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Autoimmune Disorder and Autism

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1. Introduction

1.1 Diagnosis of ASD

Autism (also known as classic autism or autism disorder) is a common neurodevelopmental disorder. Typically diagnosed before three years old, autistic children usually present with significant language delays, social and communication impairments, as well as abnormal repetitive and restrictive behaviors. Autism spectrum disorders (ASD) however, refers to a boarder definition of autism. Based on the severity of the clinical conditions, ASD is further divided into three subgroups namely autism (the most severe type of ASD), Asperger syndrome and pervasive developmental disorder – not otherwise specified (PDD-NOS; also called atypical autism) [1-3].

Of note, current diagnosis criteria of these disorders are based on behavior tests, no single biomarker has been clinically accepted, which mainly due to the difficulties for studying cellular and molecular etiology of ASD. First, subjects among different researches lack of comparability because of the diagnostic heterogeneity [4]. Second, the prevalence of ASD is relatively low therefore sample sizes are usually too small for statistical analysis. Third, comparing with other diseases, the young ages of the autistic subjects make biological study difficult. Forth, valid control groups require age-, gender-, IQ- and socioeconomic status-matched developmentally normal subjects, which most studies failed to satisfy with [5].

1.2 Epidemiology

ASD is reported to occur in all racial, ethnic and socioeconomic groups, and are about four times more likely to occur in boys than in girls probably due to the extremes of typical male neuroanatomy of autism [6, 7]. Studies in Asia, Europe and North America have identified individuals with ASD with an approximate prevalence of 6/1,000 to over 10/1,000 [8]. Chronologically, the prevalence of ASD increased from 0.8/1,000 in 1983 to 4.6/1,000 in 1999 in Western Australia, while this ratio increased from 6.6/1,000 in 2000 to 9/1,000 in 2006 in United States [9-11]. 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 [12, 13].

2. Immune disorders and autism

The relationship between immune disorders and ASD has been proposed for decades. Based on the epidemiological data, higher rate of autoimmune conditions, such as rheumatoid

arthritis, autoimmune thyroid disease, asthma, ulcerative colitis, exits in parents of autistic children [14-17]. Another line of evidence supporting immune dysfunction at least partly responsible for ASD comes from large population studies, which suggest maternal immune dysfunctions may be related to a later diagnosis of ASD in the offspring [18]. Furthermore, cumulative evidences support the theory that ASD is caused by a loss of self-tolerance to one or more neural antigens during early childhood. Using western blot for the presence of IgG antibodies against protein extracts from human brain or sera, multiple brain-specific autoantibodies are detected [19, 20]. Other groups measured the plasma concentration of immunoglobulins and/or cytokines, autistic subjects exclusively exhibited abnormal immunoglobin and/or cytokine profiles [21-24]. It's not known yet whether immune activation plays an initiating or ongoing role in the pathology of ASD. But investigations of dynamic adaptive cellular immune function suggested dysfunctional immune activation, which may be linked to disturbances in behavior and developmental functioning [25].

2.1 Autoimmune diseases

Autoimmune diseases are the most common type of immune disorders. And its relationship with autism has been widely studied. Very early study reported an increased number of autoimmune disorders in some families with autism, suggesting immune dysfunction plays a role in autism pathogenesis [26]. Consistent with this result, Sweeten et al investigated the frequency of autoimmune disorders in families that have probands with pervasive developmental disorders and autism, compared with control groups. Autoimmunity was increased significantly in families with pervasive developmental disorders compared with those of healthy and autoimmune control subjects [27]. More persuasive evidence comes from a multicenter study of 308 children with Autism Spectrum Disorder. Regression was significantly associated with a family history of autoimmune disorders. But the only specific autoimmune disorder found to be associated with regression was autoimmune thyroid disease [28].

2.2 Cytokines and chemokines

Cytokines and chemokines are thought to mediate the pathogenesis of autism, although the exact mechanism remains unclear. Jyonouchi group determined innate and adaptive immune responses in children with developmental regression and autism spectrum disorders, developmentally normal siblings, and controls. Their results indicated excessive innate immune responses in a number of ASD children that may be most evident in TNF-alpha production [29]. Similarly, Molloy et al reported children with ASD had increased activation of both Th2 and Th1 arms of the adaptive immune response, with a Th2 predominance, and without the compensatory increase in the regulatory cytokine IL-10 [30]. But Li et al showed that proinflammatory cytokines (TNF-alpha, IL-6 and GM-CSF), Th1 cytokine (IFN-gamma) and chemokine (IL-8) were significantly increased in the brains of ASD patients compared with the controls, but not the Th2 cytokines (IL-4, IL-5 and IL-10). The Th1/Th2 ratio was also significantly increased in ASD patients. Based on these results, the author concluded that ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggesting that localized brain inflammation and autoimmune disorder may be involved in the pathogenesis of ASD [31]. Most recently, Ashwood group used larger number of participants than previous studies and found that significant increases in plasma levels of a number of cytokines, including IL-1beta, IL-6, IL-8

and IL-12p40 in the ASD group compared with typically developing controls [32]. All these findings suggest that inflammatory responses may be related to disturbances in behavior. And the characterization of immunological parameters in ASD has important implications for diagnosis, therefore should be considered when designing therapeutic strategies to treat ASD.

2.3 Immunoglobulin

Using human fetal and adult brains as antigenic substrates, maternal serum antibodies transferred through placenta are detected by four independent research groups, suggesting an association between the transfer of IgG autoantibodies during early neurodevelopment and the risk of developing of autism in some children [33-37].

Singh et al provided more confirmative evidence by studying regional distribution of antibodies to rat caudate nucleus, cerebral cortex, cerebellum, brain stem and hippocampus of 30 normal and 68 autistic children. Autistic children, but not normal children, had antibodies to caudate nucleus (49% positive sera), cerebral cortex (18% positive sera) and cerebellum (9% positive sera). Brain stem and hippocampus were negative. Since a significant number of autistic children had antibodies to caudate nucleus, the author proposed that an autoimmune reaction to this brain region may cause neurological impairments in autistic children [38]. Agreed with this result, Trajkovski et al measured plasma concentration of IgA, IgM, IgG classes, and IgG1, IgG2, IgG3, and IgG4 subclasses in children with autism. Plasma concentrations of IgM and IgG in autistic children were significantly higher in comparison with their healthy brothers or sisters. Children with autism had significantly higher plasma concentrations of IgG4 compared to their siblings. Increased plasma concentration of IgG1 was found in autistic males as compared with their healthy brothers. Plasma concentrations of IgG and IgG1 in autistic females were increased in comparison with IgG and IgG1 in their healthy sisters [39]. More recently, Enstrom et al report significantly increased levels of the IgG4 subclass in children with autism compared with typically developing control children and compared with developmental delayed controls [40].

However, No consensus has been reached regarding the immunoglobin levels in autistic subjects. Morris and colleagues failed to find any useful biomarker in a small group of subjects, posing question to the current theory [41]. Stern et al found in their study most of the autistic children had normal immune function, suggesting that routine immunologic investigation is unlikely to be of benefit in most autistic children [42].

2.4 Gastrointestinal disorders

The report regarding the relationship between autism and gastrointestinal disorders was seen as early as 1971, when Goodwin et al described 6 of 15 randomly selected autistic children with symptoms of malabsorption [43]. Later Horvath et al investigated 412 autistic children, of which 84.1% had at least one of the eight abnormal gastrointestinal symptoms, comparing with 31.2% of the healthy siblings [44]. However, disagreements exit. Kuddo group and Molloy group failed to find any association between chronic gastrointestinal symptoms and autism based on the literature search or their own sample [45, 46]. Fernell et al tested two independent biomarkers of inflammatory reactions (faecal calprotectin and rectal nitric oxide) in 24 autistic children, but didn't find clear link between active intestinal inflammation and autism [47].

Morphological and histological studies provided consistent results with the clinical manifestations. Ileocolonoscopic examinations in 60 children with autism and other developmental disorders revealed that 8% (4/51) affected children but none in controls presented with active ileitis. Chronic colitis was identified in 88% (53/60) affected children compared with 4.5% (1/22) controls [48]. Similarly, another group conducted upper gastrointestinal endoscopy in 36 autistic subjects. 69.4% (25/36) of whom presented with grade I or II reflux esophagitis, 41.7% (15/36) with chronic gastritis, and 66.7% with chronic duodenitis [49].

In addition, biochemical researches reported evidences of abnormal intestinal cytokine profiles. Ashwood et al found enhanced pro-inflammatory cytokine production present in 21 ASD children compared with 65 controls [50]. Furthermore, they investigated the peripheral blood and mucosal CD3+ lymphocyte cytokine profiles in 18 autistic children with gastrointestinal symptoms. In both peripheral blood and mucosa, CD3+ TNFalpha+ and CD3+ IFNgamma+ were increased, while CD3+ IL-10+ were markedly lower in ASD children. And mucosal CD3+ IL-4+ cells were increased in ASD compared with NIC [51]. Similarly, Jyonouchi et al provided evidence that intrinsic defects of innate immune responses in ASD children with gastrointestinal symptoms, suggesting a possible link between GI and behavioral symptoms mediated by innate immune abnormalities [52]. However, DeFelice et al assessed levels of proinflammatory cytokines, interleukin (IL)-6, IL-8, and IL-1beta, produced by intestinal biopsies of children with pervasive developmental disorders but failed to find significant difference between autistic and control groups [53].

How do the gastrointestinal disorders affect brain functions? Currently available pathophysiological studies provided partial explanations. D'Eufemia et al investigated the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children without known intestinal disorders. They found increased intestinal permeability in 43% (9/21) autistic patients, but in none of the 40 controls, which suggested an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioral abnormalities [54].

3. Genetics of autism

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 and tuberous sclerosis [55]. Second, the relative risk of a newborn child to have autism, if he or she has an affected sibling, increases at least 25 folds comparing with general population [56]. 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 [57, 58]. However, based on a large scale study of 503 ASD twins in California, Liu *et al* suggest the heritability has been largely overestimated [59]. 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 [56].

3.1 Genetic methodology

However, 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 [60]. 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 [61]. However, extreme caution must be paid when interpreting CNV analysis since it is very dependent on the specific methods employed, which may partly account for the low replicability among studies [62].

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 [63]. However, linkage studies are unable to identify mutations in critical genes in highly heterogeneous disorders involving many different genes and chromosomal loci [64].

Genetic association studies, including case-control and family-based studies, examine differences in allele or genotype frequencies between two groups [63]. 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 [61]. 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 [63, 64].

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) habor 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 [65-69]. 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 [70].

3.2 Potential loci in autism

3.2.1 Genome wide linkage analysis

Although there is accumulating evidence supporting a genetic component to ASD, the specific genes involved have yet to be totally clarified. 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 be due to the genetic and clinical heterogeneity present in ASD [71]. The noted effects of heterogeneity of the samples on the corresponding results, have led to attempts to decrease sample heterogeneity by various ways which include narrowing inclusion criteria and studies of specific, autism-related endophenotypes.

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 [71, 72], while association tests for specific candidate genes in the chromosome 2q31-q33 region led to negative results [73]. Additional support for the presence of susceptibility loci on chromosome 2q is given by overlapping positive linkage findings in four other independent genomic scans [74-77].

There are three reports about gene variants on chromosome 5. Philippi 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 [78]. 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 [79, 80].

Chromosome 16 linkage results have been fairly consistent in showing a peak at 16p11-13, which strongly suggested a gene in this region may contribute to the risk of ASD [81, 82]. 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 [83-86]. 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 [80, 87-90], including some evidence of linkage to the X chromosome [91]. However, there is little overlap of these potential loci involving potential candidate genes, suggesting that the genetic background of ASD is full of complexity.

3.2.2 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 [100-102]. 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.

Chrom-osome	Loci	Candidate genes	Ref.
1	1p34.2	Regulating Synaptic Membrane Exocytosis 3(*RIMS3)*	[90]
2	2q		[71, 72]
	2q31-2q33	*GAD1,STK17B,ABI2,CTLA4,CD28,NEUROD1, PDE1A,HOXD1, DLX2*	[73]
	2q31	*SLC25A12*	[92]
	2q24-2q33	*SLC25A12, CMYA3*	[75]
	2q24-2q33	*SLC25A12, STK39, ITGA4*	[77]
	2q34	Neuropilin-2 (*NRP2*)	[74]
3	3q25-3q27	HTR3C	[48]
5	5q31	Paired-like homeodomain transcription factor 1(*PITX1*)	[78]
	5p14.1		[79]
	5p15	*SEMA5A*	[80]
6	6q	Abelson's Helper Integration 1 (*AHI1*)	[88]
	6q27		[80]
7	7q22.1-7q31		[93]
	7q31	Laminin Beta-1 (*LAMB1*), Neuronal cell adhesion molecule (*NRCAM*)	[94, 95][96]
	7q32	NADH-ubiquinone oxidoreductase 1 alpha subcomplex 5 *(NDUFA5)*	[48]
	7q31-7q33	wingless-type MMTV integration site family member 2 (*WNT2*)	[97]
11	11p12-p13		[76]
12	12q14		[87]
15	15q11-q13	Angelman syndrome gene (*UBE3A*)	[85]
	15q11-q13		[83]
	15q13	Amyloid precursor protein-binding protein A2 (*APBA2*)	[84]
16	16p11-13	4-Aminobutyrate Aminotransferase (*ABAT),* CREB-binding protein *(CREBBP),*	[98]
	16p11.2	Glutamate receptor, ionotropic, NMDA 2A *(GRIN2A)*	[81, 82, 90]
17	17q11.2		[99]
19	19p13		[99]
20	20q13		[80]
22	22q13	*SHANK3*	[89]
X	Xp22.11	*PTCHD1*	[91]

Table 1. Loci identified by genome wide linkage analysis

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 [102]. A Korean group recently reported deletion CNVs at 8p23.1 and 17p11.2 using whole-genome aCGH [103]. Using aCGH with a mean 19 kb resolution, 51 autism-specific CNV were identified in 397 unrelated ASD subjects [100]. Similarly, Qiao and colleagues performed aCGH on 100 autistic subjects and identified 9 CNVs, three of which were unique to their cohort [104]. A Spanish group recently reported the identification of 13 CNVs containing 24 different genes in their sample of 96 ASD subjects [105].

Single-nucleotide polymorphism (SNP) array analysis, primarily developed to determine linkage, now is also employed to determine genomic CNVs [106]. Marshall 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 [101]. 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 1,984 ASD probands of European ancestry [107]. 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 [108, 109].

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 [106]. 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 the higher resolution for analysis of CNVs in the future.

3.3 Selected candidate genes

As it 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 [110]. Function-targeted studies, mainly by association that focus exclusively on the candidate genes, including some of the most widely studied will be reviewed in the following section (table 2).

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 [203-205]. 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 [206-208].

Given the critical functions of reelin in brain development, and knowing there are neuroanatomical abnormities in autism [209], 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 [210-212]. Genome-wide scans also identified 7q22 as an autism critical region, where *RELN* is located [213].

Genes	Loci	Positive results	Negative/Unconfirmed results
RELN	7q22	[111-120]	
SLC6A4	17q11.1-17q12	[121-127]	[128-140]
GABR	15q11-15q13	[141-154]	[155-157]
NLGN	3q26(*NLGN1*), 17p13 (*NLGN2*), Xq13 (*NLGN3*), Xp22.3 (*NLGN4*), Yq11.2 (*NLGN4Y*)	[158-163]	[164-169]
OXTR	3p24-3p25	[170-174]	
MET	7q31.2	[175-179]	
SLC25A12	2q31	[180-183]	[184-186]
GluR6	6q21	[187-189]	[190]
CNTNAP2	7q35	[191-196]	
GLO1	6p21.3-6p21.2	[197, 198]	[199, 200]
TPH2	12q21.1	[201]	[197, 202]

Table 2. Selected candidate genes

i. Reelin gene (RELN)

Additionally, case-control and family-based studies provided further evidence supporting the association of *RELN* and ASD. Persico identified a *RELN*–related polymorphic GGC repeat located immediately 5′ of the ATG initiator codon in Italian and American subjects [120]. Using the similar methods and 126 multiplex ASD families, Zhang *et al* examined the polymorphic CGG-repeat of *RELN* [118]. Family-based association tests showed that larger *RELN* alleles (≥11 repeats) were transmitted more often than expected to autistic children. Independant studies regarding the CGG-repeat of *RELN* have also supported its contribution to the genetic risk of autism [112, 113, 115]. Others have also reported significant differences in the transmission of the reelin alleles of exon 22 and intron 59 SNPs to autistic subjects [114]. However, results have not been uniformly positive. Krebs *et al* performed a transmission disequilibrium test (TDT) analysis of the CGG-repeat polymorphism in 167 Caucasian families and found no evidence of linkage or association [119]. Similarly, another two groups failed to find a significant association of *RELN* CGG repeat polymorphisms with liability to autism [116, 117].

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 [111].

ii. Human serotonin transporter gene (SLC6A4)

The human serotonin transporter, encoded by *SLC6A4,* localizes to chromosome 17q11.1-q12 and consists of 15 exons [214]. *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 [215, 216]. Using the TDT, positive associations of a 5-HTTLPR polymorphism found in the promoter region of the *SLC6A4* gene with autism have been identified by 4 family-based studies and 2 case-control studies [121, 123, 125-127]. Other groups have performed both family-based and case-control analysis and found significant associations of the *SLC6A4* polymorphism with autism [122, 124]. In contrast to these positive reports, 9 family-based studies failed to find evidence for associations of the *SLC6A4* polymorphism with autism [130, 132-134, 136-140], as well as a case-control study [128]. An Indian group performed a series of studies but found no persuasive evidence of the association of the *SLC6A4* polymorphisms with autism [129, 135, 217]. In addition, a systematic review and meta-analysis failed to find a significant overall association of the serotonin polymorphisms examined and autism [131].

iii. Gamma-aminobutyric acid receptor gene (GABR)

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 [144]. 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 [156].

The region 15q11-q13 was originally associated with ASD based on several studies which reported a common duplication of this region in ASD subjects [147, 148, 152, 154]. A chromosome-engineered mouse model for human 15q11-13 duplication was developed with autistic features [141, 143, 153]. Cook *et al* examined markers across this region for linkage disequilibrium in 140 families with ASD, detecting significant linkage disequilibrium between *GABRB3* and ASD [218]. This finding was confirmed by others as well [145, 146, 151]. Also, two SNPs located within the *GABRG3* gene were associated with ASD using the Pedigree Disequilibrium Test (PDT) [144]. An independent study demonstrated nominally significant associations between six markers across the *GABRB3* and *GABRA5* genes [142]. Moreover, using ordered-subset analysis (OSA) another group provided evidence of increased linkage at the *GABRB3* locus [149]. Other research has also identified significant association and gene-gene interactions of GABA receptor subunit genes in autism [150].

Nonetheless, conflicting evidence has also been reported. Other groups have reported limited or no association between GABA receptor polymorphisms and autism [155, 156]. 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 [157]. Thus the linkage results are at best inconclusive.

iv. Neuroligin genes (NLGN)

The marked difference in sex ratio for ASD justifies the exploration of genes on the sex chromosome, among which the neuroligin genes (*NLGN*) 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 neuroligans, essential for the formation of functional neural synapses [163, 169].

The earliest report regarding the potential association of *NLGN* genes and ASD came from the study of multiple Swedish families [163]. 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 [162]. 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 concluded that it was unlikely that the allelic variants in these genes would be major risk factors for autism [166]. Others have also failed to obtain positive results, casting doubt on the earlier conclusion [164, 165, 167-169].

Other reports about mutations of *NLGN3* or *NLGN4* have identified splice variants in both genes [161]. 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 [158-160].

v. Human oxytocin receptor gene (OXTR)

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 [219, 220]. Both animal experiments and clinical research have confirmed the role oxytocin plays in social and repetitive behaviors [221]. Therefore the oxytocin system might be potentially involved in the pathogenesis of ASD, and the human oxytocin receptor gene (*OXTR*) 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* have been reported to confer risk for ASD in different ethnic groups [170, 172-174]. They have also been associated with IQ and adaptive behavior scale scores [172]. 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 [171].

vi. MET

The human *MET* gene encodes a transmembrane receptor tyrosine kinase of the hepatocyte growth factor/scatter factor (HGF/SF) [222]. Though primarily identified as an oncogene, MET plays crucial roles in neuronal development [222-224]. Moreover, impaired MET signaling causes abnormal interneuron migration and neural growth in the cortex, as well as decreased proliferation of granule cells, which matches many of the features found in autistic brains [223, 225].

Campbell and colleagues 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 [179]. Then they found significantly decreased MET protein levels and increased mRNA expression for proteins involved in regulating MET signaling activity [226]. 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 [178]. Most recently, they found that the *MET* C allele influences two of the behavioral domains of the autism triad [175]. Other groups have also provided supportive evidence that *MET* gene variations may play a role in autism susceptibility [176, 177].

vii. SLC25A12

SLC25A12 locates in 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 [227]. Recently mitochondrial hyperproliferation and partial respiratory chain block were found in two autistic patients, suggesting *SLC25A12* could be a promising candidate gene [228].

Following this report, several studies for genetic variants of the gene were performed. Three different ethnic groups reported linkage and association between ASD and two SNPs (i.e. rs2056202 and rs2292813) in *SLC25A12* [180, 182, 183], while another three independent groups failed to reveal significant association [184-186]. Another group associated one SNP (rs2056202) with ASD but not the other [181]. Thus, the findings so far are inconclusive.

viii. 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 [229]. 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 [187-189]. Another report failed to find any association of *GRIK2* with autism in an Indian population [189].

Contactin associated protein-2 (*CNTNAP2*) belongs to the neurexin family, within which several members have been identified as being related to autism [230]. A recent research report identified a homozygous mutation of *CNTNAP2* in Amish children with pervasive developmental disorders, seizures, and language regression [196]. Five other studies have supported this finding that *CNTNAP2* may be a genetic susceptibility factor in autism [191-195]. Another group found that *CNTNAP2* provided a strong male affection bias in ASD [193].

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 [198], although this conclusion was not confirmed by other studies [199, 200]. In addition, one group found a protective effect of the A419 allele of *GLO1* [197].

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 [197, 201, 202].

4. Environmental factors

4.1 Prenatal factors

The association between prenatal insults and the pathogenesis of autism has been reported recent decades. Early in 2005, Beversdorf *et al*. conducted surveys regarding incidence and timing of prenatal stressors. They found a higher incidence of prenatal stressors in autism at 21-32 weeks gestation, which peaks at 25-28 weeks. Their finding supported the hypothesis of prenatal stressors as a potential contributor to autism, and the timing was consistent with the embryological age suggested by neuroanatomical findings seen in the cerebellum in autism [231]. More specifically, Meyer *et al* demonstrate that the effects of maternal immune challenge between middle and late gestation periods in mice are dissociable in terms of several neuropsychiatric disorders including autism [232]. However, this conclusion was challenged by another group of scientists. Ploeger *et al*. proposed pleiotropic effects during a very early and specific stage of embryonic development, namely early organogenesis (day 20 to day 40 after fertilization) in order to explain the effect of uterine disturbances to the development of autism [233]. They provided ample evidence from literature for the association between autism and many different kinds of physical anomalies such as limb deformities, craniofacial malformations, brain pathology, and anomalies in other organs, which agrees with the hypothesis that pleiotropic effects are involved in the development of autism.

Drugs are the most important prenatal factors affecting embryo and fetal development. Cumulating data support the relationships between maternal medication and fetogeneous diseases including autism. The obnoxious drug thalidomide turned out not only to relate to fetal abnormality but also to autism. Stromland group retrospectively investigated 100 Swedish thalidomide embryopathy cases and found possible association of thalidomide embryopathy with autism [234]. Another example of drug relating to autism is valproate. Williams *et al* reported six cases whose clinical phenotype was compatible with both fetal valproate syndrome (FVS) and autism. Although the sample size is small, the authors claimed the association between this known teratogen and autism had both clinical and research implications [235]. Similarly, Rasalam group provided another line of evidence that prenatal exposure to sodium valproate is a risk factor for the development of an ASD [236].

Another prenatal factor is intrauterine inflammation. Kannan *et al* conducted an animal study to demonstrate intrauterine inflammation results in alterations in cortical serotonin and disruption of serotonin-regulated thalamocortical development in the newborn brain therefore resulting in impairment of the somatosensory system, such as autism [237]. More persuasive evidence comes from Girard's report. According to their results, end of gestation exposure of pregnant rats to systemic microbial product such as lipopolysacharide (LPS) is an independent risk factor for neurodevelopmental diseases such as cerebral palsy, mental deficiency, and autism. And coadministration of IL-1 receptor antagonist with LPS alleviated the detrimental effects caused by LPS [238].

In addition, maternal complications of pregnancies are proved to be associated with autism. One group performed a discriminant analysis to explore perinatal complications as predictors for autism. They found three maternal medical conditions including urinary infection, high temperatures, and depression to be highly significant and contribute to the separation between the autistic and normal subjects [239].

4.2 Postnatal factors

Heavy metals have also been generally considered to contribute to the pathogenesis of autism. Mercury is one of the most widely studied heavy metals. Palmer *et al* studied the association between environmentally released mercury, special education and autism rates in Texas using data from the Texas Education Department and the United States Environmental Protection Agency, and found there was a significant increase in the rates of special education students and autism rates associated with increases in environmentally released mercury. They reported a 43% increase in the rate of special education services and a 61% increase in the rate of autism [240]. Windham group included 284 children with ASD and 657 controls from the San Francisco Bay area in order to explore possible associations between autism spectrum disorders (ASD) and environmental exposures. Their results suggested a potential association between autism and estimated metal concentrations including mercury, cadmium, nickel [241]. Consistent with previous results, Geier *et al* conducted a prospective study which provided biochemical/genomic evidence for mercury susceptibility/toxicity in ASDs indicating a causal role for mercury [242, 243], and they further explored the threshold effect of mercury in a recent publication [244]. In spite of these different pieces of evidence, disagreement exists. IP *et al* performed a cross-sectional cohort study to compare the hair and blood mercury levels of autistic children and a group of normal children. There was no difference in the mean mercury levels. Thus, they concluded that there is no causal relationship between mercury as an environmental neurotoxin and autism [245].

In addition of mercury, lead is also associated with autism. Very early evidence came from a case report, which explored the interaction and possible casual relationship of an elevated blood-lead and autism, as well as treatment of the behavioral symptoms [246]. Later, Canfield *et al* concluded that blood lead concentrations, even those below 10 microgram per deciliter, were inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ were greater at these concentrations than at higher concentrations [247]. Supporting these results, Yorbik group reported that autism could be associated with significant decrease in excretion rate of lead [248].

Hazardous air pollutants have long been related to the development of autism and more evidences have begun to emerge in recent years. Kalkbrenner *et al* conducted a case-control study to screen perinatal exposure to 35 hazardous air pollutants using 383 children with autism spectrum disorders and, as controls, 2,829 children with speech and language impairment. Although the results were biased by exposure misclassification of air pollutants and the use of an alternate developmental disorder as the control group, they provided evidence based on their analysis that methylene chloride, quinoline, and styrene were the plausible candidate exposures for autism spectrum disorders [249]. In another study conducted by Windham group, trichloroethylene, and vinyl chloride have also been related to autism [241].

However, one should notice that the currently available data are mainly derived from epidemiological studies. Considering the limited sample sizes and the different populations,

the previous results are hardly conclusive. Further research is needed to explore the possible mechanisms underlying these results.

5. Mouse models for autism research

Mouse models provide a powerful strategy to explore experimentally candidate genes for autism susceptibility, and to use environmental challenges to induce gene mutations and cell pathology early in development. Mouse models have also been used to investigate the effects of alterations in signaling pathways on neuronal migration, neurotransmission and brain anatomy, which are relevant to findings in autistic subjects [250]. These models have elucidated neuropathology that might underlie the autism phenotype.

There are currently several mouse models for autism research, most of which are primarily developed by knocking out different candidate genes for other neuropsychiatric diseases such as fragile X syndrome [250, 251], Rett syndrome [252], but now are used as autistic models because of their autistic-like behaviors. Other examples include *Engrailed 1&2* and *PTEN* genetic mice [253, 254]. In addition, there is another group of models constructed by surgical or toxic treatments of candidate regions in the brain, in general during development [255]. Some other reports regarding autistic-like behaviors in BALB/c and A/J mice have also been seen [250, 256-258].

Here the author would like to stress an inbred mouse strain for autistic research. BTBR T(+)*tf/J* mouse, also named as BTBR mouse, is an inbred strain with black top coat and blond undercoat. Anatomically BTBR mice get total absence of the corpus callosum, and severely reduced hippocampal commissure, which are also attributed to their phenotypes [259-262]. Although primarily used as type 2 diabetes model [263-268] and phenylketonuria (PKU) model [269-274], BTBR mice were recently found to be a promising mice model for autism research because they exhibited the three core symptoms for diagnosing autism [275-282]. Using this strain, several groups have begun to explore the pathogenesis of autism. It was well documented that circulating corticosterone is higher in the BTBR than in B6. And higher basal glucocorticoid receptor mRNA and higher oxytocin peptide levels were detected in the brains of BTBR as compared to B6, although their relationship to autism remain disputable [283, 284]. In the meanwhile, potential treatments for autism have been proposed based on the experimental results using BTBR mice. Two independent groups confirm the efficacy of the SERT blocker, fluoxetine for enhancement of social interactions [285, 286]. Another experiment reported repetitive self-grooming behavior in the BTBR mouse model of autism was blocked by the mGluR5 antagonist Methyl-6-phenylethynyl-pyridine (MPEP) [287]. Behavioral therapies offer another option for autism treatment, Young group reported social peers rescued autism-relevant sociability deficits in adolescent BTBR mice, but not cross-fostering [288, 289].

However, the tools to analyze these animals are not yet standardized, and an important effort needs to be made. Crawley *et al* proposed three standards to evaluate animal model, namely face validity (i.e. resemblance to the human symptoms), construct validity (i.e. similarity to the underlying causes of the disease) and predictive validity (i.e. expected responses to treatments that are effective in the human disease) [290]. Using these standards, newly developed tests are used to screen more animal models for autism research.

6. Summary and conclusions

Autism spectrum disorders (ASD) is a common neurodevelopment disorder. Diagnosed before three years old, autistic children present significant language delays, social and

communication challenges, as well as abnormal repetitive and restrictive behaviors. It is reported that ASD occur in all racial, ethnic and socioeconomic groups, yet are about four times more likely to occur in boys than in girls probably due to the extremes of typical male neuroanatomy of autism.

The relationship between immune disorders and ASD has been proposed based on series of evidences.Secondly, genetic predisposition is considered to be involved in the etiology of ASD. Cumulative evidences indicated ASD had a strong genetic background, both gene-gene and gene-environment interactions attribute to the etiology of autism. Also, it's now generally accepted that ASD is a group of multi-genetic diseases, in which environmental factors play an important part. Given the early onset of the symptoms, prenatal exposures to environmental challenges are considered the major risk factors leading to subsequent mortality of ASD. Various factors have been proven to be potentially detrimental to early neurosystem development, including maternal use of pharmaceutical agents with neurotoxic effects, intrauterine exposure to viral infections or maternal stress , as well as exposure to high levels of environmental pollutants such as heavy metals . Similarly, neonatal exposure to such risk factors may also lead to mortality of ASD, which has been proven in animal studies as well as clinical reports.

At last, ASD animal models provide a feasible and relatively easy way to morphologically and functionally study the etiology of ASD in different levels, and to testify the effectiveness of the potential interventions. Recent advances in this field provide both inbred strains such as BTBR *T+ tf/J* mice and mutant lines. Other mice models for fragile X syndrome, Rett syndrome have also been used for autism related studies due to the autistic-like behaviors exhibited in these patients.

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.

7. References

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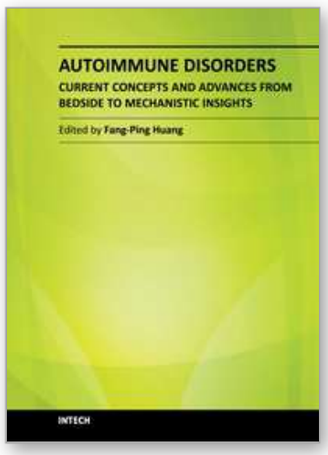

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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