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Review

Genes associated with autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a heterogeneous grouping of neurodevelopmental disorders characterized by impairment in social interaction, verbal communication and repetitive/stereotypic behaviors. Much evidence suggests that ASD is multifactorial with a strong genetic basis, but the underlying mechanisms are far from clear. Recent advances in genetic technologies are beginning to shed light on possible etiologies of ASD. This review discusses current evidence for several widely studied candidate ASD genes, as well as various rare genes that supports their relationship to the etiology of ASD. The majority of the data are based on molecular, cytogenetic, linkage and association studies of autistic subjects, but newer methods, including whole-exome sequencing, are also beginning to make significant contributions to our understanding of autism.

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Contents

1. Introduction

Autism (also known as classic autism or autistic disorder) has come to be recognized as a common neurodevelopmental disorder. Typically diagnosed before 3 years of age, autistic subjects usually present with significant language delays, social and communication impairments, and abnormal repetitive and stereotypic behaviors. Autism spectrum disorder (ASD), however, refers to a boarder definition of autism. Based on the severity of the clinical condition, it includes three subgroups; namely autism (the most severe type of ASD), pervasive developmental disorder – not otherwise specified (PDD-NOS; also called atypical autism), and high functioning autism or Asperger syndrome where significant language delays need not be present (Lord et al., 1989, 1994; Van Naarden et al., 2007).

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ASD is reported to occur in all ethnic and socioeconomic groups, and is about 4 times more likely to occur in boys than in girls (Lintas and Persico, 2009; Baron-Cohen et al., 2005). Studies in Asia, Europe and North America have identified ASD individuals with an approximate prevalence of 6/1000 to over 10/1000 (Williams et al., 2006). In Western Australia, the ASD identified prevalence increased from 0.8/1000 in 1983 to 4.6/1000 in 1999, while this ratio increased from 6.6/1000 in 2000 to 9/1000 in 2006 in United States (Anon., 2007a,b, 2009). This increase is probably because of changes and broadening of the diagnostic criteria and due to heightened awareness, but may also reflect, in part, a true increase due to environmental factors acting upon a genetically vulnerable background (Lintas and Persico, 2009; Nonkin et al., 2010; King and Bearman, 2009).

Similar to several other complex diseases, autism was not widely considered to have a strong genetic component until the 1980s. But increasing numbers of epidemiological and genetic studies are deepening our understanding of the genetic contribution autism. First, it is estimated that about 10% of children with ASD have an identifiable co-occuring genetic, neurologic or metabolic disorder, such as the fragile X syndrome or tuberous sclerosis (Caglayan, 2010). Second, the relative risk of a newborn child to have autism, if he or she has an affected sibling, increases at least 25-fold compared with the general population risk (Abrahams and Geschwind, 2008). Third, independent twin studies have suggested identical twins have a 60–90% chance to be concordantly diagnosed with autism, and this risk decreases sharply to the sibling risk of 0–24% in non-identical twins (Bailey et al., 1995; Steffenburg et al., 1989). However, based on a large scale study of 503 ASD twins in California, Liu et al. (2010a) suggest the heritability has been largely overestimated. They found the concordance rate for monozygotic male twins was 57% and for females 67%, while for same sex dizygotic twins the rate was 33%. Fourth, cumulative reports have confirmed mutations or structural variations of a number of specific genes significantly increase the risk of ASD (Abrahams and Geschwind, 2008). Taken together, ASD appears to have a strong genetic basis, however, with both gene–gene and gene–environmental interactions are likely to contribute significantly.

2. Genetic studies of ASD

Unlike monogenic Mendelian disorders, the genetic and clinical heterogeneity of ASD poses a difficult challenge to precisely define the underlying genetics. This complexity has been blamed for the lack of replicability of the many reported chromosomal susceptibility regions. Therefore, multiple parallel approaches are needed for the exploration of the potential loci underlying the etiology of ASD.

In general, there are a number of methods available for genetic studies of ASD, with each having different advantages as well as limitations. The most widely used methods include cytogenetic analysis, linkage and association studies, copy number variation and DNA micro-array analysis.

A cytogenetic study is the most “classic” of genetic methods. Based on the assumption that ASD is a result of unique rare mutations that present sporadically or “de novo” in the population and are not usually inherited, cytogenetics helps to determine the contribution of chromosomal abnormalities in childhood diseases. Cytogenetics has transitioned from light microscopy to molecular cytogenetics to DNA-based microarray detections of structural variations (Hoffman and State, 2010). Copy number variation (CNV) analysis is a newer molecular cytogenetic approach, aiming to detect the insertion or deletion of DNA fragments typically larger than 50 kb (Piggot et al., 2009). However, extreme caution must be paid when interpreting CNV analysis since it is very dependant on the specific methods employed, which may partly account for the low replicability among studies (Levitt and Campbell, 2009).

Differing from cytogenetics, linkage studies trace genetic loci that are transmitted with autism in the families of affected individuals. Parametric and non-parametric linkage studies are two typical designs. While parametric analysis requires a model for the disease (i.e. frequency of disease alleles and penetrance for each genotype), and therefore is typically employed for single gene disorders and Mendelian forms of complex disorders, “model-free” non-parametric linkage analysis evaluates whether segregation at specific locations is “not-random”. Given the uncertainty of the mode of inheritance in ASD, non-parametric linkage is more widely used, providing suggestive evidence of linkage on almost all of the chromosomes (Kumar and Christian, 2009). However, linkage studies are unable to identify mutations in critical genes in highly heterogeneous disorders involving many different genes and chromosomal loci (Betancur et al., 2009).

Genetic association studies, including case–control and family-based studies, examine differences in allele or genotype frequencies between two groups (Kumar and Christian, 2009). Typically, several microsatellite markers or SNPs are chosen based on linkage studies or biological evidence. The seemingly countless potential candidates make it hard to determine the causative relations between genes and ASD (Piggot et al., 2009). In addition, although association studies are suitable to identify common susceptibility alleles present in large numbers of patients compared to controls, they usually fail to identify rare, causal mutations (Kumar and Christian, 2009; Betancur et al., 2009).

Rapid advances in micro-array technologies have substantially improved our ability to detect submicroscopic chromosomal abnormalities. These tools have allowed for high-output and high-resolution detection of rare and de novo changes in a genome-wide manner. Moreover, newly developed, commercially available whole-exome arrays are increasingly being employed to detect de novo mutations in complex disorders. Based on the fact that the protein coding regions of genes (i.e. exons) harbor approximately 85% of the mutations of disease-related traits, whole-exome sequencing offers the possibility to identify disease-causing sequence variations in small kindreds for phenotypically complicated, genetically heterogeneous diseases when traditional linkage studies are impossible (Vissers et al., 2010; Choi et al., 2009; Robinson, 2010; Bilguvar et al., 2010; Sanders, 2011). As such, studies in this realm have been increasing in the past several years and there will surely benefit the etiological diagnosis and genetic counseling of ASD in the near future (Betancur, 2011).

3. Recent genetic findings of candidate genes and potential loci in autism

3.1. Genome wide linkage analysis

Although there is accumulating evidence supporting a genetic component to ASD, the specific genes involved have yet to be totally characterized. Genome-wide screening of autistic subjects and their first-degree relatives offers an attractive means to search for susceptibility genes. However, there has been a disappointing lack of replication of many of the reported susceptibility regions. The reason for this could be due to the epistasis of many interacting genes. But it may also due to the genetic and clinical heterogeneity present in ASD (Buxbaum et al., 2001). The noted effects of heterogeneity of the samples on the corresponding results, has led to attempts to decrease sample heterogeneity by various ways including by narrowing inclusion criteria and studies of specific, autism-related endophenotypes.

Table 1
Loci identified by genome wide linkage analysis.

Chromosome	Loci	Candidate genes	Ref.
1	1p34.2	Regulating synaptic membrane exocytosis 3 (*RIMS3*)	Kumar et al. (2010)
2	2q		Buxbaum et al. (2001); Shao et al. (2002)
	2q31–2q33	*GAD1*, *STK17B*, *ABI2*, *CTLA4*, *CD28*, *NEUROD1*, *PDE1A*, *HOXD1*, *DLX2*	Rabionet et al. (2004)
	2q31	*SLC25A12*	Segurado et al. (2005)
	2q24–2q33	*SLC25A12*, *CMYA3*	Blasi et al. (2006a)
	2q24–2q33	*SLC25A12*, *STK39*, *ITGA4*	Ramoz et al. (2008)
	2q34	Neuropilin-2 (*NRP2*)	Wu et al. (2007)
3	3q25–3q27	HTR3C	Noor et al. (2010)
5	5q31	Paired-like homeodomain transcription factor 1 (*PITX1*)	Philippi et al. (2007)
	5p14.1		Ma et al. (2009)
	5p15	*SEMA5A*	Weiss et al. (2009)
6	6q	Abelson's helper integration 1 (*AHI1*)	Alvarez et al. (2008)
	6q27		Weiss et al. (2009)
7	7q22.1–7q31		Cukier et al. (2009)
	7q31	Laminin beta-1 (*LAMB1*), Neuronal cell adhesion molecule (*NRCAM*)	Sakurai et al. (2006); Hutcheson et al. (2004); Marui et al. (2009)
	7q32	NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 (*NDUFA5*)	Noor et al. (2010)
	7q31–7q33	Wingless-type MMTV integration site family member 2 (*WNT2*)	Marui et al. (2010)
11	11p12–p13		Szatmari et al. (2007)
12	12q14		Ma et al. (2007)
15	15q11–q13	Angelman syndrome gene (UBE3A)	Nurmi et al. (2001)
	15q11–q13		Kim et al. (2008)
	15q13	Amyloid precursor protein-binding protein A2 (*APBA2*)	Sutcliffe et al. (2003)
16	16p11–13	4-Aminobutyrate aminotransferase (*ABAT*), CREB-binding protein (*CREBBP*), glutamate receptor, ionotropic, NMDA 2A (*GRIN2A*)	Barnby et al. (2005)
	16p11.2		Shinawi et al. (2010); Kumar et al. (2008, 2010)
17	17q11.2		McCauley et al. (2005)
19	19p13		McCauley et al. (2005)
20	20q13		Weiss et al. (2009)
22	22q13	*SHANK3*	Qin et al. (2009)
X	Xp22.11	*PTCHD1*	Noor et al. (2010)

A substantial body of evidence has resulted from genome-wide screening for the susceptibility genes of ASD (Table 1). Significant replicability has been found for several chromosomal loci including 2q, 5, 7q, 15q and 16p. Two studies provided suggestive evidence for linkage to chromosome 2q using a two-stage genome screen (Buxbaum et al., 2001; Shao et al., 2002), while association tests for specific candidate genes in the chromosome 2q31–q33 region led to negative results (Rabionet et al., 2004). Additional support for the presence of susceptibility loci on chromosome 2q is given by overlapping positive linkage findings in four other independent genomic scans (Wu et al., 2007; Blasi et al., 2006a; Szatmari et al., 2007; Ramoz et al., 2008).

There are three reports about gene variants on chromosome 5. Philippi et al. (2007) found strong association with autism for allelic variants of "paired-like homeodomain transcription factor 1" (*PITX1*), a key regulator of hormones within the pituitary–hypothalamic axis. Two other groups used genome-wide linkage and association mapping studies to analyze chromosome 5 gene variations finding that SNPs located at 5p14.1 and 5q15, respectively, were significantly associated with autism (Ma et al., 2009; Weiss et al., 2009).

Chromosome 16 linkage results have been fairly consistent in showing a peak at 16p11–13, which strongly suggests a gene or genes in this region may contribute to the risk of ASD (Shinawi et al., 2010; Kumar et al., 2008). 15q11–q13 is another frequently identified locus by linkage studies. Several genes located in this region have been intensively studied and some have provided very promising results (Kim et al., 2008; Sutcliffe et al., 2003; Nurmi et al., 2001; Shen et al., 2010). But in all of these linkage reports there is a certain lack of reproducibility, and therefore they require further validation based on using a combination of several methods.

Besides these "hot spots", there are other reports regarding associations of other loci with ASD (Weiss et al., 2009; Ma et al., 2007; Alvarez et al., 2008; Qin et al., 2009; Kumar et al., 2010), including some evidence of linkage to the X chromosome (Noor et al., 2010). However, there is little overlap of these potential loci involving potential candidate genes, suggesting that the genetic background of ASD is full of complexity.

3.2. Copy number variation (CNV)

Rapid advances in genomic DNA microarray technologies have substantially improved our ability to detect submicroscopic chromosomal abnormalities. Novel rare variants have been detected in association with ASD and these can be either de novo or inherited. De novo or noninherited CNVs are found in 7–10% of ASD samples from simplex families (having only one child affected, the majority), in 2–3% from multiplex families, and in ~1% in non-ASD controls. Further, about 10% of ASD subjects with de novo CNVs carry two or more CNVs (Christian et al., 2008; Marshall et al., 2008; Sebat et al., 2007). Inherited CNVs reportedly are found in up to 50% of ASD subjects for whom one of the presumably normal parents also has the duplication/deletion. These familial CNVs may include candidate genes relevant to ASD where they are rare in the normal population.

Array comparative genomic hybridization (aCGH) is the most widely used method for detection of CNVs. A seminal early report used aCGH, with a mean resolution of one probe every 35 kb, to study a sample of 264 ASD families. After validation by higher-resolution microarray scans, G-banded karyotype, FISH, and microsatellite genotyping, 17 de novo CNVs were confirmed (Sebat et al., 2007). A Korean group recently reported deletion CNVs at 8p23.1 and 17p11.2 using whole-genome aCGH (Cho et al., 2009). Using aCGH with a mean 19 kb resolution, 51 autism-specific CNV were identified in 397 unrelated ASD subjects (Christian et al., 2008). Similarly, Qiao et al. (2009) performed aCGH on 100 autistic subjects and identified 9 CNVs, three of which were unique to their cohort. A Spanish group recently reported the identification

Table 2
Selected candidate genes.

Genes	Loci	Positive results	Negative/unconfirmed results
RELN	7q22	Li et al. (2008); Ashley-Koch et al. (2007); Dutta et al. (2007a); Serajee et al. (2006); Skaar et al. (2005); Devlin et al. (2004); Li et al. (2004); Zhang et al. (2002); Krebs et al. (2002); Persico et al. (2001)	
SLC6A4	17q11.1–17q12	Sutcliffe et al. (2005); Coutinho et al. (2004, 2007); Cook et al. (1997); Anderson et al. (2009); Cho et al. (2007); McCauley et al. (2004a); Coutinho et al. (2004)	Zhong et al. (1999); Guhathakurta et al. (2009); Ma et al. (2010); Huang and Santangelo (2008); Persico et al. (2000); Wu et al. (2005a); Ramoz et al. (2006a); Guhathakurta et al. (2008); Tordjman et al. (2001); Maestrini et al. (1999); Klauck et al. (1997); Betancur et al. (2002); Koishi et al. (2006)
GABR	15q11–15q13	Takumi (2010); McCauley et al. (2004b); Nakatani et al. (2009); Menold et al. (2001); Buxbaum et al. (2002); Kim et al. (2006); Kwasnicka-Crawford et al. (2007); Bolton et al. (2004); Shao et al. (2003); Ma et al. (2005); Yoo et al. (2009); Cai et al. (2008); Aldinger and Qiu (2010); Depienne et al. (2009)	Curran et al. (2005); Martin et al. (2000); Maestrini et al. (1999)
NLGN	3q26(*NLGN1*), 17p13 (*NLGN2*), Xq13 (*NLGN3*), Xp22.3 (*NLGN4*), Yq11.2 (*NLGN4Y*)	Zhang et al. (2009); Pampanos et al. (2009); Yan et al. (2008); Talebizadeh et al. (2006); Yan et al. (2005); Jamain et al. (2003)	Wermter et al. (2008); Blasi et al. (2006b); Ylisaukko-oja et al. (2005); Gauthier et al. (2005); Vincent et al. (2004); Talebizadeh et al. (2004)
OXTR	3p24–3p25	Liu et al. (2010b); Gregory et al. (2009); Lerer et al. (2008); Jacob et al. (2007); Wu et al. (2005b)	
MET	7q31.2	Campbell et al. (2006, 2008, 2010); Jackson et al. (2009); Sousa et al. (2009)	
SLC25A12	2q31	Turunen et al. (2008); Silverman et al. (2008); Segurado et al. (2005); Ramoz et al. (2004)	Chien et al. (2010); Rabionet et al. (2006); Blasi et al. (2006a)
GluR6	6q21	Kim et al. (2007); Shuang et al. (2004); Jamain et al. (2002)	Dutta et al. (2007b)
CNTNAP2	7q35	Poot et al. (2010); Arking et al. (2008); Alarcon et al. (2008); Bakkaloglu et al. (2008); Rossi et al. (2008); Strauss et al. (2006)	
GLO1	6p21.3–6p21.2	Sacco et al. (2007); Junaid et al. (2004)	Wu et al. (2008); Rehnstrom et al. (2008)
TPH2	12q21.1	Coon et al. (2005)	Sacco et al. (2007); Ramoz et al. (2006b)

RELN: reelin; *SLC6A4*: the serotonin transporter gene; *GABR*: the Bacillus subtilis ycnF; *NLGN*: neuroligin; *OXTR*: oxytocin receptor; *MET*: hepatocyte growth factor receptor; *SLC25A12:* calcium-binding mitochondrial carrier protein Aralar1; *GluR6*: glutamate receptor *CNTNAP2*: contactin-associated protein-like 2; *GLO1*: lactoylglutathione lyase; *TPH2*: tryptophan hydroxylase 2.

of 13 CNVs containing 24 different genes in their sample of 96 ASD subjects (Cusco et al., 2009).

Single-nucleotide polymorphism (SNP) array analysis, primarily developed to determine linkage, now is also employed to determine genomic CNVs (Babatz et al., 2009). Marshall et al. (2008) performed a genome-wide assessment via SNP array analysis. They genotyped proximately 500,000 SNPs for each sample and detected 13 loci with recurrent or overlapping CNVs in a sample of 427 ASD cases. Using SNP markers, another group identified 6 CNVs within a 2.2-megabase (Mb) intergenic Chr 2 region between cadherin 10 (CDH10) and cadherin 9 (CDH9) in a combined sample set of 1984 ASD probands of European ancestry (Wang et al., 2009). In addition, SNP array analysis offers some special advantages in the exploration of potentially relevant gene networks. Two recent reports have provided strong evidence for the involvement of certain genes in important gene networks including neuronal cell-adhesion, ubiquitin degradation and GTPase/Ras signaling (Pinto et al., 2010; Glessner et al., 2009).

Currently available aCGH methods for identifying CNV typically assay the genome in the 40-kb to several mb range. Methodological improvements that employ oligonucleotides are providing a high potential resolution down to approximately the 5-kb resolution level for aCGH with genome-wide detection of CNVs (Babatz et al., 2009). Thus, SNP or oligonucleotide aCGH analysis can detect a CNV as small as a few kilobases. Therefore, it is clear that the higher-density oligonucleotide or SNP arrays offer significantly higher resolution for analysis of CNVs in the future.

3.3. Selected candidate genes

As is becoming apparent, a genetic predisposition to ASD may involve one or more interconnected genetic networks involving neurogenesis, neuronal migration, synaptogenesis, axon pathfinding and neuronal or glial structure regionalization (Geschwind and Levitt, 2007). Function-targeted studies, mainly by association that focus exclusively on the candidate genes, including the some of the most widely studied will be reviewed in the following section (Table 2).

3.3.1. Reelin (RELN) gene

Reelin is an extracellular matrix glycoprotein responsible for guiding the migration of several neural cell types and the establishment of neural connection. In the 1980s, it was discovered that reelin plays important roles in the positioning of neuronal cells in the inferior olivery complex, cerebral cortex and cerebellum early in embryonic development (Goffinet, 1983a,b, 1984). Further research has confirmed and further extended our knowledge about the widespread functions reelin plays in laminated regions of the brain, both embryonically and postnatally (D'Arcangelo et al., 1995; Del et al., 1997; Curran and D'Arcangelo, 1998).

Given the critical functions of reelin in brain development, and knowing there are neuroanatomical abnormities in autism (Bailey et al., 1998), the reelin gene (*RELN*) was a plausible candidate to investigate in ASDs. Significantly reduced levels of reelin in the human cortex, cerebellum and peripheral blood were confirmed in ASD at both the protein and mRNA levels (Fatemi et al., 2001, 2002, 2005). Genome-wide scans also identified 7q22 as an autism critical region, where *RELN* is located (Scherer et al., 2003).

Additionally, case–control and family-based studies provided further evidence supporting the association of *RELN* and ASD. Persico et al. (2001) identified a *RELN*-related polymorphic GGC repeat located immediately 5′ of the ATG initiator codon in Italian and American subjects. Using the similar methods and 126 multiplex ASD families, Zhang et al. (2002) examined the polymorphic

GGC-repeat of *RELN*. Family-based association tests showed that larger *RELN* alleles (≥11 repeats) were transmitted more often than expected to autistic children. Independent studies regarding the GGC-repeat of *RELN* have also supported its contribution to the genetic risk of autism (Ashley-Koch et al., 2007; Dutta et al., 2007a; Skaar et al., 2005). Others have also reported significant differences in the transmission of the reelin alleles of exon 22 and intron 59 SNPs to autistic subjects (Serajee et al., 2006). However, results have not been uniformly positive. Krebs et al. (2002) performed a transmission disequilibrium test (TDT) analysis of the GGC-repeat polymorphism in 167 Caucasian families and found no evidence of linkage or association. Similarly, another two groups failed to find a significant association of *RELN* GGC repeat polymorphisms with liability to autism (Devlin et al., 2004; Li et al., 2004).

The association between *RELN* and ASD were also found in other ethnic groups besides Caucasian populations. Recently, a significant genetic association between the RELN SNP2 (located in intron 59) and ASD was reported in a Chinese Han population, and the combination of RELN SNP1/SNP2/SNP3/SNP4, all in strong linkage disequilibrium, were reported to have a significant association with ASD (Li et al., 2008).

3.3.2. Human serotonin transporter (SLC6A4) gene

The human serotonin transporter, encoded by *SLC6A4*, localizes to chromosome 17q11.1–q12 and consists of 15 exons (Ramamoorthy et al., 1993). *SLC6A4* was considered as a candidate gene for autism primarily based on the elevated blood serotonin levels found in a number of autistic probands, as well as the efficacy of potent serotonin transporter inhibitors in reducing rituals and routines (Kim et al., 2002; McDougle et al., 1996). Using the TDT, positive associations of a 5-HTTLPR polymorphism found in the promotor region of the SLC6A4 gene with autism have been identified by 4 family-based studies and 2 case–control studies (Sutcliffe et al., 2005; Cook et al., 1997; Cho et al., 2007; McCauley et al., 2004a; Coutinho et al., 2004). Other groups have performed both family-based and case–control analysis and found significant associations of the *SLC6A4* polymorphism with autism (Coutinho et al., 2007; Anderson et al., 2009). In contrast to these positive reports, 9 family-based studies failed to find evidence for associations of the *SLC6A4* polymorphism with autism (Ma et al., 2010; Persico et al., 2000; Wu et al., 2005a; Ramoz et al., 2006a; Tordjman et al., 2001; Maestrini et al., 1999; Klauck et al., 1997; Betancur et al., 2002; Koishi et al., 2006), as well as a case–control study (Zhong et al., 1999). An Indian group performed a series of studies but found no persuasive evidence of the association of the *SLC6A4* polymorphisms with autism (Guhathakurta et al., 2006, 2008, 2009). In addition, a systematic review and meta-analysis failed to find a significant overall association of the serotonin polymorphisms examined and autism (Huang and Santangelo, 2008).

3.3.3. Gamma-aminobutyric acid receptor (GABR) gene

Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the brain, acting by binding to a GABA receptor. The receptor is a multimeric transmembrane receptor that consists of five subunits arranged around a central pore. The GABA receptor subunits are homologous, but are both structurally and functionally diverse (Menold et al., 2001). Three of the GABA receptor subunit genes (*GABRB3*, *GABRA5* and *GABRG3*) are localized to chromosome 15q11–q13, one of the most complex regions in the genome involved with genome instability, gene expression, imprinting and recombination (Martin et al., 2000).

The region 15q11–q13 was originally associated with ASD based on several studies which reported a common duplication of this region in ASD subjects (Kwasnicka-Crawford et al., 2007; Bolton et al., 2004; Cai et al., 2008; Depienne et al., 2009). A chromosome-engineered mouse model for human 15q11–q13 duplication was developed with autistic features (Takumi, 2010; Nakatani et al., 2009; Aldinger and Qiu, 2010). Cook et al. examined markers across this region for linkage disequilibrium in 140 families with ASD, detecting significant linkage disequilibrium between *GABRB3* and ASD (Cook et al., 1998). This finding was confirmed by others as well (Buxbaum et al., 2002; Kim et al., 2006; Yoo et al., 2009). Also, two SNPs located within the *GABRG3* gene were associated with ASD using the pedigree disequilibrium test (PDT) (Menold et al., 2001). An independent study demonstrated nominally significant associations between six markers across the *GABRB3* and *GABRA5* genes (McCauley et al., 2004b). Moreover, using ordered-subset analysis (OSA) another group provided evidence of increased linkage at the *GABRB3* locus (Shao et al., 2003). Other research has also identified significant association and gene–gene interactions of GABA receptor subunit genes in autism (Ma et al., 2005).

Nonetheless, conflicting evidence has also been reported. Other groups have reported limited or no association between GABA receptor polymorphisms and autism (Curran et al., 2005; Martin et al., 2000). Similarly, another group conducted a full genome search for autism susceptibility loci including seven microsatellite markers from 15q11–q13, and found no significant evidence of association or linkage (Maestrini et al., 1999). Thus the linkage results are at best inconclusive.

3.3.4. Neuroligin (NLGN) genes

The marked difference in sex ratio for ASD justifies the exploration of genes on the sex chromosome, among which the neuroligin (*NLGN*) genes are perhaps the most widely studied. Five *NLGN* have been identified in the human genome, which are localized at 3q26(*NLGN1*), 17p13 (*NLGN2*), Xq13 (*NLGN3*), Xp22.3 (*NLGN4*), and Yq11.2 (*NLGN4Y*), respectively. They encode a family of cell-adhesion molecules, the neuroligins, essential for the formation of functional neural synapses (Jamain et al., 2003; Talebizadeh et al., 2004).

The earliest report regarding the potential association of *NLGN* genes and ASD came from the study of multiple Swedish families (Jamain et al., 2003). The authors screened for *NLGN3* mutations in 36 affected sib-pairs and 122 trios with ASD. They found one de novo mutation in NLGN4 in one family. This mutation creates a stop codon leading to premature termination of the protein. In another family, a C to T transition in *NLGN3* was identified that changed a highly conserved arginine residue into cysteine (R451C) within the esterase domain. It was inherited from the mother. Following this report, several other groups studied this gene but found little support for common mutations of the gene. Limited support came from a Portuguese group, who found missense changes in *NLGN4* as well as the protein-truncating mutations in ASD (Yan et al., 2005). A Finnish group conducted a molecular genetic analysis of *NLGN1, NLGN3, NLGN4*, and *NLNG4Y*. Their results suggested neuroligin mutations most probably represent rare causes of autism and that it was unlikely the allelic variants in these genes would be major risk factors for autism (Ylisaukko-oja et al., 2005). Others have also failed to obtain positive results, casting doubt on the earlier conclusion (Wermter et al., 2008; Blasi et al., 2006b; Gauthier et al., 2005; Vincent et al., 2004; Talebizadeh et al., 2004).

Other reports about mutations of *NLGN3* or *NLGN4* have identified splice variants in both *genes* (Talebizadeh et al., 2006). Three groups recently reported one missense variant and two single substitutions in independent autistic samples, indicating that a defect of synaptogenesis may predispose to autism (Zhang et al., 2009; Pampanos et al., 2009; Yan et al., 2008).

3.3.5. Human oxytocin receptor (OXTR) gene

Oxytocin is a nine amino acid peptide synthesized in the hypothalamus. Apart from regulating lactation and uterine contraction, oxytocin acts as a neuromodulator in the central nervous

system (Lucht et al., 2009; Yamasue et al., 2009). Both animal experiments and clinical research has confirmed the role oxytocin plays in social and repetitive behaviors (Green and Hollander, 2010). Therefore the oxytocin system might be potentially involved in the pathogenesis of ASD, and the human oxytocin receptor (*OXTR*) gene has been regarded as a most promising candidate gene to study.

Indeed, research pertaining to the potential association between *OXTR* and autism has come to positive conclusions. Using family-based and population-based association tests, SNPs and haplotypes in the *OXTR* gene have been reported to confer risk for ASD in different ethnic groups (Liu et al., 2010b; Lerer et al., 2008; Jacob et al., 2007; Wu et al., 2005b). They have also been associated with IQ and adaptive behavior scale scores (Lerer et al., 2008). Furthermore, a recent study identified significant increases in the DNA methylation status of OXTR in peripheral blood cells and temporal cortex, as well as decreased expression of *OXTR* mRNA in the temporal cortex of autism cases, suggesting that epigenetic dysregulation may be involved in the pathogenesis of ASD (Gregory et al., 2009).

3.3.6. *MET*

The human *MET* gene encodes a transmembrane receptor tyrosine kinase of the hepatocyte growth factor/scatter factor (HGF/SF) (Powell et al., 2001). Though primarily identified as an oncogene, MET plays crucial roles in neuronal development (Powell et al., 2001; Streit and Stern, 1997; Park et al., 1986). Moreover, impaired MET signaling causes abnormal interneuron migration and neural growth in the cortex, as well as decreased proliferation of granule cells, which could help explain matches many of the features found in autistic brains (Streit and Stern, 1997; Levitt et al., 2004).

Campbell et al. (2006) have done a series of studies regarding the association between MET signaling and autism. They first reported the genetic association of a common C allele in the promoter region of *MET*, which results in significant decrease in *MET* promoter activity and altered binding of specific transcription factor complexes. Then they found significantly decreased MET protein levels and increased mRNA expression for proteins involved in regulating MET signaling activity (Campbell et al., 2007). Furthermore, they screened the exons and 5′ promoter regions for variants in the five genes encoding the proteins that regulate *MET* expression, finding that genetic susceptibility impacting multiple components of the MET signaling pathway contributes to ASD risk (Campbell et al., 2008). Most recently, they found that the *MET* C allele influences two of the behavioral domains of the autism triad (Campbell et al., 2010). Other groups have also provided supportive evidence that *MET* gene variations may play a role in autism susceptibility (Jackson et al., 2009; Sousa et al., 2009).

3.3.7. *SLC25A12*

SLC25A12 locates to the chromosome 2q31 region, encoding the mitochondrial aspartate/glutamate carrier (AGC1), a key protein involved in mitochondrial function and ATP synthesis. Since the physiological function of neurons greatly depends on energy supply, any alteration in mitochondrial function or ATP synthesis could lead to corresponding changes in neurons (Del and Satrustegui, 1998). Recently mitochondrial hyperproliferation and partial respiratory chain block were found in two autistic patients, suggesting *SLC25A12* could be a promising candidate gene (Filipek et al., 2003).

Following this report, several studies for genetic variants the gene were performed. Three different ethnic groups reported linkage and association between ASD and two SNPs (i.e. rs2056202 and rs2292813) in *SLC25A12* (Turunen et al., 2008; Segurado et al., 2005; Ramoz et al., 2004), while another three independent groups failed to reveal significant association (Chien et al., 2010; Rabionet et al., 2006; Blasi et al., 2006a). Another group associated one SNP (rs2056202) with ASD but not the other (Silverman et al., 2008). Thus, the findings so far are inconclusive.

3.3.8. *Other candidate genes*

The glutamate receptor 6 gene (*GRIK2* or *GluR6*) is located at chromosome 6q21. Given that glutamate is the principal excitatory neurotransmitter in the brain and it is involved in cognitive functions such as memory and learning, *GRIK2* was proposed as a gene candidate for ASD (Shimizu et al., 2000). Unfortunately, the limited reports have very different results. Genetic studies in a Caucasian population, Chinese Han and Korean trios provided positive evidence, but using different SNPs (Kim et al., 2007; Shuang et al., 2004; Jamain et al., 2002). Another report failed to find any association of *GRIK2* with autism in an Indian population (Jamain et al., 2002).

Contactin associated protein-2 (*CNTNAP2*) belongs to the neurexin family, within which several members have been identified as being related to autism (Burbach and van der Zwaag, 2009). A recent research report identified a homozygous mutation of *CNTNAP2* in Amish children with pervasive developmental disorders, seizures, and language regression (Strauss et al., 2006). Five other studies have supported this finding that *CNTNAP2* may be a genetic susceptibility factor in autism (Poot et al., 2010; Arking et al., 2008; Alarcon et al., 2008; Bakkaloglu et al., 2008; Rossi et al., 2008). Another group found that *CNTNAP2* provided a strong male affection bias in ASD (Alarcon et al., 2008).

Glyoxalase 1 is a cytosolic, ubiquitously expressed, zinc metalloenzyme enzyme involved in scavenging toxic α-oxoaldehydes formed during cellular metabolic reactions. Proteomics analysis found glyoxalase 1 increased in autism brains, and subsequent sequencing of its gene (*GLO1*) identified that homozygosity for a polymorphism of the gene, A419 *GLO1*, resulted in decreased enzyme activity and association with autism (Junaid et al., 2004), although this conclusion was not confirmed by other studies (Wu et al., 2008; Rehnstrom et al., 2008). In addition, one group found a protective effect of the A419 allele of *GLO1* (Sacco et al., 2007).

TPH1 and *TPH2* encode rate-limiting enzymes that control serotonin biosynthesis. TPH1 is primarily expressed peripherally, while TPH2 is found exclusively in brain tissue. However, despite evidence for the potential involvement of the serotonin system in the etiology of autism, only one of three reports to date conservatively has supported the notion that *TPH2* plays a role in autism susceptibility (Sacco et al., 2007; Coon et al., 2005; Ramoz et al., 2006b).

4. Conclusions

It is clear that ASD has a strong genetic component. But attempts to clarify the underlying genetic mechanisms confront great challenges. First, the inclusion criteria vary between studies due to the phenotypic heterogeneity of ASD. Indeed, among the original research we reviewed, some studied exclusively subjects with classic autism while others included all ASD subjects. Additionally, diagnostic criteria differ from one study to another, which may partly account for the inconsistent results. Second, different sample sizes undermine the comparability among reports. It has been suggested that about 40,000 samples will be needed to ensure that important but subtle common genetic risks will be identified and that the role of rare variants will be illuminated (O'Roak and State, 2008). Small-sized studies lacking adequate statistical power lead not only to the underestimation of small-to-moderate effects, but also to overestimation of the observed effects. Unfortunately, most of the current studies fail to satisfy this requirement. Third, international databases greatly facilitate autism research. But at the same time, they further challenge the interpretation of the data because

of the differing allelic frequencies of many polymorphisms in different ethnic groups. As a result, validations of positive studies are difficult without cautious analysis.

However, even the most critical observers admit that substantial progress has been achieved in this realm during the past decade. The most promising genes, such as *NLGN* and *SLC6A4*, are involved in the physiological and pathophysiological processes of neurogenesis, neuronal migration, and synaptogenesis. However, analysis of newly discovered variants may also play important roles in helping to elucidate the underlying networks and pathways involved in ASD.

In conclusion, data remain inconclusive for the majority of candidate genes tested so far. Still, we have good reason to be optimistic regarding gene discovery in ASD now and in the future. Cytogenetic, linkage, association studies and array analysis have provided promising results. Emerging genetic technologies and analysis tools offer even more powerful approaches for developing insights into the etiology of ASD. In addition, genetic studies facilitate other autism research such as biochemical and neuroimaging studies, which will, in turn, provide evidence and valuable clues to direct future genetic studies.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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