RESEARCH ARTICLE

pISSN: 0126-074X | eISSN: 2338-6223
https://doi.org/10.15395/mkb.v58.4867
Majalah Kedokteran Bandung. 2026;58(2):95–102

Majalah Kedokteran Bandung (MKB)

Received: March 27, 2026
Accepted: June 9, 2026
Available online: June 30, 2026

Whole-Exome Sequencing Reveals SHANK3 and CHD8 Variants in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder associated with synaptic dysfunction and chromatin remodeling abnormalities. Among the genes implicated in ASD, SHANK3 and CHD8 play essential roles in synaptic organization and neurodevelopmental regulation. This study aimed to investigate genetic variants in SHANK3 and CHD8 and evaluate their possible association with ASD susceptibility. A case-control study was conducted on twenty (20) participants, including ten (10) clinically diagnosed ASD patients according to DSM-5 criteria and ten (10) age- and sex-matched neurotypical controls. Whole-exome sequencing was performed using the Illumina NovaSeq platform with a mean coverage depth of 95× and more than 98% of target regions covered at ≥20×. Detected variants were annotated and analyzed for missense, splice-site, synonymous, and intronic alterations. Structural bioinformatics and protein interaction analyses were applied to assess the biological significance of the identified variants. A total of eighteen (18) variants were detected in SHANK3 and CHD8 genes. Two variants showed higher frequencies in ASD patients, including a missense variant (p.Ile320Thr) and a splice-site variant potentially affecting RNA processing. Structural modeling suggested that the p.Ile320Thr substitution may reduce SHANK3 protein stability. Protein interaction analyses indicated functional connectivity between SHANK3 and CHD8 through NRXN1, SYNGAP1, and GRIN2B pathways. In conclusion, the findings provide preliminary evidence supporting the involvement of SHANK3 and CHD8 variants in ASD pathogenesis through synaptic and chromatin-related mechanisms. Further studies with larger cohorts are recommended to validate these findings.

Keywords: Autism spectrum disorder, chromatin remodeling, neurodevelopment, synaptic transmission, whole-exome sequencing

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, accompanied by restricted and repetitive patterns of behavior, interests, or activities.[1] Symptoms typically appear during early childhood and affect cognitive, behavioral, and social functioning with varying degrees of severity. The global prevalence of ASD has increased substantially during the past two decades because of improved diagnostic awareness, expanded screening programs, and refinement of diagnostic criteria.[2,3] Despite advances in clinical diagnosis, the molecular mechanisms underlying ASD pathogenesis remain incompletely understood, limiting the development of precise diagnostic and therapeutic strategies. Therefore, understanding the genetic and molecular basis of ASD has become a major focus in neurodevelopmental research.

Genetic factors estimated to account for a substantial proportion of ASD susceptibility, with family and twin studies consistently demonstrating high heritability.[4] Advances in next-generation sequencing technologies, particularly whole-exome sequencing (WES), have enabled the identification of numerous ASD-associated genes involved in synaptic organization, neuronal connectivity, chromatin remodeling, transcriptional regulation, and neuronal differentiation.[5] In addition to inherited variants, rare de novo mutations have emerged as important contributors to ASD risk, particularly those affecting genes essential for brain development and synaptic function.[6] These findings support the concept that ASD is genetically heterogeneous and involves multiple

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interacting molecular pathways.

Among the most extensively studied ASD-associated genes are SHANK3 and CHD8. SHANK3 encodes a postsynaptic scaffold protein that plays a critical role in synaptic organization and excitatory neurotransmission. Mutations or deletions in SHANK3 have been associated with synaptic dysfunction, impaired dendritic spine maturation, Phelan–McDermid syndrome, and ASD-related phenotypes.[7,8] Experimental studies have shown that disruption of SHANK3 adversely affects neuronal connectivity and synaptic signaling during brain development. In contrast, CHD8 encodes a chromatin-remodeling factor involved in transcriptional regulation during neurodevelopment. Loss-of-function mutations in CHD8 are considered among the strongest genetic risk factors for ASD because they can cause widespread dysregulation of neurodevelopmental gene expression.[8,9] Furthermore, functions as a regulatory hub controlling the expression of numerous ASD-associated genes, highlighting its critical role in coordinating neuronal developmental pathways.[10]

Although substantial progress has been achieved in ASD genomics, the contribution of rare coding variants remains insufficiently characterized in underrepresented populations, including Middle Eastern cohorts. Most genomic studies have focused predominantly on European and North American populations, resulting in limited genetic data from Arab populations. Consequently, identifying ASD-associated variants in different ethnic backgrounds may improve understanding of population-specific genetic architecture and reveal novel disease mechanisms. Integrating genomic findings with structural and functional analyses may also provide additional insights into the biological significance of identified variants.

Therefore, the present study aimed to investigate genetic variants in the SHANK3 and CHD8 genes in individuals with ASD using whole-exome sequencing. In addition, structural bioinformatics and protein interaction analyses were performed to evaluate the potential functional significance of the identified variants and to explore molecular pathways linking synaptic organization and chromatin remodeling in ASD pathogenesis.

Methods

This exploratory case-control study included 20 participants, consisting of 10 individuals clinically diagnosed with autism spectrum disorder (ASD) and 10 age- and sex-matched neurotypical controls. Participants were recruited from specialized neurodevelopmental clinics in Misan, Iraq, between September 2024 and February 2025 using convenience sampling. Diagnosis of ASD was based on Diagnostic and Statistical Manual of Mental Disorders–5th edition (DSM-5) criteria established through established use of standardized clinical assessment tools used for the diagnosis of ASD including Childhood Autism Rating Scale (CARS) as well as Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2) based on established guidelines for the extent to which an individual's functioning meets criteria for determination of severity of ASDs. Participants had similar ethnic backgrounds. Controls had no known neurological or psychiatric disorders.

Written informed consent was obtained from the parents or legal guardians of all participants before enrollment. The study protocol was approved by the Institutional Ethics Review Board of the University of Misan, College of Science (Approval No. Dept362, 2024). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Peripheral venous blood samples (5 mL) were collected aseptically into EDTA-containing tubes. Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Germany) according to the manufacturer's instructions. DNA concentration and purity were measured using a NanoDrop spectrophotometer (Thermo Fisher Scientific), and DNA integrity was assessed by electrophoresis on a 1% agarose gel. DNA samples with an A260/A280 ratio of 1.8–2.0 and concentration >100 ng/μL were considered suitable for sequencing analysis.[11]

Whole-exome sequencing was performed using the Illumina NovaSeq 6000 platform with paired-end 150-bp reads. Libraries were prepared using the Agilent SureSelect Human All Exon V7 capture kit according to the manufacturer's recommendations. Sequencing achieved a mean coverage depth of 95×, with more than 98% of targeted regions covered at ≥20×. Raw sequencing reads were assessed using FastQC version 0.11.9. Adapter trimming and quality filtering were performed using Trimmomatic version 0.39. High-quality reads were aligned to the human reference genome GRCh38 using BWA-MEM version 0.7.17. Variant calling was performed using GATK HaplotypeCaller version 4.4.0.0 following the

GATK Best Practices workflow. Variants were annotated using ANNOVAR release 2023-07-24 and Ensembl Variant Effect Predictor version 110The process by which variants were filtered to produce potentially disease-causing variants consisted of multiple filtering steps. Variants with a minor allele frequency (MAF) greater than 1% in population databases, including gnomAD and the 1000 Genomes Project, were excluded, as rare variants (MAF <1%) are more likely to contribute to highly penetrant neurodevelopmental disorders.[13] Additional criteria for selecting variants included predicted functional consequence (e.g., missense, nonsense, frameshift and splice site variants) and evolutionary conservation of the allele assessed by PhyloP and GERP++. Variant pathogenicity was assessed using multiple prediction algorithms. Variants were considered potentially deleterious when they met one or more of the following criteria: SIFT score <0.05, PolyPhen-2 score >0.85 (probably damaging), MutationTaster prediction classified as disease-causing, and CADD Phred-scaled score ≥20. Priority was given to variants supported by at least two independent prediction tools. (SIFT, PolyPhen-2, MutationTaster and Combined Annotation Dependent Depletion (CADD)). The variants in and around the coding regions of SHANK3 and CHD8 were given priority for further structural and functional studies.

As part of the investigation of variant proteins with varying levels of potential functional impact, we performed structural modelling analyses on moderate/High impact variants to evaluate the potential impact of the variants on protein stability and conformation. To evaluate the potential structural effects of candidate variants, protein structures were obtained from AlphaFold2 prediction models. Structural comparisons between wild-type and mutant proteins were performed using PyMOL (v2.5.5; Schrödinger, LLC) and FoldX (v5.0) structural modelling software. The impact of amino acid substitutions on protein conformation and stability was assessed through analysis of hydrogen-bonding patterns, root mean square deviation (RMSD), and predicted changes in folding free energy (ΔΔG). The results of this functional modelling analysis can therefore be correlated to determine the potential impact of the variant protein on the folding and function of the corresponding protein Figure 1.

Protein–protein interaction networks were constructed using the STRING database version 12.0. Interactions with a confidence score ≥0.70 were retained for downstream analysis. Network visualization and topological analyses were performed using Cytoscape version 3.10.1. ASD-related genes were curated from established

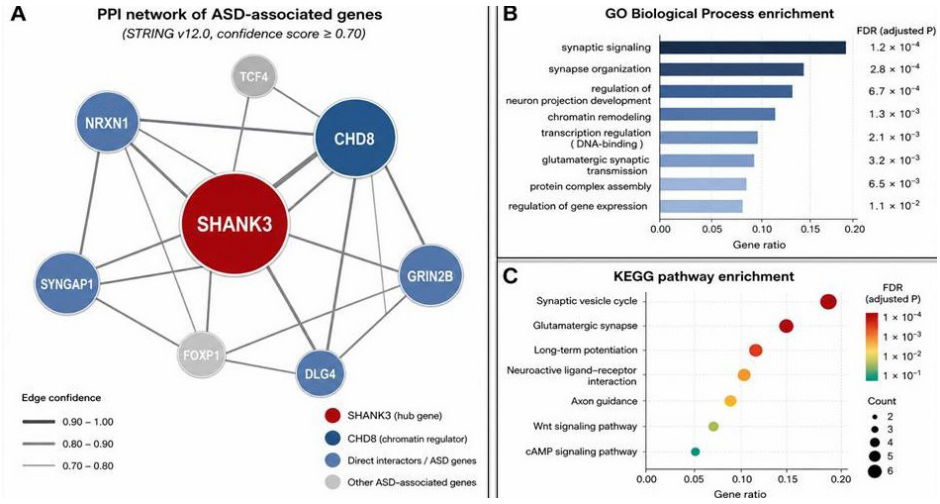

Figure 1 Protein–Protein Interaction Network of ASD-Associated Genes

(A) High-confidence protein–protein interaction network constructed using STRING v12.0 and visualized in Cytoscape v3.10.1. SHANK3 and CHD8 are highlighted as key ASD-associated genes. Network edges represent experimentally validated or predicted functional interactions with a confidence score ≥0.70. (B) Gene Ontology enrichment analysis of genes included in the interaction network. (C) KEGG pathway enrichment analysis showing significant enrichment of synaptic signaling and neurodevelopmental pathways

genomic resources, including the SFARI Gene database. Functional enrichment analyses were performed using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway annotations to evaluate biological processes and pathways associated with the identified variants.

All statistical analyses were performed using SPSS version 27 and GraphPad Prism version 10. Descriptive statistics were presented as mean±standard deviation. Because of the limited sample size and non-normal data distribution, non-parametric statistical methods were applied. Fisher's exact test was used to compare variant frequencies between ASD patients and controls. Spearman's rank correlation analysis was used to evaluate the relationship between SHANK3 variant burden and Childhood Autism Rating Scale (CARS) scores. A p-value <0.05 was used as a nominal threshold for statistical significance. Given the exploratory pilot nature of the study, the findings were interpreted as hypothesis-generating rather than confirmatory and require validation in larger population-based studies.

Results

All 20 participants, including 10 individuals with autism spectrum disorder (ASD) and 10 age- and sex-matched neurotypical controls, underwent successful whole-exome sequencing. Sequencing generated a mean coverage depth of 95×, with more than 98% of targeted regions covered at ≥20×. The mean read-mapping rate was 99.2%, indicating adequate sequencing quality for downstream variant analysis.

Variant were annotated using ANNOVAR and Ensembl Variant Effect Predictor. Population frequency was assessed using public databases, including gnomAD and dbSNP. A total of 18 unique variants were identified in the SHANK3 and CHD8 genes, including missense, splice-site, synonymous, intronic, and untranslated-region variants (Table 1).

Most detected variants were intronic or synonymous and were classified as benign or variants of uncertain significance according to the American College of Medical Genetics and Genomics (ACMG) criteria. A smaller subset of variants was predicted to have potential functional effects and was therefore prioritized for further analysis (Figure 2).

Table 2 summarizes the distribution of variant types between ASD participants and neurotypical controls. Predicted functional variants, including missense, splice-site, and frameshift variants, were observed more frequently among ASD participants, whereas synonymous variants were observed primarily among controls. Intronic or modifier variants were identified in both groups. Because of the small sample size, these findings should be interpreted descriptively, and formal statistical comparisons were limited (Figure 3).

Gene-level burden analysis showed that

Table 1 Annotated Variants Identified in *SHANK3* and *CHD8* Genes

Sample	Group	Gene	HGVS cDNA	HGVS Protein	Variant Type	Predicted Effect	Zygosity
P1	ASD	*SHANK3*	c.565-97dupG	–	Intronic	Modifier	HET
P1	ASD	*SHANK3*	c.673+16G>A	–	Intronic	Modifier	HOM
P1	ASD	*SHANK3*	c.959T>C	p.Ile320Thr	Missense	Moderate	HOM
P1	ASD	*SHANK3*	c.165+1_166-1delCG	–	Splice-site	High	HOM
C1	Control	*SHANK3*	c.565-28C>T	–	Intronic	Modifier	HET
C1	Control	*SHANK3*	c.1527+44G>A	–	Intronic	Modifier	HOM
C1	Control	*SHANK3*	c.1527+106C>A	–	Intronic	Modifier	HOM
C1	Control	*SHANK3*	c.1798+18T>C	–	Intronic	Modifier	HOM
C1	Control	*SHANK3*	c.1874+18G>A	–	Intronic	Modifier	HOM
C1	Control	*CHD8*	c.3477G>A	p.Val1159Val	Synonymous	Low	HOM
C1	Control	*CHD8*	c.2908-45C>G	–	Intronic	Modifier	HOM
P1	ASD	*CHD8*	c.1968+64_1968+67delATTT	–	Intronic	Modifier	HET

Note: ASD = autism spectrum disorder; HET = heterozygous; HOM = homozygous; HGVS = Human Genome Variation Society. Gene symbols are presented according to HGVS nomenclature

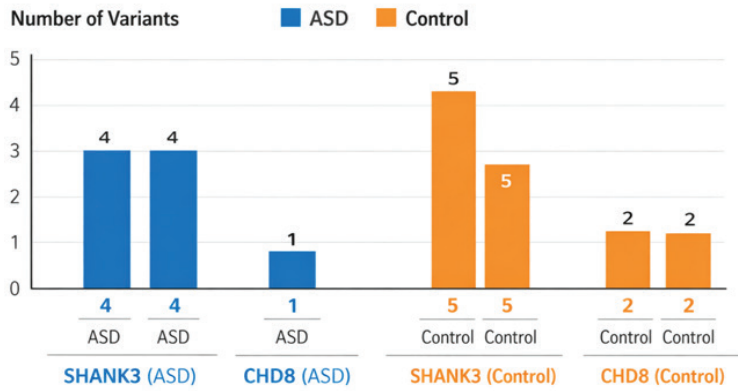

Figure 2 Distribution of Rare Variants in SHANK3 and CHD8 in ASD and Control Samples
The ASD sample uniquely carried a missense and a splice-site variant in SHANK3, whereas the majority of variants detected in both groups were intronic variants with predicted modifier effects

Table 2 Distribution of Detected Variants Across *SHANK3* and *CHD8* Genes

Gene	Variant Category	ASD (n=10)	Controls (n=10)
SHANK3	Missense	1	0
SHANK3	Splice-site	1	0
SHANK3	Frameshift	1	0
SHANK3	Synonymous	0	1
SHANK3	Intronic / Modifier	7	6
CHD8	Splice-proximal	2	0
CHD8	Synonymous	0	1
CHD8	Intronic / Modifier	6	5

two ASD participants carried SHANK3 variants predicted to have moderate or high functional impact, whereas no such variants were detected among controls (Table 3). After Haldane–Anscombe correction, the estimated odds ratio for predicted functional SHANK3 variant carriage in ASD participants was 6.18; however, this difference was not statistically significant by Fisher's exact test (p=0.14). No high-impact

Table 3 Gene-Level Variant Burden Analysis

Gene	ASD Carriers	Control Carriers	Fisher p-value
SHANK3	2	0	0.14
CHD8	0	0	-

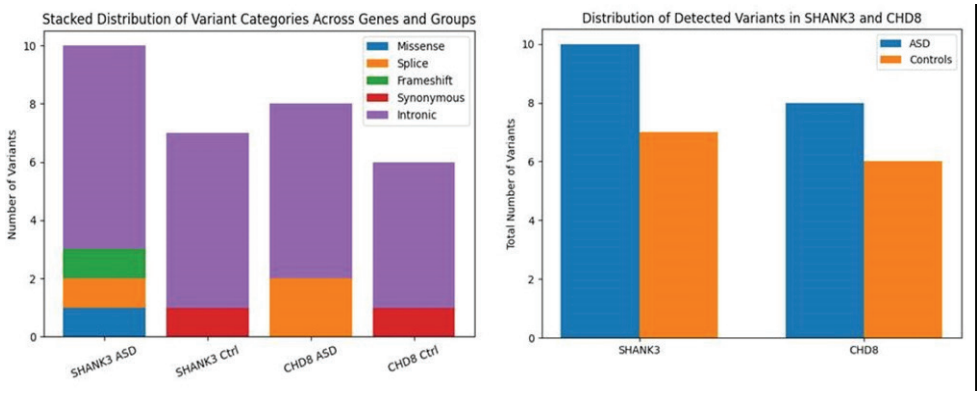

Figure3 Distribution of Variants in *SHANK3* and *CHD8* Among ASD and Control Participants
Variants identified in *SHANK3* and *CHD8* are categorized by variant type. Missense, splice-site, and frameshift variants were detected only in ASD participants, whereas synonymous and intronic/ modifier variants were identified in both ASD and control participants

Table 4 Prioritized Candidate Variants

Gene	Variant	Consequence	Prediction Effect	Protein Domain
SHANK3	p.Ile320Thr	Missense	Damaging	Ankyrin repeat domain
SHANK3	c.165+1_166-1delCG	Splice-site	Predicted pathogenic*	Exon–intron boundary
CHD8	Splice-proximal variant	Splicing	Possible	Regulatory region

Note: Variant pathogenicity was predicted using in silico analyses and has not been experimentally validated

CHD8 variants were detected in either group.

Based on predicted functional consequence and domain location, three candidate variants were prioritized for further analysis: SHANK3 p.Ile320Thr, a SHANK3 splice-site deletion at the exon–intron boundary, and a splice-proximal CHD8 variant (Table 4).

Modeling the structure of the protein showed that the p.Ile320Thr substitution in SHANK3 is found in the ankyrin repeat domain, which is important for how the protein interacts with other proteins at the postsynaptic density; thus, it is likely that it has an effect on both the stability of the structure and the nature of the interfaces with other proteins. Analyses of the interaction of proteins suggest that at least some similarities exist between SHANK3 and CHD8 and other neurodevelopmental genes (NRXN1, SYNGAP1, TCF4 and GRIN2B), all of which are thought to be involved in signaling mechanisms at synapses and the development of neurons.

Spearman correlation analysis showed a positive correlation between SHANK3 variant burden and clinical severity measured using CARS scores (r=0.42, p=0.046). Given the small sample size, this finding should be interpreted cautiously and requires validation in larger cohorts.

Discussion

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder in which both rare and common genetic variants contribute to disease susceptibility. W In this exploratory whole-exome sequencing study, rare coding and regulatory variants were identified in two ASD-associated genes, SHANK3 and CHD8, among 10 individuals with ASD and 10 neurotypical controls. In SHANK3, two candidate variants were prioritized, including a missense variant, p.Ile320Thr, and a splice-site variant. In CHD8, most detected variants were located in intronic or regulatory regions, suggesting possible effects on gene regulation rather than direct protein-coding changes.[11,12]

The SHANK3 p.Ile320Thr variant lies within a functional domain of the protein and may affect protein stability and interactions within the postsynaptic density (PSD). Previous studies have linked SHANK3 dysfunction to altered synaptic organization, dendritic spine morphology, and excitatory synaptic transmission, which are consistent with ASD-related phenotypes.[13,14] However, the biological effect of the p.Ile320Thr variant in the present study remains uncertain because functional validation was not performed.

In CHD8, the observed variants are consistent with previously reported regulatory and splice-related alterations that may contribute to transcriptional dysregulation during neurodevelopment. CHD8 has been implicated in controlling large gene networks involved in neuronal proliferation, cortical development, and synaptic maturation.[15,16]

Network analysis further suggested functional convergence between SHANK3 and CHD8 through intermediate neurodevelopmental genes such as NRXN1, SYNGAP1, GRIN2B, and TCF4, all of which are involved in synaptic signaling and neuronal plasticity.[17,18] Additionally, the Wnt/β-catenin signaling pathway may represent a mechanistic link between chromatin regulation and synaptic function, as CHD8 regulates β-catenin–associated transcriptional programs, while SHANK3 participates in activity-dependent synaptic remodeling.[19–24] However, these findings are based on bioinformatic analyses and should be interpreted as hypothesis-generating.

Although predicted functional SHANK3 variants were observed more frequently among ASD participants than controls, gene-level burden analysis did not reach statistical significance. Therefore, the present findings do not establish a definitive association between SHANK3 or CHD8 variants and ASD. Instead, they identify candidate variants that may warrant further investigation

in larger cohorts. This cautious interpretation is particularly important given the limited sample size and exploratory nature of the study.

The study is limited by its small cohort, lack of statistical power, and absence of functional validation (e.g., Sanger confirmation or in vitro assays). Despite these limitations, the integration of WES data, structural prediction, and network analysis provides a useful framework for identifying candidate variants and understanding potential molecular convergence in ASD.

In conclusion, this exploratory study identified candidate SHANK3 and CHD8 variants in individuals with ASD and suggested possible convergence between synaptic scaffolding and chromatin-mediated transcriptional regulation in ASD-related neurodevelopmental pathways. However, because of the small sample size and lack of statistically significant gene-level associations, the findings remain preliminary and require validation in larger, independent cohorts with functional and molecular confirmation.

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