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Investigation of *Pogz* Gene Variants in Non-Syndromic Autism Spectrum Disorder

Jülide TOZKIR[1], Gökberk YILDIRIM[2], Selma DEMİR[3], Orkide PALABIYIK[1], Işık GÖRKER[4], Hakan GÜRKAN[3]

[1]Trakya University Vocational School of Health Services, Edirne, Turkey
[2]Atlascro Clinical Research Coordinator, Edirne, Turkey
[3]Trakya University Faculty of Medicine, Department of Medical Genetics, Edirne, Turkey
[4]Trakya University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Edirne, Turkey

ABSTRACT

Introduction: Genetic factors play an important role in the etiopathogenesis of autism spectrum disorder (ASD). The Pogo Transposable Element with ZNF Domain protein (*POGZ*) gene (MIM*614787) has been reported to be one of the most frequently mutated genes associated with ASD. This study aims to analyze the exonic regions of the *POGZ* gene in individuals diagnosed with non-syndromic ASD.

Methods: Fifty-one non-syndromic cases diagnosed with ASD according to the DSM-V diagnostic criteria, aged 2–18 years, were included in the study. The healthy control group consisted of 50 children of similar age groups without neurodevelopmental problems. Amplicons produced using deep intronic primers covering the mRNA-encoded regions of the *POGZ* gene from at least 50 base pairs were sequenced by Next Generation Sequencing Analysis.

Results: No pathogenic or likely pathogenic variants reported in open-access databases (ClinVar, HGMD, etc.) were detected in the case group. In the ASD and healthy control groups, rs113396244, rs11204811, rs779479223, rs772352054, rs3831142, rs112072925, rs227453 and rs142860188 variants were determined. The rs3831142, rs112072925, rs2274535, rs142860188 variants were found statistically significant in the ASD group. The distribution of the cases with detected single nucleotide polymorphisms (SNPs) according to gender was not statistically significant.

Conclusion: The variants identified as statistically significant within the patient group are situated in regions that encompass both the HP1-ZNF and DDE domains of the protein. Given the crucial role that the DDE domain plays, particularly in fetal brain development and neurogenesis, these four variants may potentially possess modifying and/or predisposing effects in the context of ASD.

Keywords: Autism spectrum disorder, next generation sequencing, *POGZ*

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INTRODUCTION

Autism spectrum disorder (ASD) [MIM209850] is a severe lifelong neurodevelopmental disorder characterised by limited or absent verbal communication, lack of responsiveness, limited social interaction and stereotyped and ritualised repetitive behaviour patterns (1,2). ASD is both genetically and phenotypically heterogeneous and affects around 1% of children. While the prevalence of ASD used to be 1/1000 in previous years, current reports indicate a prevalence of approximately 1/50. ASD is four times more common and has an earlier onset in males than females, with a mean age at diagnosis of four years (3–5). Although definitive ASD treatment is not yet possible, studies are being conducted in the field of special education to alleviate other symptoms accompanying the disorder and enhance the individual's quality of life. To enhance treatment effectiveness, it is imperative to diagnose ASD at the earliest opportunity and establish the individual's tailored educational plan expeditiously (6).

Highlights

- **The *POGZ* gene is one of the most frequently mutated genes in ASD.**
- **Variants rs3831142, rs112072925, rs2274535, rs142860188 in *POGZ* are different in ASD.**
- **The variants identified in *POGZ* are in the sequence encoding functional regions.**

Genetic factors play a crucial role in the etiopathogenesis of ASD (7). While multiple genetic factors interact with one another, both prenatal and postnatal factors contribute to the complexity of the etiopathogenesis (1). The estimated heritability of ASD presents complex risk architecture due to de novo mutations as well as epigenetic and environmental factors (8). Despite the remarkable heterogeneity of ASD, most genetic variants linked to the disorder are found in genes evaluated within specific functional networks, including synaptic function, neuronal activity, neuronal cell adhesion, Wnt signalling during neurogenesis and chromatin remodelling (9–11). Previous studies have highlighted a correlation between pogo transposable element with ZNF domain

Correspondence Address: Jülide Tozkır, Trakya Üniversitesi Sağlık Hizmetleri MYO, Balkan Yerleşkesi, Merkez, Edirne, Turkey • **E-mail:** julideduymaz@trakya.edu.tr
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protein (POGZ) (MIM*614787) and ASD (12–17). Several mutations in POGZ have been detected in diverse groups of cases with ASD, intellectual disability, neurodevelopmental disorders or schizophrenia (12,13,16–20). In a meta-analysis of studies involving families impacted by ASD and developmental delay (DD), de novo microdeletions or single nucleotide polymorphisms (SNPs) of POGZ were identified as a potential risk gene for neurodevelopmental conditions (13,14,16,21).

The POGZ gene is located on chromosome 1q21. The POGZ protein, which has not been extensively studied, contains a zinc finger cluster, a centromere protein (CENP)-B-like DNA binding domain, and a DDE domain derived from a pogo-like DNA transposon. One of the functional domains is between 791–850 amino acids within the zinc-finger cluster, which binds to the human heterochromatin protein 1 (HP1). The HP1-binding zinc-finger-like (HPZ) domain plays a crucial role in POGZ's interaction with heterochromatin. The binding of the POGZ protein to chromatin alters how tightly regions of DNA are packaged (22,23). POGZ is therefore part of the processes that change chromatin structure. The transposase-derived DDE domain, spanning amino acids 1117–1323, constitutes another functional segment of the protein, considered to actively contribute to foetal brain development and neurogenesis (24). When the expression of the POGZ gene is silenced in the human cell, proper cell growth and division are damaged. The regulation of gene expression in chromatin due to the POGZ protein is important for brain development. Many anomalies have been reported, such as lack of motor development and coordination in individuals with POGZ mutations and hypothalamus-pituitary structural lesions in paediatric individuals (15,21,24). Although the role of POGZ protein in the physiological and pathological context is not fully understood, POGZ knockout mice show abnormal brain development, smaller absolute brain, altered neurogenesis in embryo and adult mice, growth delay as well as abnormal motor, cognitive and social behaviour (25).

The POGZ gene is widely cited as one of the most commonly mutated genes in ASD (14,17,18). De novo mutations in POGZ are believed to impede the DNA binding capabilities of the protein, subsequently affecting gene expression (26,27). In the present study, we aimed to scrutinise the exonic regions of the POGZ gene in cases diagnosed with ASD by utilising the next generation sequencing (NGS), with the intention of examining the potential impact of any variants on the phenotype.

METHOD

The research involved 51 paediatric cases aged 2 to 18 who were diagnosed with ASD according to DSM-V diagnostic criteria among. The cases had applied to Trakya University Health Research and Application Centre Child and Adolescent Mental Health outpatient clinic with a prediagnosis of ASD. The healthy control group consisted of 50 children of similar age group without neurodevelopmental problems. Among these cases, 14 were between the ages of 1–3 years and 37 were between the ages of 4–18 years. Fourteen cases in the 1–3 age range were evaluated as autism risk group with the Modified Checklist for Autism in Toddlers (M-CHAT). The M-CHAT was developed by Robins and colleagues in 2001 (28). Its validity study in Türkiye was conducted by Yikgec in 2005 (29). The test consists of twenty-three questions, all of which parents answer with a "Yes" or "No". Thirty-seven cases between the ages of 4–18 years were evaluated with the Childhood Autism Rating Scale (CARS). The CARS is a behavioral evaluation scale with 15 parts developed by Schopler and colleagues (30). It has the validity study in Turkish and is widely used to distinguish the autistic children from other children with developmental delay (31). For each item: 1 indicates not autistic; 2 mild autistic; 3 moderate autistic; and 4 indicates severe autistic. The total score range is between 15 and 60. In the general sum, scores like 15–29 means "not autistic", 30–36 mild-moderate autistic, and 37–60 indicates severe autism. The results of chromosome analysis, Fragile X syndrome-related FMR1 gene analysis and comparative genomic hybridisation (array CGH) analysis of the cases included in the study were normal.

Table 1. Primers designed for *POGZ* Exon (s) and annealing temperatures

Exon (s)		Primer	Annealing Temperature
2	Primer F	TTGGAAATGGAGGAAGGCTAGAGGATATG	57°C
	Primer R	GGATGAGGAAACTGAGGTTTTCACAGAC	
3	Primer F	TAGGAGGAGAAATCACATGAACAGTTGG	57°C
	Primer R	GAAACACCAGTACCGAGTCAGCA	
4	Primer F	GGTCACTTAAATCATGAGAGTCAGGGTG	57°C
	Primer R	GTCATCTTCCTTGTCTCCCAAAGGTC	
5	Primer F	CCCCACCCCCACTTCTGTTCATTTA	55°C
	Primer R	TGTCTCCTGGCTCAACTGTAGACAATTC	
6,7	Primer F	GCTGCCCAGGTTATTTTGTCAACAT	55°C
	Primer R	CTCAACCTGAAGATCTCTCTACCAAATCC	
8	Primer F	TGGTAGCTGGGCTGGATTTGATCTGT	57°C
	Primer R	CATTTTAGAGCCCCTGCTTACAAGCTTCC	
9,10	Primer F	ACCTAAGACAGGCAGGAGGGAGAAAT	57°C
	Primer R	CGCCCCTAACAATTCAGGATCTAACACT	
11,12	Primer F	TGGTAAGACAGGAGGATGCTGAATTAGG	57°C
	Primer R	AGCCTTACTAGGCACCCAGAATAGC	
13,14,15	Primer F	CAAGTCAGGAAAGGATGATTTGAGAACTT	55°C
	Primer R	TACTTGAATAGCAAGGCCCTATGAAATTAG	
16,17	Primer F	GTATTAGGTGGGAGCTTGTTAGAAATGCTG	57°C
	Primer R	TCAACAGTGAATGAGTGAGGCCAAGTAG	
18,19	Primer F	GTTGAGATGTGCTGGACCTAATTAGAAACC	55°C
	Primer R	AGCTCCTTGGCTCAGACGTGATTACTATT	

POGZ: Pogo transposable element with ZNF domain protein.

Table 2. Distribution of variants identified in the *POGZ* gene in healthy control and ASD groups

POGZ **Gene Variants**	**Healthy Control n/N (%)**	**ASD n/N (%)**	**p**	**OR (95% CI)**
rs113396244	45/48 (93.8)	50/51 (98)	0.279	3.33 (0.33–33.2)
rs11204811	47/50 (94)	44/51 (86.3)	0.194	0.4 (0.09–1.64)
rs779479223	2/50 (4)	0/51	0.149	0.96 (0.9–1.01)
rs772352054	46/50 (92)	45/51 (88.2)	0.527	0.65 (0.17–2.46)
rs3831142	28/50 (56)	48/51 (94.1)	0.0001	12.5 (3.45–45.81)
rs112072925	24/50 (48)	47/51 (92.2)	0.0001	12.73 (3.98–40.6)
rs2274535	0/50	8/51 (15.7)	0.004	1.186 (1.05–1.33)
rs142860188	0/50	5/51 (9.8)	0.023	1.10 (1.01–1.21)

ASD: Autism Spectrum Disorders; POGZ: Pogo transposable element with ZNF domain protein.

Table 3. Genotypic distribution of variants significantly differentiated in the OSB group

POGZ **gene variants and genotypes**	**Healthy control n/N (%)**	**ASD n/N (%)**	**p**	**OR (95% CI)**
rs3831142				
AA	22 (44)	3 (5.9)	0.0001	12.5 (3.45–45.81)
A/-	27 (54)	20 (39.2)		
-/-	1 (2)	28 (54.9)		
Total	28/50 (56)	48/51 (94.1)		
rs112072925				
AA	26 (52)	4 (7.9)	0.0001	12.73 (3.98–40.6)
A/-	24 (48)	12 (23.5)		
-/-	0	35 (68.6)		
Total	24/50 (48)	47/51 (92.2)		
rs2274535				
GG	50	43 (84.3)	0.004	1.186 (1.05–1.33)
GA	0	5 (9.8)		
AA	0	3 (5.9)		
Total	0/50	8/51 (15.7)		
rs142860188				
AA	50	46 (90.2)	0.023	1.10 (1.01–1.21)
AC	0	3 (5.9)		
CC	0	2 (3.9)		
Total	0/50	5/51 (9.8)		

ASD: Autism Spectrum Disorders; POGZ: Pogo transposable element with ZNF domain protein.

Ethical approval of the study was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee with the approval number 2016-185. The study followed the guidelines set forth in the Helsinki Declaration II (32). The informed consent forms of all the cases who participated in the study were signed by their parents.

Genomic DNA (gDNA) was isolated from peripheral blood samples using the protocol provided by the Qiagen kit on a QIAGEN EZ1 Advanced XL (Serial No: L122A1010) isolation device. The concentrations of the isolated gDNAs were measured at 260nm and 280nm using NanoDrop (ThermoScientific, USA) and samples with a 260/280 ratio between 1.8–2 were included in the study. Deep intronic primers encompassing at least 50 base pairs of the mRNA-encoded regions of the POGZ gene were designed using the NCBI primer blast tool (Table 1). Primer design was performed in accordance with the sequence NM_015100.4, the longest transcript in the databases. Amplicons produced by polymerase chain reaction were sequenced by NGS. The obtained data were stored in. Binary Alignment Map (BAM) BAM Index (BAI) format for analysis, which was performed with the Integrative Genomics Viewer (IGV) 2.3.91. The American College of Medical Genetics 2015 (ACMG 2015) criteria were used to evaluate the variations in terms of pathogenicity.

Statistical Analysis

The statistical comparison of the obtained data between the groups was evaluated by using chi-square test in IBM Statistical Package for Social Sciences (SPSS) version 22 programme. The results were accepted as significant when the P value was less than 0.05.

RESULTS

Amongst our cases, 31 have been identified as severely autistic, and 6 as mildly autistic. In 46 cases, mental retardation comorbidity was determined and 3 cases were diagnosed with severe mental retardation, 33 cases with moderate mental retardation and 10 cases with mild mental retardation. In 5 cases, intelligence level was found to be within normal limits. Of the 51 cases diagnosed with ASD, 37 (72.5%) were male and 14 (27.5%) were female; 20 (40%) of the healthy control group were male and 30 (60%) were female.

As a result of the bioinformatics analysis, no pathogenic, likely pathogenic or novel variants present in the open access databases (ClinVar, HGMD, etc.) were detected in the case group. In the study group, which included 51 cases and 50 healthy controls, SNPs, such as rs113396244, rs11204811, rs779479223, rs772352054, rs3831142, rs112072925, rs227453 and rs142860188, as well as indel variants, were identified. The distribution

of the detected SNPs and indel variations is provided in Table 2 for both the case and healthy control groups. It was not possible to sequence the intronic region that contains the rs113396244 SNP at the desired depth in two healthy control group samples; it was, thus, not included in the planned statistical analysis. Therefore, the rs113396244 SNP was compared between 48 healthy controls and 51 ASD cases in a statistical analysis. The rs3831142, rs112072925, rs2274535 and rs142860188 variants showed significant statistical differences in the ASD group. Table 3 provides the genotypic distributions of these variants. There was no statistically significant difference in the distribution of the identified SNPs and indel variants based on gender.

DISCUSSION

ASD is highly hereditary, and since clinical findings are used in the diagnostic process of ASD, and the degree of these findings varies between cases, it is important to elucidate the genetic basis of the disorder to enable early diagnosis and to reveal parameters that may change treatment options. Variants in hundreds of different genes associated with ASD have been reported. These variants cover a wide spectrum of mutations ranging from single base pair changes (SNVs) to microdeletions or microduplications (copy number variants [CNVs]) (33).

POGZ is classified as one of the ASD risk genes that exhibit high reliability in all exome sequencing studies that screened large cohorts of cases (14,16,17,21). The HGMD Professional 2023.2 database lists 173 POGZ-related mutations; 163 are in the coding region, and 10 are in the non-coding region. Among the 173 mutations, 89 were identified as missense-nonsense, 8 splicing, 46 small deletions and 23 small insertions/duplications (http://www.hgmd.org). In the literature, POGZ was identified as a possible gene linked to ASD through two distinct family studies conducted by Iossifov et al., in which cases with ASD were compared to their healthy siblings (13,16).

DNA packaging by chromatin regulators such as POGZ is a dynamic process that determines the transcriptional potential of a cell. Genetic variants that can disrupt the function of chromatin regulatory genes have been reported to be linked to neurodevelopmental disorders, including ASD and developmental delay. ASD-associated variants in the DNA binding domain of POGZ have been shown to disrupt POGZ-DNA binding dynamics (27). Homozygous deletion of POGZ is embryonically lethal in mice, whereas heterozygous and conditional knockout mice have been reported to exhibit cortical neuron development and social and anxiety-related avoidance behaviours (14,15,21,34). Considering the ASD-POGZ-related data reported in the literature, in our study, we designed deep intronic primers to detect possible variants in exonic, exon-intron (splicing) and deep intronic regions of POGZ and analysed POGZ in the case and control groups through the NGS method. As a result of bioinformatic analysis, rs113396244, rs11204811, rs779479223, rs772352054, rs3831142, rs112072925, rs227453 and rs142860188 single nucleotide polymorphisms (SNPs) and indel variants were detected.

Stessman et al. (17) investigated POGZ-related variants in cases with intellectual disability and ASD and observed that the clinical diagnosis of cases with mutations was ID/DD and ASD was a comorbidity in these cases. White et al. (35) reported that POGZ-related truncation mutations caused syndromic intellectual disability. In our study, we did not detect any pathogenic (P), likely pathogenic (LP) and variants of uncertain clinical significance (VUS) in POGZ. We speculate that this result may be related to the fact that our case group did not include cases diagnosed with ID/DD and/or syndromic ASD, who were diagnosed with ASD only according to DSMV criteria.

The rs3831142, rs112072925, rs2274535 and rs142860188 variants, which were found to be statistically significant in the case group, are located within the regions covering the HPZ and DDE domains of the protein. In the literature, phenotype-genotype relationship between rs3831142 and rs142860188 variants and intellectual disability-microcephaly-strabismus-behavioral anomaly syndrome was investigated but no significant relationship was found (36,37). There is no data on the biological effects that other variants (rs112072925 and rs2274535) may cause and/or their frequency in other diseases. Considering that especially the DDE domain plays a role in foetal brain development and neurogenesis, these four variants may have modifying and/or predisposing effects in ASD (23).

Zhao et al. (24) examined the rare missense variants of POGZ in 2926 individuals with ASD and identified 66 exonic, inherited and non-de novo pathogenic variants. It is possible that the absence of any ASD-linked pathogenic variant in POGZ within our study could be attributed to the small sample size. If we conduct further studies by increasing the sample size in our population, it is likely that the POGZ-associated P and LP variants could be identified.

Yalçintepe et al. investigated FOXP2, GRIN2B, KATNAL2 and GABRA4 genes, which are reported to have a significant association with ASD in the literature, in 96 cases and reported different intronic variants of unknown clinical significance in 50 cases (38).

Görker et al. reported 2 pathogenic and 7 variants of undetermined significance (VUS) in their study investigating CNVs in the genome in 53 cases with ASD (39).

The main reason why our study results differ from the results of other studies reported in the literature may be related to the fact that our case group consisted of cases with comorbid and/or non-syndromic ASD. Ethnic differences between populations, different inclusion criteria and different molecular genetic analysis methods may be other limiting factors. The impact of the rs3831142, rs112072925, rs2274535 and rs142860188 phenotype variations, which displayed statistical significance amongst the case group in our research, requires further functional investigations.

Ethics Committee Approval: Ethical approval of the study was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee with the approval number 2016-185.

Informed Consent: The informed consent forms of all the cases who participated in the study were signed by their parents.

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REFERENCES

1. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;392(10146):508–520. [Crossref]
2. Emre O, Eshraghi RS, Danesh A, Mittal R, Eshraghi AA. Central auditory processing disorders in individuals with autism spectrum disorders. Balkan Med J. 2018;35(5):367–372. [Crossref]
3. National Academies of Sciences, Engineering, and Medicine; Institute of Medicine; Board on the Health of Select Populations; Board on Children, Youth, and Families; Committee to Evaluate the Supplemental Security Income Disability Program for Children with Mental Disorders; Boat TF and Wu JT, editors. Mental Disorders and Disabilities Among Low-Income Children. Washington, DC: The National Academies Press; 2015. [Crossref]

4. Hyman, S. L., Levy, S. E., Myers, S. M. Council On Children With Disabilities, Section On Developmental And Behavioral Pediatrics. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics 2020;145:1. [Crossref]
5. Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. Neurosci Bull. 2017;33(2):183–193. [Crossref]
6. Genovese A, Butler MG. Clinical assessment, genetics, and treatment approaches in autism spectrum disorder (ASD). Int J Mol Sci. 2020;21(13):4726. [Crossref]
7. Manoli DS, State MW. Autism spectrum disorder genetics and the search for pathological mechanisms. Am J Psychiatry. 2021;178(1):30–38. [Crossref]
8. Du X, Gao X, Liu X, Shen L, Wang K, Fan Y, et al. Genetic diagnostic evaluation of trio-based whole exome sequencing among children with diagnosed or suspected autism spectrum disorder. Front Genet. 2018;9:594. [Crossref]
9. Kumar S, Reynolds K, Ji Y, Gu R, Rai S, Zhou CJ. Impaired neurodevelopmental pathways in autism spectrum disorder: a review of signaling mechanisms and crosstalk. J Neurodev Disord. 2019;11(1):10. [Crossref]
10. Murtaza N, Cheng AA, Brown CO, Meka DP, Hong S, Uy JA, et al. Neuron-specific protein network mapping of autism risk genes identifies shared biological mechanisms and disease-relevant pathologies. Cell Rep. 2022;41(8):111678. [Crossref]
11. Lasser M, Sun N, Xu Y, Wang S, Drake S, Law K, et al. Pleiotropy of autism-associated chromatin regulators. Development. 2023;150(14). [Crossref]
12. Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature. 2012;485(7397):242–245. [Crossref]
13. Iossifov I, Ronemus M, Levy D, Wang Z, Hakker I, Rosenbaum J, et al. De novo gene disruptions in children on the autistic spectrum. Neuron. 2012;74(2):285–299. [Crossref]
14. Sanders SJ, He X, Willsey AJ, Ercan-Sencicek AG, Samocha KE, Cicek AE, et al. Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. Neuron. 2015;87(6):1215–1233. [Crossref]
15. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature. 2014;515(7526):209–215. [Crossref]
16. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, Levy D, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014;515(7526):216–221. [Crossref]
17. Stessman HAF, Willemsen MH, Fenckova M, Penn O, Hoischen A, Xiong B, et al. Disruption of POGZ is associated with intellectual disability and autism spectrum disorders. Am J Hum Genet. 2016;98(3):541–552. [Crossref]
18. Bruno LP, Doddato G, Valentino F, Baldassarri M, Tita R, Fallerini C, et al. New candidates for autism/intellectual disability identified by whole-exome sequencing. Int J Mol Sci. 2021;22(24). [Crossref]
19. Nagy D, Verheyen S, Wigby KM, Borovikov A, Sharkov A, Slegesky V, et al. Genotype-phenotype comparison in POGZ-related neurodevelopmental disorders by using clinical scoring. Genes (Basel). 2022;13(1):154. [Crossref]
20. Balakrishna T, Curtis D. Assessment of potential clinical role for exome sequencing in schizophrenia. Schizophr Bull. 2020;46(2):328–335. [Crossref]
21. Deciphering Developmental Disorders S. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519(7542):223–228. [Crossref]
22. Nozawa RS, Nagao K, Masuda HT, Iwasaki O, Hirota T, Nozaki N, et al. Human POGZ modulates dissociation of HP1alpha from mitotic chromosome arms through Aurora B activation. Nat Cell Biol. 2010;12(7):719–727. [Crossref]
23. Bartholomeeusen K, Christ F, Hendrix J, Rain JC, Emiliani S, Benarous R, et al. Lens epithelium-derived growth factor/p75 interacts with the transposase-derived DDE domain of PogZ. J Biol Chem. 2009;284(17):11467–11477. [Crossref]
24. Zhao W, Tan J, Zhu T, Ou J, Li Y, Shen L, et al. Rare inherited missense variants of POGZ associate with autism risk and disrupt neuronal development. J Genet Genomics. 2019;46(5):247–257. [Crossref]
25. Suliman-Lavie R, Title B, Cohen Y, Hamada N, Tal M, Tal N, et al. Pogz deficiency leads to transcription dysregulation and impaired cerebellar activity underlying autism-like behavior in mice. Nat Commun. 2020;11(1):5836. [Crossref]
26. Matsumura K, Nakazawa T, Nagayasu K, Gotoda-Nishimura N, Kasai A, Hayata-Takano A, et al. De novo POGZ mutations in sporadic autism disrupt the DNA-binding activity of POGZ. J Mol Psychiatry. 2016;4:1. [Crossref]
27. Matsumura K, Seiriki K, Okada S, Nagase M, Ayabe S, Yamada I, et al. Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes. Nat Commun. 2020;11(1):859. [Crossref]
28. Robins DL, Fein D, Barton ML, Green JA. The modified checklist for autism in toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. J Autism Dev Disord. 2001;31:131–144. [Crossref]
29. Yıkgeç A. A validity study of the modified checklist for autism in toddlers (M-CHAT) on a Turkish sample. Yayınlanmamış Yüksek Lisans Tezi. İstanbul: Boğaziçi Üniversitesi Sosyal Bilimler Enstitüsü; 2005.
30. Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: childhood autism rating scale (CARS). J Autism Dev Disord. 1980;10(1):91–103. [Crossref]
31. Sucuoğlu B, Öktem F, Akkök F, Gökler B. Otistik çocukların değerlendirilmesinde kullanılan ölçeklere ilişkin bir çalışma. 3P Psikiyatri Psikoloji Psikofarmakoloji Dergisi 1996;4(2):116-121.
32. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014;81(3):14–8.
33. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI Jr, Hallmayer JF. Autism genetics: opportunities and challenges for clinical translation. Nat Rev Genet. 2017;18(6):362–376. [Crossref]
34. Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An J-Y, et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell. 2020;180(3):568–584. e23. [Crossref]
35. White J, Beck CR, Harel T, Posey JE, Jhangiani SN, Tang S, et al. POGZ truncating alleles cause syndromic intellectual disability. Genome Med. 2016;8(1):3. [Crossref]
36. ClinVar. Genomic variation as it relates to human health 25/04/2022. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/1327429/?oq=((1317941[AlleleID]))&m=NM_015100. 4(POGZ):c.1927-17del
37. National Library of Medicine MedGen. Intellectual disability-microcephaly-strabismus-behavioral abnormalities syndrome (MRD37; WHSUS): Available from: https://www.ncbi.nlm.nih.gov/medgen/C4225351/
38. Yalcintepe S, Görker I, Demir S, Atli EI, Engin A, Tozkir H, et al. Investigation the relationship of autism spectrum disorder and FOXP2, GRIN2B, KATNAL2, GABRA4 genes. Noro Psikiyatr Ars. 2021;58(3):171–175. [Crossref]
39. Görker I, Gürkan H, Ulusal S, Atli E, Ayaz G, Ceylan C, et al. Investigation of copy number variation by array CGH in Turkish children and adolescents diagnosed with autism spectrum disorders. Arch Neuropsychiatry 2018;55:215–219.