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Genetic Biomarkers in the Neurexin3 gene May Confer Protection Against Autism Spectrum Disorder

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ABSTRACT

Objective: To explore whether individual or interacting neurexin3 variants may have a potential effect on autistic spectrum disorders (ASD).

Methods: ASD symptoms and severity were evaluated using Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) criteria and the Childhood Autism Rating Scale. Genomic DNA was extracted from buccal cells from 84 cases and 78 healthy controls. These samples were then analyzed, matching for age and gender, using TaqMan genotyping assays for the rs8019381 (T>C) and rs2270964 (C>A) SNPs in the NRXN3 gene. Most suitable mode of inheritance for these genotypic data was then analyzed and identified using SNPstats.

Results: SNPs in our Saudi controls were in Hardy-Weinberg equilibrium. We found an apparent protective effect at rs8019381(C>T) in ASD cases compared with controls (11% versus 29%, respectively), whereas no statistically significant difference was observed at rs2270964 (OR = 1.47, 95% CI, 0.78-2.79; P = 0.24). Furthermore, the genotype frequencies for rs8019381(T>C) showed a significant difference between cases and controls under the log-additive model (OR 2.89, 95% CI 1.04-8.01; P = 0.028). However, the distribution of rs2270964 genotypes was relatively similar between the two groups across the various inheritance models. Among the four possible haplotypes at rs8019381(C>T) and rs2270964(C>A) loci, the T-A haplotype showed an overall frequency of 19.44%, indicating a significant difference between the cases and controls (OR = 2.89, 95% CI, 1.04-8.03; P = 0.048). Furthermore, the global haplotype association showed no significant difference between cases and controls (P = 0.12). The two SNPs showed a weak negative linear correlation in linkage disequilibrium (D' = 0.4393, r = -0.0867; P = 0.3677).

Conclusion: Our results clearly show that the NRXN3 rs8019381 biomarker is protective against ASD, whereas rs2270964 shows no significant risk. Additional studies are required to identify potential genes and genetic variants.

Keywords: Molecular; Saudi community; Autism spectrum disorder; Polymorphism; Population genetics; TaqMan genotyping

Background

Neurexin and neuroligin interact, establishing a connection between two neurons and facilitating synapse formation[1]. The various combinations of neurexin-neuroligin pairs, along with the alternative splicing of neurexin and neuroligin genes, govern the binding interactions between neurexins and neuroligins, thereby contributing to synapse specificity[2]. Nevertheless, neurexins alone can attract neuroligins to the dendritic surface of postsynaptic cells, leading to clustering of neurotransmitter receptors and other proteins and machinery associated with the postsynaptic area.

Neurexins are present in neurons and are predominantly located at presynaptic terminals, where they facilitate synaptic signalling and impact neural networks through their synapse-specific roles[3]. Initially recognized as receptors for α-latrotoxin (derived from black widow venom)[4], they function as presynaptic cell adhesion molecules[5], playing a crucial role in regulating neurotransmitter release and stabilizing synapses, including glutamatergic synapses, which are essential in Alzheimer's disease research[6,7].

In humans, changes in the genes that encode neurexins are associated with autism spectrum disorders (ASDs) and various cognitive disorders, including Tourette syndrome and schizophrenia[8,9]. Neurexin genes rank among the most crucial genes (exceeding 1 million bp) within the human genome, with three neurexin splice variants NRXN1, NRXN2 and NRXN3 that encode for thousands of different isoforms, set against a backdrop of long α-neurexin and short β-neurexin produced through the utilization of different promoters[10]. In postmortem analyses of human brains, alphaNRXN3 mRNA expression in the frontal cortex was 5 times higher than that of betaNRXN3[11]. Both isoforms were expressed at varying levels in the hippocampus, substantia nigra, midbrain, caudate and putamen. In the cerebellum, the expression of beta-NRXN3 was more than five times higher than that of alpha-NRXN3[11].

Autism is a neurodevelopmental disorder known to exhibit by significant deficits in social interaction, frequently accompanied by restricted and repetitive behavioral patterns[12]. It can be divided into three groups of disorders: Asperger syndrome (AS), childhood disintegrative disorder (CDD) and pervasive developmental disorder. A limited number of individuals with ASD carries a single mutation in genes encoding the neuroligin-neurexin cell adhesion molecules. Neurexin is essential for synaptic connectivity and function, demonstrated by the diverse array of neurodevelopmental phenotypes seen in individuals with neurexin deletions[9], which presents compelling evidence that neurexin deletions contribute to an elevated risk of ASDs and suggests that synaptic dysfunction may be a potential origin of autism[13].

We hypothesized that specific NRXN3 genetic variants were associated with ASD. Our study specifically explored the associations of the rs8019381 (T>C) and rs2270964 (C>A) SNPs with risk of ASD in the Western region of Saudi Arabia. The purpose of this research study was to investigate the association of these genetic loci with the risk of childhood ASD in a Saudi population.

Study Population and Methods

Ethical approval

The study received approval from the Institutional Biomedical Ethics Committee at Medicine College, Umm Al-Qura University (reference #HAPO-02-K-012) (http://bioethics.kacst.edu.sa/About.aspx?lang=en-US). Consents were provided by parents/ guardians of all participants. This research was carried out with unrelated Saudi patients diagnosed with ASD, chosen from neuropsychiatric clinics, in addition to healthy controls with no history of mental disorders, epilepsy or behavioural illnesses.

Study population

The study included unrelated individuals diagnosed with ASD and healthy control participants from the Saudi population. The case group comprised 84 patients (73 males and 11 females) aged 5-15 years, collected from neuropsychiatric clinics in the Western governorates of Saudi Arabia. ASD cases were identified according to the criteria from the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), family information, clinical data, medical records[14]. All cases met DSM-V criteria and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) diagnostic tools and the required scores on the Autism Diagnostic Interview-Revised (ADI-R)[12,15]. Moreover, the Childhood Autism Rating Scale (CARS) can assess the severity of ASD behaviors; scores of 30-36 indicated mild to moderate autism and scores of 37-60 indicated severe autism[16]. Cognitive functions were estimated via Wechsler IQ scales, based on age and clinical condition. Cases with any neuropsychiatric disorders were excluded. In addition to that patients with family history of a known genetic disorder were excluded (e.g., fragile X syndrome, microdeletion chromosomal abnormalities, etc.)[17] or a positive. Healthy controls (78 individuals; 67 males, 11 females) were selected after having CARS scores within the normal range (unpublished data) and for having no family history of mental disorders, behavioral illnesses or epilepsy[18].

DNA isolation enomic DNA was isolated from buccal cells using Oragene DNA-OGR-575 kits designed for non-invasive samples (DNA Genotek Inc., Ottawa, ON, Canada). The entire collection of buccal cells was completed within 30 minutes and the samples were promptly sealed. The cells were incubated in OGR-lysis buffer at 53°C to facilitate DNA release. Then it was precipitated with ethanol and reconstituted in elution buffer[19].

TaqMan genotyping analysis

We employed TaqMan genotyping assays to determine the genotypes of individuals for specific SNPs in the NRXN3 gene using a 7500 Fast Dx Real-Time PCR System (Thermo Fisher Scientific, USA). Probes were obtained from Applied Biosystems.

The assay IDs for rs8019381 and rs2270964 SNPs were C__29283249_10 and C__2270964_20, respectively (Thermo Fisher Scientific, SA). All DNA samples were included in the genotyping process. Additionally, 10% of the samples were genotyped twice, with identical results in all cases.

Statistical analysis

Variants from cases and control were tested for Hardy-Weinberg equilibrium (HWE) using chi-square ($\chi 2$) test; P values < 0.05 indicated deviation from HWE. We performed statistical analysis of the examined SNPs using SNPStats (https://www.snpstats.net) and evaluated inheritance models:

codominant, dominant, recessive and overdominant. Moreover, a log-additive genetic model was used to assess how a gene's effect changes on a log scale across the examined genotypes. Logistic regression analyses of genotypic distributions and allelic frequencies in ASD cases and controls were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). The lowest Akaike information criterion (AIC) value was selected as the best model for inheritance. Demographic and clinical characteristics, such as age, gender, IQ and CARS score, were analyzed using Student's t-test and the chi-square test (https://www.medcalc.org/en/calc/relative_risk.php) (Ver. 23.4.5, 2025). A two-tailed P value of ≤ 0.05 was used for statistically significant data.

Results

Study population

A total of 84 unrelated Saudi individuals diagnosed with ASD were recruited for the study, comprising 11 females and 73 males (female-to-male ratio 1:6.6), along with 78 healthy Saudi controls (11 females and 67 males; ratio 1:6.1). The mean age of participants with ASD was 8.05 ± 2.08 years and did not differ significantly from that of the control group (t = −0.96, 95% CI: 22.9–47.0; P = 0.34). The overall mean CARS score among ASD cases was 41.56 ± 7.20, with individuals exhibiting severe autism (CARS ≥37) significantly outnumbering those with mild to moderate presentations (CARS <37) (67.9% vs. 32.7%; χ^2 = 28.6; 95% CI: 22.9–47.0; P < 0.0001). In addition, the average IQ score was markedly lower in the ASD group compared with controls (56.1 ± 6.5 vs. 63.4 ± 7.8), a difference that was highly statistically significant (t = 7.4; 95% CI: 5.4–9.2; P < 0.0001), as summarized in **(Table 1)**.

Allele frequencies of the examined NRXN3 loci

Table 2 shows the allele frequencies for rs8019381 (T>C) and rs2270964 (C>A) polymorphisms. The odds ratio for the allelic variants was 0.29 (95% CI, 0.29-0.54; P < 0.0001) for rs8019381 and 1.47 (95% CI, 0.78-2.79; P = 0.0001) for rs2270964 (Table 2). Regarding rs8019381, the T-allele variant was significantly more common in controls than in cases (29% versus 11%). Conversely, rs2270964 showed a higher frequency of the A-allele in cases compared to controls (16% versus 12%) **(Table 2)**.

Table 1: Epidemiologic and clinical data of cases and controls.

Parameter	ASD Cases (N = 84)	Controls (N = 78)	Statistical Test (95% CI)	P value
Age range (years)	5 – 15	6 – 17	—	—
Mean age ± SD (years)	8.05 ± 2.08	7.77 ± 2.62	t = 0.96 (−0.9 to 0.3)[a]	0.34
Male sex, n (%)	73 (87.3%)	67 (86.3%)	—	—
Mean IQ ± SD	56.1 ± 6.5	63.4 ± 7.8	t = 7.4 (5.4–9.2)[a]	< 0.0001**
CARS score range	31 – 60	—	—	—
Mean CARS ± SD	41.56 ± 7.20	—	t = 53.3 (40.2–43.0)[a]	< 0.0001**
Mild–moderate ASD (CARS < 37), n (%)	34 (32.7%)	—	—	—
Severe ASD (CARS ≥ 37), n (%)	76 (67.9%)	—	χ^2 = 28.6 (22.9–47.0)[b]	< 0.0001**
	n = 17 (incomplete)			

[a] Student's t-test (data expressed as mean ± SD). [b] Chi-square test.
*P > 0.05: not significant; *P < 0.0001: very highly significant.
[c] Number of subjects, with percentages in parentheses.

Genotypic distribution of the examined NRXN3 loci

Healthy controls exhibit consistent findings with Hardy-Weinberg equilibrium at rs8019381 T>C (χ2 = 1.92, P = 0.167), whereas this is not the case forrs2270964 C>A (χ2 = 4.73, P = 0.03). The best interactive inheritance model was identified as the one with the lowest AIC value. Regarding the genotypic distribution of rs8019381, the most appropriate interactive statistical models were dominant (OR = 4.09; 95% CI, 1.1614.50; P = 0.023) and log-additive (OR = 2.89; 95% CI, 1.04-8.01; P = 0.028). Conversely, the genotypic distribution of rs2270964 did not reveal any statistically significant differences between cases and controls across the inheritance models evaluated (P > 0.05) **(Table 2)**.

Table 2: Genotype distribution and allele frequencies of NRXN variants and their associations with ASD among cases and controls.

Genetic Model	Genotype	Patients n = 84	Controls n = 78	Logistic regression		
				OR (95% CI)	P-value	AIC
NRXN3 rs8019381T>C (MAF, Tallele):						
Codominant	C/C	69 (82.1)	42 (53.9)	1		
	C/T	12 (14.3)	27 (34.6)	3.85 (0.97-15.31)	0.001	75.4
	T/T	3 (3.6)	9 (11.5)	5.08 (0.46-55.81)	0.022	
Dominant	C/C	69 (82.1)	42 (53.9)	1		
	C/T-T/T	15 (17.9)	36 (46.1)	4.09 (1.16-14.50)	0.023	73.5
Recessive	C/C-T/T	81 (96.4)	69 (88.5) 9 (11.5)	1		
	T/T	3 (3.6)		3.58 (0.34-37.99)	0.26	77.4
Overdominant	C/C-T/T	72 (85.7)	51 (65.4)	1		
	C/T	12 (14.3)	27 (34.6)	3.29 (0.85-12.79)	0.075	75.5
log-additive	---	---	---	2.89 (1.04-8.01)	0.028	73.8

Allele:	C	150 (0.89)	111 (0.71)	1		
	T	18 (0.11)	45 (0.29)	0.29 (0.16-0.54)	0.0001	NA
NRXN3 rs2270964C>A (MAF, A-allele):						
Dominant	C/C	63 (75.0)	63 (80.8)	1		
	A/C-A/A	21 (75.0)	15 (19.2)	1.4 (0.66-2.96)	0.38	78.3
Recessive	C/C-A/C	78 (92.9)	75 (96.2)	1		
	A/A	6 (7.1)	3 (3.8)	1.9 (0.46-7.97)	0.37	78.2
Overdominant	C/C-A/A	69 (82.1)	66 (84.6)	1		
	A/C	15 (17.9)	12 (15.4)	1.2 (0.52-2.74)	0.8	78.6
log-additive	---	---	---	0.70 (0.26-1.92)	0.49	78.2
Allele:	C	141 (0.84)	138 (0.89)	1		
	A	27 (0.16)	18 (0.12)	1.47 (0.78-2.79)	0.24	NA

NRXN: Neurexin gene, ASD: autism spectrum disorder or: odds ratio, SNP: single nucleotide polymorphism, CI: confidence interval. AIC, corresponds to the minimal expected entropy. Bold numbers (P < 0.05). Underlined data indicate the best mode of inheritance having lowest AIC score.

Haplotype analysis

The results from the haplotype analysis, along with the comparisons of possiple haplotypes among the groups, are detailed in **(Table 3)**. From the four possible haplotypes at rs8019381 (C>T) and rs2270964 (C>A) loci, the T-A haplotype showed an overall frequency of 19.44%, indicating a significant difference between the cases and controls (OR = 2.89, 95% CI, 1.04-8.03; P = 0.048) **(Table 4)**.

Table 3: Haplotype frequencies estimation (n = 162).

Haplotype	*NRXN3* rs8019381C>T	*NRXN*3 rs2270964C>A	Total	ASD cases *n* = 84	Control N = 78	Cumulative frequency
1	C	A	0.6803	0.8115	0.6346	0.7222
2	T	A	0.1944	0.0992	0.2885	0.9169
3	C	C	0.1252	0.0813	0.0769	1
4	T	C	0.0136	**0.0079**	0	1

Table 4: Haplotype association with response (n = 16, adjusted by age).

Haplotype *NRXN3 NRXN3 Frequency* **rs8019381C>T rs2270964C>A**	OR (95% CI)	P-value
1 C A 0.6803	1	---
2 T A 0.1944	2.89 (1.04-8.03)	**0.048**
3 C C 0.1252	0.99 (0.22-4.45)	0.99
4 T C 0.0136	inf (-inf-inf)	< 0.0001

NRXN3: Neurexin3 gene. CI, confidence interval; OR = odds ratio. Bold numbers show statistically significant P values (P < 0.05). Statistical analysis was conducted using logistic regression.

Furthermore, the global haplotype association showed no significant difference between cases and controls (P = 0.12). Moreover, the physical distance separating the two SNPs (rs8019381 and rs2270964) within the NRXN3 gene on chromosome 14 is relatively small, approximately 885,860 kb, i.e., less than one centiMorgan (< 1 cM) (https://genome.ucsc.edu). Additionally, the two SNPs displayed a weak negative linear correlation in linkage disequilibrium (D' = 0.4393, r = -0.0867; P = 0.3677).

Discussion

This case-control study examined the association between the rs8019381 (T>C) and rs2270964 (C>A) SNPs in the NRXN3 gene and ASD in the Saudi population. The current results suggested that rs8019381 (T>C) may act as a statistically significantly protective biomarker in ASD cases, whereas rs2270964 (C>A) was not associated with ASD. Additionally, the genotype distributions significantly differed between cases and controls under the log-additive model for rs8019381 (T>C). In contrast, the distribution of rs2270964 genotypes showed no significant difference between cases and controls across the tested inheritance models.

Our results showed that although the genotypic distribution of rs8019381 differed significantly under both codominant and dominant models, the homozygous variant genotype (T/T) present more commonly in healthy controls compared to cases, suggesting a protective effect. In contrast, the rs2270964 SNP showed increased expression of homozygous variant genotypes in cases across all inheritance models, but there were no statistically significant differences compared to controls. Six studies on that SNP have been published; four focused on its connection with drug dependence and alcoholism[11,20-22]. The remaining studies concentrated on Alzheimer's and neuropsychiatric disorders[23,24].

Neurexin genes have two leading promoters that produce long forms (α-neurexin) and short forms (β-neurexins), each with five and two splicing sites, respectively. Alleles of rs8019381 generate splice variants that include or exclude exon 23, which is essential for the solubility of NRXN3 isoforms. It was found that the intronic SNP, located near exon 23 splice site, is strongly associated with alcohol dependence (P = 0.0007 or = 2.46)[11]. This may be because rs8019381, which carries the T-allele, produces fewer isoforms lacking exon 23, potentially affecting the protein's synaptic function.20 Additionally, individuals having the T-allele at rs8019381 are more likely to be in the alcohol-dependent group than those who are homozygous C/C[11]. Another study reported a significant association between the NRXN3 rs8019381 SNP and Alzheimer's disease (AD). Conversely, Hashimoto, et al.[24]. showed that the minor allele

at rs8019381 (Tallele) was significantly more frequent in cases with AD compared to controls (45% versus 18%, respectively).

Moreover, we have observed genetic overlap between ASDs and various genes, including glutamate receptors, synaptic regulators, a transcription factor and the RNAbinding protein FMR1[25]. This damaging effect may be significant, as abnormalities in white matter integrity could be relevant to the pathophysiology of ASD and schizophrenia[26,27].

Limitations of the Study

Pinning down the NRXN3 gene polymorphisms for ASD has been challenging due to inconsistent replication across studies. Firstly, few studies have focused on these NRXN3 genetic variants and/or their reports do not specifically involve ASD.

Secondly, different studies have included various SNPs that were not in HardyWeinberg equilibrium (HWE) in controls, which could have introduced bias, leading to either false-positive or false-negative associations. Thirdly, we could not increase the number of samples, as doing so would take time.

Conclusion

Few reports have explored genetic variants within NRXN3 and ASD. With rising prevalence, ASD imposes significant economic and emotional burdens on affected families and communities. To our knowledge, this is the first study to explore the potential association of the NRXN3 rs8019381T>C and rs2270964 (C>A) with ASD. Based on our findings, the rs8019381 genetic biomarker clearly has a protective effect among cases with ASD in the Western Saudi community. These results should not be taken at face value, as ASD is a complex, multifactorial disorder and thus, other genes are also involved in its development. This study provides a reference for ASD in the Saudi population and will support future association studies with larger samples.

Declarations Ethical Approval

The study received approval from the Institutional Biomedical Ethics Committee at Medicine College, Umm Al-Qura University (reference #HAPO-02-K-012) (http://bioethics.kacst.edu.sa/About.aspx?lang=en-US). All participants' parents provided informed consent.

Consent for Publication

Written informed consent was obtained from the parents or legal guardians of all study participants for publication of the results.

Availability of Data and Materials

The data sets analysed in this study are available from the corresponding author whenever possible.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Author's Contributions

AHM designed the study, conducted the practical work, analysed the statistical data and wrote the draft and revised the final manuscript.

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