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WHOLE-EXOME SEQUENCING OF MONOZYGOTIC TWINS WITH EPILEPSY AND AUTISM SPECTRUM DISORDER IN A KAZAKHSTANI FAMILY: A CASE REPORT

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ABSTRACT

Epilepsy and autism spectrum disorder (ASD) frequently co-occur and share complex genetic determinants. However, molecular diagnosis remains challenging because of incomplete penetrance, variable expressivity, and the limited representation of Central Asian populations in genomic reference databases. This case report describes a Kazakhstani family with 9-year-old monozygotic twin girls who developed focal seizures with secondary generalization at approximately one year of age and were subsequently diagnosed with ASD. Family-based whole-exome sequencing was performed for both affected twins and their clinically unaffected, non-consanguineous parents. No pathogenic or likely pathogenic variant explaining the shared epilepsy–ASD phenotype was identified. A paternally inherited NPRL3 missense variant, c.121A>G (p.Lys41Glu), was considered biologically plausible because of the established association of NPRL3 with focal epilepsy. However, it remained a variant of uncertain significance (VUS), was not reported in the queried gnomAD dataset, and had an AlphaMissense score of 0.14. Additional heterozygous VUS were identified in SPTBN4, ANK2, VPS33A, SLC25A46, and GFM1. Two ZC2HC1C variants inherited from different parents supported a possible biallelic hypothesis, but their clinical significance was uncertain. We interpreted a heterozygous pathogenic ALDOB variant as an incidental carrier finding unrelated to the presenting phenotype. This case illustrates the distinction between candidate variants and a molecular diagnosis. Further evaluation may include periodic exome reanalysis, copy-number analysis, genome sequencing, and targeted validation where justified. Broader population reference resources could improve variant interpretation in Kazakhstan.

Keywords: Epilepsy, autism spectrum disorder, whole-exome sequencing

INTRODUCTION

Epilepsy is a long-term disorder that causes neurobiological, cognitive, and psychological effects. It is one of the most common neurological conditions and can affect anyone, regardless of age, race, or location. Epilepsy involves sudden disruptions in normal brain activity, known as seizures, which are caused by excessive electrical activity in the brain and can change behavior [1] [2]. More than 50 million people worldwide have epilepsy, making it a leading serious brain disorder across all populations [3]. According to the Global Burden of Disease study, idiopathic epilepsy accounted for about 13.5 million disability-adjusted life-years in 2016 [4]. An epileptic seizure is a brief event with clear signs and symptoms that result from abnormal, excessive, or synchronized brain activity, and it has a definite beginning and end [5]. Increasing inhibition and reducing excitation can also stop seizures [6].

Epilepsy has many causes, but genetics play a major role, especially in childhood-onset cases and in developmental and epileptic encephalopathies (DEE) [7]. As research has progressed, genetic factors have become recognized as important in both the development of epilepsy and how patients respond to treatment. About 70-80% of epilepsy cases are linked to genetic factors [8] . In the past 15 years, many genes related to epilepsy have been discovered, and now over 1000 genes are associated with monogenic epilepsy [9–11].

Epilepsy and autism are both complex conditions with different causes and features [12]. There is a well-known link between epilepsy and autism spectrum disorder (ASD): about 20% of children with ASD develop epilepsy, and 20–30% of children with epilepsy also meet criteria for ASD [13,14]. This connection is partly due to shared genetic factors. However, this genetic overlap makes genetic variants harder to interpret because of incomplete penetrance and variable expressivity. Many studies show a genetic tendency toward autism, as seen in higher concordance rates among monozygotic twins compared to dizygotic twins [15].

Genomic data on pediatric epilepsy in Kazakhstan is limited. The first pilot study on early-onset pediatric epilepsy found pathogenic variants in epilepsy-related genes in 14 of 20 patients [16]. However, family-based studies in epilepsy are still rare. Also, the absence of a Kazakhstani reference database and the limited representation of Central Asian ancestry in the Genome Aggregation Database (gnomAD) make it harder to interpret variants accurately for this population [17,18].

This study describes a Kazakhstani family with monozygotic twins who have focal epilepsy and ASD. Both twins were born to a clinically unaffected, non-consanguineous family. We present the family-based whole-exome sequencing (WES) results in this case.

MATERIALS AND METHODS

Recruitment of patients and ethics. Recruitment was con-

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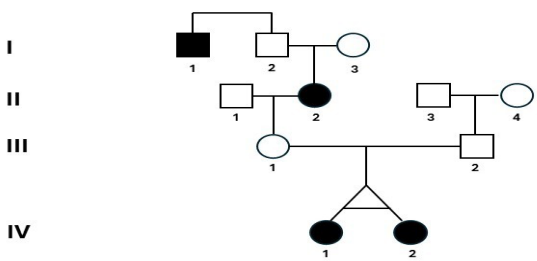
ducted at the NJSC «National Center for Children's Rehabilitation». Patients were recruited according to the inclusion and exclusion criteria defined by the local ethics committee. Inclusion criteria were families with at least one proband clinically diagnosed with epilepsy accompanied by seizures.

This study was approved by the Local Ethics Committee of the National Laboratory Astana (No. 03-2024 from October 2, 2024) and conducted in accordance with the Declaration of Helsinki. Recruited patients attended individualized information sessions, which included an oral explanation of the genetic testing procedure, likely outcomes, and ethical aspects related to participation. Written informed consent was obtained from all adult participants before enrollment. For the two minor participants, written informed consent for participation and genetic testing was obtained from their parents.

Biomaterial sampling and DNA Isolation. Blood samples were collected into tubes containing K_2EDTA (for blood cells and plasma) and tubes with a coagulation activator gel. Genomic DNA (gDNA) was isolated from whole blood samples according to Illustra Blood GenomicPrep Mini Spin Kit (Cytiva, Marlborough, MA, USA) protocol. The quality and quantity of the isolated DNA were assessed using spectrophotometry NanoDrop 2000 (ThermoFisher Scientific, Waltham, MA, USA) and fluorometry Qubit 2.0 (ThermoFisher Scientific, Waltham, MA, USA). Samples that did not meet the established quality and concentration criteria were re-extracted until they met the criteria. The gDNA integrity and purity were evaluated by gel electrophoresis on a 1% agarose gel.

Whole-Exome Sequencing. Whole-exome sequencing (WES) was performed on an Illumina NovaSeq6000 high-throughput sequencing platform, following the Illumina DNA Prep with Exome 2.0 Plus Enrichment protocol (Illumina Inc., San Diego, CA, USA). Library quality and fragment size were assessed using the Agilent DNA 1000 Kit on a BioAnalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA). Library pool concentrations were quantified using a Qubit dsDNA High Sensitivity Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA) on a Qubit 2000 Fluorometer.

Bioinformatic Analysis and variant interpretation. All sequencing reads were mapped to the human reference genome assembly GRCh38 (hg38) using the DRAGEN Platform (Illumina, v.4.4.4). Per-sample variant calling was performed within the DRAGEN pipeline, and variants were emitted in gVCF format. Sequencing quality and coverage metrics, including mean target-region sequencing depth, target coverage at ≥20×, the proportion of bases with a Phred quality score ≥30 (Q30), and mapping rate, were assessed using DRAGEN built-in reports. Only variants with a PASS status following DRAGEN quality filtering were retained for downstream analysis. The principal germline quality filters included DRAGENSnpHardQUAL and DRAGENIndelHardQUAL (QUAL <3.0103), LowDepth (DP ≤1), LowGQ (GQ = 0), and StrandArtifact (FS >80, SOR >4, and QD <2). Variant annotation was performed using Variant Effect Predictor (VEP) release 116.0. Variants with a population-maximum allele frequency (popmax AF) <0.01, as well as variants absent from gnomAD, were retained for further prioritization [19]. Candidate variants were prioritized using a family-based approach integrating variant consequence, population frequency, segregation, inheritance pattern, computational evidence, and gene–phenotype relevance. We preferentially evaluated protein-altering variants, including missense, nonsense, frameshift, and splice-site variants. Segregation across the four family members was assessed to identify variants shared by both affected twins and to evaluate de novo, autosomal dominant, autosomal recessive, X-linked, and potential compound-heterozygous inheritance models. Particular consideration was given to variants shared by both affected twins as potential contributors to their concordant phenotype. For missense variants, computational evidence was assessed using CADD and AlphaMissense [20,21]. The clinical significance of identified variants was assessed in accordance with the 2015 American College of Medical Genetics and Genomics (ACMG) and the Association of Molecular Pathology (AMP) guidelines, using the online databases of ClinVar and the Franklin by Genoox platform for independent classification confirmation (accessed on 23 September 2026).



Member	Age, Diagnosis
I : 1	No information, Epilepsy, DD
I : 2	No information
I : 3	No information
II : 1	No information
II : 2	No information, epilepsy
II : 3	No information
II : 4	No information
III : 1	31, healthy
III : 2	32, healthy
IV : 1	9, epilepsy, ASD
IV : 2	9, epilepsy, ASD
DD: developmental delay; ASD: autism spectrum disorder.	

Figure 1. Family pedigree. Squares denote males and circles females; filled symbols indicate affected individuals. The monozygotic twin daughters (IV-1; IV-2) are concordantly affected by focal epilepsy and autism spectrum disorder. On the maternal side, the grandmother (II-2) had epilepsy. The maternal great-grandfather's brother (I-1) was reported to have epilepsy and developmental delay. Only III-1, III-2, IV-1, and IV-2 underwent whole-exome sequencing.

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Table 1. Whole-exome sequencing quality and coverage metrics for the four family members

Sample	Mean target depth (×)	Target ≥20× (%)	Q30 bases (%)	Mapped reads (%)	Duplicate reads (%)
Mother	126.24	97.67	94.17	99.54	18.06
Father	108.49	97.07	93.02	99.52	17.55
Twin 1	83.20	96.30	94.81	99.61	15.24
Twin 2	116.40	97.30	94.10	99.57	17.45

RESULTS

Clinical characteristics and family history. The family comprised four individuals: two monozygotic twins (9 y.o.) and clinically unaffected biological parents (mother, 31 y.o., and father, 32 y.o., at the time of recruitment). Neither parent had a reported history of epilepsy or neurological disorders. Both sisters were diagnosed with epilepsy at approximately one year of age. Seizures were characterized by focal onset with loss of consciousness, tonic involvement of the extremities, and deviation of the head to the left, followed by generalization. Seizures lasted approximately 3 minutes and occurred 2–3 times per year. EEG demonstrated epileptiform discharges lasting approximately 0.5–2 seconds. Both sisters were also diagnosed with autism spectrum disorder (ASD; ICD-10: F84). The patients were treated with levetiracetam (Keppra) at 1000 mg/day, increased to 1500 mg/day in 2025.

The maternal family history was notable: the maternal grandmother of the twins had epilepsy, and a brother of the maternal great-grandfather had epilepsy with developmental delay. None of these affected relatives were available for genetic testing. Given the highly concordant phenotype in the monozygotic twins and the positive maternal family history, we performed family-based WES on both affected sisters and both unaffected parents. Figure 1 shows the pedigree.

Sequencing. Whole-exome sequencing generated high-quality sequencing data across all four family members. Mean sequencing depth over the target regions ranged from 83.20× to 126.24×, with 96.30–97.67% of target regions covered at ≥20×. The proportion of bases with a Phred quality score ≥30 (Q30) ranged from 93.02% to 94.81%, while 99.52–99.61% of reads were mapped to the reference genome (Table 1).

WES findings. Family-based WES analysis yielded 4 Pathogenic/Likely pathogenic variants, 86 variants of uncertain significance (VUS), 19 loss-of-function variants, 1 in silico prioritized variant, 1 de novo candidate, 35 autosomal-recessive candidates, 6 X-linked candidates, and 22 compound-heterozygous candidate pairs (Table 2).

Table 2. Summary of WES identified variants.

Variant category	Number of variants/pairs
ClinVar P/LP	4 (1 after re-assessment)
VUS	86
Loss-of-function	19
In-silico prioritized	1
De novo	1
Autosomal recessive candidates	35
X-linked candidates	6
Compound-heterozygous pairs	22
P/LP: Pathogenic/likely pathogenic; VUS: variant of uncertain significance	

After quality and population-frequency filtering, variants were prioritized according to functional consequence, inheritance pattern, familial segregation, and gene–phenotype relevance. Because both affected twins presented with epilepsy and ASD, the primary analysis focused on protein-altering variants shared by both twins in genes associated with epilepsy, ASD, or other neurological and neurodevelopmental disorders. Six rare heterozygous variants meeting these prioritization criteria were selected for further evaluation (Table 3). A heterozygous variant in *NPRL3*, specifically c.121A>G (p.Lys41Glu; rs1299719512), was passed down from the clinically unaffected father. Heterozygous missense variants inherited from the mother were found in *SPTBN4* (p.Ala1711Val), *ANK2* (p.Ala589Thr) and *VPS33A* (rs574910295). None of these variants has been classified as likely pathogenic. We also identified rare heterozygous variants with autosomal recessive inheritance in SLC25A46 (rs772739765) and *GFM1* (rs200244667). These variants are associated with neurological or neurometabolic disorders.

No pathogenic or likely pathogenic variant explaining the shared epilepsy–ASD phenotype was identified in established developmental and epileptic encephalopathy or high-confidence ASD genes.

Pathogenic and likely pathogenic variants. After initial annotation, results showed 4 pathogenic/likely patho-

Table 3. Principal candidate variants identified in both affected twins

Gene	Variant	RefSeq transcript	Inheritance	Popmax AF	CADD / AlphaMissense	ClinVar
NPRL3	c.121A>G (p.Lys41Glu), missense; rs1299719512	NM_001077350.3	Paternal	Not reported	23.2 / 0.14	VUS
SPTBN4	c.5132C>T (p.Ala1711Val), missense; rs372386329	NM_020971.3	Maternal	7.7×10^{-5}	25.7 / 0.38	VUS
ANK2	c.1765G>A (p.Ala589Thr), missense; rs1288246947	NM_001148.6 |	Maternal	3.4×10^{-6}	24.4 / 0.10	VUS
VPS33A	c.1387T>C (p.Tyr463His); missense; rs574910295	NM_022916.6	Maternal	4.0×10^{-4}	26.5 / 0.97	VUS

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SLC25A46	c.849G>C (p.Gln283His); missense; rs772739765	NM_138773.4	Paternal	2.4×10^{-4}	23.9 / 0.73	VUS
GFM1	c.1384G>T (p.Asp462Tyr); missense; rs200244667	NM_024996.7	Paternal	4.9×10^{-5}	33 / 0.43	VUS

AF: allele frequency; CADD: Combined Annotation Dependent Depletion score; VUS: variant of uncertain significance.

Table 4. Potential compound-heterozygous ZC2HC1C variants identified in both affected twins

Gene	Variant	RefSeq transcript	Inheritance	Popmax AF	CADD / AlphaMissense	ClinVar
ZC2HC1C	c.348del (p.Trp116CysfsTer26), frameshift; rs759570636	NM_024643.4	Compound heterozygous	Not reported	17.7 / -	VUS
ZC2HC1C	c.1208T>A (p.Leu403Gln), missense; rs143341334	NM_024643.4	Compound heterozygous	6.9×10^{-3}	26.5 / 0.55	VUS

AF: allele frequency; CADD: Combined Annotation Dependent Depletion score; VUS: variant of uncertain significance.

genic variants. Nevertheless, after re-query, only one is confirmed pathogenic. The *ALDOB* c.1013C>T (p.Ala338Val, NM_000035.4) is classified as pathogenic by multiple submitters. Inherited from the unaffected father, indicating heterozygous carrier for autosomal recessive fructose intolerance.

Another potentially significant discovery was found in *ZC2HC1C*. Both twins affected by the condition possessed two rare variants of this gene: a frameshift variant inherited from the mother, p.Trp116CysfsTer26, and a missense variant inherited from the father, p.Leu403Gln (Table 4). The parental variant distribution is consistent with a possible compound-heterozygous model. However, the clinical significance of these variants remains unclear, and their phase and functional implications need further validation.

A low-confidence candidate call in *DGKQ* (c.2221C>T, p.Gln741Ter, NM_001347.4) was found in one of the affected twins but was not present in the second affected twin or either parent. However, this variant is only supported by 5% of reads in a single twin.

DISCUSSION

This report examines a Kazakhstani family with monozygotic twins affected by epilepsy and autism spectrum disorders. Focal seizures with generalization began at one year of age. Family history indicates aggregation of the phenotype on the maternal side, with an affected maternal grandmother and an affected maternal great-uncle. The maternal family history is compatible with an inherited predisposition but cannot currently be genetically linked to the identified variants because the affected maternal relatives were not available for testing.

SPTBN4 is a gene associated with a recently described autosomal-recessive disorder. βIV-spectrin is a non-erythrocytic member of the β-spectrin family and has a vital role in the organization of axonal initial segments and nodes of Ranvier [22]. Mutations in this gene cause congenital hypotonia, motor neuropathy, central deafness, and sometimes seizures [23]. *SPTBN4* (rs372386329) was inherited from the mother, but only a single heterozygous missense variant is present. Therefore, it cannot be considered causative for epilepsy. The severe congenital hypotonia, neuromuscular weakness, and auditory abnormalities that characterise biallelic *SPTBN4* disorder were not reported in children's phenotype. Because *ANK2*, which codes for ankyrin-B, is one of the genes most strongly linked to ASD in large exome studies, is categorized as a high-confidence ASD gene in SFARI Gene database and is highly intolerant of loss-of-function variation (LOEUF 0.28), the maternally inherited *ANK2* variant c.1765G>A (p.Ala589Thr) was also reviewed [24,25]. However, this variant is a missense change inherited from the unaffected mother and is expected to be benign (AlphaMissense 0.10). ASD-associated *ANK2* variants are primarily de novo protein-truncating variants.

VPS33A and *SLC25A46* are best described as heterozygous variants of uncertain significance. Established *VPS33A*-related disease is autosomal recessive and presents as mucopolysaccharidosis-plus syndrome, a severe multisystem lysosomal disorder characterized by developmental delay, hypotonia, skeletal and renal abnormalities, and hematologic manifestations. It is caused predominantly by the recurrent p.Arg498Trp founder variant [26,27]. Although AlphaMissense predicts that the p.Tyr463His variant has a negative effect (0.97), a single heterozygous allele is insufficient to demonstrate causality for the epilepsy-ASD phenotype observed here, and its presence in the clinically unaffected mother points out the importance of considering penetrance and phenotype specificity when interpreting rare candidate variants.

The paternally inherited *SLC25A46* missense variant, p.Gln283His, is also interpreted as a carrier finding: biallelic *SLC25A46* variants cause an optic-atrophy spectrum disorder with hereditary motor and sensory neuropathy and, in some patients, progressive myoclonic ataxia [28,29]. This variant is unlikely to be causal because it is the only heterozygous allele and was inherited from an unaffected parent. Similarly, the paternally inherited *GFM1* variant, p.Asp462Tyr, is notable because biallelic *GFM1* variants cause combined oxidative phosphorylation deficiency 1, a severe hepatoencephalopathy that frequently includes epileptic encephalopathy [30]. However, the second allele is absent, and the children did not report early-onset metabolic or hepatic features.

The heterozygous *NPRL3* variation c.121A>G (p.Lys41Glu) deserves special attention. *NPRL3* encodes a component of the GATOR1 complex, which is a negative regulator of mTORC1 signalling, and loss-of-function variants in *NPRL3*, *NPRL2*, and *DEPDC5* are well-known causes of familial focal epilepsy with variable foci and other focal epilepsy syndromes, which frequently include focal cortical

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dysplasia [31–33]. Patients with *NPRL3*-related epilepsy exhibit focal seizures and, in a considerable subset, cognitive or neurobehavioral comorbidities, which are consistent with the clinical picture described in the family. However, GATOR1-related focal epilepsies have significantly lower penetrance — estimated at 60-80% for *DEPDC5* and even lower for *NPRL3* — which is compatible with paternal transmission of the variant from a clinically unaffected carrier [33]. However, evidence for the variant is scarce. The p.Lys41Glu variant is missing from gnomAD but is expected to be benign by AlphaMissense (0.14) [14].

The identification of a compound-heterozygous configuration in *ZC2HC1C* provides an additional hypothesis for the shared phenotype observed in the twins. Both siblings inherited a loss-of-function variant (p.Trp116CysfsTer26) from their mother and a missense variant (p.Leu403Gln) from their father, suggesting a possible biallelic mechanism. However, the biological significance of this observation remains unclear because evidence linking *ZC2HC1C* to neurodevelopmental disorders is limited. Previous studies have reported biallelic loss-of-function *ZC2HC1C* variants in individuals with neurodevelopmental phenotypes, including autism spectrum disorder, highlighting the need for further investigation of this gene [34] . To clarify the contribution of these variants to the family's phenotype, we need to evaluate the pathogenicity of each variant and identify additional cases with biallelic *ZC2HC1C* alterations.

The low-confidence *DGKQ* variant identified in one monozygotic twin is another finding of interest. The variant allele frequency (VAF) is ~ 5%, which could indicate postzygotic mosaicism. Given that both twins exhibit an epilepsy phenotype, a genuine mosaic mutation could theoretically point to shared mosaicism within the neuroectodermal lineage, coupled with uneven cellular distribution [35]. However, careful evaluation of sequencing metrics suggests this is a technical artefact or sequencing noise rather than true biological mosaicism. The variant call is supported by an alternate allele depth of only 3 reads out of a total depth of 62 reads (AD=59,3), yielding a low genotype quality score (GQ=11) and an exceptionally low quality-by-depth score (QD=0.10).

Our study supports the use of NGS and WES to uncover the genetic basis of pediatric epilepsy. However, diagnostic yield is approximately 27-50%, leaving some families with unsolved cases and underscoring the need for specific diagnostic strategies for complex cases [36].

This study has several limitations. First, epilepsy with autism has a complex genetic background, and the traits seen in this family may be due to multiple genes rather than a single Mendelian variant, which whole exome sequencing (WES) cannot fully detect. Second, WES is less effective at finding copy-number and structural variants, repeat expansions, deep intronic and regulatory variants, and regions with low coverage or similar sequences. Therefore, genome sequencing or at least chromosomal microarray would be a logical next step. Third, we did not have other affected relatives available for clinical or genetic testing, so we could not assess segregation beyond the immediate family. Finally, we used gnomAD to filter allele frequencies by population, but Central Asian and Kazakh groups are underrepresented. Thus, some variants considered rare may be more common in these populations.

CONCLUSION

Family-based WES in monozygotic twin girls with focal epilepsy and ASD did not identify a pathogenic or likely pathogenic variant explaining their shared phenotype. NPRL3 was biologically plausible, but c.121A>G (p.Lys41Glu) remained a VUS. The other heterozygous VUS and exploratory ZC2HC1C findings did not establish a diagnosis. The pathogenic ALDOB variant represented an unrelated carrier finding. This case illustrates the need to integrate clinical findings, inheritance, population frequency, and variant-level evidence while communicating an unresolved genetic result. Additional phenotype assessment and appropriately selected genomic investigations may help clarify the etiology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization - A.G., A.D., Zh.M., N.S., A.K., S.A., A.G., A.A., D.Y.; Data curation – A.G., A.D., A.K., A.A., D.Y.; Formal Analysis – A.G., A.D., D.Y.; Investigation – A.G., Zh.M., N.S., S.A., A.A., D.Y.; Validation – A.G., A.D., S.A., A.G., A.A., D.Y.; Methodology – A.G., Zh.M., N.S., S.A., A.G., D.Y.; Resources – S.A., AG., A.A., D.Y.; Supervision – D.Y.; Visualization – A.G., A.G., D.Y.; Funding Acquisition – D.Y.; Writing – A.G., D.Y.; Writing – review & editing – A.G., D.Y.;

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ҚАЗАҚСТАНДЫҚ ОТБАСЫДАҒЫ ЭПИЛЕПСИЯ ЖӘНЕ АУТИЗМ СПЕКТРІНІҢ БҰЗЫЛЫСЫ БАР МОНОЗИГОТАЛЫ ЕГІЗДЕРГЕ БҮКІЛ ЭКЗОМДЫ СЕКВЕНИРЛЕУ ЖҮРГІЗУ: КЛИНИКАЛЫҚ ЖАҒДАЙ СИПАТТАМАСЫ

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АҢДАТПА

Эпилепсия мен аутизм спектрінің бұзылысы (АСБ) жиі қатар кездеседі және оларға ортақ күрделі генетикалық факторлар тән. Дегенмен, пенетранттылықтың толық болмауы, экспрессивтіліктің әртүрлілігі және эталондық геномдық дерекқорларда Орталық Азия популяцияларының жеткіліксіз қамтылуына байланысты молекулалық диагностика қиындықтар тудырады. Бұл клиникалық жағдайда Қазақстандағы бір отбасы сипатталады: онда 9 жасар бір жұмыртқалы (монозиготалы) егіз қыздарда шамамен бір жас шамасында екіншілік генерализациямен сипатталатын фокальды ұстамалар пайда болып, кейіннен оларға АСБ диагнозы қойылған. Ауруға шалдыққан егіздер мен олардың клиникалық тұрғыдан сау, туыстық байланысы жоқ ата-аналарына отбасылық талдаумен қоса, бүкіл экзомды секвенирлеу жүргізілді. Байқалған фенотипті (эпилепсия мен аутизм спектрінің бұзылысының үйлесімі) түсіндіретін патогенді немесе патогенді болуы ықтимал нұсқа анықталған жоқ. *NPRL3* геніндегі әкесінен тұқым қуалаған, аминқышқылының алмасуына әкелетін (миссенс) c.121A>G (p.Lys41Glu) нұсқасы, *NPRL3* пен фокальды эпилепсия арасындағы белгілі байланыс ескеріле отырып, биологиялық тұрғыдан маңызды деп бағаланды. Дегенмен, ол маңыздылығы белгісіз нұсқа (VUS) ретінде жіктелді, gnomAD дерекқорында кездеспеді және AlphaMissense көрсеткіші 0,14-ті құрады. *SPTBN4*, *ANK2*, *VPS33A*, *SLC25A46* және *GFM1* гендерінде қосымша гетерозиготалы VUS нұсқалары анықталды. *ZC2HC1C* геніндегі әртүрлі ата-анадан тұқым қуалаған екі нұсқа биаллельді тұқым қуалау мүмкіндігін туындатты, алайда олардың клиникалық маңыздылығы белгісіз болып қалды. *ALDOB* геніндегі гетерозиготалы патогендік нұсқа бастапқы фенотипке қатысы жоқ кездейсоқ табылған жағдай (тасымалдаушылық мәртебесі) ретінде жіктелді. Бұл жағдай кандидаттық нұсқалар мен нақтыланған молекулалық диагноз арасындағы айырмашылықты көрсетеді. Қосымша тексерулерге экзом деректерін мерзімді түрде қайта талдау, көшірме санының өзгеруін (CNV) талдау, толық геномды секвенирлеу және қажет болған жағдайда нәтижелерді мақсатты түрде растау кіруі мүмкін. Популяциялық анықтамалық ресурстарды кеңірек пайдалану Қазақстандағы генетикалық нұсқалардың интерпретациясын жақсартуға ықпал етер еді.

Түін сөздер. Эпилепсия, аутизм спектрінің бұзылысы, бүкіл экзомды секвенирлеу

ПОЛНОЭКЗОМНОЕ СЕКВЕНИРОВАНИЕ МОНОЗИГОТНЫХ БЛИЗНЕЦОВ С ЭПИЛЕПСИЕЙ И РАССТРОЙСТВОМ АУТИСТИЧЕСКОГО СПЕКТРА В КАЗАХСТАНСКОЙ СЕМЬЕ: ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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АННОТАЦИЯ

Эпилепсия и расстройство аутистического спектра (РАС) часто встречаются совместно и имеют общие сложные генетические детерминанты. Однако молекулярная диагностика сопряжена с трудностями из-за неполной пенетрантности, вариабельной экспрессивности и недостаточной представленности популяций Центральной Азии

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в референсных геномных базах данных. В данном клиническом случае описывается семья из Казахстана, в которой у 9-летних однояйцевых близнецов женского пола в возрасте около одного года развились фокальные приступы с вторичной генерализацией, а впоследствии было диагностировано РАР. Было проведено полноэкзомное секвенирование с анализом семьи для обеих больных близнецов и их клинически здоровых родителей, не состоящих в родстве. Патогенный или вероятно патогенный вариант, объясняющий наблюдаемый фенотип (сочетание эпилепсии и РАС), выявлен не был. Миссенс-вариант c.121A>G (p.Lys41Glu) в гене *NPRL3*, унаследованный от отца, рассматривался как биологически значимый ввиду установленной связи *NPRL3* с фокальной эпилепсией. Однако он был классифицирован как вариант с неопределенным клиническим значением (VUS), отсутствовал в базе данных gnomAD, а его оценка по алгоритму AlphaMissense составила 0,14. Дополнительные гетерозиготные варианты VUS были выявлены в генах *SPTBN4*, *ANK2*, *VPS33A*, *SLC25A46* и *GFM1*. Два варианта в гене ZC2HC1C, унаследованные от разных родителей, допускали гипотезу о биаллельном наследовании, однако их клиническое значение оставалось неопределенным. Гетерозиготный патогенный вариант в гене *ALDOB* был расценен как случайная находка (носительство), не связанная с основным фенотипом. Данный случай иллюстрирует различие между вариантами-кандидатами и установленным молекулярным диагнозом. Дальнейшее обследование может включать периодический повторный анализ экзома, анализ вариаций числа копий (CNV), секвенирование генома и, при наличии показаний, целевую валидацию результатов. Использование более обширных популяционных референсных ресурсов могло бы улучшить интерпретацию генетических вариантов в Казахстане.

Ключевые слова. Эпилепсия, расстройство аутистического спектра, полноэкзомное секвенирование