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## Genomics and Autism Spectrum Disorder

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### Abstract

**Purpose**—To present the current state of the evidence regarding translation of genetics (the study of single genes) and genomics (the study of all genes and gene-gene or gene-environment interactions) into health care of children with autism spectrum disorder (ASD).

**Methods**—This article presents an overview of ASD as an international health challenge, the emerging science related to broad diagnostic criteria, and the role of the nurse in research, education, and practice.

**Findings**—Much progress is being made in the understanding of genetics and genomics of ASD. Environmental factors are thought to contribute to the risk of developing ASD by interacting with a number of genes in different ways, thus suggesting causal heterogeneity. The rising identified prevalence of ASD, the changing diagnostic criteria for ASD, and the complexity of the core and associated features have made it difficult to define the ASD phenotype (observable behaviors that result from gene-environment interaction). Because early identification improves opportunities for intervention, researchers are looking for a useful biomarker to detect ASD. This search is complicated by the likelihood that there are multiple causes for multiple expressions that are defined as the autism spectrum.

**Conclusions**—To date, genetic and genomic research on ASD have underscored the complexity of the causes of ASD indicating that there are very complex genetic processes involved that are still not well understood.

**Clinical Relevance**—Nurses will benefit from new knowledge related to early identification, diagnosis, and implications for the family to promote early intervention. Families who have a child with ASD will require nursing support for advocacy for optimal health outcomes.

## Keywords

Autism; autism spectrum disorder; genetics; genomics

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Autism spectrum disorder (ASD) is a collective term for pervasive neurodevelopmental conditions characterized by atypical development in socialization, communication, and behavior (American Psychiatric Association [APA], 2000). Ongoing research focuses both on determining biomarkers to detect ASD, and on genetic etiology and the environmental influences involved in the cause(s) of the disorder (Caronna, Milunsky, & Tager-Flusberg, 2008). Early diagnosis of ASD affords the best outcomes for children and families (Agency for Healthcare Research and Quality [AHRQ], 2011). The purpose of this article is to present the current state of the evidence regarding translation of genetics and genomics into healthcare of children with ASD. It begins with an overview of ASD as an international public health problem, followed by a description of the emerging science related to early identification, diagnosis, and the role of the nurse in research, education and practice.

## Overview of Autism Spectrum Disorder

### Defining ASD

Kanner (1943) first described autism as a disorder of unusual social and communication development as well as of restrictive and repetitive behaviors that begins early in life. However, autism was classified as a form of early-onset schizophrenia in the APA's *Diagnostic and Statistical Manual* (DSM) until 1980 (APA, 1952, 1968, 1980). The DSM-III (APA, 1980) severed the connection to schizophrenia and distinguished autism as a developmental disability or "pervasive developmental disorder" (PDD). The specific criteria consisted of social, communication, and behavioral symptoms. The lowest threshold PDD diagnosis of PDD-Not Otherwise Specified was added in the revised DSM III-R (APA, 1987). Asperger's disorder was added as a PDD in the DSM-IV and the DSM-IV TR (APA, 1994, 2000), mirroring the broadening of conditions included as PDDs for the International Classification of Diseases, 10th edition (ICD-10; World Health Organization, 1992). Another revision of the diagnostic criteria for autism and related conditions will appear in the fifth edition of the DSM ([www.dsm5.org](http://www.dsm5.org)), anticipated for 2013. The current proposed criteria collapse several of the PDD subtypes into one category of ASDs.

### Prevalence of Autism Spectrum Disorder

With the redefining and recognition of ASD, there have been increases in the numbers of people identified with an ASD. From the 1940s until the 1980s, autism primarily referred to more severely affected individuals with autistic disorder, and it was thought to be rare, affecting approximately 1 in every 2,000 children (0.05%; Fombonne, 2009). Several studies using the ICD-10 and DSM-IV have been done in industrialized countries identifying not only autism, but also the wider spectrum with surprising consistency, indicating a best estimate now of combined ASD prevalence at 6 or 7 of every 1,000 children (0.6%–0.7%; Fombonne, 2009). These estimates are more than 10 times higher than estimates using earlier criteria. However, some of the most recent population-based studies have documented even higher ASD prevalence estimates of > 1% (Centers for Disease Control

and Prevention [CDC], 2012) and even as high as 2.6% (Kim et al., 2011) among children in areas of Asia, Europe, and North America. A consistent finding across many prevalence studies is that four to five boys are affected for every girl (CDC, 2012; Fombonne, 2009).

### **Autism Spectrum Disorder Phenotype**

Today, there is an increasing appreciation of the causal heterogeneity (diversity) in the expression of ASDs, along numerous phenotypic dimensions (Walsh, Elsabbagh, Bolton, & Singh, 2011). For example, one child with ASD may display speech delay and co-occurring gastrointestinal (GI) issues, while another child with ASD may have full speech and no GI comorbidity. In the clinical and research fields, there is a move away from the categorical identification of autism as being present or not present, with the recognition that some of the core domains associated with ASDs are distributed in a more continuous way in the population (Constantino, 2011). For example, autistic characteristics such as attention to detail are adaptive, with mild phenotypic expression, but are problematic when severely expressed or in interaction with other genetic or environmental factors (Constantino, 2011).

One focus of research relates to the definition of an ASD phenotype of specific autistic traits (endophenotypes) such as deficits in social expressiveness or presence of repetitive behaviors, rather than conceptualizing ASD as a unitary disorder. The research may lead to the discovery of different genotypes that match different ASD phenotypes. Furthermore, standardized approaches for diagnosis are needed to move toward the establishment of these endophenotypes as markers for familial risk of ASD, which can be important for causal discovery. As it stands now, the diagnostic criteria of ASD have not led to meaningful phenotypes that relate to cause or predict course.

### **Heritability**

It is widely accepted that ASDs are highly heritable (Kumar & Christian, 2009; Myers et al., 2011). The genetic influence of ASD has been identified in twin studies. Identical twins shared 60% to 90% of autistic traits compared with fraternal twins, who only shared 0% to 10% (Rosenberg et al., 2009). Studies estimate sibling recurrence risk from 2% to 8%, but a recent study that followed the development of infant siblings of children already diagnosed with ASD estimate sibling recurrence as high as 19% (Ozonoff et al., 2011). In addition, co-occurrence of ASD and single gene disorders (e.g., tuberous sclerosis) has also been observed, adding to the evidence that genetic factors play a significant role in the pathogenesis of ASD (Freitag, Staal, Klauck, Duketis, & Waltes, 2010).

At this point, it is clear that shifts in the diagnostic criteria and awareness of ASD have had an impact on the identified prevalence; however, a true increase in risk is also possible. There are likely multiple identification and risk factors that have affected the identified ASD prevalence. To date, no single risk factor explains the changes identified in ASD prevalence over time (Rice, 2011). For example, although changes in perinatal risk factors (i.e., low birth weight, preterm, breech, multiple, and cesarean births, and use of assisted reproductive technology) have been found to be associated with ASDs, the contribution of many of these factors to the recently observed ASD increase is unknown (Schieve et al., 2011).

## Environment

Environmental factors (influences other than genetic mutations) play a part in determining whether ASD will develop in a particular individual (Hallmayer et al., 2011). Studies have implicated exposure to high levels of environmental pollutants, such as pesticides (Shelton, Hertz-Picciotto, & Pessah, 2012). Two other studies looked at complications during pregnancy and found a positive relationship between viral infections and maternal stress and an increased incidence of ASD (Atladottir et al., 2010; Kinney, Munir, Crowley, & Miller, 2008). Likewise, artificial insemination and ovulation-inducing drugs were significantly associated with having a child with ASD in mothers 35 years old (Lyll, Pauls, Spiegelman, Santangelo, & Ascherio, 2012).

An exciting new area of research relates to environmental epigenetics, the study of the factors that control gene expression by chemicals that surround a gene's DNA that affect genetic activity. Shulha et al. (2012) found hundreds of places in the genome (in post-mortem brains) where histone methylation (addition of a methyl group to DNA that alters gene expression) is different on genes regulating neuronal connectivity, social behaviors, and cognition in persons with ASD. Another study (The Early Autism Risk Longitudinal Investigation [EARLI; [www.earlistudy.org](http://www.earlistudy.org)]) is exploring how epigenetic changes from methylation related to environment exposure during pregnancy increase the risk for ASD.

## Genetics

Genetics (single gene research) has focused on looking for susceptibility genes for ASD (genes that cause ASD that run in families), and newer models are looking to see if ASD is acquired through de novo (new, spontaneous) mutations (Sebat et al., 2007). Research efforts for each method follow below.

**Genetic susceptibility**—A systematic effort across support networks and the Interagency Autism Coordinating Committee in the United States (<http://iacc.hhs.gov/>) has organized large groups of patients, families, and researchers in an effort to biobank genetic materials and facilitate inquiry using large family- and population-based samples. Studies of these samples have focused on susceptibility loci and candidate genes, both for children with idiopathic (no known cause) and syndromic ASD. Although at this time no definitive genetic mutations leading to autism susceptibility have been established, several kinds of genes are being carefully analyzed and have shown potential to be involved in the autism phenotype. Five of these genes are *EN2* (Engrailed 2 gene), which is involved in cerebellum development; *GABR* (gamma amino butyric acid receptor genes), which regulate brain cell migration, differentiation, and synapse formation; *OXTR* (oxytocin receptor genes), which is involved in the response to stress and in social skills such as empathy; *RELN* (Reelin gene), which is involved in neuronal migration in the developing brain; and *SLC6A4*, a serotonin transporter gene that could account for phenotypic expression of happiness (Sakurai, Cai, Grice, & Buxbaum, 2011). Researchers have noted the differences between causal loci and susceptibility loci that increase the risk for ASD. Specific gene mutations that are causal loci have been identified on chromosomes 2, 3, 15, 16, 17, and 22 (Table 1). Table 1 also includes several copy number variants (CNVs).

**De novo mutations**—Recently published results from multiple studies have confirmed the importance of de novo mutations in the etiology of ASDs. A number of studies have focused on de novo CNVs and found higher rates of spontaneous CNVs in affected children than in their nonaffected siblings. Sanders et al. (2012) found significant associations of ASDs with de novo duplications of the 7q11.23 Williams-Beuren syndrome region (people with Williams-Beuren syndrome are actually deleted for a copy of this region rather than duplicated). Findings from these studies highlight that there may be hundreds of CNV regions on the human genome where de novo mutations could increase the risk for ASDs.

Exome sequencing (selectively sequencing the region of the genome that code for genes), as distinguished from whole genome sequencing, has also identified several de novo mutations in sporadic ASDs. O’Roak et al. (2011) sequenced the exomes of 20 individuals with sporadic ASD and their parents and identified 21 de novo mutations, 11 of which were protein altering. These findings again suggest that de novo mutations may contribute substantially to the genetic etiology of ASDs and open up significant possibilities for future research in gene discovery.

**Associated syndromes and medical conditions**—An estimated 5% to 10% of cases of ASD occur as part of a syndrome (McMahon, Baty, & Botkin, 2006). Investigating whether the genetic factors associated with the syndromes are linked to ASD may lead to a better understanding of the genetics of ASD. Autism may also coexist with other chromosomal abnormalities and single gene disorders. For example, a chromosomal condition involving duplication of regions on 15q (tetrasomy15q11q13) is associated with autistic-like features (Battaglia, Parrini, & Tancredi, 2010). Additionally, there is an increased risk for ASD in the sex chromosome trisomies, XYY and Klinefelter syndrome (XXY), at a rate substantially above population levels (Bishop et al., 2011), with X-linked and Y-linked neurologins hypothesized to play a role. Neurologins are proteins involved in the synapses, which allow information to travel between cells in the nervous system.

Several syndromes may have associated ASD symptoms. These include Fragile X syndrome, Rett syndrome, tuberous sclerosis, Smith-Magenis syndrome (Laje et al., 2010), Angelman syndrome and Prader-Willi syndrome (Nurmi et al., 2001), Smith-Lemli-Opitz syndrome (Opitz, Penchaszadeh, Holt, Spano, & Smith, 1994), and velocardiofacial syndrome, which is more commonly called deletion 22q11.2 syndrome (Fine et al., 2005). Among the syndromes, Fragile X, Rett syndrome, and tuberous sclerosis are the most common. The features, incidence, cause, and prevalence of associated ASD symptoms of these syndromes are presented below.

**Fragile X syndrome**—Fragile X syndrome is a common cause of inherited intellectual disability (Auerbach, Osterweil, & Bear, 2011). It occurs in 1 in 3,600 males and 1 in 8,000 females. It is caused by an abnormally increased number of CGG trinucleotide repeats within the *FMR1* (Fragile X Mental Retardation-1) gene on chromosome Xq27.3 (Cornish, Turk, & Levitas, 2007), which affects synaptic proteins (Auerbach et al., 2011). Jones, Skinner, Friez, Schwartz, and Stevenson (2008) found that abnormal methylation pattern plays a role in fragile X. Those with fragile X syndrome are diagnosed with autism at a rate of 15% to 30% (Harris, 2011).

**Rett syndrome**—Rett syndrome is a degenerative condition that primarily affects females and has an onset in early childhood. It occurs in 1 in 10,000 to 1 in 15,000 live female births (Hagberg, 1985). It is caused by a mutation in the X-linked gene *MECP2*, which produces methyl cytosine binding protein 2 (Amir et al., 1999). Approximately 25% to 40% of individuals with Rett syndrome are also diagnosed with autism (Harris, 2011), and ASD and Rett syndrome are currently in the same classification of disorders (APA, 2000).

**Tuberous sclerosis**—Tuberous sclerosis is a multisystem autosomal-dominant disorder that results from a loss of function mutation in either the *TSC1* gene on chromosome 9q34 or the *TSC2* gene on chromosome 16p13.3 (Curatolo, Bombardieri, & Jozwiak, 2008). It occurs in 1 in 6,000 live births (O’Callaghan, 1999). The gene product of *TSC1* is known as hamartin, and the product of *TSC2* is tuberin. Approximately 10% to 30% of cases of tuberous sclerosis are due to mutations in *TSC1*, with the remainder due to mutations in *TSC2*. Approximately 25% to 60% of individuals with tuberous sclerosis have autism (Harris, 2011).

There are other syndromes that have autism as a clinical characteristic. Further study is needed in order to explain how mutations in *FMRI*, *MECP2*, *TSC1-TSC2*, and the various genes involved in other syndromes can result in an autism phenotype. In addition, ASDs can co-occur across the whole range of intellectual functioning and with other developmental and medical conditions, for example, epilepsy. Intellectual disability co-occurs with ASD in about 40% of children identified (CDC, 2012).

## Genomics

Advances in genomic research (gene-gene, whole genome, and gene-environment) have enabled a number of different approaches to be used in order to characterize genetic determinants of ASD (Kumar & Christian, 2009). Early studies used chromosome banding, a technique whereby chromosomes are treated to reveal characteristic patterns of horizontal bands (Mefford et al., 2012). This method enabled identification of cytogenetically visible chromosome rearrangements such as translocations, deletions, or duplications (Mefford et al., 2012). These findings were significant in facilitating the understanding of the molecular basis for conditions such as Prader-Willi syndrome and Angelman syndrome (deletion of 15q11-q13; Butler, Meaney, & Palmer, 1986), but not autism. Genome-wide linkage studies to identify regions of the genome that are shared between affected family members with autism were also conducted and identified several susceptibility loci that show up in multiple studies, including 2q24–2q31, 7q and 17q11–17q21 (Abrahams & Geshwind, 2008). More recently, the introduction of genome-wide techniques has enabled identification of submicroscopic CNVs (Mefford et al., 2012). CNVs are segments of DNA that are present in fewer or more copies (deletions or duplications), as compared with the number of copies in a reference human genome.

Analysis of genome-wide CNVs has led to an increase in the discovery of several common recurrent CNVs, such as 16p11.2 (Weiss et al., 2008) and 17q12 (Moreno-De-Luca et al., 2010). Most of these variations appear not to be inherited but have resulted from spontaneous mutations (permanent changes in DNA sequences that makes up genes; Sebat

et al., 2007). Yet, while a number of chromosome and genetic loci have been implicated, there is little evidence that any one of these is responsible for a large proportion of cases (Freitag et al., 2010).

Similarly, nongenetic clinical features, such as head size and differences in brain function, have been frequently associated with ASD (Elder, Dawson, Toth, Fein, & Munson, 2008; Walsh et al., 2011). Yet, no findings are present in the majority of people with ASD, and a number have been associated with a range of neurodevelopmental conditions other than ASD (Walsh et al., 2011). The current evidence therefore points to ASD being a highly complex process involving multiple contributing loci, genetic heterogeneity, gene-gene interactions, and gene-environment interactions (Freitag et al., 2010). The Interagency Autism Coordinating Committee has assembled a strategic research plan for autism and offers an annual summary of promising research findings (<http://iacc.hhs.gov/>).

## Nursing Implications

### Research

Nurses need to know of the genetic and genomic research methodologies as nurses inform and counsel clients for participation in clinical trials. Nurses caring for families of persons with ASD need to understand the implications of participation in different areas of research. ASD affects people's functioning in virtually every domain; therefore, research involves behavioral and biological approaches. Multiple approaches take into consideration many factors, including nursing perspectives and knowledge. The International Society for Autism Research is a professional organization that fosters the necessary interdisciplinary collaboration (<http://www.autism-insar.org/>).

Multiple efforts are underway to increase the power of genetic studies through collaborative consortiums (e.g., The Autism Genetic Resource Exchange, <http://agre.autismspeaks.org/>; The Simons Foundation Autism Research Initiative, <http://sfari.org/>; The Autism Genome Project, [www.autismgenome.org](http://www.autismgenome.org/); and The National Database for Autism Research, [http://ndar.nih.gov](http://ndar.nih.gov/)). The parents and children with ASD participating in the Simons Simplex Community Research are referred to as "simplex" families since they have only one child with ASD (Fischbach & Lord, 2010). This research helps identify whether genetic changes are inherited from the parent (already present in the family) or are the result of a de novo mutation in the child, resulting in the potential to connect environmental and genetic links to ASD (Sebat et al., 2007). Autism Genetic Resource Exchange research families participate in research looking for ASD candidate genes ([http://agre.autismspeaks.org](http://agre.autismspeaks.org/)).

In some cases, the intent of research may only be to aggregate the findings of potential genetic associations across patients for reports in scientific literature (Miller, Hayeems, & Bytautas, 2010), not to provide individual-level data that explain symptomatology for that participant. Informed consent can be achieved when there is an understanding and acceptance by the participant that individual results may not be offered, and if offered, may not be clinically useful. For example, research findings may show that a child has a chromosome abnormality, but the clinical implications of what that means for the child's symptoms and prognosis may not be known. Despite participant expectations, an

explanation that such research will not help with any therapeutic interventions, at least in the relatively short term, is important. To date, the reason for the lack of clarity in prognosis relates to the complex nature of aligning genes with the behavioral symptoms of ASD, which also limits the development of a clinically valid genetic test (McMahon et al., 2006).

## Education

Education on ASD and genetic literacy are needed for nurses to have the adequate knowledge and skills to assess genetic risk for ASD and to advocate for at-risk families. One educational resource to help meet this goal is the National Genetics Education and Development Center (<http://www.tellingstories.nhs.uk/>). A story on the Web site describes autism as a condition with multifactorial etiology. The story also has a link to a nursing competency in genetics and outlines key aspects of nursing's role in genetics and genomics. By grounding the science in a real-life example, practicing nurses can conceptualize how to apply complicated science of genetic risk to cases with real clients.

Several educational Web sites inform both families and nursing practice. These include The Autism Society of America ([www.autism-society.org](http://www.autism-society.org)), Autism Speaks ([www.autismspeaks.org](http://www.autismspeaks.org)), The Centers for Disease Control and Prevention ([www.cdc.gov/autism](http://www.cdc.gov/autism)), and the National Autistic Society ([www.autism.org.uk](http://www.autism.org.uk)). Another source for health literature on autism and genes is the National Institutes of Health (<http://health.nih.gov/topic/Autism>).

In order for services to be directed to those in need, nurses and other healthcare professionals must know what risk factors there are for ASD, how to identify possible signs of ASD, and referral sources for additional assessment and intervention. A comprehensive family history is essential and should include information on the broader autism phenotype in apparently unaffected family members, across generations. Of particular interest is a history of the occurrence of syndromes (as described above) with autism characteristics. A family history of, for example, fragile X syndrome, might help in diagnosing the basis for the autism phenotype in the proband undergoing the evaluation for ASD.

## Practice

Nurses can also assess for possible ASD in all child encounters. Determining whether a child's developmental profile is consistent with ASD requires consideration of the way the child communicates, interacts, behaves, learns, and plays and is guided by diagnostic criteria. Recent efforts have focused on improving the early recognition of autism and for screening all children for developmental disabilities in the first few years of life using screening algorithms in the United States (Johnson & Myers, 2007) and in the United Kingdom (National Collaborating Centre for Women's and Children's Health, 2011). As key healthcare professionals, nurses play an important role in proactive screening, listening to parents' concerns, and referral for further assessment and intervention.

ASD is typically identified by either parent or professional concern about delayed or unusual language, limited interactions with others, or the presence of unusual behaviors during the first 3 years of life. Although concerns about development are often noted before the age of 2 years, diagnosis is often delayed until after 4 years of age (CDC, 2012). Children who

have some evidence of ASD should be referred for a comprehensive diagnostic evaluation with behavioral observation assessment tools (Johnson & Myers, 2007), such as the Autism Diagnostic Observation Schedule (Lord, Rutter, DiLavore, & Risi, 2012). The ADOS quantifies social, communication, and behavioral features associated with autism.

A timely diagnosis of ASD is important so that children can begin receiving evidence-based therapies as soon as possible. Early diagnosis and evidence-based therapies improve chances of optimal functioning (AHRQ, 2011). The CDC has information and materials available to new parents, healthcare professionals, and early childhood education providers on early developmental milestones, concerns needing follow-up, the importance of early developmental screening, and the importance of starting developmental therapies as early as possible ([www.cdc.gov/actearly](http://www.cdc.gov/actearly)).

It is also important that a child's access to services and supports is not delayed while waiting for a diagnostic assessment. One referral source is through the public education system. The Individuals with Disabilities Education Act (<http://idea.ed.gov/>) enables early intervention or special education assessment to begin at any time there is a developmental concern. The National Dissemination Center for Children with Disabilities (<http://nichcy.org/>) has a great deal of resource information.

Nursing research has focused on the parental perception of the cause of their child's autism. In a review of the literature, Hebert and Koulouglioti (2010) found that without a definitive cause for ASD, parents are left to come to their own interpretations for the cause (e.g., environmental toxins or vaccinations). The authors found that the parent's beliefs about the cause of their child's ASD affected future decision making, for example, the decision to immunize. Nurses have an important role in providing accurate information to help families make informed decisions (<http://www.cdc.gov/vaccines/hcp.htm>).

Parental stress is another area of nursing research for parents of children with ASD. Parents experience great distress during the year or two typically needed to assess all factors and make a diagnosis (Giarelli, Sounders, Pinto-Martin, Bloch, & Levy, 2005). During this time, the ethical obligation of nurses is to provide parents and families with care that promotes psychological and social adjustment to the possibility of living with a chronic, possibly debilitating condition. One strategy is to develop protocols that incorporate essential information about the genetics of ASD with information about life-long care. Regardless of the etiology, the affected individual will require life-long behavioral interventions, and healthcare plans must accommodate the client with special needs.

## Summary

ASD researchers work to identify which genes are involved in ASD. Current evidence suggests several genes on different chromosomes may be involved. ASD can co-occur with other chromosomal disorders and syndromes, suggesting that these disorders are risk factors for ASD. Collaborative efforts of researchers continue to search for a clinically useful biomarker for the disorder that will standardize the approach to diagnosis, which is necessary to optimize outcomes for children and families. Nurses will continue to play an

important role in research, education and practice for families of children with ASD through advocacy for persons with ASD and their families.

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### Clinical Resources

- National Health Service: <http://www.nhs.uk/conditions/Autistic-spectrum-disorder>
- National Human Genome Research Institute. National Institutes of Health. Learning about Autism: <http://www.genome.gov/25522099>

**Table 1**

## Genes, Deletions, Copy Number Variations, and Associated Features

Gene function/outcome	Brain region	Gene	Chromosome	Reference
Pattern forming genes that guide body plans	Brainstem and cerebellum development	<i>38 HOX</i>	2	Elsea & Eikler, 2011; Ingram et al., 2000
Social behaviors	Amygdala	<i>OXTR</i>	3	Ylisaukko-Oja et al., 2006
Speech and language disorders	Cerebellar development	<i>EN2 AUT1, AUT2 FOXP2</i>	7	Lai, Fisher, Hurst, Vargh-Khadems, & Monaco, 2001; Schumann et al., 2011
Migration of neuronal cells for neural connections	Encodes for a protein in neural connections	<i>RELN</i>	7q	Skaar et al., 2005
Anxiety, epilepsy	Synapses	<i>GABR</i>	15 q 15	Cook et al., 1998 Muhle, Trentacoste, & Rapin, 2004
Developmental disabilities, and intellectual and developmental disabilities	Not known	Duplication Several copy number variants (deletions and duplications)	15q11q13 16 16p11.2	Battaglia et al., 2010 Marshall et al., 2008; Ullmann et al., 2007; Weiss et al., 2008
Obsessions and compulsions, depression	Synapses	<i>SLC64A</i>	17q11.2	Lister Hill Center for Biomedical Communication, 2012
Cognitive deficits, language and speech disorder	Synapses	Duplication <i>SHANK3</i>	22q11.2	Durand et al., 2007; Itsara et al., 2009