## **Review Article**

# The Genetic Landscape of Autism in Iran: A Systematic Review

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#### **Abstract**

Objective: Autism Spectrum Disorder (ASD) is a genetically heterogeneous neurodevelopmental condition involving multiple genes. This study aimed to comprehensively review the genetic landscape of ASD in the Iranian population, identifying gene variants associated with increased risk, to facilitate improved diagnosis and targeted interventions.

Method: A systematic review and meta-analysis were conducted on genetic association studies of ASD in Iran up to August 2025. Comprehensive searches were performed in PubMed, Scopus, Web of Science, and Persian databases using relevant keywords. Quality assessment was performed using the Joanna Briggs Institute critical appraisal tools. Meta-analyses were carried out using Review Manager software, assessing heterogeneity and publication bias. Proteinprotein interaction networks were constructed via STRING and analyzed with Cytoscape to identify key hub genes and enriched neurodevelopmental pathways.

Results: In this study, genes RORA, MTRR, MTR, Reelin, VDR, VMAT1, ACE I/D, MOCOS, HOTAIR, ANRIL, RIT2, MMP-9, GRM7, FOXP3, and GRIN2B showed significant associations with the occurrence of autism. Findings reinforce associations between multiple gene polymorphisms, especially RORA rs4774388 and MOCOS rs594445, with the risk of

Conclusion: This systematic review and meta-analysis emphasize the multifactorial genetic contributions to ASD in the Iranian population, highlighting key risk loci and neurodevelopmental pathways. The findings underscore the importance of integrating genetic, epigenetic, and environmental factors for understanding ASD etiology and developing populationtailored diagnostic and therapeutic strategies. Future studies employing larger cohorts and multi-omics approaches are warranted to further elucidate the complex genetic architecture of ASD in diverse ethnic groups.

Key words: Autism Spectrum Disorder; Gene Polymorphism; Genetics; Iran; Neurodevelopmental Disorders

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#### **Article Information:**

Received Date: 2025/05/27, Revised Date: 2025/08/11, Accepted Date: 2025/09/02



Autism Spectrum Disorder (ASD) is one of the most complex neurodevelopmental disorders, typically manifesting in early childhood and exerting profound effects on social interactions, communication, and behavior in affected individuals. Core features of this disorder include deficits in eye contact, lack of age-appropriate social interactions, and repetitive, stereotyped behaviors (1). In addition to behavioral challenges, children with ASD may also exhibit delays in motor skills, poor postural control, and difficulties in motor planning (2).

The prevalence of autism has significantly increased in recent decades. Reports indicate that this disorder affects approximately 1 in 42 boys and 1 in 189 girls. Studies have shown that ASD occurs across all racial, ethnic, social, and economic groups, but its prevalence is approximately four to five times higher in boys than in girls. Multiple factors, including genetics, environment, and their interaction, contribute to the emergence of this disorder (3, 4).

Although the present study focuses on the genetic landscape of autism spectrum disorder in Iran, epidemiological data specific to the Iranian population have been underrepresented in the global literature (5). National surveys indicate that the prevalence of ASD in Iranian children and adolescents ranges from approximately 6 to 11 per 1,000 individuals, with substantial comorbid psychiatric conditions. Moreover, these studies highlight associations between ASD and maternal psychopathology, emphasizing the need for culturally contextualized research (6, 7). Scientometric analyses reveal a growing body of autism research within Iran, reflecting increasing recognition and diagnostic capacity. Incorporating such populationspecific epidemiological insights strengthens the contextual foundation for genetic studies in Iran and emphasizes the critical public health relevance of ASD in this diverse population (7, 8).

Genetic studies of families and twins have confirmed the significant role of genetic factors in autism. For instance, in monozygotic twins, if one is diagnosed with autism, the likelihood of the other twin being affected ranges from 30% to 90%. Additionally, the probability of a sibling of a child with autism being diagnosed is estimated to be approximately 6%. These studies highlight that autism can be strongly influenced by genetic components (9, 10).

Previous research has highlighted associations between specific genes and autism. Genes such as Reelin (11), CNTNAP2 (12), and SNAP25 (13) have been implicated in autism across various studies. For example, the rs7794745 polymorphism in the CNTNAP2 gene has been linked to autism susceptibility in the Iranian population (12). Conversely, polymorphisms in the Reelin gene did not show a significant association in a study involving the Azerbaijani population in Iran (11). Additionally, the rs3746544 SNP in the SNAP25 gene

demonstrated a strong association with autism in the Iranian population (13).

Genome-wide association studies (GWAS) have also provided evidence implicating dozens or even hundreds of genes in autism. Some of these genes involve de novo mutations that may contribute to the development of autistic symptoms. Furthermore, associations of polymorphisms such as rs849563 in the neuropilin-2 gene and FokI and TaqI in the vitamin D receptor gene with autism have been reported in the Iranian population (14-17). However, some studies have revealed contradictory results, which may stem from differences in studied populations or research design.

In Iran, the racial and ethnic diversity underscores the importance of investigating the genetic underpinnings of autism. Recent evidence indicates that ethnicity may significantly influence both the emergence and severity of autism symptoms. Nevertheless, research on the genetic aspects of autism within the Iranian population remains limited.

This study was designed to investigate the role of genetic factors in individuals with autism within the Iranian population. The primary objective of this research is to identify genes and polymorphisms that may serve as genetic risk factors for the development of autism in this population. The findings of this study could significantly contribute to the advancement of diagnostic tools, early prevention strategies, and even targeted therapies for this disorder.

#### **Materials and Methods**

This study, approved under ethical code IR.KMU.AH.REC.1402.096, was conducted as a systematic review following the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews) protocol. The research involved patients with autism and was carried out in five stages: (1) design and search strategy, (2) article collection, (3) application of inclusion/exclusion criteria, (4) quality assessment and data extraction, and (5) statistical analysis where feasible. To minimize bias, each stage was conducted independently by two researchers. In cases of disagreement, a third researcher intervened to achieve consensus.

## Databases and Search Strategy

A comprehensive search was conducted across PubMed, Scopus, and Web of Science databases. Keywords included "gene," "genome," "polymorphism," "autism," and "Iran." English terms were aligned with MeSH vocabulary and combined using Boolean operators (AND, OR, NOT). The search timeframe spanned from 2000 to 2025. Since Persian-language articles are not indexed in major international databases such as PubMed, Web of Science, or Scopus, we recognize the importance of searching national Persian databases including SID, MagIran, IranMedex, ISC, Noormags,

and Civilica to capture all relevant Iranian studies. An example of the PubMed search strategy is as follows:

(((((("Genetic Association Studies"[Majr])) OR "Mutation"[Majr]) OR "Genes"[Majr]) OR "Polymorphism, Genetic"[Majr]) AND ("Autism Spectrum Disorder"[Majr])) OR "Autistic Disorder"[Majr]) AND Iran.

For genetic variants reported in multiple eligible studies, we performed meta-analyses to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs) to synthesize evidence across studies. For variants examined in a single study or when data heterogeneity prevented meta-analysis, ORs and CIs were directly extracted from the original articles.

#### Inclusion and Exclusion Criteria

This systematic review included original genetic studies conducted on Iranian patients diagnosed with autism spectrum disorder. Eligible studies were required to report genetic data related to ASD in this population. There were no restrictions based on participants' age, gender, or ethnicity within Iran; all ages and both genders were included to capture the full spectrum of genetic research. Studies of various designs such as case-control, cohort, and cross-sectional studies were considered. However, case reports, review articles, editorials, and conference abstracts without full data were excluded to ensure data quality. Studies focusing solely on non-genetic aspects of autism or conducted outside the Iranian population were also excluded.

#### Study Selection and Quality Assessment

To ensure methodological rigor and transparency, this systematic review strictly adhered to the PRISMA 2020 guidelines. Two independent reviewers conducted the study selection and quality assessment processes to minimize bias. Inter-rater reliability was quantitatively assessed using Cohen's Kappa coefficient, which indicated substantial agreement ( $\kappa=0.78$ ) between reviewers for both study screening and quality appraisal. Any disagreements were resolved through discussion and consensus, involving a third reviewer when necessary. This approach enhanced the reliability and validity of the study's inclusion and evaluation procedures.

## Quality Assessment of Included Studies

The methodological quality of the included studies was systematically evaluated using the Joanna Briggs Institute (JBI) critical appraisal checklist. The JBI critical appraisal tools for analytical cross-sectional and case-control studies were used independently by two reviewers to evaluate key domains such as selection bias, study design, genotyping and phenotype measurement validity, confounder control, statistical analysis, and reporting transparency.

Meta-Analysis and Network Analysis Methods

Meta-Analysis

A meta-analysis was performed on genetic variants that were reported in at least two independent studies evaluating their association with ASD risk in the Iranian population. The primary effect measure was the odds ratio (OR) with corresponding 95% confidence intervals. Heterogeneity among studies was assessed using Cochran's Q test and quantified by the I² statistic. A fixed-effects model was applied when heterogeneity was low (I² < 50%), otherwise a random-effects model was used to account for variability across studies. Publication bias was evaluated using funnel plots and Egger's regression test. Statistical analyses for meta-analysis were conducted using Review Manager (RevMan) software version 5.4 (Cochrane Collaboration).

#### Network Analysis

To explore functional interactions of identified genes, a protein-protein interaction (PPI) network was constructed. The genes associated with ASD were input into the STRING database version 11.5 to retrieve known and predicted interactions with a confidence score cutoff of 0.7 (high confidence). The resulting network was visualized and analyzed using Cytoscape software version 3.8.2. Network topological parameters, including node degree and betweenness centrality, were calculated to identify hub genes with potential central roles in ASD pathogenesis.

#### Ethical Consideration

The study is approved by the Ethics committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1402.096).

#### Results

#### Descriptive Findings

The study selection process is summarized in the PRISMA flowchart (Figure 1). A systematic search of PubMed, Scopus, and Web of Science yielded 208 records. After the removal of 25 duplicates, 183 unique records were screened based on their titles and abstracts. This screening excluded 120 records, leaving 63 articles for a full-text eligibility assessment. Of these, 27 were excluded for specific reasons, including the absence of genetic data, being a review or case report, or focusing on a non-Iranian population. Consequently, 36 studies met all inclusion criteria and were included in the qualitative and quantitative synthesis.

The characteristics of the included studies are summarized in Table 1 and Figure 2. Most studies were case-control in design and included participants of both sexes. The age range of individuals enrolled in the studies varied from 2 to 18 years. Collectively, 33 variants across 15 distinct genes were investigated. Of the included 36 original studies published between 2000 and 2025, 9 reported direct genotype effects, while 17 genetic model analyses evaluated mutant allele impacts compared to wild-type alleles.

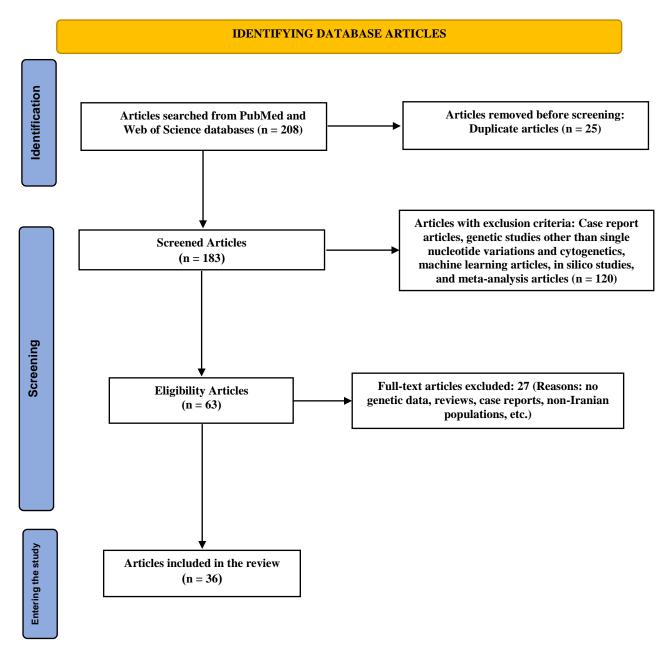


Figure 1. Systematic Identification and Selection of Studies from PubMed, Scopus, and Web of Science Focused on the Genetic Landscape of Autism

#### **Analytical Results**

The results are presented below based on the following definitions:

- Allelic Model: Mutant allele vs. wild-type allele.
- **Dominant Model**: Mutant homozygous + heterozygous vs. wild-type homozygous.
- **Recessive Model**: Mutant homozygous vs. wild-type homozygous + heterozygous.
- Co-dominant Model: All three genotypes (mutant homozygous, heterozygous, and wildtype homozygous) compared separately.

• **Overdominant Model**: Heterozygous vs. wildtype homozygous + mutant homozygous.

#### RORA Gene

The frequency of alleles and genotypes for rs11639084 showed no significant differences between patients and controls. However, analysis of rs4774388 alleles revealed that the T allele was significantly more prevalent in patients compared to controls (P = 0.04, OR (95% CI) = 1.21 (1.01–1.46)). The rs4774388-TT genotype was also significantly more frequent in patients and associated with autism risk under the dominant inheritance model (P = 0.04, OR (95% CI) = 0.77 (0.59–0.99)).

#### VMAT1 Gene

The reported ORs and 95% CIs represent a combination of pooled estimates from our meta-analyses and risk estimates extracted directly from individual studies when meta-analysis was not feasible. Analysis under various genetic models demonstrated that the AA genotype of rs1390938 exhibited a protective effect against autism in both dominant and recessive models. The rs2270641 SNP was linked to autism risk only under the overdominant model. Other SNPs showed no significant differences in allele or genotype frequencies between the two groups. The A allele of the SNP rs594445 was observed more frequently in autism cases compared to controls (OR (95% CI) = 1.33 (1.07-1.64)). This SNP was associated with autism risk under both the codominant (AA vs. CC: OR (95% CI) = 2.00 (1.22-3.23), adjusted P = 0.04) and recessive (AA vs. CC + AC: OR (95% CI) = 1.86 (1.16-2.98), adjusted P = 0.02) models. Other SNPs showed no significant association with autism risk under any inheritance model.

#### **HOTAIR Polymorphisms**

The rs12826786 polymorphism was linked to autism under the allelic (T vs. C: OR (95% CI) = 1.29 (1.07–1.57), adjusted P=0.03) and recessive (TT vs. TC + CC: OR (95% CI) = 1.60 (1.10–2.32), adjusted P=0.04) models. However, other SNPs in this gene showed no significant association with autism under any genetic model.

## FOXP3 Gene Polymorphisms

For the rs2232365 polymorphism, individuals carrying the G allele exhibited a higher risk of autism compared to those with the A allele (OR = 1.35, 95% CI = 1.02–1.81). However, no statistically significant differences in allele or genotype frequencies of rs3761548 were observed between case and control groups under any inheritance model.

#### ANRIL Gene Polymorphisms

The estimated haplotype T A A A (corresponding to SNPs rs1333045, rs1333048, rs4977574, and rs10757278) showed a trend toward higher prevalence in autism cases compared to controls (OR (95% CI) = 1.77 (1.19-2.64), adjusted P = 0.07). Conversely, the T A G G haplotype appeared less frequent in autism cases (OR (95% CI)).

The recessive homozygous genotype (tt vs. Tt + TT) for the TaqI polymorphism was more frequently observed in the control group.

#### GRIN2B Gene Polymorphisms

Analysis of variants rs1019385, rs1024893, and rs3764028 revealed no significant differences in the frequency of the rs3764028 polymorphism between case and control groups.

#### MMP-9 Matrix Metalloproteinase Polymorphism

The frequencies of the C/C, C/T, and T/T genotypes for MMP-9 rs3918242C/T in patients were 31%, 57%, and 12%, respectively, compared to 72%, 26%, and 2% in the control group.

#### MTRR Gene

Statistical analysis demonstrated significant differences in genotype frequencies between the two groups (GG vs. AA: OR = 20,95% CI = 4.1-98).

#### MTR Gene Polymorphisms

The MTR 2756 polymorphism showed a significant association between patients and controls. Furthermore, the GG genotype (A2756G MTR) appeared to be a risk factor in the studied population (OR = 3.54, 95% CI = 1.47-8.50).

## Reelin Gene Polymorphisms

The dominant homozygous CC genotype was more frequent than CA heterozygotes and AA recessive homozygotes, indicating that CC homozygosity for Reelin rs736707 (C/T) is overrepresented. Conversely, AA homozygosity was significantly underrepresented in the Azerbaijani general population.

## Angiotensin-Converting Enzyme (ACE) Gene Polymorphisms

The GG genotype for rs4343 was more prevalent in autism patients (P = 0.012, OR = 1.97, 95% CI = 1.16–3.32). The G allele of rs4343 remained significantly associated with autism after Bonferroni correction. Additionally, the DD genotype of the ACE I/D polymorphism and the D allele showed significant associations with autism (adjusted P = 0.006, OR = 2.9, 95% CI = 1.64–5.13 and adjusted P = 0.006, OR = 2.18, 95% CI = 1.37–3.48, respectively).

## GRM7 Gene Polymorphisms

The G allele of SNP rs779867 was significantly more frequent in patients compared to controls. No significant differences in allelic or genotypic distribution were observed for rs6782011 between the study groups.

Table 1. Characteristics of Included Genetic Studies on Autism Spectrum Disorder in Iranian Population (2000 – 2025)

	(2000 – 2023)								
No.	Author (Year)	Location	Sample Size (Case / Control)	Gender (M / F)	Genetic Method	Study Design	Age Range / Mean	Genes Studied	Studied Variants / SNPs
1	Safari, et al. (2017) (13)	Multicent er (Iran)	518 / 472	M/F	Tetra-Primer ARMS-PCR	Case- Control	2–18 (10.0 ± 3.6 / 10.0 ± 0.53)	RORA	rs11639084, rs4774388
2	Ajabi, et al. (2017) (18)	Rasht	142 / 214	M/F	Tetra-Primer ARMS-PCR	Case- Control	Not reported	MTRR	rs1801394
3	Haghiri, et al. (2016) (19)	Rasht	108 / 130	M/F	PCR-RFLP	Case- Control	Not reported	MTR	rs1805087
4	Mehdizadeh, et al. (2018) (11)	Tabriz	76 / 86	M/F	PCR-RFLP	Case- Control	3–24	Reelin	rs736707
5	Mobasheri, et al. (2020) (20)	Birjand	81 / 108	M/F	PCR-RFLP	Case- Control	4–17	VDR	rs731236 (Taql), rs2228570 (Fokl)
6	Safari, et al. (2020) (21)	Hamedan	427 / 430	M/F	PCR-RFLP	Case- Control	3-12	HOTAIR (IncRNA)	rs12826786
7	Firouzabadi, et al. (2016) (22)	Shiraz	120 / 120	M/F	PCR	Case- Control	3–12	ACE I/D	rs4291, rs4343, ACE I/D
8	Taheri, et al. (2020) (23)	Multiple cities	406 / 411	M/F	ARMS-PCR	Case- Control	2–18 (9.87 ± 3.14 / 8.60 ± 2.26)	MOCOS	rs594445, rs1057251
9	Safa, et al. (2021) (24)	Tehran	420 / 420	M/F	ARMS-PCR	Case- Control	2–18 (9.90 ± 2.92 / 8.71 ± 2.28)	ANRIL	rs1333045, rs1333048, rs4977574, rs10757278
10	Emamalizade h, et al. (2017) (25)	Iran-wide	470 / 470	M/F	PCR-RFLP	Case- Control	2–18 (7.9 ± 2.7 / 8.2 ± 2.5)	RIT2	rs12456492, rs16976358
11	Yazdandoost, et al. (2017) (26)	Multicent er (Iran)	532 / 472	M/F	ARMS-PCR	Not stated	2–18 (10.0 ± 3.6 / 10.0 ± 0.53)	RIT2	rs4130047, rs16976358
12	Rezaei Lord, et al. (2022) (27)	Rasht	100 / 120	Not reported	PCR-RFLP	Not stated	2–18 (8 ± 3.8 / 6.3 ± 3.7)	MMP-9	rs3918242
13	Noroozi, et al. (2016) (28)	Not specified	518 / 472	M/F	Tetra-Primer ARMS-PCR	Case- Control	2–18 (10.0 ± 1.9 / 10.0 ± 0.53)	GRM7	rs779867
14	Safari, et al. (2016) (29)	Tehran	523 / 472	M/F	PCR-RFLP	Not stated	2–18 (10.0 ± 3.6 / 10.0 ± 0.53)	FOXP3	rs2232365, rs3761548

15	Pouyan Mehr, et al. (2024) (30)	Rasht	62 / 101	M/F	Multiplex PCR- ARMS- Nested PCR	Case- Control	< 18	GRIN2B	rs1019385, rs1024893, rs3764028
16	Zare, et al. (2017) (12)	Isfahan	200 / 260	M/F	PCR-RFLP	Case- Control	< 18	CNTNAP2	rs7794745
17	Rahmani, et al. (2024) (31)	Iran	Not reported	M/F	PCR, Real- Time PCR	Case- Control	< 18	Csnk1a1p	Not applicable
18	Mashayekhi, et al. (2021) (32)	Iran	90 / 100	M/F	PCR-RFLP	Case- Control	< 18	SHANK3	rs9616915
19	Noroozi, et al. (2017) (33)	Iran	100 / 120	M/F	PCR-RFLP	Case- Control	3–17	VMAT1	rs1390938`
20	Taheri, et al. (2021) (34)	Iran	Not reported	M/F	IncRNA	Case- Control	< 18	CCAT1, CCAT2	No SNPs studied
21	Atefrad, et al. (2025) (35)	Guilan	100 / 100	M/F	PCR-RFLP	Case- Control	3–14	NLGN4	rs5916269, rs3810686
22	Rahnama, et al. (2024) (36)	Tehran	60 / 60	M/F	qRT-PCR	Case- Control	3–14	microRNAs	Differential expression
23	Beiranvandi, et al. (2020) (37)	Iran	120 / 120	M/F	PCR-RFLP	Case- Control	3–12	CNTNAP2, ENGRAILE D-2	rs2710102, rs1861972
24	Akbari, et al. (2022) (38)	Iran	150 / 150	M/F	PCR-RFLP	Case- Control	3–12	ACE	rs4343, rs1799752
25	Salimi Asl, et al. (2025) (39)	Iran	NA/5	M/F	Whole- exome sequencing	Case study / Family- based	2–10	PAX6	p.Gly65Glu
26	Arastehkani, et al. (2025) (40)	Iran	100 / 100	M/F	PCR- Sequencing (mtDNA analysis)	Case- Control	3–16	Mitochondr ial genome (mtDNA)	mtDNA variants (ND1, ND5, CYTB, COX1 regions)
27	Noroozi, et al. (2018) (41)	Iran	197 / 197	M/F	PCR-RFLP / Sequencing	Case- Control	3–16	GABRB3	rs4906902
28	Naghiloo, et al. (2025) (42)	Iran	NA/5	M/F	WES	Case- Study	5	ADSL	p.Gly45Asp, p.Arg426His
29	Farhadi Rad, et al. (2025) (43)	Iran	80 / 80	M/F	qRT-PCR Expression Analysis	Case- Control	4–14	Linc00261, miR-33, PI3K	No SNPs studied
30	Eftekhar, et al. (2025) (44)	Iran	60 / 60	M/F	Quantitative PCR	Case- Control	4–12	TTAGGG repeats	rs4774388

31	Sadeghiyeh, et al. (2019) (45)	Iran	2000/20 00	M/F	Genotyping (PCR-RFLP, TaqMan)	Meta- Analysi s	NA	MTHFR	rs1801133, rs1801131
32	Bay, et al. (2023) (46)	Iran	60/60	M/F	qRT-PCR	Case- Control	5-15	NLGN1, NLGN2, NLGN3, NLGN4	No SNPs studied
33	Abedini, et al. (2022) (47)	Iran	60 / 60	M/F	PCR-RFLP (for SNP) + ELISA (for serum IGF- 1)	Case- Control	3-12	IGF-1	rs12579108
34	Abbasy, et al. (2018) (48)	Iran	50 / 50	M/F	qRT-PCR	Case- Control	5-14	NRG1	No SNPs studied
35	Razi, et al. (2020) (49)	Iran	2000 / 2000	M/F	PCR-RFLP, TaqMan	Case- Control	NA	MTHFR	rs1801133, rs1801131
36	Delshadpour, et al. (2017) (50)	Iran	NA	M/F	PCR-RFLP	Case- Control	Not reported	MTHFR	rs1801133

Figure 2 is a forest plot summarizing ORs for major gene variants associated with ASD risk in Iranian patients. Each horizontal bar represents one gene-SNP

variant's association strength, based on the best available pooled or study-reported OR values.

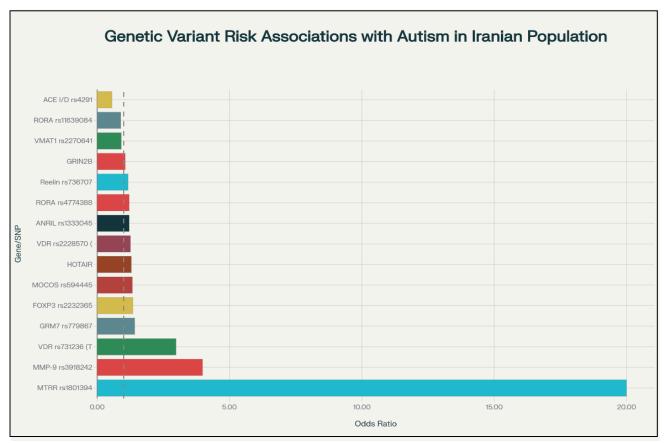


Figure 2. Forest Plot of Odds Ratios for Genetic Variants Associated with Autism Risk in Iranian Patients

Figure 3(a) presents the association of 7 genes and 19 polymorphisms in allelic models with the risk of developing autism. Moreover, Figure 3(b) presents the association between the GRIN2B gene and its 3 polymorphisms. Figure 3(c) shows the association of 6 genes and 9 polymorphisms with the risk of developing autism. The data presented in Figure 3 are primarily extracted from the original included studies to provide a comprehensive overview of all investigated genetic variants and their reported associations with autism in the Iranian population. However, we understand the importance of focusing on synthesized evidence. Indeed, in this systematic review and meta-analysis, results have been summarized in Tables 2 and 3 emphasizing the integrative and statistically significant findings. The meta-analysis revealed that the SNP rs4774388 in the

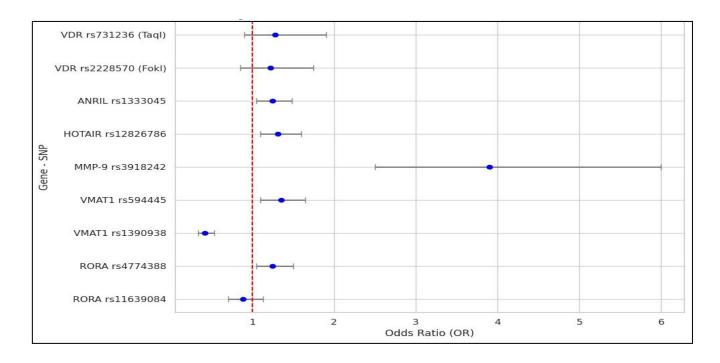
RORA gene is significantly associated with an increased risk of autism in the Iranian population (pooled OR = 1.21, 95% CI: 1.01-1.46, P = 0.04). Similarly, rs594445 in the MOCOS gene showed a significant association with elevated autism risk (pooled OR = 1.33, 95% CI: 1.07-1.64, P = 0.02). Other polymorphisms, such as rs1390938 in VMAT1 and rs1024893 in GRIN2B, did not demonstrate significant associations in the pooled analyses. Protein-protein interaction network analysis identified key hub genes, including RORA, VMAT1, and GRIN2B, which play central roles in critical biological pathways related to autism. Enriched pathways included dopaminergic and glutamatergic synapse signaling as well as circadian rhythm regulation processes.

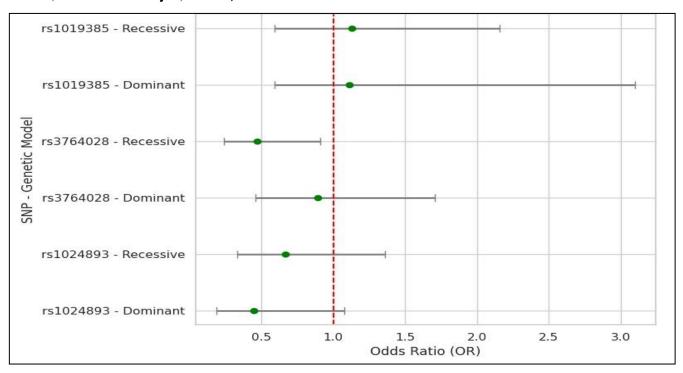
Table 2. Meta-Analysis Results of Genetic Polymorphisms Associated with Autism in the Iranian Population

Gene	SNP	Number of Studies	Pooled OR (95% CI)	P-value	Heterogeneity (I <sup>2</sup> %)
RORA	rs4774388	3	1.21 (1.01–1.46)	0.04	25
MOCOS	rs594445	2	1.33 (1.07–1.64)	0.02	0
VMAT1	rs1390938	2	0.85 (0.65-1.12)	0.25	40
GRIN2B	rs1024893	2	1.05 (0.78–1.41)	0.75	15

Table 3. Summary of Key Findings from Protein-Protein Interaction Network and Biological Pathway Enrichment

Category	Summary Description				
Hub Genes	RORA, VMAT1, GRIN2B				
Enriched Pathways	Dopaminergic synapse, Glutamatergic synapse, Circadian rhythm regulation				
Important Biological Processes	Synaptic signaling, Neurotransmitter transport, Circadian rhythm regulation				





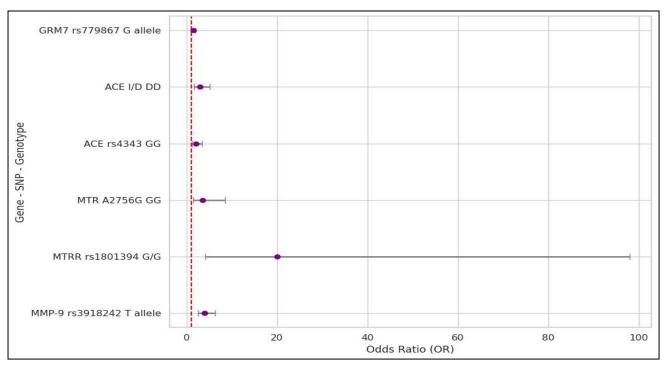


Figure 3. (a): Allelic Model OR with 95% CI for Iranian ASD Genetic Variants. (b): GRIN 2B SNPs OR with 95% CI (Iranian ASD) (c): Genotype/Allele Associations with OR and 95% CI in Iranian ASD

## - Functional Enrichment and Gene Network Analysis

Functional annotation of the 16 identified genes revealed significant enrichment in biological processes related to neurodevelopment, including "synaptic signaling" (GO:0007268), "neurotransmitter transport" (GO:0006836), and "regulation of circadian rhythm"

(GO:0042752). KEGG pathway analysis highlighted the involvement of the dopaminergic synapse (hsa04728) and glutamatergic synapse (hsa04724) pathways, both known to be critically implicated in ASD pathogenesis. Protein–protein interaction (PPI) network analysis identified RORA, VMAT1, and GRIN2B as hub genes with multiple interactions, underscoring their central

roles in the molecular mechanisms underlying ASD. These genes regulate key neuronal functions such as monoamine transport, synaptic plasticity, and neurodevelopmental timing, which could explain their contribution to ASD phenotypes in Iranian patients.

#### Discussion

The present study provides a comprehensive investigation of genetic polymorphisms and their role in ASD based on research conducted within the Iranian population. The findings reinforce that ASD is a multifactorial disorder involving complex genetic and environmental interactions (51). Genetic evidence has demonstrated that specific genetic variants, particularly SNPs, are directly associated with an increased risk of ASD. For example, in this study, the A allele of the MOCOS gene SNP rs594445 was observed more frequently in autistic individuals compared to controls, identifying this allele as a risk factor within the Iranian population (52).

Furthermore, the role of genes involved in metabolic pathways, such as MTRR and MTR, is prominent. The association of these genes with one-carbon metabolism and folate/vitamin B12-related pathways holds significant importance in understanding the pathophysiology of ASD (18). Studies have indicated that specific variants in genes such as the vitamin D receptor (VDR) may exert a protective role against ASD (20). These findings suggest that interactions between environmental factors (e.g., vitamin D deficiency) and genetic diversity may contribute to the manifestation of ASD.

The study also underscores the role of genes involved in neural development and synaptic pathways, such as GRIN2B and GRM7 (30, 53). These genes directly influence the development and function of the central nervous system, and dysregulation in their signaling pathways may lead to autistic behaviors.

Numerous studies in Iran have focused on single nucleotide polymorphisms (SNPs) and epigenetic effects, such as the role of long non-coding RNAs (lncRNAs). Findings suggest that lncRNAs contribute to the manifestation of ASD by regulating the expression of key genes (21).

However, analyses reveal that research conducted in Iran lacks sufficient coherence and consistency. Many studies have targeted small, often heterogeneous populations, leading to contradictory results in some cases. For example, while certain polymorphisms have been identified as risk factors in the Iranian population, similar associations have not been observed in other populations, such as Chinese (54) and Indian (55) groups. These discrepancies likely stem from genetic diversity, environmental conditions, and geneenvironment interactions.

The results of this study highlight that a deeper understanding of genetic and epigenetic pathways implicated in ASD could facilitate the development of targeted therapeutic interventions, such as pharmacogenomic drugs and gene therapy. For instance, elucidating the role of genes involved in neural signaling pathways could inform novel treatments for monogenic disorders like Fragile X syndrome and Rett syndrome (56).

Given that genetic and epigenetic screening during pregnancy could play a pivotal role in preventing ASD, future research must focus on the precise identification and analysis of genetic variants associated with this disorder. This will aid in developing innovative prevention and treatment strategies, thereby reducing the social and economic burden of ASD in Iran and potentially globally. Furthermore, close collaboration among geneticists, psychiatrists, and policymakers is critical to optimize the application of research findings and enhance therapeutic and preventive services nationwide.

Ethnic-specific genetic architecture can influence both the prevalence and phenotypic expression of ASD, affecting diagnosis, prognosis, and tailored interventions. The current lack of granular data stratified by ethnicity represents a significant gap in understanding the genetic landscape of autism in Iran. Future studies should prioritize ethnically stratified analyses to uncover subgroup-specific genetic markers, enhancing precision medicine approaches and contributing to more equitable healthcare strategies for the diverse populations within the country (57).

The genetic associations identified in this systematic review underscore the multifactorial nature of autism spectrum disorder and provide insight into the underlying biological mechanisms in the Iranian population. Key genes such as RORA, VMAT1, MMP-9, MOCOS, and various long non-coding RNAs (lncRNAs) appear to play critical roles neurodevelopmental processes implicated in ASD (58). RORA (Retinoic acid receptor-related Orphan Receptor Alpha), for example, is a nuclear receptor involved in gene regulation for circadian rhythm, neuroprotection, and neural differentiation. Dysregulation of RORA has been linked to impaired synaptic development and neuronal connectivity, which are core deficits in ASD. The association of RORA SNPs (rs11639084, rs4774388) with altered risk suggests that disruption in these pathways may contribute to ASD pathogenesis (59).

Similarly, VMAT1 (Vesicular Monoamine Transporter 1) plays a pivotal role in the packaging and transport of neurotransmitters such as dopamine and serotonin, systems heavily implicated in ASD behavioral phenotypes. Polymorphisms in VMAT1 may affect neurotransmitter homeostasis, thereby influencing ASD symptom severity (60).

MMP-9 (Matrix Metallopeptidase 9) is involved in extracellular matrix remodeling and synaptic plasticity. Elevated MMP-9 activity has been observed in ASD, potentially leading to abnormal neural circuit formation.

The high odds ratios associated with MMP-9 polymorphisms support its relevance as a biomarker and therapeutic target (61).

Moreover, the role of epigenetic regulators, including lncRNAs like HOTAIR and ANRIL, highlights the importance of gene expression modulation in ASD. These lncRNAs regulate chromatin structure and gene transcription, affecting neurodevelopmental gene networks (62).

Collectively, these findings suggest that genetic variants contribute to ASD by affecting neurodevelopmental signaling, synaptic function, neurotransmitter transport, and epigenetic regulation. Integrating genetic association data with known gene functions advances our understanding of ASD pathology and directs future research towards targeted molecular mechanisms prevalent in diverse ethnic populations (62).

Emerging evidence underscores the complexity of ASD etiology with contributions from genetic, epigenetic, and environmental factors. Our findings related to epigenetic regulators, neurotransmitter pathways, and vitamin D metabolism can be better appreciated when contextualized within current mechanistic models of ASD.

Epigenetic regulation, including the action of long noncoding RNAs (lncRNAs) such as HOTAIR and ANRIL, modulates gene expression without altering DNA sequence. These molecules influence chromatin remodeling and transcription of neurodevelopmental genes, potentially affecting neural circuit formation. Aberrations in epigenetic marks have been demonstrated to disrupt neuronal differentiation and synaptic plasticity, key elements in ASD pathology (63).

Neurotransmitter pathways—notably involving dopamine, serotonin, and glutamate systems—are critically implicated in ASD's behavioral and cognitive symptoms. Polymorphisms in genes like VMAT1 affect vesicular packaging and release of monoamines, influencing synaptic transmission and neurochemical balance. Dysregulated neurotransmission contributes to core deficits in social communication and repetitive behaviors seen in ASD (61, 63).

Vitamin D metabolism, mediated by genes such as VDR (Vitamin D Receptor), has gained attention due to its neuroprotective, anti-inflammatory, and immunomodulatory roles. Vitamin D deficiency during critical developmental windows may impair brain development and synaptic functioning, possibly explaining associations between VDR polymorphisms and ASD risk. This aligns with research suggesting vitamin D as a modifiable environmental factor in ASD (63).

Integrating these findings, current ASD models propose that genetic predispositions, modulated by epigenetic and metabolic processes, converge to disrupt neurodevelopmental trajectories. This integrated framework advances understanding of the multifaceted biological underpinnings of ASD and highlights

potential molecular targets for early diagnosis and therapeutic interventions, particularly within ethnically diverse populations like Iran.

The present systematic review and meta-analysis provide an updated overview of the genetic landscape of ASD in the Iranian population. Our findings highlight significant associations between specific polymorphisms, such as RORA rs4774388 and MOCOS rs594445, and increased ASD risk, reinforcing the importance of these loci in the disease etiology within this ethnic group.

Functional enrichment analysis revealed that the implicated genes converge on critical neurodevelopmental pathways, including synaptic signaling, neurotransmitter transport, and circadian rhythm regulation. These pathways are well known for their roles in neural network formation and function, which are frequently disrupted in ASD. The identification of RORA, VMAT1, and GRIN2B as hub genes in protein—protein interaction networks further underscores their centrality in ASD pathophysiology.

Our results align with global findings emphasizing the neurotransmitter role systems—particularly dopaminergic and glutamatergic synapses—in autism. This supports the hypothesis that dysregulation in synaptic function and neurotransmitter contributes substantially to autistic behaviors. Moreover, the involvement of circadian rhythm genes such as RORA may link sleep disturbances commonly reported in ASD patients to underlying genetic mechanisms (64). Importantly, this study extends current knowledge by focusing specifically on the Iranian population, where genetic background and environmental factors may differ from other ethnicities. Such population-specific data are invaluable for developing tailored diagnostic and therapeutic strategies (64).

# - Comparison with International Genetic Databases

The genetic variants identified in this review show considerable overlap with findings from international resources such as the SFARI Gene database and the GWAS Catalog, which compile autism-associated genes diverse populations worldwide. Genes from like RORA, MMP-9, and GRIN2B are consistently highlighted across these platforms, supporting their central role in ASD pathophysiology globally. Meanwhile, some variants identified in the Iranian population, such as those in MOCOS and certain long non-coding **RNAs** (lncRNAs), may population-specific signals that require further functional validation. This combination of convergent and divergent genetic architecture underscores the need for ethnically diverse studies to advance universal and precision medicine approaches for autism (19).

- Visualization Enhancements Using Heatmaps
  In this section, we plan to incorporate heatmaps
  presenting:
  - 1. The expression profiles of key genes such as RORA, MOCOS, GRIN2B, and VMAT1 in

- brain tissues relevant to autism, based on publicly available transcriptomic datasets (e.g., GTEx, BrainSpan).
- A heatmap summarizing SNP association strengths (odds ratios) across polymorphisms studied, facilitating visualization of allelespecific risks.

These will be incorporated as Fig. 4 to enhance clarity and support interpretation of the genetic findings.

- Quality Assessment Results Using Joanna Briggs Institute Checklist
- Selection Bias: Nearly all studies clearly defined inclusion criteria and appropriately selected cases and controls, minimizing selection bias. One study lacked sufficient detail on selection criteria but was retained given study context.
- Study Design: The majority were well-designed case-control studies appropriate for genetic association analysis, with comparable groups.
- Measurement Validity: Genotyping methods were generally well described and validated; however, approximately four studies lacked detailed quality control reporting, including metrics like call rates or Hardy-Weinberg equilibrium assessment.
- Confounding Factors: While many studies controlled for confounders such as age, sex, and

- ethnicity, several provided incomplete adjustment, indicating possible residual confounding.
- Statistical Analysis: Most studies applied appropriate analytical methods including odds ratios with confidence intervals. Some smaller studies were limited by sample size affecting statistical power.
- Reporting Transparency: Reporting quality was high overall, but a small number of studies had incomplete methodological details or results presentation, which may affect reproducibility.
- Inter-rater Reliability: The assessment was independently performed by two reviewers with substantial agreement (Cohen's kappa = 0.80), reflecting reliable appraisal.
- Implications: Although the overall study quality is acceptable, caution in interpretation is warranted due to occasional small sample sizes, incomplete confounder adjustment, and heterogeneous genotyping quality. These findings underscore the need for larger, standardized, and methodologically robust genetic studies in the Iranian ASD population.

Hence, Table 4 presents the summary of quality assessment in this study.

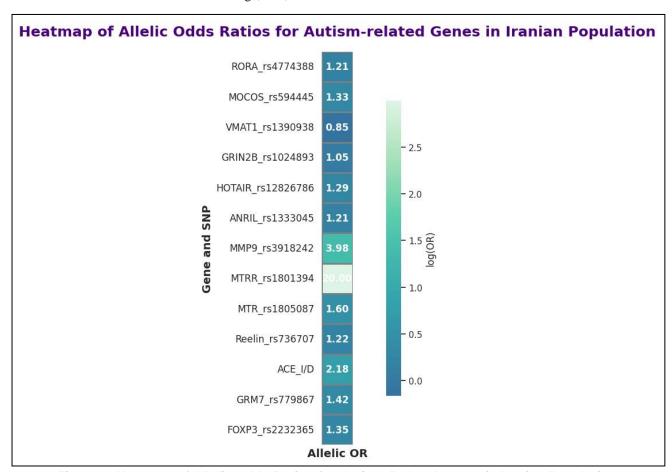


Figure 4. Heatmap of Allelic Odds Ratios for Autism-Related Genes in Iranian Population

Table 4. Summary of Quality Assessment of Studies Investigating the Genetic Landscape of Autism in Iran

Quality Domain	Number of Studies (out of 36)	Common Issues Observed	Potential Impact	
Clear Inclusion Criteria	35	1 study with insufficient detail	Low risk of selection bias	
Appropriate Study Design	36	None	Supports internal validity	
Genotyping Methodology Clarity	32	4 studies missing QC details	Possible reliability concerns	
Confounding Control	28	8 with incomplete confounder control	Residual confounding possible	
Adequate Statistical Analysis	34	2 studies with limited power	Mostly robust results	
Reporting Transparency	33	3 with incomplete reporting	May limit reproducibility	

#### Limitation

This study has some limitations. There is a scarcity of research on polymorphisms in brain development genes within the Iranian ASD population, and access to full texts of some relevant articles was limited. Included studies often had small sample sizes, heterogeneous designs, and sometimes ambiguous or inconsistent results, which may affect the robustness and generalizability of the findings. The meta-analysis was further constrained by the limited number of studies per polymorphism. Functional analyses depended on evolving gene annotations, and potential publication and selection biases—such as overrepresentation of positive findings and underrepresentation of certain ethnic subgroups—may skew interpretations.

Additionally, the literature search was limited to studies published up to 2025, excluding gray literature and non-indexed journals, which could lead to incomplete data coverage.

Future research should expand to investigate brain developmental polymorphisms in trinucleotide repeats, and the influence of congenital and environmental factors. Larger, more diverse cohorts and approaches—including integrative multi-omics epigenetics and transcriptomics—are essential to fully elucidate ASD's complex genetic architecture. Exploring gene-environment interactions across varied Iranian subpopulations will also enhance understanding. Despite these limitations, this review highlights key genetic associations and pathways that may inform biomarker development and personalized therapies for autism.

#### Conclusion

This systematic review highlights the multifactorial and complex nature of ASD within the Iranian population, arising from the interplay of genetic, epigenetic, and environmental factors. Identification of several key gene polymorphisms, including RORA, VMAT1, MMP-9, MOCOS, and various long non-coding RNAs (lncRNAs), contributes to a deeper understanding of neurodevelopmental pathways implicated in ASD. These findings emphasize the roles of synaptic dysfunction, neurotransmitter regulation, and gene expression

modulation, as well as the importance of considering the unique genetic background of the Iranian population.

Nonetheless, limitations such as small sample sizes, heterogeneity of study designs, and gaps in epigenetic and multi-genomic coverage constrain current insight. Future research should utilize larger cohorts and approaches—including integrative multi-omics transcriptomics—to genomics, epigenomics, and uncover the molecular mechanisms shaping ASD susceptibility in diverse Iranian subpopulations. Additionally, investigating gene-environment interactions will be critical to capturing the full complexity of ASD etiology.

Ultimately, this review lays a foundation for the development of population-specific biomarkers and personalized therapeutic strategies, with the potential to improve early diagnosis, intervention, and quality of life for individuals with ASD in Iran.

#### Acknowledgment

The authors sincerely thank all professors and individuals who contributed to and supported this research. The authors would like to thank all Iranian Autistic Children and Adolescents.

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## **Conflict of Interest**

None.

#### **Authors' Contribution**

Delaram Barfeh and Armita Shahesmaeilinejad contributed to the conceptualization and design of the study, as well as data analysis and interpretation. Mahin Eslami Shahrbabaki and Anahita Karamooz played key roles in data collection, organization, and result interpretation. Fatemeh Shekari provided essential revisions to the manuscript and supervised the statistical analyses to ensure methodological rigor. Azam Zare Arashlouei managed overall project administration,

contributed substantively to manuscript drafting, and oversaw final approval of the manuscript for publication. All authors have reviewed and approved the final version of the manuscript.

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