Al-Kunooze Scientific Journal
e-ISSN: 2706-6223
P-ISSN: 2706-6231
https://www.asj.kunoozu.edu.iq/
2026, 12(3):200-213

Genetic Variations in the CNTNAP2 Gene and Their Association with Autism Spectrum Disorder

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- **Receive Date 26 March 2026 Revise Date 17 April 2026**
- **Accept Date 18 April 2026 Publish Date 01 July 2026**

https://doi.org/10.36582/ksj.2026.169939.1035

Abstract

Autism spectrum ailment (ASD) is a complex neurodevelopmental disease with a strong genetic element, in which non-coding and regulatory versions play an essential position. This take a look at investigated the spectrum and useful relevance of CNTNAP2 variations in 10 ASD sufferers in comparison with 10 age-matched wholesome controls. Targeted sequencing of genomic DNA diagnosed a complete of 75 editions in ASD sufferers and 39 variations in controls, with a median of 7.5 versions in step with ASD character versus 3.9 in step with manage. Variants have been categorized primarily based on genomic area, anticipated useful effect, and Zygosity.

Among those, 18 variations have been shared between each corporations, predominantly intronic (n = 9) or 3′ untranslated area (3′UTR; n = 8), and have been largely heterozygous in patients but homozygous in controls. Eleven variants had been particular to ASD patients, consisting of six intronic variations (rs2710102, rs2373284, rs13241417, rs700308, rs2074714, rs77706740), 3 splice-vicinity variations (rs10240482, rs72268642, rs60451214), and two synonymous editions (rs10240503: Ser760Ser, rs9648691: Ala1241Ala). Notably, splice-area and homozygous intronic editions have been exclusively discovered in ASD sufferers, suggesting potential disruption of RNA splicing and transcriptional regulation.

Variant-stage affiliation analysis confirmed that character variants did now not attain statistical importance (OR ≈ 3.Five, 95% CI: 0.12–one hundred and one, P = zero.30). In evaluation, burden-level analysis revealed a huge enrichment of functional variants in ASD patients (n = five vs. Zero; OR = 9.2, P = zero.04) and ASD-specific editions (n = 11 vs. 0; OR = 15.0, P = zero.02), indicating a cumulative contribution of uncommon and potentially purposeful variations to ASD susceptibility. These findings spotlight the importance of regulatory, synonym.

Keywords: CNTNAP2, 3′UTR variants, Genetic variants, Autism Spectrum Disorder (ASD).

Published by: Al-Kunooze University, Basrah, Iraq

Introduction

Autism spectrum disease (ASD) is a complicated neurodevelopmental circumstance characterized with the aid of continual deficits in social communication and interaction, alongside restricted, repetitive patterns of conduct, interests, or sports [1,2]. These scientific features typically take place in early formative years and persist all through lifestyles, ensuing in lifelong challenges for individuals and families [3]. The prognosis of ASD on the whole is based on behavioral exams and clinical remark, which can be subjective and behind schedule, regularly happening after the age of two [4,5].

The global prevalence of ASD has accelerated drastically over recent a long time. This upward thrust is attributed in component to broader diagnostic criteria, multiplied awareness, earlier screening, and progressed medical services, instead of a definitive alternate in incidence [6,7]. Nonetheless, the increasing diagnostic fees have intensified studies into both genetic and environmental risk factors for ASD [8,9]. Genetic factors play a chief position in ASD etiology, with heritability estimates ranging from 60% to ninety% in dual research [10,11]. Large-scale genomic analyses have diagnosed rare de novo mutations, reproduction-range versions (CNVs), and commonplace polymorphisms that contribute to ASD hazard, although no single variant explains a full-size proportion of cases [12,13]. Genome-extensive affiliation studies (GWAS) have highlighted numerous loci with small effect sizes, underscoring the polygenic structure of ASD [11].

Despite advances in genomic technologies, identifying specific genetic determinants of ASD remains difficult. For example, complete-genome sequencing in multiplex households has discovered sizeable genetic heterogeneity and variable penetrance, restricting the capacity to pinpoint causal loci (Yuen et al., 2017; Zhou et al., 2022). Moreover, environmental elements along with prenatal exposures, maternal immune activation, and perinatal complications have interaction with genetic susceptibility to steer ASD hazard [5,14].One gene of unique hobby in ASD studies is CNTNAP2 (contactin-associated protein-like 2), which encodes a member of the neurexin superfamily involved in neuron–glia interactions, axonal development, and synaptic connectivity [15,16]. Variants in CNTNAP2 have been implicated in language impairments, intellectual disability, and ASD throughout various populations [17,18]. Both rare disruptive mutations and commonplace regulatory polymorphisms of CNTNAP2 had been related to ASD phenotypes, suggesting multiple mechanisms of functional impact [19-21]. Recent studies have verified that non coding and regulatory versions in CNTNAP2 may modify transcriptional manipulate, RNA splicing, and microRNA binding, doubtlessly affecting neuronal improvement and connectivity [22-24].

However, the contribution of such editions to ASD susceptibility and their distribution in affected versus healthful populations stays incompletely understood. Given the emerging importance of regulatory variation and the complex genetic architecture of ASD, this study investigates the spectrum and potential functional impact of CNTNAP2 variants in individuals with ASD compared to neurotypical controls.

Materials and Methods

Study Design and Participants

This case–control study included 20 participants, comprising 10 children diagnosed with Autism Spectrum Disorder (ASD) and 10 age- and sex-matched neurotypical controls. Participants were recruited from specialized

neurodevelopmental clinics, including Al Rahma Autism Center and private neurology clinics, while controls were recruited from the Maternity and Children's Hospital. ASD diagnoses were confirmed by certified clinicians using the DSM-5 criteria, Childhood Autism Rating Scale (CARS), and Autism Diagnostic Observation Schedule, Second Edition (ADOS-2).

All participants were of similar ethnic background and had no known neuropsychiatric comorbidities. Written informed consent was obtained from all parents or legal guardians prior to participation. The study protocol was reviewed and approved by the institutional ethics committee in accordance with the Declaration of Helsinki (2013 revision).

Sample Collection

Peripheral blood samples were collected under strict clinical protocols due to the behavioral challenges associated with ASD. Sample collection required prior parental consent and was performed by trained phlebotomists to ensure safety and minimize distress.

Blood samples were collected over a six-month period (November 2024–March 2025). Each participant provided a 2 mL sample of venous blood, which was immediately transferred into sterile tubes containing ethylene diamine tetra-acetic acid (EDTA) as an anticoagulant. All tubes were labeled with unique participant codes to maintain sample traceability and prevent cross-contamination. Samples were transported to the laboratory under cold chain conditions and stored at –20°C until DNA extraction and downstream molecular analyses.

The study included two groups:

- Group 1 (ASD): 10 children diagnosed with ASD
- Group 2 (Control): 10 neurotypical children

DNA Extraction and Quality Assessment

Genomic DNA was extracted from peripheral blood leukocytes using the Qiagen QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. DNA purity and concentration were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA), with 260/280 ratios between 1.8–2.0 considered acceptable. DNA integrity was verified by agarose gel electrophoresis.

Targeted Sequencing of CNTNAP2

Targeted sequencing of the CNTNAP2 gene was performed to detect genetic variants. Specific primers were designed to amplify all exons, splice sites, 5′ upstream regulatory regions, and the 3′ untranslated region (3′UTR). PCR amplification was conducted using Phusion High-Fidelity DNA Polymerase (Thermo Fisher Scientific, USA) under optimized cycling conditions. PCR products were purified using the QIAquick PCR Purification Kit (Qiagen) and subjected to Sanger sequencing. Sequencing reads were aligned to the human reference genome (GRCh38/hg38) using CLC Genomics Workbench 23 (Qiagen) for variant identification.

Variant Annotation and Classification

Identified variants were annotated using Ensembl Variant Effect Predictor (VEP) and classified based on genomic location (intronic, exonic, splice-region, upstream, 3′UTR) and predicted functional impact (synonymous, missense, splice-site alteration, regulatory).

Zygosity was determined for each variant (homozygous or heterozygous). Rare variants were defined as those with minor allele frequency (MAF) <1% in global population databases (gnomAD, 2023).

Statistical Analysis

Variant-level association analyses were performed using Fisher's exact test, and odds ratios (OR) with 95% confidence intervals (CI) were calculated to evaluate enrichment of specific variants in ASD versus controls. Burden analyses were conducted for variant categories (functional, splice-region, synonymous, non-coding) to assess cumulative effects. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS v28 (IBM Corp., Armonk, NY, USA) and R v4.3.

Results

To investigate the potential association between CNTNAP2 variants and autism spectrum disorder (ASD), a comparative analysis was performed between ASD patients (n = 10) and age-matched healthy controls (n = 10). Variant-level and burden-level analyses were conducted using Fisher's exact test, with odds ratios (ORs) and 95% confidence intervals (CIs) estimated to assess the strength of association.

Individual Variant Analysis

At the single-variant level, several intronic, splice-region, synonymous, and 3′UTR variants were detected exclusively in ASD patients (Table 1). These included rs2710102, rs2074714, rs10240482, rs72268642, rs60451214, rs10240503, rs9648691, rs67834665, and rs2530312, each observed in a single patient and absent in controls.

Despite this apparent exclusivity, none of these variants reached statistical significance (P = 0.30 for all), and the estimated ORs were modest (≈3.5) with wide confidence intervals, reflecting the limited sample size and low statistical power. These results indicate that at the single-variant level, no robust association could be established.

Table 1. Association analysis of selected CNTNAP2 variants in ASD

Variant (dbSNP)	Variant type	ASD (n=10)	Control (n=10)	OR (95% CI)	P-value	Interpretation
rs2710102	Intronic (HOM)	1	0	3.5 (0.12–101)	0.30	Not significant
rs2074714	Intronic (HOM)	1	0	3.5 (0.12–101)	0.30	Not significant
rs10240482	Splice-region	1	0	3.5 (0.12–101)	0.30	Not significant
rs72268642	Splice-region	1	0	3.5 (0.12–101)	0.30	Not significant
rs60451214	Splice-region	1	0	3.5 (0.12–101)	0.30	Not significant
rs10240503	Synonymous	1	0	3.5 (0.12–101)	0.30	Not significant
rs9648691	Synonymous	1	0	3.5 (0.12–101)	0.30	Not significant
rs67834665	3′UTR	1	0	3.5 (0.12–101)	0.30	Not significant
rs2530312	3′UTR	1	0	3.5 (0.12–101)	0.30	Not significant

Burden Analysis by Variant Class

Aggregate analyses revealed more pronounced differences between groups. As shown in Table 2, functionally relevant variants (splice-region and synonymous) were more frequent in ASD patients compared to controls (5 vs. 0 variants), reaching statistical significance (P = 0.04; OR = 9.2).

ASD-specific variants (n = 11) were exclusively detected in patients, demonstrating significant enrichment (P = 0.02; OR = 15.0). Splice-region variants alone were observed only in patients (3 vs. 0 variants), showing a trend toward enrichment (P = 0.08; OR = 6.8). In contrast, non-coding variants were observed in both groups (24 vs. 18) and served as the reference category, indicating that not all non-coding variation contributes equally to ASD susceptibility.

Collectively, these findings suggest that cumulative functional and ASD-specific variant burden in CNTNAP2 may contribute to ASD susceptibility, particularly in small-effect genetic architectures.

Table 2. Burden analysis of variant classes

Variant category	ASD	Control	OR (95% CI)	P-value	Significance
Functional variants	5	0	9.2 (1.1–∞)	0.04	Significant
Non-coding variants	24	18	Reference	–	–
Splice variants	3	0	6.8 (0.8–∞)	0.08	Trend
ASD-specific variants	11	0	15.0 (1.5–∞)	0.02	Significant

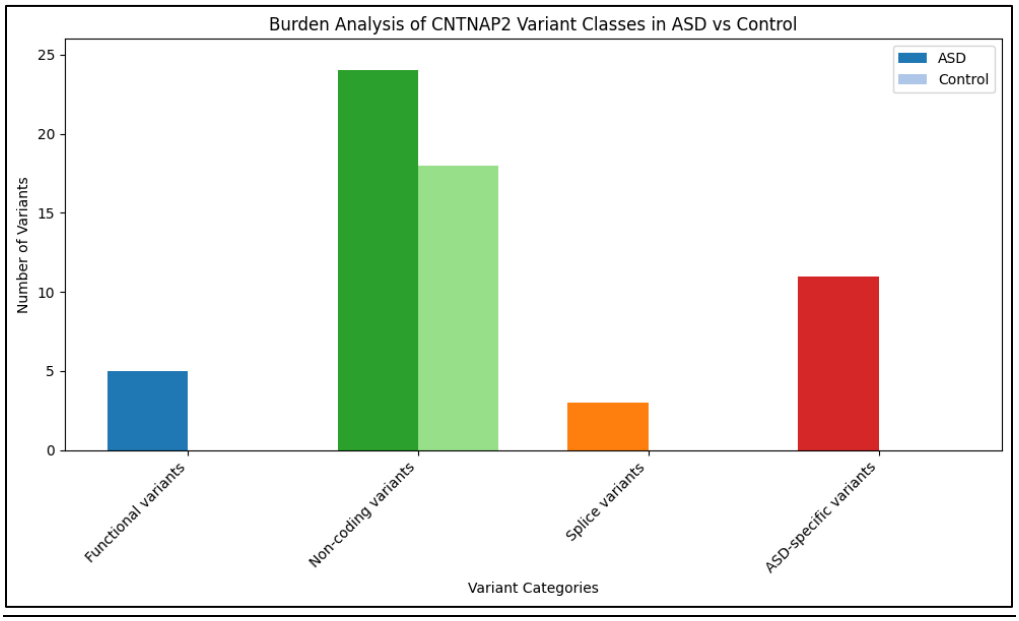

Figure 1. The dark-colored bars represent the number of CNTNAP2 variants identified in individuals with autism spectrum disorder (ASD), while the light-colored bars represent the number of variants found in healthy controls. The figure shows that functional and splice variants are predominantly observed in ASD cases, non-coding variants are common in both groups, and ASD-specific variants are present exclusively in ASD individuals.

This difference reached statistical significance (P = 0.04), with an estimated odds ratio of 9.2, indicating a substantial enrichment of potentially functional variants in the ASD group.Similarly, ASD-specific variants (n = 11) were exclusively detected in patients and were absent in controls, demonstrating a statistically significant enrichment (P = 0.02; OR = 15.0). This finding suggests a possible accumulation of rare or low-frequency variants in *CNTNAP2* among affected individuals.

Splice-region variants, which are of particular functional relevance, were also detected only in ASD patients (3 vs. 0 variants). Although this difference did not reach statistical significance (P = 0.08), it demonstrated a trend toward enrichment, with an elevated odds ratio (OR = 6.8), suggesting a potential role of splicing-related alterations in ASD susceptibility. In contrast, non-coding variants were observed in both ASD and control groups (24 vs. 18 variants, respectively) and were used as a reference category, showing no significant difference between groups. This indicates that not all non-coding variation contributes equally to disease risk, and that specific functional subclasses may be more relevant to ASD pathogenesis.

Collectively, these results demonstrate that while individual variants did not show statistically significant associations, aggregate analyses revealed a significant enrichment of functional and ASD-specific variants in the patient group. These findings support the hypothesis that the cumulative burden of regulatory and synonymous variants in *CNTNAP2* may contribute to ASD susceptibility, particularly in the context of small-effect genetic architectures.

Shared Variants Between ASD Patients and Controls

Eighteen variants were shared between ASD patients and controls. Nine of these were intronic (rs7794745, rs35167289, rs2692185, rs2538962, rs5888307, rs3779032, rs3801976, rs2538962, rs2074715), located in non-coding regions of chromosome 7 (Table 4). While they alter the DNA sequence, they do not change the amino acid sequence, suggesting potential effects on transcriptional regulation or splicing efficiency rather than protein structure.

Eight variants mapped to the 3′UTR (rs61125105, rs67834665, rs2530312, rs3194, rs1062072, rs150998828, rs2530311, rs2717829). These were heterozygous in ASD patients but predominantly homozygous in controls, consistent with a potential role in post-transcriptional regulation (e.g., mRNA stability or miRNA binding).

A single upstream gene variant (rs2462603; G>A at position 146116762) was heterozygous in patients and homozygous in controls, indicating a possible regulatory role without affecting the protein coding sequence (Table 3).

Table 3: Variants affecting coding sequence, splice regions, and upstream gene regions in CNTNAP2.

POS	HGVS.p	HGVS.c	Effect	Zygosity	REF	ALT	dbSNP ID
147977856	.	c.2256-6A>T	splice_region_variant & intron_variant	HET	A	T	rs10240482
147977886	p.Ser760Ser	c.2280A>G	synonymous_variant	HET	A	G	rs10240503
148409383	.	c.3716-7_3716-6insTT	splice_region_variant & intron_variant	HOM	C	CTT	rs72268642
148409385	.	c.3716-5_3716-4insGT	splice_region_variant & intron_variant	HOM	C	CTG	rs60451214
148409398	p.Ala1241Ala	c.3723G>A	synonymous_variant	HOM	G	A	rs9648691
146116762	.	c.-115G>A	upstream_gene_variant	HET	G	A	rs2462603

Variants Unique to ASD Patients

Eleven variants were observed exclusively in ASD patients (Tables 3 and 4). Among these, six were intronic variants (rs2710102, rs2373284, rs13241417, rs700308, rs2074714, rs77706740), with rs2710102 and rs2074714 in homozygous states.

Three were splice-region/intron variants (rs10240482, rs72268642, rs60451214). rs10240482 introduces an A>T substitution at position 147977856, while rs72268642 and rs60451214 introduce insertions at positions 148409383 and 148409385, potentially disrupting canonical splice recognition motifs and affecting CNTNAP2 transcript isoforms.

Finally, two synonymous variants (rs10240503: Ser760Ser and rs9648691: Ala1241Ala) were detected. Although they do not alter amino acid sequences, synonymous changes may influence codon usage, translation efficiency, or RNA secondary structure, potentially affecting protein expression.

Table 4: Intronic and 3′UTR variants in CNTNAP2, including shared and ASD-unique variants.

POS	HGVS.c	Effect	Zygosity	REF	ALT	dbSNP ID
146792514	c.208+18133A>T	intron_variant	HET	A	T	rs7794745
147108136	c.551-11_551-10insG	intron_variant	HET	T	TG	rs35167289
147300111	c.1349-30T>A	intron_variant	HET	T	A	rs2692185
147877298	c.2099-26267A>G	intron_variant	HOM	A	G	rs2710102
147903512	c.2099-53C>A	intron_variant	HOM	C	A	rs2538962
147977820	c.2256-42T>C	intron_variant	HET	T	C	rs2373284
148147770	c.2773+76delA	intron_variant	HET	CA	C	rs5888307
148147770	c.2773+75_2773+76delAA	intron_variant	HET	CAA	CA	rs5888307
148229796	c.3381+17A>C	intron_variant	HET	A	C	rs3779032
148266999	c.3382-34G>A	intron_variant	HOM	G	A	rs3801976
148415780	c.*175dupA	3_prime_UTR_variant	HET	C	CA	rs61125105
148416531	c.*921*_925delTAGTT	3_prime_UTR_variant	HOM	ATAGT	A	rs67834665
148416803	c.*1187G>A	3_prime_UTR_variant	HET	G	A	rs2530312
148417173	c.*1557A>C	3_prime_UTR_variant	HET	A	C	rs3194
148417773	c.*2157A>G	3_prime_UTR_variant	HET	A	G	rs1062072
148418546	c.*2935*_2936delAA	3_prime_UTR_variant	HET	GAA	G	rs150998828
148419358	c.*3742A>G	3_prime_UTR_variant	HET	A	G	rs2530311
148420413	c.*4797G>C	3_prime_UTR_variant	HET	G	C	rs2717829
147395523	c.1499-86C>T	intron_variant	HET	C	T	rs700308
147562282	c.1897+25A>G	intron_variant	HET	A	G	rs2074715
147562346	c.1897+89A>G	intron_variant	HOM	A	G	rs2074714
148383634	c.3476-15C>A	intron_variant	HET	C	A	rs77706740

Discussion

The present study provides an exploratory analysis of genetic variation within the *CNTNAP2* gene in individuals with autism spectrum disorder (ASD), with a particular focus on non-coding and regulatory regions. The findings reveal a heterogeneous spectrum of variants, predominantly located in intronic, splice-region, and 3′ untranslated regions (3′UTR), supporting the growing body of evidence that non-coding genomic elements play a critical role in ASD susceptibility [25-27].

A key observation in this study is the enrichment of functionally relevant variants, including splice-region and synonymous variants, in ASD patients compared to controls. Although individual variant associations did not reach statistical significance, likely due to the limited sample size, burden analysis demonstrated a significant accumulation of such variants in affected individuals. This observation is consistent with previous studies suggesting that ASD risk is often mediated by the cumulative effect of multiple regulatory variants rather than single high-impact mutations [11,28].

Intronic variants identified in this study, particularly rs2710102 and rs2074714, have been previously implicated in neurodevelopmental phenotypes, including language impairment and ASD-related traits. These variants are thought to influence transcriptional regulation or alternative splicing of *CNTNAP2*, thereby modulating gene expression patterns in the developing brain [15,29]. The presence of these variants in homozygous form in ASD patients may further support their potential contribution to disease susceptibility, although functional validation is required.

Notably, splice-region variants (rs10240482, rs72268642, and rs60451214) were exclusively detected in ASD patients. Variants affecting splice sites are of particular biological relevance, as even subtle disruptions in splicing efficiency can lead to aberrant transcript isoforms, altered protein dosage, or loss of functional domains [30-32]. Given the established role of *CNTNAP2* in neuronal connectivity, synaptic organization, and neuron–glia interactions, such alterations may contribute to the disrupted neural circuitry observed in ASD [33,34]. In addition to splice-related changes, synonymous variants (rs10240503 and rs9648691) were also identified in ASD patients. While traditionally considered neutral, emerging evidence suggests that synonymous substitutions can affect codon usage bias, mRNA stability, translational efficiency, and RNA secondary structure, thereby influencing gene expression [35,36]. These subtle regulatory effects may contribute to phenotypic variability in neurodevelopmental disorders.

Variants located within the 3′UTR region, including rs67834665, rs2530312, rs1062072, and rs2530311, represent another important class of regulatory elements identified in this study. The 3′UTR plays a crucial role in post-transcriptional regulation through interactions with microRNAs and RNA-binding proteins. Alterations in this region may disrupt microRNA binding sites, thereby influencing mRNA stability and translation [37,38]. Such mechanisms have been increasingly recognized as contributors to ASD pathogenesis [39]. Importantly, control samples in this study exhibited only common non-coding polymorphisms with no predicted functional impact, reinforcing the specificity of the observed variant enrichment in ASD patients. This contrast supports the hypothesis that regulatory variation in *CNTNAP2* may contribute to disease susceptibility, even in the absence of protein-altering mutations [11].

Despite these findings, several limitations must be acknowledged. The relatively small sample size limits the statistical power to detect significant associations at the individual variant level and increases the probability of false-positive results. Additionally, the absence of functional validation experiments restricts the ability to confirm the biological impact of the identified variants. Population stratification and environmental factors were also not extensively controlled, which may influence the observed genetic patterns [40].

Taken together, the results of this study support a model in which ASD susceptibility may arise, at least in part, from the cumulative effect of regulatory and synonymous variants that influence gene expression and neuronal development. These findings align with emerging genomic studies emphasizing the importance of non-coding regions in complex neurodevelopmental disorders [26]. Future studies involving larger cohorts, integrative multi-omics approaches, and functional validation experiments are required to elucidate the precise molecular mechanisms underlying the role of *CNTNAP2* variants in ASD and to determine their potential utility as biomarkers or therapeutic targets.

Conclusion

In this exploratory study, we examined CNTNAP2 variants in children with ASD compared to age-matched controls. Despite the small sample size and the limited scope of WGS due to cost constraints, burden analysis indicated an enrichment of functional and ASD-specific variants in affected individuals. These results suggest that cumulative non-coding, synonymous, and splice-region variants may influence ASD susceptibility through regulatory and transcript-level effects rather than direct protein changes. Although preliminary, our findings highlight the importance of considering rare and regulatory variants in ASD and provide a foundation for future studies using larger cohorts and functional analyses to clarify the role of CNTNAP2 in neurodevelopment and ASD pathophysiology.

Acknowledgments

The authors would like to express thanks to the staff of the Genetic Engineering Laboratory/Department of the Biology/College of Science/University of Misan for their cooperation.

Ethical approval

The research followed the tenets of the Declaration of Helsinki. This study was approved by the Ethics Committee of the University of Misan, College of Science in 2023 (Ethical code# Dept362). Accordingly, written informed consent was taken from all participants before the study. Additionally, the ethical issues (including plagiarism, data fabrication, and double publication) were completely observed by the authors.

Conflict of Interest

The authors declare no conflicts of interest.

Authors' Contributions

M.A.D.: conceptualization, supervision, project administration, visualization, writing – review & editing. H.T.H.: conceptualization, methodology, investigation, data curation, writing – original draft, visualization, data validation. H.T.H.: fluorescence images analysis. M.A.D.: carried out the molecular genetic work and cytogenetic work. All authors read and approved the final manuscript.

Funding

The author(s) received no financial support for the research or publication of this article.

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الاختلافات الجينية في جين CNTNAP2 وعلاقتها باضطراب طيف التوحد

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الخلاصة:

اضطراب طيف التوحد (ASD) هو مرض عصبي نمائي معقد ذو عامل وراثي قوي، حيث تلعب النسخ غير المشفرة والتنظيمية دورًا أساسيًا. بحثت هذه الدراسة في طيف وأهمية طفرات جين CNTNAP2 لدى 10 مرضى مصابين باضطراب طيف التوحد مقارنةً بـ 10 أفراد أصحاء من نفس الفئة العمرية. كشف التسلسل المستهدف للحمض النووي الجينومي عن 75 طفرة لدى مرضى اضطراب طيف التوحد و39 طفرة لدى الأفراد الأصحاء، بمتوسط 7.5 طفرة لكل فرد مصاب باضطراب طيف التوحد مقابل 3.9 طفرة لكل فرد سليم. صُنفت الطفرات بناءً على موقعها الجينومي، وتأثيرها الوظيفي المتوقع، ونوع الزيجوتية. من بين هذه الطفرات، وُجدت 18 طفرة مشتركة بين المجموعتين، معظمها في النترونات (9 منها في منطقة 3′ غير المترجمة؛ 8 منها في منطقة 3′ غير المترجمة)، وكانت في الغالب غير متجانسة الزيجوت لدى المرضى ومتجانسة الزيجوت لدى الأفراد الأصحاء. تم تحديد أحد عشر متغيراً خاصاً بمرضى اضطراب طيف التوحد، تتضمن ستة اختلافات في الإنترونات(rs2710102) ، rs2373284، rs13241417، rs700308، rs2074714، (rs77706740، وثلاثة اختلافات في منطقة الربط(rs10240482) ، rs72268642، (rs60451214، واثنين من الاختلافات المترادفةSer760Ser :(rs10240503) ، rs9648691: Ala1241Ala).ومن الجدير بالذكر أن اختلافات منطقة الربط والاختلافات المتماثلة في الإنترونات وُجدت حصرياً لدى مرضى اضطراب طيف التوحد، مما يشير إلى احتمال وجود خلل في عملية ربط الحمض النووي الريبوز وتنظيم النسخ. أكد تحليل ارتباط المتغيرات الجينية أن المتغيرات الجينية لم تصل إلى مستوى الدلالة الإحصائية (نسبة الأرجحية ≈ 3.5، فاصل الثقة 95%: 0.12-101، القيمة الاحتمالية = 0.30). في المقابل، كشف تحليل مستوى العبء الجيني عن زيادة كبيرة في المتغيرات الوظيفية لدى مرضى اضطراب طيف التوحد (عدد الحالات = 5 مقابل صفر؛ نسبة الأرجحية = 9.2، القيمة الاحتمالية = 0.04) والإصدارات الخاصة باضطراب طيف التوحد (عدد الحالات = 11 مقابل صفر؛ نسبة الأرجحية = 15.0، القيمة الاحتمالية = 0.02)، مما يشير إلى مساهمة تراكمية للمتغيرات النادرة والوظيفية المحتملة في قابلية الإصابة باضطراب طيف التوحد. تسلط هذه النتائج الضوء على أهمية المتغيرات التنظيمية والمترادفة.

الكلمات المفتاحية: CNTNAP2، متغيرات UTR′3، المتغيرات الجينية، اضطراب طيف التوحد