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Association between autism and various genes: Review and summarize

Linjin Bai

Shanxi Medical University, Jinzhong City, Shanxi Province, China

2941580819@qq.com

Abstract. Autism has emerged as a prominent health concern among humans. The genes related to autism risk are crucial in developing this disorder. This research examined prior investigations focused on identifying the candidate genes linked to autism. A systematic search was conducted across electronic databases and scientific literature papers. Eventually, we consolidated and presented the ten genes connected with autism.

Keywords: autism risk genes, autism spectrum disorder, gene sequencing, mouse model

1. Introduction

Autism Spectrum Disorder (ASD) is designated as a developmental condition, with supporting evidence derived from studies showing a high concordance rate among monozygotic twins, ranging between 73% and 95%. Furthermore, twin studies have highlighted a remarkable heritability of over 90% for ASD. Additionally, there is a notable risk of recurrence within sibling pairs, with approximately 5-6% of siblings manifesting the complete disorder and a broader spectrum of ASD affecting around 15-25% of them [1]. The core characteristics of Autism Spectrum Disorder (ASD) encompass deficiencies in social interaction and verbal communication, coupled with repetitive and rigid behaviours.

2. Background

Autism exhibits a polygenic inheritance pattern. Genetic anomalies, including abnormal chromosomes or candidate genes associated with autism, give rise to abnormal expression of proteins, glycoproteins, enzymes, receptors, and neurotransmitters crucial for neurological development. Consequently, this abnormal expression disrupts the typical development of both the cerebrum and cerebellum, establishing a biological foundation for autism. In combination with additional factors, these disruptions ultimately culminate in specific neurodevelopmental disorders, manifesting as the characteristic symptoms of autism.

3. Methodology

To reassess the autism candidate genes and provide a robust review of the published evidence, we systematically searched China Knowledge, Web of Science, etc., and used the following strategy to search the databases: (ALL=(ASD)) OR ALL=(autism)) OR ALL=(autism genetics)) OR ALL=(autism risk gene)) OR ALL=(pervasive developmental disorder)) OR ALL = (autism risk gene)) OR ALL=(autism candidate gene)) OR ALL=(autism genetic variation)) OR ALL=(autism shank3)) OR ALL=(autism RELN). A total of 72 articles were identified through the initial search. After duplicates were removed, 65 articles were screened for eligibility. Of the remaining 48 articles that were fully reviewed, 21 eligible articles were selected for data extraction (Figure 1).

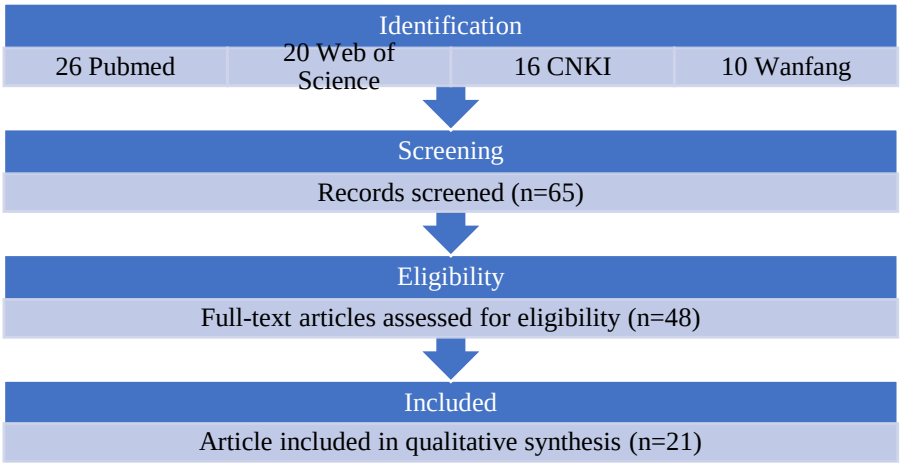

Figure 1. Flow chart of literature identification and selection

4. Finding

We extracted the information by searching China Knowledge, Web of Science, etc., and summarized the risk genes related to autism, such as *SHANK3*, *TRIM33*, *RELN*, *CHD8*, *NRXN1*, and *ZNF804A*, intending to evaluate the candidate genes of autism once again and provide a powerful overview of the published evidence(Table1). Investigations into potential ASD genes have leveraged next-generation sequencing (NGS) and animal models as key strategies. NGS has facilitated the discovery of disruptive genetic variations across the protein-coding segments of the genome. In conjunction with extensive cohorts and advanced statistical techniques, these NGS approaches have transformed the landscape of ASD gene identification. Additionally, NGS has played a pivotal role in generating functional genetic information, including gene expression profiles, which aids in elucidating the neurobiological ramifications of disrupting ASD-linked genes [2]. Mice with *SHANK3* mutations, specifically those lacking the *SHANK3* gene, have offered fresh perspectives on the brain's higher functions specifically linked to *SHANK3*, as well as on developmental and psychiatric disorders associated with *SHANK3* alterations.

Zhang et al. found that the genetic variant rs10497655 exhibited a statistically significant association with autism spectrum disorder (ASD) (P=0.007851), exerting a notable influence on *ZNF804A* expression [3]. Specifically, individuals homozygous for the T-risk allele demonstrated decreased levels of *ZNF804A* expression in human fetal brains. This finding was observed in a cohort comprising a total of 427 trio families. Li et al. identified a statistically significant genetic correlation between autism and four SNPs within the *DAB1* gene: rs12035887 (G allele, $p = 0.0006$), rs3738556 (G allele, $p = 0.0044$), rs1202773 (A allele, $p = 0.0048$), and rs12740765 (T allele, $p = 0.0196$) [4]. These results imply that variations in *DAB1* may be associated with autism and potentially elevate the risk for the condition. Cuchillo-Ibáñez et al. showed that children diagnosed with autism exhibited higher concentrations of Reelin (0.44 ± 0.03 ng/ml, $n = 40$) in comparison to those without autism spectrum disorder (ASD), who had lower levels (0.32 ± 0.03 ng/ml, $n = 19$) [5]. This difference was statistically significant ($p < 0.01$).

Table 1. Information on risk genes is included in the review.

Genes	Result	Materials and Methods
ZNF804A	*ZNF804A* CNV was observed in patients with autism.	Examine the genetic association and CNVs of *ZNF804A* in 841 families [6]
RELN	Variations in the form of single nucleotide polymorphisms (SNPs) within the Reelin gene (*RELN*) represent plausible contributors to the risk of developing autism.	PCR-RFLP and sequencing detected *RELN* gene polymorphisms in 367 Chinese Han subjects [7]
DAB1	Genetic variations in *DAB1*, which participates in the *RELN* signalling cascade, could potentially influence the susceptibility to autism in individuals of Chinese Han ethnicity.	Genotyped for SNPs of 239 Chinese Han family trios (autistic individuals diagnosed with singleton disorder, along with their biologically related, unaffected parents) [4]
SHANK3	*SHANK3* is crucial for the typical development of neuronal connectivity, and mutations in the *SHANK3* gene have been implicated in inducing autism-like behaviours in murine models.	Cellular, electrophysiological, and biochemical analyses with *SHANK3* mutant mouse model [8]

Table 1. (continued).

CHD8	*CHD8* affects neurodevelopment and interacts with environmental and heredity factors.	Develop different *CHD8* mutant mouse models [9]
NRXN1	Mutations within the *NRXN1* gene may pose a risk factor for the development of non-syndromic autism spectrum disorder (ASD).	Thirty individuals, ranging from children to adolescents aged 3 to 18 years, present with non-syndromic autism [10]
CACNA1G	Within a localized context, a statistically significant correlation between *CACNA1G* and autism spectrum disorder (ASD) has been established.	Most common alleles in 284 MO trios [11]
GABRB3	Particular variants within the *GABRB3* gene might plausibly have associations with autism spectrum disorder (ASD). Notably, an increased level of *GABRB3* expression could potentially contribute to the progression of ASD pathology in certain individuals.	356 DSM-IV-diagnosed ASD patients, confirmed by ADI-R, and 386 unrelated controls [12]
THBS1	Both frequent and uncommon variations within the *THBS1* gene have been linked to an increased risk of autism.	Sanger sequencing was used on 313 autistic patients and 350 normal controls to analyze variants [13]
SETD5	The conservation of *SETD5* activity across evolutionary timelines offers additional support for its crucial role in regulating molecular processes.	Zebrafish heterozygous *SETD5* mutants [14]

5. Discussion

In recent years, advancements in high-throughput genomic technologies have enabled scientists to uncover numerous genes that pose risks for autism spectrum disorder. These genes may encompass common variations like single nucleotide polymorphisms (SNPs) or rare genetic anomalies. This discussion focuses on the identified risk genes.

SHANK3: Among the structural chromosomal variations frequently observed in autism spectrum disorder, 22q stands out as a prominent one. The condition arising from the terminal deletion of the 22q segment is known as 22q13.3 deletion syndrome. *SHANK3* is a compelling candidate gene implicated in the causation of 22q13.3 deletion syndrome [15]. Durand et al. showed that in ASD families, people with absent language and mental retardation carried the deletion of 22q13 [16]. The breakpoint of the deletion was identified within intron 8 of the *SHANK3* gene. Furthermore, patients diagnosed with bipolar disorders were found to have duplications of the *SHANK3* gene. Mice overexpressing *Shank3* exhibited synaptic abnormalities and displayed manic-like behavioural phenotypes [17].

CHD8: Genetic alterations in the gene that encodes the chromodomain helicase DNA-binding protein 8 (*CHD8*) represent a potent risk factor for autism spectrum disorder (ASD). Heterozygous mutant mice lacking one functional copy of the *Chd8* gene exhibit macrocephaly heightened anxiety-related behaviours, perturbations in social interactions, and cognitive impairments [18]. In Chd8+/− mice, there are observable changes. Specifically, brain growth is modified, and the expression of crucial neurodevelopmental genes, which are responsible for governing long-distance brain connections, is reduced. Subsequently, unique abnormalities surface in the functional connectivity of the brain. Suetterlin et al. reported that heterozygous *Chd8* mutant mice exhibited an enlargement of brain size, delayed motor development, increased interocular distance (hypertelorism), marked hypoactivity, and aberrant responses to social cues [19].

RELN: Reelin, a secreted extracellular matrix protein, is pivotal in neuronal migration and cortical lamination during embryonic brain development. Encoded by the *RELN* gene situated on chromosome 7q22, its expression is tightly regulated by intricate epigenetic mechanisms. Mutations within the *RELN* gene have been implicated in the pathogenesis of autism spectrum disorders [20]. Reelin has been identified as a potential gene associated with autism. Researchers have noted a correlation between an increased number of CGG repeats within the 5' untranslated region (5'UTR) of the *RELN* gene and decreased expression of Reelin. Importantly, these genetic variants are more frequently observed in individuals diagnosed with autism [21].

6. Conclusion

In conclusion, ten candidate genes were identified from the extracted data. Autism spectrum disorder (ASD) encompasses a multifaceted aetiology and biochemical anomalies that remain incompletely understood. The intricate causes and biochemical disturbances of ASD necessitate further elucidation, highlighting the paramount importance of ASD prevention. Investigating

autism risk genes will furnish clinicians and healthcare policymakers with pertinent evidence-based data to advance the prevention and management of ASD.

7. Challenge

Certain genetic sequence variations remain unknown in the pathogenesis of autism, and numerous studies have yielded preliminary findings due to constraints such as limited sample sizes and incomplete functional annotation of missense variants. Validation of these results necessitates larger sample sizes and independent replication studies. Given that the investigation of autism risk genes will furnish crucial evidence-based insights for clinicians and healthcare policymakers, future research on autism spectrum disorder (ASD) holds particular significance.

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