsy in autism. Lancet Neurol. 1**,** 352-8.

Turner, G., Partington, M., Kerr, B., Mangelsdorf, M., Gecz, J., 2002. Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARX gene mutation. Am J Med Genet. 112**,** 405-11.

Udwin, O., 2002. Williams and Smith-Magenis syndromes. In Outcomes in Neurodevelopmental and Genetic Disorders, P. Howlin, O. Udwin, eds. Cambridge University, New York, NY, pp. 299-325.

Ullmann, R., Turner, G., Kirchhoff, M., Chen, W., Tonge, B., Rosenberg, C., Field, M., Vianna-Morgante, A.M., Christie, L., Krepischi-Santos, A.C., Banna, L., Brereton, A.V., Hill, A., Bisgaard, A.M., Muller, I., Hultschig, C., Erdogan, F., Wieczorek, G., Ropers, H.H., 2007. Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation. Hum Mutat. 28**,** 674-82.

Unique, 2008. 2p15p16.1 microdeletions. http://www.rarechromo.org. Accessed August 4, 2010.

Unique, 2009a. 15q13.3 microdeletion syndrome. http://www.rarechromo.org. Accessed August 4, 2010.

Unique, 2009b. Kleefstra syndrome. http://www.rarechromo.org. Accessed August 4, 2010.

van Bon, B.W., Mefford, H.C., Menten, B., Koolen, D.A., Sharp, A.J., Nillesen, W.M., Innis, J.W., de Ravel, T.J., Mercer, C.L., Fichera, M., Stewart, H., Connell, L.E., Ounap, K., Lachlan, K., Castle, B., Van der Aa, N., van Ravenswaaij, C., Nobrega, M.A., Serra-Juhe, C., Simonic, I., de Leeuw, N., Pfundt, R., Bongers, E.M., Baker, C., Finnemore, P., Huang, S., Maloney, V.K., Crolla, J.A., van Kalmthout, M., Elia, M., Vandeweyer, G., Fryns, J.P., Janssens, S., Foulds, N., Reitano, S., Smith, K., Parkel, S., Loeys, B., Woods, C.G., Oostra, A., Speleman, F., Pereira, A.C., Kurg, A., Willatt, L., Knight, S.J., Vermeesch, J.R., Romano, C., Barber, J.C., Mortier, G., Perez-Jurado, L.A., Kooy, F., Brunner, H.G., Eichler, E.E., Kleefstra, T., de Vries, B.B., 2009. Further delineation of the 15q13 microdeletion and duplication syndromes: a clinical spectrum varying from non-pathogenic to a severe outcome. J Med Genet. 46**,** 511-23.

van Bon, B.W., Koolen, D.A., Brueton, L., McMullan, D., Lichtenbelt, K.D., Ades, L.C., Peters, G., Gibson, K., Moloney, S., Novara, F., Pramparo, T., Dalla Bernardina, B., Zoccante, L., Balottin, U., Piazza, F., Pecile, V., Gasparini, P., Guerci, V., Kets, M., Pfundt, R., de Brouwer, A.P., Veltman, J.A., de Leeuw, N., Wilson, M., Antony, J., Reitano, S., Luciano, D., Fichera, M., Romano, C., Brunner, H.G., Zuffardi, O., de Vries, B.B., 2010. The 2q23.1 microdeletion syndrome: clinical and behavioural phenotype. Eur J Hum Genet. 18**,** 163-70.

Van Buggenhout, G., Van Ravenswaaij-Arts, C., Mc Maas, N., Thoelen, R., Vogels, A., Smeets, D., Salden, I., Matthijs, G., Fryns, J.P., Vermeesch, J.R., 2005. The del(2)(q32.2q33) deletion syndrome defined by clinical and molecular characterization of four patients. Eur J Med Genet. 48**,** 276-89.

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

van Karnebeek, C.D., van Gelderen, I., Nijhof, G.J., Abeling, N.G., Vreken, P., Redeker, E.J., van Eeghen, A.M., Hoovers, J.M., Hennekam, R.C., 2002. An aetiological study of 25 mentally retarded adults with autism. J Med Genet. 39**,** 205-13.

van Rijn, S., Swaab, H., Aleman, A., Kahn, R.S., 2008. Social behavior and autism traits in a sex chromosomal disorder: Klinefelter (47XXY) syndrome. J Autism Dev Disord. 38**,** 1634-41.

Varga, E.A., Pastore, M., Prior, T., Herman, G.E., McBride, K.L., 2009. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. Genet Med. 11**,** 111-7.

Vazna, A., Havlovicova, M., Sedlacek, Z., 2008. Molecular cloning and analysis of breakpoints on ring chromosome 17 in a patient with autism. Gene. 407**,** 186-92.

Veltman, M.W., Craig, E.E., Bolton, P.F., 2005. Autism spectrum disorders in Prader-Willi and Angelman syndromes: a systematic review. Psychiatr Genet. 15**,** 243-54.

Verri, A., Maraschio, P., Devriendt, K., Uggetti, C., Spadoni, E., Haeusler, E., Federico, A., 2004. Chromosome 10p deletion in a patient with hypoparathyroidism, severe mental retardation, autism and basal ganglia calcifications. Ann Genet. 47**,** 281-7.

Vervoort, V.S., Beachem, M.A., Edwards, P.S., Ladd, S., Miller, K.E., de Mollerat, X., Clarkson, K., DuPont, B., Schwartz, C.E., Stevenson, R.E., Boyd, E., Srivastava, A.K., 2002. AGTR2 mutations in X-linked mental retardation. Science. 296**,** 2401-3.

Vorstman, J.A., Morcus, M.E., Duijff, S.N., Klaassen, P.W., Heineman-de Boer, J.A., Beemer, F.A., Swaab, H., Kahn, R.S., van Engeland, H., 2006. The 22q11.2 deletion in children: high rate of autistic disorders and early onset of psychotic symptoms. J Am Acad Child Adolesc Psychiatry. 45**,** 1104-13.

Vostanis, P., Harrington, R., Prendergast, M., Farndon, P., 1994. Case reports of autism with interstitial deletion of chromosome 17 (p11.2 p11.2) and monosomy of chromosome 5 (5pter-->5p15.3). Psychiatr Genet. 4**,** 109-11.

Wada, T., Gibbons, R.J., 2003. ATR-X syndrome. In Genetics and Genomics of Neurobehavioral Disorders, S. Fisch G, ed. Humana Press, Totowa, NJ, pp. 309-334.

Wang, L.W., Berry-Kravis, E., Hagerman, R.J., 2010. Fragile X: leading the way for targeted treatments in autism. Neurotherapeutics. 7**,** 264-74.

Wassink, T.H., Piven, J., Patil, S.R., 2001. Chromosomal abnormalities in a clinic sample of individuals with autistic disorder. Psychiatr Genet. 11**,** 57-63.

Weaving, L.S., Christodoulou, J., Williamson, S.L., Friend, K.L., McKenzie, O.L., Archer, H., Evans, J., Clarke, A., Pelka, G.J., Tam, P.P., Watson, C., Lahooti, H., Ellaway, C.J., Bennetts, B., Leonard, H., Gecz, J., 2004. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet. 75**,** 1079-93.

Weidmer-Mikhail, E., Sheldon, S., Ghaziuddin, M., 1998. Chromosomes in autism and related pervasive developmental disorders: a cytogenetic study. J Intellect Disabil Res. 42**,** 8-12.

Weiss, L.A., Shen, Y., Korn, J.M., Arking, D.E., Miller, D.T., Fossdal, R., Saemundsen, E., Stefansson, H., Ferreira, M.A., Green, T., Platt, O.S., Ruderfer, D.M., Walsh, C.A., Altshuler, D., Chakravarti, A., Tanzi, R.E., Stefansson, K., Santangelo, S.L., Gusella, J.F., Sklar, P., Wu, B.L., Daly, M.J., 2008. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med. 358**,** 667-75.

Willatt, L., Cox, J., Barber, J., Cabanas, E.D., Collins, A., Donnai, D., FitzPatrick, D.R., Maher, E., Martin, H., Parnau, J., Pindar, L., Ramsay, J., Shaw-Smith, C., Sistermans, E.A., Tettenborn, M., Trump, D., de Vries, B.B., Walker, K., Raymond, F.L., 2005. 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. Am J Hum Genet. 77**,** 154-60.

Williams, P.G., Hersh, J.H., 1998. Brief report: the association of neurofibromatosis type 1 and autism. J Autism Dev Disord. 28**,** 567-71.
Williams, S.R., Aldred, M.A., Der Kaloustian, V.M., Halal, F., Gowans, G., McLeod, D.R., Zondag, S., Toriello, H.V., Magenis, R.E., Elsea, S.H., 2010. Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. Am J Hum Genet. 87**,** 219-28.
Wisniowiecka-Kowalnik, B., Nesteruk, M., Peters, S.U., Xia, Z., Cooper, M.L., Savage, S., Amato, R.S., Bader, P., Browning, M.F., Haun, C.L., Duda, A.W., 3rd, Cheung, S.W., Stankiewicz, P., 2010. Intragenic rearrangements in NRXN1 in three families with autism spectrum disorder, developmental delay, and speech delay. Am J Med Genet B Neuropsychiatr Genet. 153B**,** 983-93.
Wolanczyk, T., Banaszkiewicz, A., Mierzewska, H., Czartoryska, B., Zdziennicka, E., 2000. [Hyperactivity and behavioral disorders in Sanfilippo A (mucopolysaccharidosis type IIIA)--case report and review of the literature]. Psychiatr Pol. 34**,** 831-7.
Wolff, D.J., Clifton, K., Karr, C., Charles, J., 2002. Pilot assessment of the subtelomeric regions of children with autism: detection of a 2q deletion. Genet Med. 4**,** 10-4.
Wong, V., 2006. Study of the relationship between tuberous sclerosis complex and autistic disorder. J Child Neurol. 21**,** 199-204.
Wu, J.Y., Kuban, K.C., Allred, E., Shapiro, F., Darras, B.T., 2005. Association of Duchenne muscular dystrophy with autism spectrum disorder. J Child Neurol. 20**,** 790-5.
Wu, Y., Arai, A.C., Rumbaugh, G., Srivastava, A.K., Turner, G., Hayashi, T., Suzuki, E., Jiang, Y., Zhang, L., Rodriguez, J., Boyle, J., Tarpey, P., Raymond, F.L., Nevelsteen, J., Froyen, G., Stratton, M., Futreal, A., Gecz, J., Stevenson, R., Schwartz, C.E., Valle, D., Huganir, R.L., Wang, T., 2007. Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. Proc Natl Acad Sci U S A. 104**,** 18163-8.
Wuyts, W., Waeber, G., Meinecke, P., Schuler, H., Goecke, T.O., Van Hul, W., Bartsch, O., 2004. Proximal 11p deletion syndrome (P11pDS): additional evaluation of the clinical and molecular aspects. Eur J Hum Genet. 12**,** 400-6.
Xu, S., Han, J.C., Morales, A., Menzie, C.M., Williams, K., Fan, Y.S., 2008. Characterization of 11p14-p12 deletion in WAGR syndrome by array CGH for identifying genes contributing to mental retardation and autism. Cytogenet Genome Res. 122**,** 181-7.
Yatsenko, S.A., Kruer, M.C., Bader, P.I., Corzo, D., Schuette, J., Keegan, C.E., Nowakowska, B., Peacock, S., Cai, W.W., Peiffer, D.A., Gunderson, K.L., Ou, Z., Chinault, A.C., Cheung, S.W., 2009. Identification of critical regions for clinical features of distal 10q deletion syndrome. Clin Genet. 76**,** 54-62.
Yntema, H.G., Hamel, B.C., Smits, A.P., van Roosmalen, T., van den Helm, B., Kremer, H., Ropers, H.H., Smeets, D.F., van Bokhoven, H., 1998. Localisation of a gene for non-specific X linked mental retardation (MRX46) to Xq25-q26. J Med Genet. 35**,** 801-5.
Yoon, G., Rosenberg, J., Blaser, S., Rauen, K.A., 2007. Neurological complications of cardio-facio-cutaneous syndrome. Dev Med Child Neurol. 49**,** 894-9.
Yoshimura, I., Sasaki, A., Akimoto, H., Yoshimura, N., 1989. [A case of congenital myotonic dystrophy with infantile autism]. No To Hattatsu. 21**,** 379-84.
Young, H.K., Barton, B.A., Waisbren, S., Portales Dale, L., Ryan, M.M., Webster, R.I., North, K.N., 2008. Cognitive and psychological profile of males with Becker muscular dystrophy. J Child Neurol. 23**,** 155-62.
Yzer, S., van den Born, L.I., Schuil, J., Kroes, H.Y., van Genderen, M.M., Boonstra, F.N., van den Helm, B., Brunner, H.G., Koenekoop, R.K., Cremers, F.P., 2003. A Tyr368His RPE65 founder mutation is associated with variable expression and progression of early onset retinal dystrophy in 10 families of a genetically isolated population. J Med Genet. 40**,** 709-13.
Zafeiriou, D.I., Ververi, A., Salomons, G.S., Vargiami, E., Haas, D., Papadopoulou, V., Kontopoulos, E., Jakobs, C., 2008. L-2-Hydroxyglutaric aciduria presenting with severe autistic features. Brain Dev. 30**,** 305-7.

Zaffanello, M., Zamboni, G., Fontana, E., Zoccante, L., Tato, L., 2003. A case of partial biotinidase deficiency associated with autism. Child Neuropsychol. 9**,** 184-8.

Zappella, M., Meloni, I., Longo, I., Canitano, R., Hayek, G., Rosaia, L., Mari, F., Renieri, A., 2003. Study of MECP2 gene in Rett syndrome variants and autistic girls. Am J Med Genet B Neuropsychiatr Genet. 119**,** 102-7.

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

Zweier, C., de Jong, E.K., Zweier, M., Orrico, A., Ousager, L.B., Collins, A.L., Bijlsma, E.K., Oortveld, M.A., Ekici, A.B., Reis, A., Schenck, A., Rauch, A., 2009. CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. Am J Hum Genet. 85**,** 655-66.

Zweier, M., Gregor, A., Zweier, C., Engels, H., Sticht, H., Wohlleber, E., Bijlsma, E.K., Holder, S.E., Zenker, M., Rossier, E., Grasshoff, U., Johnson, D.S., Robertson, L., Firth, H.V., Ekici, A.B., Reis, A., Rauch, A., 2010. Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression. Hum Mutat. 31**,** 722-33.

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
POMGNT1	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)
RPE65	retinal pigment epithelium-specific protein	1p31.3	Leber congenital amaurosis	AR	(Coppieters et al., 2010; Yzer et al., 2003)
NRXN1	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)
NPHP1	nephrocystin-1	2q13	Joubert syndrome 4 and nephronophthisis (see *AHI1* below, 6q23.3)	AR	(Tory et al., 2007)†
*MBD5**	methyl-CpG binding domain protein 5	2q23.1	*MBD5* is the only gene deleted in all subjects with the 2q23.1 microdeletion syndrome	AD	(Jaillard et al., 2009; van Bon et al., 2010)
SCN1A	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)
*SATB2**	SATB homeobox 2	2q33.1	Haploinsufficiency of *SATB2* causes some of the clinical features of the 2q33.1 microdeletion syndrome, including severe ID, cleft palate and tooth anomalies. *SATB2* was disrupted in an individual with ASD carrying a balanced translocation	AD	(Marshall et al., 2008; Van Buggenhout et al., 2005)
FOXP1	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)
BTD	biotinidase	3p24.3	Biotinidase deficiency	AR	(Zaffanello et al., 2003)†
PRSS12	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)†
NIPBL	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 *NIPBL* (60%), *SMC1A* (5%), and *SMC3* (1 patient). ASD has been reported in subjects with *NIPBL* and *SMC1A* 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)
*MEF2C**	myocyte enhancer factor 2C	5q14.3	*MEF2C* 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)
ALDH7A1	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 *ALDH7A1* 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
*NSD1**	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)
ALDH5A1	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)
AHI1	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)
SYNGAP1	synaptic Ras GTPase activating protein 1	6p21.32	Non-syndromic ID	AD	(Pinto et al., 2010)†
HOXA1	homeobox A1	7p15.2	*HOXA1* 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)
BRAF	B-Raf	7q34	Cardio-facio-cutaneous syndrome is caused by gain of function mutations in *KRAS*, *BRAF*, *MEK1*, or *MEK2*. 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)
CNTNAP2	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 *CNTNAP2* 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)
CHD7	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)
VPS13B	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)
POMT1	protein-O-mannosyltransferase 1	9q34.13	Limb-girdle muscular dystrophy with ID; Walker-Warburg syndrome	AR	(D'Amico et al., 2006)†

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
TSC1	tuberous sclerosis 1	9q34.13	Tuberous sclerosis is caused by mutations in the *TSC1* or *TSC2* 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)
*EHMT1**	euchromatic histone-lysine N-methyltransferase 1	9q34.3	*EHMT1* 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)
PTEN	phosphatase and tensin homolog	10q23.31	PTEN hamartoma-tumor syndrome (including Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome); ID and ASD with macrocephaly. The frequency of *PTEN* mutations in children with ASD and macrocephaly is unknown; in one study, 15% (4/26) of children with *PTEN* 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)
FGFR2	fibroblast growth factor receptor 2	10q26.13	Apert syndrome	AD	(Morey-Canellas et al., 2003)†
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene	11p15.5	Costello syndrome	AD	(Kerr et al., 2006)†
*IGF2**	insulin-like growth factor 2	11p15.5	Aberrant imprinting of *IGF2* is associated with Beckwith-Wiedermann syndrome and Silver-Russell syndrome, characterized by growth abnormalities. Both disorders have been reported in ASD; 7% (6/87) of children with Beckwith-Wiedermann syndrome have ASD	AD	(Kent et al., 2008a)
DHCR7	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)
SHANK2	SH3 and multiple ankyrin repeat domains 2	11q13.3	3 *de novo* 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)
CACNA1C	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)
KRAS	c-K-ras2	12p12.1	Cardio-facio-cutaneous syndrome	AD	(Nava et al., 2007; Nystrom et al., 2008)
CEP290 (NPHP6)	centrosomal protein 290kDa	12q21.32	Joubert syndrome 5; Leber congenital amaurosis (see *AHI1* above, 6q23.3)	AR	(Coppieters et al., 2010; Perrault et al., 2007; Tory et al., 2007)
PAH	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)
PTPN11	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)
FOXG1	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)
L2HGDH	L-2-hydroxyglutarate dehydrogenase	14q22.1	L-2-hydroxyglutaric aciduria	AR	(Zafeiriou et al., 2008)†

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
*UBE3A**	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 *UBE3A* 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)
GATM (AGAT)	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)†
MAP2K1 (MEK1)	mitogen-activated protein kinase kinase 1	15q22.31	Cardio-facio-cutaneous syndrome	AD	(Nava et al., 2007)
TSC2	tuberous sclerosis 2	16p13.3	Tuberous sclerosis is caused by mutations in the *TSC1* or *TSC2* genes (see *TSC1* above, 9q34.13)	AD	(Fombonne et al., 1997; Gillberg et al., 1994; Lewis et al., 2004; Muzykewicz et al., 2007; Wong, 2006)
*CREBBP**	CREB binding protein	16p13.3	Rubinstein-Taybi syndrome (ID, characteristic facial features, broad thumbs and great toes). Mutations in *EP300* can also cause Rubinstein-Taybi syndrome (in 3%) but have not been reported in ASD	AD	(Schorry et al., 2008)
RPGRIP1L	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)
*PAFAH1B1**	platelet-activating factor acetylhydrolase, isoform Ib, subunit 1	17p13.3	Deletions or point mutations of *PAFAH1B1* (*LIS1*) result in isolated lissencephaly; extended deletions including *YWHAE* cause Miller-Dieker syndrome; microduplications of *PAFAH1B1* cause ID and subtle brain abnormalities. 30% (12/40) of patients with *PAFAH1B1* point mutations or intragenic deletions have moderate to severe autistic features	AD	(Bi et al., 2009; Bruno et al., 2010; Saillour et al., 2009)
*YWHAE**	tyrosine 3/tryptophan 5 - monooxygenase	17p13.3	Deletions including *YWHAE* are associated with Miller-Dieker syndrome, a contiguous gene syndrome; *YWHAE* is thought to be responsible for the more severe brain phenotype compared to deletions affecting only *PAFAH1B1*; 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)
GUCY2D	guanylate cyclase 2D, membrane	17p13.1	Leber congenital amaurosis	AR	(Coppieters et al., 2010)†
*RAI1**	retinoic acid induced 1	17p11.2	Deletions or mutations of *RAI1* 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)
RNF135	ring finger protein 135 isoform 1	17q11.2	Mutations in *RNF135*, which is within the *NF1* microdeletion region, cause overgrowth, ID, and dysmorphic features, demonstrating that haploinsufficiency of *RNF135* contributes to the phenotype of *NF1* microdeletion cases	AD	(Douglas et al., 2007)

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
*NF1**	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)
SGSH	N-sulfoglucosamine sulfohydrolase	17q25.3	Sanfilippo syndrome A (mucopolysaccharidosis III A)	AR	(Petit et al., 1996; Ritvo et al., 1990; Wolanczyk et al., 2000)
NFIX	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)
GAMT	guanidinoacetate N-methyltransferase	19p13.3	Guanidine acetate methyltransferase (GAMT) deficiency (brain creatine deficiency, synthesis defect)	AR	(Sempere et al., 2009b)
DMPK	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)
MKKS	McKusick-Kaufman syndrome	20p12.2	Bardet-Biedl syndrome is a ciliopathy, like Joubert syndrome	AR	(Barnett et al., 2002; Moore et al., 2005)
*TBX1**	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)†
ADSL	adenylosuccinate lyase	22q13.1	Adenylosuccinate lyase deficiency; ~50% present autism/autistic features	AR	(Jaeken and Van den Berghe, 1984; Spiegel et al., 2006)
*SHANK3**	SH3 and multiple ankyrin repeat domains 3	22q13.33	22q13 deletion syndrome (Phelan-McDermid syndrome) is caused by deletions of *SHANK3*; ASD or autistic features are frequent. *SHANK3* 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)
NLGN4X	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)
MID1	midline 1	Xp22.2	Opitz syndrome (Opitz/BBB syndrome)	XL	(Cox et al., 2000; Hsieh et al., 2008)
AP1S2	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)‡
NHS	Nance-Horan syndrome	Xp22.13	Nance-Horan syndrome (congenital cataracts and dental anomalies)	XL	(Toutain et al., 1997)(PARIS study, unpublished)
CDKL5	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)
PTCHD1	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)
ARX	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)
IL1RAPL1	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)

Gene	Description	Cytoband	Disorder	Inheritance pattern	References reporting ASD/autistic traits
DMD	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)
OTC	ornithine carbamoyltransferase	Xp11.4	Ornithine transcarbamylase deficiency	XL	(Gorker and Tuzun, 2005)†
CASK	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)†
NDP	norrin	Xp11.3	Norrie Disease (occuloacousticocerebral dysplasia)	XL	(Halpin and Sims, 2008; Schuback et al., 1995)
ZNF674	zinc finger family member 674	Xp11.3	Non-syndromic X-linked ID	XL	(Lugtenberg et al., 2006)†
PQBP1	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)
SYN1	synapsin I	Xp11.23	X-linked epilepsy with variable learning disabilities and behavior disorders	XL	(Garcia et al., 2004)†
ZNF81	zinc finger protein 81	Xp11.23	Non-syndromic X-linked ID	XL	(Kleefstra et al., 2004)†
FTSJ1	FtsJ homolog 1	Xp11.23	Non-syndromic X-linked ID	XL	(Froyen et al., 2007a)‡
CACNA1F	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)
JARID1C	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)†
IQSEC2	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)
SMC1A	structural maintenance of chromosomes 1A	Xp11.22	Cornelia de Lange syndrome (see *NIPBL* above, 5p13.2)	XL	(Deardorff et al., 2007)†
PHF8	PHD finger protein 8	Xp11.22	Siderius–Hamel syndrome (ID with cleft lip or cleft palate)	XL	(Qiao et al., 2008)‡
FGD1	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)
OPHN1	oligophrenin 1	Xq12	ID with cerebellar and vermis hypoplasia	XL	(Al-Owain et al., 2010; Froyen et al., 2007b)
MED12	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)
NLGN3	neuroligin 3	Xq13.1	Mutations in *NLGN3* 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)‡
KIAA2022	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
ATRX	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)
PCDH19	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)
ACSL4 (FACL4)	acyl-CoA synthetase long-chain family member 4	Xq22.3	Non-syndromic X-linked ID	XL	(Longo et al., 2003; Meloni et al., 2002)
DCX	doublecortin	Xq22.3	Type 1 lissencephaly	XL	(Leger et al., 2008)
AGTR2	angiotensin II receptor, type 2	Xq23	Non-syndromic X-linked ID	XL	(Vervoort et al., 2002)
UPF3B	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)
LAMP2	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)†
GRIA3	glutamate receptor, ionotrophic, AMPA 3	Xq25	Non-syndromic X-linked ID; mutations as well as 3 cases of partial duplication of *GRIA3* 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)
OCRL	phosphatidylinositol polyphosphate 5-phosphatase	Xq25	Lowe syndrome or oculo-cerebro-renal syndrome (ID, bilateral cataract and renal Fanconi syndrome)	XL	(Fisher, 2005; Steffenburg et al., 2003)
SLC9A6	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)
PHF6	PHD finger protein 6	Xq26.2	Borjeson-Forssman-Lehmann syndrome (ID, epilepsy, and hypogonadism)	XL	(de Winter et al., 2009)†
ARHGEF6	Rac/Cdc42 guanine nucleotide exchange factor 6	Xq26.3	Non-syndromic X-linked ID	XL	(Kutsche et al., 2000; Yntema et al., 1998)
FMR1	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)
AFF2	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)
SLC6A8	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 *SLC6A8*, or by defects in the biosynthesis of creatine (*GAMT* and *GATM* 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
L1CAM	L1 cell adhesion molecule	Xq28	Syndromic X-linked ID, MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs) syndrome	XL	(Simonati et al., 2006)†
*MECP2**	methyl CpG binding protein 2	Xq28	*MECP2* mutations or deletions cause Rett syndrome in females, and congenital encephalopathy or non-syndromic ID in males; *MECP2* 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)
RAB39B	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[a]	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, *MBD5.* 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 *SATB2* 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 *HDAC4* 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 *HDAC4*	(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[a]	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 *MEF2C*. 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 *NSD1*. 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 *NSD1*. 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 *GATA4*) 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 *EHMT1* 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 *GATA3* causes the HDR syndrome (hypoparathyroidism, deafness, renal disease)	(Lindstrand et al., 2010; Verri et al., 2004)	

Disorder	Cytoband	Genomic coordinates[a]	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 *CDKNIC* have been reported in BWS. Paternal 11p15.5 duplications of the *H19* and *IGF2* 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 *EXT2* and *ALX4* 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[a]	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 *UBE3A*; 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 *CHRNA7*, 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)[b]	
15q26 overgrowth syndrome	15q26.3	97,175,493-100,338,915	15q26 duplications cause an overgrowth syndrome; the causal gene is *IGF1R*		(Bonati et al., 2007)
Rubinstein-Taybi syndrome, 16p13.3 duplication syndrome	16p13.3	3,721,465-3,801,247	16p13.3 deletions including *CREBBP* 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[a]	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 *PAFAH1B1* gene cause isolated lissencephaly; larger deletions including *YWHAE* 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 *PAFAH1B1* or *YWHAE* 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 *RAI1*; 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 *NF1* and other genes. The NF1 microdeletion syndrome is characterized by a more severe phenotype than that observed in patients with intragenic *NF1* mutations; haploinsufficiency of *RNF135* 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 *HNF1B* 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[a]	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 *SHANK3*. 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 *SHANK3* 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 (*MECP2* duplication syndrome)	Xq28,	152,403,094-153,044,193	The Xq28 duplication syndrome is caused by the duplication of *MECP2*; it is mostly reported in males (females are protected by X inactivation) and is often associated with ASD or autistic features		(Ramocki et al., 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[a]	Comment	References reporting ASD/autistic traits in deletions	References reporting ASD/autistic traits in duplications
XYY 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)	

[a] 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.
[b] 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

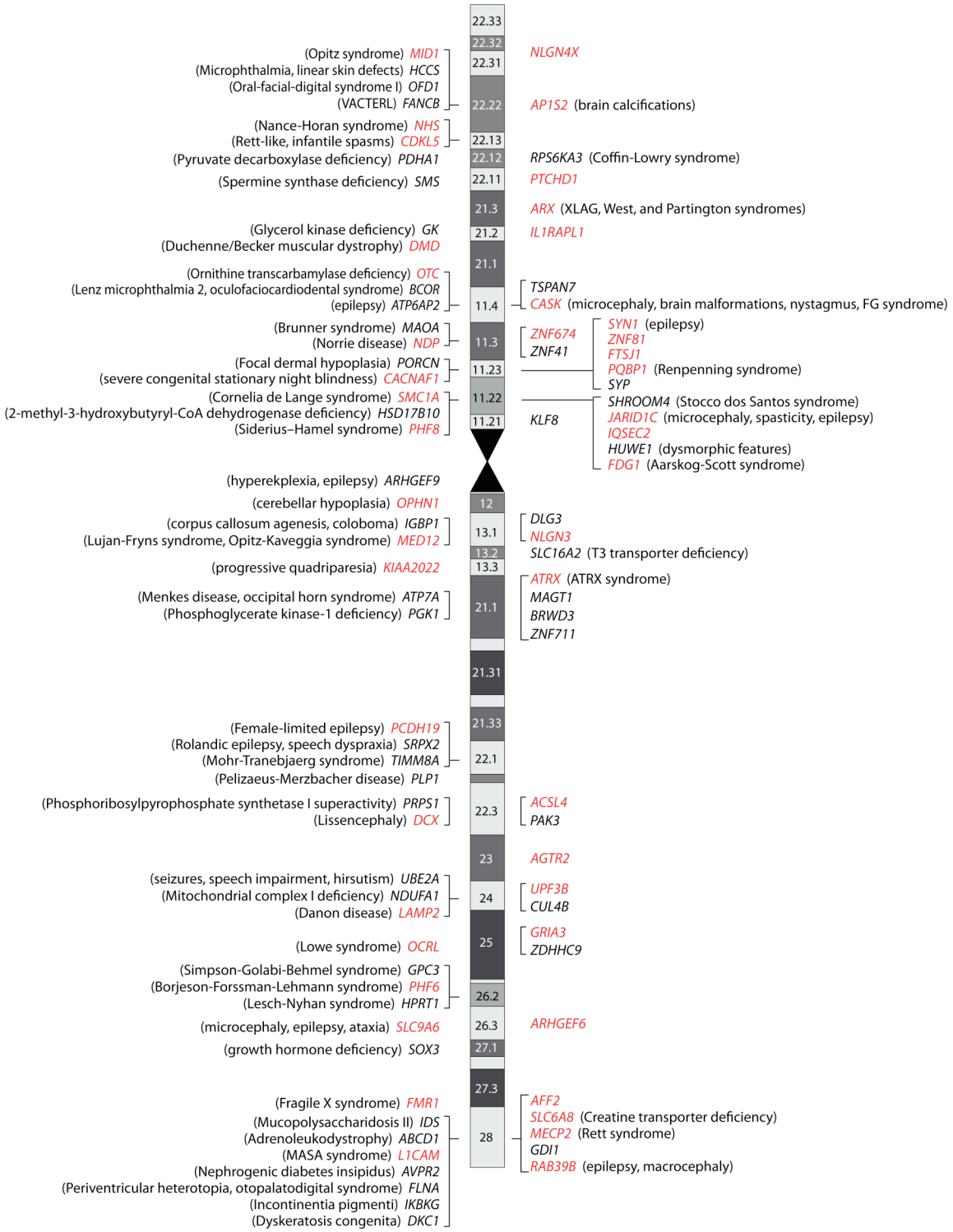


Figure 1. Genes implicated in syndromic and/or non-syndromic forms of X-linked mental retardation (XLMR) and their localization on the X chromosome. Genes that have been reported to be mutated in ASD are highlighted in red. Genes that cause syndromic forms of XLMR are shown on the left; those that can 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.