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Genetic Markers Association in Autism Spectrum Disorder

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Abstract

Although the etiology of autism spectrum disorder (ASD) is still unclear, multiple factors have been suggested to be involved in its pathogenesis. There is a strong evidence for multiple interacting genetic factors as the main cause of autism. Hundreds of genes and genetic mutations that are involved in autism development were identified, and thus serve as useful genetic markers for identification of autism. Those genes play a key role in brain development, or may code for immune proteins. Numerous studies have suggested that autism can be inherited based on earlier twins studies which showed that monozygotic (MZ) twins had higher concordance rates than dizygotic (DZ) twins for ASDs. In this review we consider the genetic factors that underlie the pathogenesis of autism and their contribution to the disease outcome. In conclusion, candidate genes studies will highlight the role of interaction between innate immunity and neuronal activity in the etiology of autism, and it may lead to earlier diagnosis and behavioral intervention which improves ASD subjects outcomes.

Keywords: Autism; Genetic markers; Neurodevelopment; Candidate genes

Introduction

Autism spectrum disorder (ASD) is a severe neurodevelopmental and neuropsychiatric disorder characterized by impaired social interaction, verbal and non-verbal communication deficit, and restricted interests and repetitive behavior [1,2]. There is a strong male bias, five times more males than females are affected [3,4]. Although the etiology of autism is still unclear; multiple factors have been suggested to be involved in its pathogenesis [5].

Autism is considered as one of autoimmune neuropsychiatric disorders. There is a strong evidence suggests that the autoimmunity plays a key role in the pathogenesis of neurodevelopmental disorders, including autism [6-9]. The immune response could play a role in the impairment of the central nervous system (CNS) that characterizes autistic children [8,10,11]. In addition, the prenatal maternal-fetal immune interaction was confirmed to affect the fetal brain development [12-14].

Nevertheless, both genetic and environmental factors are believed to contribute to the risk for the development of the disease spectrum during early development [9,15]. There is a strong evidence for multiple interacting genetic factors as the main cause of autism [16]. Those genes play a key role in brain development or associated with brain structures and neurotransmitters defects. Moreover, they may code for immune proteins [17] (Figure 1).

Researchers previously have identified hundreds of genes and genetic mutations that are involved in autism development, and served as useful genetic markers for the disease identification. Numerous studies have suggested that autism can be inherited based on earlier twins studies which showed that monozygotic (MZ) twins had higher concordance rates than dizygotic (DZ) twins for ASDs, thus confirming the influence of genetics in the cause of autism [18]. Concordance for ASD between identical twins is higher than in any other cognitive and/or behavioral disorders [18,19].

In this review we considered the genetic factors that underlie the pathogenesis of autism and their contribution to the disease outcome. A comprehensive search of PubMed database was performed, using multiple terms "autism", "gene", "genetic markers", "chromosomal abnormalities", focusing on the most commonly implicated candidate genes in autism.

The genetics of autism

Family studies have confirmed the key role of the genetic factors in the most of the idiopathic autism cases [17]. No single gene variant has been identified yet contributed to ASD susceptibility in the majority of the cases, due to the genetic complexity; multiple genetic factors are involved in the majority of cases.

Yuen and colleagues published a new study, using whole-genome sequencing analysis in quartet families. They revealed that genes linked to autism can vary among family members, as the siblings who share a diagnosis of autism carried different ASD-relevant mutations. Only one-third of siblings with autism shared similar genetic variations, which was inherited from one of their parents. This could be due to the fact that many genes are not directly associated with autism; rather they associated with specific psychological and nervous system conditions often characterizing autism [20]. In addition, they showed that the chance to develop autism in identical twins where one twin had autism was higher, because they share the same DNA [20,21].

Different approaches were used to identify common genetic risk factors and chromosomal regions that underlying autism: 1) Whole genome screens to search for common genetic markers associated with autism in multiplex families. 2) Cytogenetic studies that could point to the relevant inherited or *de novo* chromosomal abnormalities, including gene copy number variations, associated with autism in affected individuals and their families, and 3) Association studies

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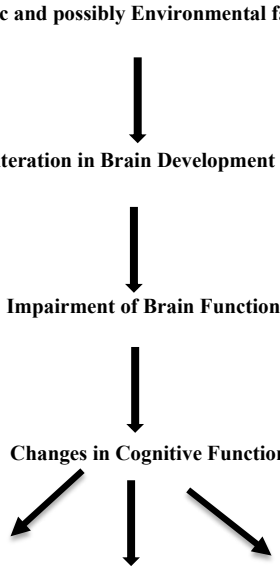

Figure 1: Schematic representation of the effect of the genetic and environmental factors in the outcome of autism.

(candidate genes studies) that could determine the selected candidate genes known to be associated with abnormal brain development or linked to the pathogenesis of autism [22].

Chromosomal abnormalities in autism

Cytogenetic studies help detection of chromosomal abnormalities to locate relevant genes for autism. A number of maternal duplications, deletions, and insertions have been reported in autistic children [23]. The most frequent chromosomal abnormality is maternal duplication 15q11-13, which accounts for ~ 1-3% of autism [24], followed by the microdeletion of 16p11.2 which accounts for ~ 0.5% of autistic patients [25]. In addition, other chromosomes have shown to have some linkage to ASD etiology such as chromosomes 2q21–33, 3q25–27, 3p25, 4q32, 6q14–21, 7q22, 7q31–36, 11p12–13, 17q11–21 [26]. Most of the genes located in those chromosomes are associated with specific symptoms, such as speech and language disorders, learning and memory deficit, communication and social difficulties, and mental retardation [21,23,24,26]. These genes include *EN2*, Reelin, serotenin transporter gene (*5HTT*), *GABRB3, FOXP2, AVPR1A, UBE3A,* and *WNT2*. Additional candidate genes that may represent risk loci for autism were identified, such as *ALDOA, DOC2A, HIRIP3, MAPK3, MAZ, PPP4C, SEZ6L2,* and *TAOK* [25], *NRXN1, CNTN4, DPP6, UBE3A, OR4N4* [26].

Candidate genes implicated in autism

The detection of genetic variants responsible for ASD outcome has thus far been elusive. However, genome wide association studies have identified a growing number of distinct and individually rare genetic variants associated with the disease outcome. Multiplex families studies confirmed the contribution of more than 10 genes in the onset of the disease, but most of them were associated with only one specific symptom suggesting the involvement of multiple genes in the disease [25]. Mutations in the genes active in early development can lead to brain malformations or severe mental retardation. In contrast, postnatal brain development requires input from the environment that triggers the release of neurotransmitter and promotes critical aspects of synaptic maturation [27].

De novo mutation appears to be contributed to the incidence of autism [28]. Genes with *de novo* mutation include *CHD8, DYRK1A, GRIN2B, KATNAL 2, RIMS1, SCN2A, POGZ, ADNP, ARID1B, ANK2, CUL3, TBR1and TBR1* [28-30]. Some of candidate genes play different roles in the pathogenesis of autism, by affecting brain structure and function, mediating different behavioral responses, impairing learning and memory process, impairing motor and cognitive development, impairing speech and language process, or affecting social behaviors. These genes include Engrailed homebox 2 (*EN2*), Reelin, serotenin transporter gene *(5HTT), GABRB3, FOXP2, AVPR1A, UBE3A, WNT2* [17,21,26,31].

De novo mutation in *SHANK2* synaptic scaffolding gene was detected in autistic children and it linked to intellectual disability. This mutation may lead to language and social communication disorders [32]. Furthermore, mutation in neuroligin genes *NLGN3* and *NLGN4* were reported in autistic children, it may affect cell-adhesive molecules at the synapse leading to autism [33].

In addition, the neuronal cell-adhesive molecules cadherin 9 (*CDH9*) and cadherin 10 (*CDH10*) were implicated in the pathogenesis of autism [34]. Another gene of interest is chromatin helicase gene (*CHD8*) which regulates brain development and controls expression of many other genes. The loss of function may contribute to autism pathology due to the reduced level of CHD8 protein, which may lead to the disruption of expression of other ASD risk genes regulated by *CHD8* protein [35-37]. Moreover, several studies indicate the involvement of the oxytocin receptor gene (*OTR*) in the pathophysiology of autism. They reported a low level of oxytocin in the plasma of autistic children; as the physiologic effects of oxytocin (OT) are exerted through its receptor. Furthermore, they postulated its contribution to the social impairment and the development of the repetitive behaviors found in autistic children [17,38].

A recent study has identified a new gene that linked to autism in females, *CTNND2*, which encodes the adhesive junction-associated δ-catenin protein. It was detected in the fetal brain more than in adults brain or other tissues, thus it may play a critical role in brain development and may be associated with other intellectual disability. Moreover, it regulates other genes functions [4].

Taken together, linkage and candidate gene association studies have implicated several genes and chromosomal regions in autism, although the replication and confirmation of some of these findings was failed. These genes play a key role in brain development, or are associated with brain structure, neurotransmitters, or neuromodulators [17]. Some of these genes are involved in the neuronal cell-adhesion pathway, they are involved in the development of the nervous system and contributed to synaptic formation such as *NRXN1, NLGN3, NLGN4, CNTNAP2* [33]. However, mutation in these genes interfere with synaptic development and plasticity, giving rise to wide range of pathologic findings that characterized autism, such as abnormalities in cortical and cerebellar development, learning and memory process deficit, language disabilities and social cognition, behavioral impairment, and increased risk of epilepsy (Table 1).

Immune-related genes

Several studies have reported an association between some autoimmune disorders and specific human leukocyte antigen (HLA) alleles and related genes which have been identified as susceptibility

Genes	Chromosomal position	Effect of mutation	Reference
GABRB3	15q11.2	Learning and memory deficits	[17,24]
FOXP2	7q31	Severe speech and language disorders, social behaviors impairments	[17]
AVPRIA	12q14	Impaired motor and cognitive development	[26]
UBE3A	15q11	Learning and memory deficit	[17,26]
WNT2	7q31	Reduced social interaction	[17,21,26]
SEZ6L6	16p11	Increased risk of epilepsy	[25]
NRXN1	2p16.3	Language disabilities and social cognition	[33]
NLGN3 &NLGN4	Xq28, Xp22.33	Language disabilities and social cognition	[33]
CNTNAP2	7q35	Seizure and language deficit	[25]
CHD8	14q11.2	Abnormal neuronal development	[35,37]
EN2	7q36	Brain structure alteration	[21,26,31]
SHANK3	22q13	Development of language and social cognition	[25,32]
CDH9 &CDH10	5q14	Impaired neuronal development	[31,34]
OXRT	3p26.2	Social impairment and development of the repetitive behaviors	[24,38]
CTNND2	5p15.2	Intellectual disability and brain development	[4]
5-HTT	17q12	Behavioral impairment	[31]
RELN	7q22	Learning and memory process deficit	[17,25,26,31]

Table 1: Selected candidate genes associated with ASD and their chromosomal location.

markers for the diseases, such as rheumatoid arthritis, hypothyroidism and type I diabetes, and autism [14,39]. In autism, several HLA alleles located in class I, class II, and class III regions, were found to be implicated in the pathogenesis of autism [40,41]. The mutations and immune dysregulation of certain HLA alleles in the developing brain may lead to the alteration of the brain connectivity and function characterizing autism [9,42].

Early familial studies reported the contribution of DR4 alleles to autism susceptibility, because it may disrupt the normal fetal brain development due to the triggered immune response [12]. Its frequency was increased in their mothers, suggesting the contribution of maternal DR4 to autism [43,44]. The reason behind that might be the interaction with other risk alleles factors for autism or environmental factors such as maternal infections and thus affect the brain development in autistic children [12]. Another study confirmed the contribution of DR4 in the disease susceptibility and also suggested a protective role of DR13 [42].

A study carried out by Lee et al. reported an interesting finding; the frequencies of DR4 alleles were significantly increased in autistic children and their mothers in a specific region [14]. This could be attributed to the exposure to some environmental factors or pathologic factors that may stimulate immune response in the mother and fetus, which in turn may lead to the development of autism [14,45].

More recently, HLA-DRB1 alleles including DR4 were associated with autism in Han Chinese population (DR4, DR11, and DR14). Those alleles have different effects on intelligence and neuropsychology tests among autistic children [46]. Recent studies reported different HLA alleles and haplotypes which were associated with autism. Autistic children exhibited a significantly higher frequency of HLA-DRB1*11 allele, and a significantly lower frequency of HLA-DRB1*03 allele compared to the controls, suggesting a significant risk association of HLA-DRB1*11 with autism, especially in families with history of autoimmune disorders, as well as a protective association of HLA-DRB1*03 [38], unlike Torres et al who reported a protective association of DR13 in Caucasians [43].

Al-Hakbany et al. demonstrated for the first time the association of number of HLA alleles and haplotypes with the disease, HLA-A∗01, A∗02, HLA-B∗07, DRB1∗1104, and the haplotypeA∗02-B∗07 were positively associated with autism, whereas DQB1∗0202, DQB1∗0302, and DQB1∗0501 were negatively associated with the disease [41]. Furthermore, an association of HLA-C*03 and HLA-DRB1*01 alleles has been reported in Macedonian autistic patients. Although some haplotypes, A*11-C*12-B*52-DRB1*15, A*24-C*03-B*55-DRB1*16, and A*24-C*03-B*55-DRB1*16, were frequently higher in autistic children but they were not statistically significant [47].

Regarding the HLA non-classical genes, the tolerogenic molecule HLA-G is known to be responsible for preventing the destruction of the fetal tissues by the maternal immune system. However, HLA-G/KIR interaction is responsible for the immune tolerance during pregnancy. The activated HLA/KIR complexes were detected in autistic children and their mothers [40,48]; it leads to the neurodevelopmental impairment presented in autism. A recent study showed that a 14-bp insertion polymorphism in the HLA-G gene was significantly associated with autism development due to the prenatal immune activation. The polymorphic gene was detected in autistic children and their mothers and not in their non-autistic siblings, supporting the notion that prenatal immune activation plays an important role in autism development [49].

Furthermore, strong association of the complement C4B null allele in HLA class III region with autism has been reported in several studies [40]. They demonstrated a significant increase in the C4B null allele in autistic children compared to controls [50-52]. Moreover, Mostafa et al. reported an increased risk of autism in the families with autoimmune disorders [52].

Conclusion

Understanding the etiology of ASD may help in the development of biomarkers for its prediction, diagnosis, prognosis, and eventually in its prevention and intervention. In addition, candidate genes studies will highlight the role of interaction between innate immunity and neuronal activity in the etiology of autism. Moreover, elucidating the genes associated with autism and the effect of their products on brain development will be useful for accurate diagnosis and earlier treatments for children with a genetic predisposition towards autism.

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