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GENETIC INSIGHTS INTO A KAZAKHSTANI FAMILY WITH MULTIPLE NEUROLOGICAL CONDITIONS: A CASE REPORT

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ABSTRACT

Introduction. Neurological disorders (ND) are diseases that affect both the central nervous system (CNS) and peripheral nervous system (PNS). The aetiology of neurological disorders is highly diverse and may involve genetic, environmental, metabolic, infectious, immune-mediated, and acquired factors. Epilepsy, cerebral palsy (CP), and autism spectrum disorder (ASD) are clinically and genetically heterogeneous neurological and neurodevelopmental conditions that frequently manifest during childhood. Although these disorders have distinct core clinical features, considerable phenotypic overlap and comorbidity are observed, suggesting they may share underlying genetic and molecular mechanisms. *Methods*. Recruitment of the family, interview and clinical data acquisition, as well as blood sample acquisition, took place at the "National Center for Children's Rehabilitation" NJSC. DNA was isolated using commercially available kits. Whole-exome sequencing (WES) was performed using DNA Prep with Exome 2.0 Plus Enrichment Kit on the NovaSeq-6000 platform. All sequencing reads were mapped to the human reference genome assembly GRCh38 (hg38) using the DRAGEN Platform. Variant annotation was performed using VEP release 116.0. *Results.* We recruited a family with multiple neurological conditions. The parents were a Kazakh male and female with no family history of neurological or neurodevelopmental conditions. Marriage is non-consanguineous. There are three probands in the family diagnosed with autism spectrum disorder (ASD), focal symptomatic epilepsy, and (ASD) and ataxic cerebral palsy (CP), respectively. Bioinformatic analysis revealed pathogenic/likely pathogenic variants in IL10, CDKN2B, GALC, and SLC12A3 genes. In addition, we identified variants of uncertain significance (VUS), loss-of-function (LoF), compound heterozygous, X-linked, and single *de novo* mutation, in many genes involved in neurological or neurodevelopmental conditions. *Conclusion*. Overall, our findings demonstrate substantial genetic heterogeneity within a single family presenting with different neurological and neurodevelopmental phenotypes. The results highlight the challenges of interpreting rare and uncertain variants identified by WES and emphasize the importance of integrating variant classification, inheritance patterns, segregation analysis, clinical phenotype, and available gene–disease evidence. Further functional studies and accumulation of additional clinical cases will be required to determine the contribution of the identified candidate variants to autism spectrum disorder, epilepsy, and other neurological manifestations in this family.

Keywords: whole-exome sequencing; neurological disorders; cerebral palsy; epilepsy; autism spectrum disorder.

INTRODUCTION

Neurological disorders (ND) are diseases that affect both the central nervous system (CNS) and peripheral nervous system (PNS) and result from structural, biochemical, or electrical abnormalities in the brain, spinal cord, peripheral nerves, neuromuscular junctions, and muscles, causing a variety of symptoms [1]. Symptoms may include paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain, tauopathies, and altered levels of consciousness [2]. They encompass a broad and heterogeneous group of conditions, such as epilepsy, stroke, neurodegenerative diseases, neurodevelopmental disorders, multiple sclerosis, and neuromuscular diseases. Collectively, neurological conditions represent a major global health burden and are among the leading causes of disability and premature mortality worldwide [3].

The aetiology of neurological disorders is highly diverse and may involve genetic, environmental, metabolic, infectious, immune-mediated, and acquired factors. Genetic factors play a particularly important role in many rare, pediatric, neurodevelopmental, and epileptic disorders [4]. Advances in genomic technologies, particularly whole-exome sequencing (WES) and whole-genome sequencing (WGS), have substantially improved identification of disease-associated genes and pathogenic variants, increasing diagnostic yield for patients with previously unexplained neurological and rare disorders [4, 5].

Epilepsy, cerebral palsy (CP), and autism spectrum disorder (ASD) are clinically and genetically heterogeneous neurological and neurodevelopmental conditions that frequently manifest during childhood. Although these disorders have distinct core clinical features, considerable phenotypic overlap and comorbidity are observed, suggesting they may share underlying genetic and molecular mechanisms [6, 7].

Epilepsy comprises a broad group of neurological disorders characterized by a persistent predisposition to epileptic seizures. Its aetiology is highly heterogeneous and includes genetic, structural, metabolic, immune, infectious, and unknown causes. Genetic factors are particularly important in early-onset epilepsies and developmental and epileptic encephalopathies, with disease-associated variants identified in

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genes involved in ion-channel function, synaptic transmission, neuronal signalling, and brain development [6].

Cerebral palsy is a group of permanent disorders affecting movement and posture that result from non-progressive disturbances of the developing fetal or infant brain. Although CP has traditionally been attributed primarily to prenatal and perinatal environmental or acquired factors, genomic studies have demonstrated a substantial genetic contribution to its aetiology [7, 8]. Exome sequencing has identified pathogenic or likely pathogenic variants in a considerable proportion of individuals with CP, particularly in patients presenting with additional neurodevelopmental features such as epilepsy, intellectual disability, or ASD [7].

ASD is a heterogeneous neurodevelopmental condition characterised by persistent difficulties in social communication and interaction together with restricted or repetitive patterns of behaviour and interests. Its genetic architecture is complex and includes common polygenic variation, copy-number variants, and rare inherited and de novo sequence variants [9, 10]. Many genes associated with ASD are involved in neuronal development, synaptic function, gene-expression regulation, and other biological processes essential for normal brain development [9, 10].

Importantly, the boundaries between these neurological phenotypes are not absolute. Epilepsy frequently co-occurs with ASD [11], while epilepsy, ASD, and intellectual disability are also common comorbidities in individuals with CP [7]. Furthermore, genetic variants associated with one neurodevelopmental phenotype may produce a broad spectrum of clinical manifestations, even within the same family. This clinical and genetic heterogeneity supports using comprehensive genomic approaches, including WES and WGS, to investigate families in which affected individuals present with different neurological phenotypes [7, 10].

In the current case report, we present the results of whole-exome sequencing in a Kazakhstani family in which cerebral palsy, epilepsy, and autism spectrum disorder (ASD) occur in different probands, with no prior family history of neurological disorders.

MATERIALS AND METHODS

Recruitment of patients and ethics. Recruitment is conducted at the "National Center for Children's Rehabilitation" NJSC (NCCR, Astana, Kazakhstan). Patient selection is performed according to predefined inclusion and exclusion criteria approved by the local bioethics committee.

Inclusion criteria were at least 2 neurological or neurodevelopmental conditions in different probands within one family.

This study was approved by the Local Ethics Committee of the National Laboratory Astana (No. 03-2024 from October 2, 2024). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Interview and clinical data acquisition. The family participated in an individualized information and genetic counselling session at the NCCR. During the session, the genetic testing procedure, possible test outcomes, methodological limitations, and relevant ethical considerations were explained in detail. Following the consultation, a clinical neurologist and a geneticist provided the family with a standardized written clinical conclusion and appropriate recommendations.

After confirming participation, we obtained written informed consent from all participants. The consent form described the purpose and nature of genetic testing, the storage of biological samples and genetic data, and participants' right to withdraw from the study at any time. All study procedures were recorded in the project research database, and each participant was assigned a unique identification code to maintain confidentiality. We established an individual clinical record for each participant, including demographic characteristics (age, ethnicity, and place of residence), medical and obstetric history, family history of hereditary disorders, and results of relevant laboratory and instrumental examinations.

Biomaterial sampling, DNA isolation, and quality control. Following a medical genetic consultation and informed consent, biological material was collected from each participant. Blood was collected into a blood collection tube containing K2EDTA (BD, Franklin Lakes, NJ, USA).

DNA was extracted from 300 µL of whole blood using the Illustra Blood Genomic Prep Spin Kit (Cytivia, Marlborough, MA, USA), according to the manufacturer's instructions, and stored at −20°C. The quality and quantity of extracted DNA were assessed using the spectrophotometric method with the NanoDrop 2000 UV spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA) and the fluorometric assay with the Qubit BR Assay Kit (ThermoFisher Scientific, Waltham, MA, USA) on a Qubit v4.0 fluorometer. Samples that did not meet the established quality and concentration criteria were re-extracted until they met the criteria.

DNA library preparation and whole-exome sequencing. DNA libraries were prepared using DNA Prep with Exome 2.0 Plus Enrichment Kit (Illumina Inc., San Diego, CA, USA), according to the manufacturer's instructions. Quality of the DNA libraries and fragment size were evaluated using DNA 1000 Kit (Agilent Technologies, Santa Clara, CA, USA) 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. Quality of the DNA library pool and fragment size were evaluated using the High Sensitivity DNA reagents Kit (Agilent Technologies, USA) on an Agilent 2100 Bioanalyzer (Agilent Technologies, USA). Whole-exome DNA libraries were sequenced on NovaSeq6000 high-throughput sequencing platform (Illumina Inc., San Diego, CA, USA) using S1 flow cell and loading pool of 40 libraries at a time.

Bioinformatic analysis. 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 metrics were assessed using DRAGEN built-in reports. Variant annotation was performed using VEP release 116.0. 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

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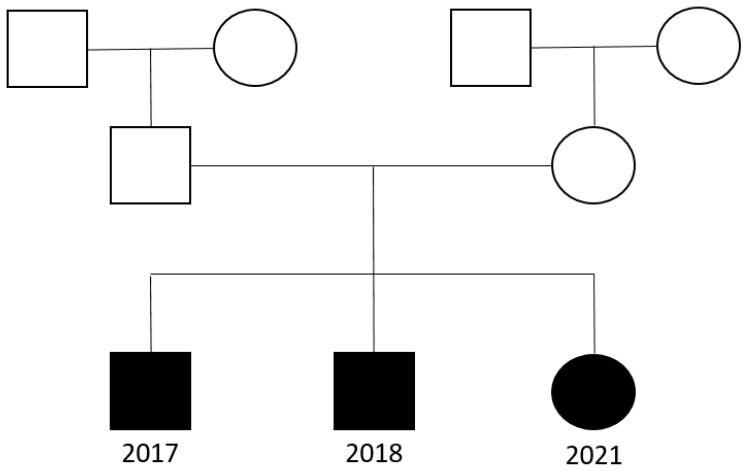


Figure 1 – Family tree of recruited participants

classification confirmation (accessed on 20 September 2026). ACMG pathogenic and likely pathogenic (P/LP) designations are standardized clinical classifications indicating that a genetic sequence variant has strong or very strong evidence of causing a Mendelian genetic disorder. Under ACMG guidelines, a variant of uncertain significance (VUS) is a genetic change with insufficient or conflicting evidence to determine whether it causes disease or is harmless. Hence, VUS cannot be considered causative. A benign variant (B) (Class 1) is a genetic sequence change with strong evidence indicating it is not disease-causing and represents a normal variant or common polymorphism.

RESULTS

Family description.

In the current study, we recruited a family with multiple neurological conditions. Both parents are healthy individuals. Father: 34-year-old male of Kazakh nationality with no family history of neurological and neurodevelopmental conditions. Mother: 31-year-old female of Kazakh nationality. Neurological and neurodevelopmental conditions were absent in the family history. Marriage is non-consanguineous. The family has three probands. The mother delivered them at ages 22, 24, and 27, respectively. All three children have neurological and neurodevelopmental conditions. Figure 1 shows the family tree.

Child 1. The proband is an 8-year-old boy (male) diagnosed with autism spectrum disorder (ASD). First child in the family from the first pregnancy. 39-week pregnancy without complications and delivered naturally. Weight at birth: 4230 g, height: 56 cm. The baby started crying immediately after birth. He was placed at the breast immediately and nursed vigorously. According to the medical history, concerns regarding neurodevelopment became apparent in early childhood and were primarily related to delayed speech and language development, sleep disruption, impaired social communication, and behavioural difficulties. Clinical evaluation revealed deficits in reciprocal social interaction and communication, accompanied by restricted and repetitive patterns of behaviour and interests. Difficulties with adaptation to changes in routine and age-appropriate social interaction were also reported. Medical history excludes seizures, and EEG is normal. The diagnosis of ASD was established following clinical assessment by appropriate specialists.

Child 2. The proband is a 6-year-old boy (male) diagnosed with focal symptomatic epilepsy. Second child in the family from the second pregnancy. 40-week pregnancy without complications and delivered naturally. Weight at birth: 3650 g, height: 54 cm. The baby started crying immediately after birth. He was placed at the breast immediately and nursed vigorously.

The child grew and developed according to age during the first year of life. First seizures were registered at the age of 1 year. Depakine was prescribed in the form of a syrup (18 uG/kg) twice a day. EEG: The bioelectrical activity of the brain is preserved in terms of the amplitude-frequency characteristics of the main cortical rhythms and corresponds to age-appropriate norms. Sleep staging and cyclicity are evident, and sleep transitions are present. During sleep, epileptiform activity is recorded as high-amplitude «sharp wave» and «sharp-slow wave» complexes in the fronto-centro-parieto-temporal leads, transitioning to low-amplitude «sharp wave» and «spike-wave» complexes in the same leads. Brain MRI showed gliotic foci in the white matter of the cerebral hemispheres. Delayed speech and language development was noted at age 2.5 years. Since age 5, episodes of freezing with a fixed stare emerged.

Child 3. The proband is a 4-year-old girl (female) diagnosed with autism spectrum disorder (ASD) and ataxic cerebral palsy (CP). Third child in the family from the third pregnancy. 38-week pregnancy without complications and delivered naturally. Weight at birth: 3220 g; height: 52 cm. The baby started crying immediately after birth. She was placed at the breast immediately and nursed vigorously.

Developmental abnormalities became apparent in early childhood, with delays in acquiring age-appropriate motor and communication skills. The clinical presentation was characterized by impaired motor coordination and balance consistent with the ataxic form of CP. The patient demonstrated gait instability, a broad-based gait, intention tremor, and/or difficulties with fine motor coordination. In addition to motor impairment, the patient demonstrated features consistent with ASD, including difficulties in social communication and reciprocal social interaction, together with restricted and repeti-

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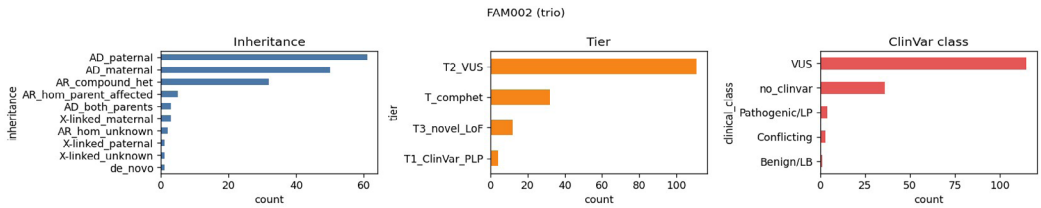


Figure 2 – Whole exome sequencing results

tive patterns of behaviour. Speech and language development was delayed. The diagnosis was established following clinical and neurological assessment. Brain MRI and EEG showed no abnormalities. At the time of evaluation, no epileptic seizures had been reported. The coexistence of ASD, developmental delay, and ataxic CP prompted further genetic investigation to assess a possible underlying genetic aetiology.

Whole exome sequencing results

All family members were successfully sequenced. Sequencing quality was consistently high, with a mean of 94.4% of bases at ≥Q30 (range 94.2-94.6%) and 99.7% of reads successfully aligned to the reference (99.64-99.71%). The mean duplicate rate was 18.3% (17.0-19.8%). Mean depth across the exome target regions was 114.7× (range 101.4-124.3×); on average, 97.4% of target regions were covered at ≥20× (96.8-97.8%) and 90.3% at ≥50× (86.0-93.0%). A mean of 30,509 variants per sample (range 30,396-30,719) passed filtering.

Bioinformatics analysis identified several P/LP variants, VUS, benign, compound heterozygous variants, loss-of-function (LoF), and de novo variants, and assigned inheritance mechanisms according to ACMG criteria. Generalized results of WES are illustrated in Figure 2.

Bioinformatic analysis revealed P/LP variants in IL10, CDKN2B, GALC, and SLC12A3 genes. IL10 gene variant (rs1800896, pathogenic) is associated with susceptibility to Leprosy and hepatitis C, according to the ClinVar database, and all three probands are homozygous for the alternative allele. The alternative homozygous allele of the CDKN2B gene (rs1063192, likely pathogenic), which is associated with coronary disease and cancer, was detected in probands 1 and 2, while proband 3 is heterozygous. Variant annotation was performed against the ClinVar release of 21 June 2026. At that time, two variants in the family were classified as P/LP: rs1800896 in IL10 (chr1:206,773,552 T>C; upstream gene variant) and rs1063192 in CDKN2B (chr9:22,003,368 G>A; 3′-UTR variant, NC_000009.12:g.22003368G>A). IL10 and CDKN2B variants have since been reclassified as benign in the current ClinVar release. GALC gene variant (rs138577661, P/LP) is heterozygous in all three probands. We identified the alternative heterozygous allele of the familial hypokalemia-hypomagnesemia-associated SLC12A3 gene variant (rs775765261, LP) only in proband 1.

We found VUS in many genes involved in neurological conditions. We found heterozygous variants in the USH2A, AFF3, and ATP9A genes in all three probands. These genes are associated with Usher syndrome type 2A, KINSSHIP syndrome, and neurodevelopmental disorder with poor growth and behavioural abnormalities, respectively. We identified heterozygous variants in AARS1, ASPM, TTN, DIAPH1, and ITCH only in proband 1. A *de novo* mutation in the GDF1 gene was found in proband 2, who was diagnosed with epilepsy. Table 1 presents all genetic variations found in the recruited family.

Table 2 summarizes common genetic variants for all three probands that are associated with neurological and neurodevelopmental conditions according to the ClinVar database, and since probands 1 and 3 share an ASD diagnosis, we added common genetic variants for probands 1 and 3 that are absent in proband 2. Interestingly, proband 3 did not have exclusive genetic variations in analyzed genes.

Table 1 – Results of bioinformatics analysis

GENE	CHR	REF (0)	ALT (1)	CONSE-QUENCE	rsID	ClinVar	ClinVar Diagnosis	Inheritance	Proband 1	Proband 2	Proband 3
Pathogenic/ Likely pathogenic											
IL10	chr1	T	C	upstream gene variant	rs1800896 (NC_000001.11:g.206773552T>C)	Pathogenic (PS4*)	Leprosy, susceptibility to; Hepatitis C virus, susceptibility to	AR hom parent affected	1/1	1/1	1/1
CDKN2B	chr9	G	A	3 prime utr variant	rs1063192 (NC_000009.12:g.22003368G>A)	Likely pathogenic (PS3*)/ Protective	Malignant tumor of breast; Three-vessel coronary disease (single submission)	AR hom parent affected	1/1	1/1	0/1
GALC	chr14	A	G	missense variant	rs138577661; (NM_000153.4(GALC):c.1901T>C)	Pathogenic/ Likely pathogenic (PM1)	Galactosylceramide beta-galactosidase deficiency; Krabbe disease (KD)	AD maternal	0/1	0/1	0/1
SLC12A3	chr16	G	A	missense variant	rs775765261 (NM_001126108.2:c.3043G>A)	Likely pathogenic (PM2)	Gitelman syndrome; Familial hypokalemia-hypomagnesemia	AD paternal	0/1	0/0	0/0
Variants of uncertain significance (VUS)											
USH2A	chr1	G	A	missense variant	rs185823130; CM149213; COSV56415541; COSV56450187	Uncertain significance	Usher syndrome type 2A; Retinitis pigmentosa 39	AD maternal	0/1	0/1	0/1
AFF3	chr2	C	G	missense variant	rs746372293	Uncertain significance	KINSSHIP syndrome	AD paternal	0/1	0/1	0/1
ATP9A	chr20	C	T	missense variant	rs760297151	Uncertain significance	Intellectual disability; Hypotonia; Motor impairment; Attention deficit hyperactivity disorder (ADHD)	AD maternal	0/1	0/1	0/1
SLC39A8	chr4	C	G	missense variant	rs1560527180	Uncertain significance	Autism Spectrum Disorders	AD paternal	0/1	0/1	0/0
ANK2	chr4	A	T	missense variant	rs776735614	Uncertain significance	ANK2-related syndrome; Developmental delay or intellectual disability; Speech and language impairment	AD paternal	0/1	0/1	0/0
PODXL	chr7	T	C	missense variant	rs770115273	Uncertain significance	Atypical Juvenile Parkinsonism; Early-Onset Parkinson's Disease	AD paternal	0/1	0/1	0/0
KMT2C	chr7	A	C	missense variant	rs2487796925	Uncertain significance	Kleefstra syndrome 2; Autism spectrum disorder	AD maternal	0/1	0/0	0/1
ATXN2	chr12	G	C	missense variant	rs149774930; COSV66482812	Uncertain significance	Spinocerebellar Ataxia Type 2 (SCA2); Amyotrophic Lateral Sclerosis (ALS)	AD paternal	0/1	0/0	0/1
AARS1	chr16	T	C	missense variant	rs762420332; COSV105851956	Uncertain significance	Charcot-Marie-Tooth disease type 2; Developmental and Epileptic Encephalopathy 29 (DEE29);	AD maternal	0/1	0/0	0/0

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Eurasian Journal of Applied Biotechnology. №.3, 2026
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ASPM	chr1	C	T	missense variant	rs375901171; COSV54127685; COSV99659844	Uncertain significance	Microcephaly 5; primary;	AD paternal	0/1	0/0	0/0
TTN	chr2	T	C	missense variant	rs1168512202	Uncertain significance	Hypertrophic cardiomyopathy 9; Dilated cardiomyopathy 1G; Autosomal recessive limb-girdle muscular dystrophy type 2J; Tibial muscular dystrophy; Myopathy; myofibrillar; 9 with early respiratory failure; Early-onset myopathy with fatal cardiomyopathy;	AD paternal	0/1	0/0	0/0
DIAPH1	chr5	C	T	missense variant	rs374788809; COSV105875275	Uncertain significance	Autosomal dominant nonsyndromic hearing loss 1; Progressive microcephaly-seizures-cortical blindness-developmental delay syndrome	AD paternal	0/1	0/0	0/0
ITCH	chr20	A	G	missense variant	rs764016207	Uncertain significance	Developmental delay; Intellectual disability	AD paternal	0/1	0/0	0/0
ALG9	chr11	T	C	missense variant	rs782350313	Uncertain significance	ALG9 congenital disorder of glycosylation	AD maternal	0/1	0/1	0/1
SH2B1	chr16	G	A	missense variant	rs375578823	Uncertain significance	Early-Onset Obesity; Insulin Resistance	AD paternal	0/1	0/1	0/1
KISS1R	chr19	C	T	missense variant	rs924223910	Uncertain significance	Hypogonadotropic hypogonadism 8 with or without anosmia;	AD maternal	0/1	0/1	0/1
PADI3	chr1	G	A	missense variant	rs150695491	Uncertain significance	Central Centrifugal Cicatricial Alopecia (CCCA)	AD paternal	0/1	0/1	0/1
PRKAG2	chr7	G	A	missense variant	rs41317142; COSV55232567	Uncertain significance	Cardiovascular phenotype; Cardiomyopathy; Hypertrophic cardiomyopathy 6; Wolff-Parkinson-White pattern; Lethal congenital glycogen storage disease of heart; PRKAG2 cardiac syndrome; Hypertrophic cardiomyopathy	AD paternal	0/1	0/1	0/0
TNFRSF13B	chr17	G	A	missense variant	rs375891337; COSV55425819	Uncertain significance	Immunodeficiency; common variable; 2	AD maternal	0/1	0/1	0/0
KCNJ16	chr17	G	A	missense variant	rs200564862; COSV52254859	Uncertain significance	Hypokalemic tubulopathy and deafness	AD paternal	0/1	0/1	0/0
PMS2	chr7	T	C	missense variant	rs2128747431	Uncertain significance	Lynch Syndrome; Hereditary cancer-predisposing syndrome;	AD maternal	0/1	0/0	0/1
RBP3	chr10	C	T	missense variant	rs782449660	Uncertain significance	Retinal dystrophy;	AD maternal	0/1	0/0	0/1
OCA2	chr15	G	A	missense variant	rs372899234; COSV100667606; COSV62337373	Uncertain significance	Tyrosinase-positive oculocutaneous albinism; skin/hair/eye pigmentation 1; blue/nonblue eyes;	AD maternal	0/1	0/0	0/1

VDR	chr12	C	T	missense variant	rs773813445; COSV57469533	Uncertain significance	Vitamin D-dependent rickets type II with alopecia; osteoporosis;	AD maternal	0/1	0/0	0/0
Loss of Function											
HRNR	chr1	C	CAG	frameshift variant	rs1557842699	no clinvar	Psoriasis & Ichthyosis; Atopic Dermatitis (Eczema)	AR hom parent affected	1/1	1/1	1/1
HLA-DRB1	chr6	G	A	stop gained; splice region variant	rs17882084; COSV106513787; COSV63512913	no clinvar	Multiple Sclerosis	AR hom unknown	1/1	-/-	1/1
OR52E1	chr11	C	T	stop gained	rs117343856	no clinvar	Parkinson's Disease; Alzheimer's Disease	AD maternal	0/1	0/0	0/1
ZNF45	chr19	C	CG	frameshift variant	rs1353073818	no clinvar	Schizophrenia and developmental dyslexia; Alcohol Use Disorder (AUD)	AD paternal	0/1	0/0	0/1
SPATA31A3	chr9	G	A	stop gained	rs1185140274	no clinvar	Autism Spectrum Disorders (ASD);	AD paternal	0/1	0/0	0/0
SLC4A3	chr2	G	GC	frameshift variant	rs766665904	no clinvar	Short QT Syndrome 7 (SQTS7); Idiopathic Generalized Epilepsy (IGE)	AD paternal	0/0	0/1	0/0
USP17L15	chr4	G	A	stop gained	rs181172003	no clinvar	Cancers; Inflammation;	AR hom parent affected	1/1	1/1	1/1
TRIM7	chr5	G	A	stop gained	-	no clinvar	Cancers and Tumor Progression	AD maternal	0/1	0/1	0/1
LILRB3	chr19	A	C	stop gained	rs16985497	no clinvar	Inflammation; Cancers;	AD both parents	0/1	0/1	0/1
SPANXC	chrX	T	TTGGC	frameshift variant		no clinvar	Cancers and Tumor Progression	X-linked paternal	0/1	0/0	0/1
SUMO3	chr21	ACAAGCCCTGGAAAGGAAAGCAGTGGCCATTAGTCTCACTGG	A	splice acceptor variant; coding sequence variant; intron variant	rs1448853522	no clinvar	Achalasia-Addisonianism-Alacrimia syndrome; Familial hypoparathyroidism; Brachydactyly Type A1	AD paternal	0/1	0/1	0/1
HS3ST6	chr16	C	CG	frameshift variant	rs573199046	no clinvar	Hereditary Angioedema (HAE)	AD maternal	0/1	0/0	0/0
Compound Heterozygous											
ANK2	chr4	G	A	missense variant	rs141013157; COSV99999594	Conflicting	Cardiovascular phenotype; Long QT syndrome; Cardiac arrhythmia; ankyrin-B-related	AR	0/1	0/0	0/1
	chr4	A	T	missense variant	rs776735614	VUS	Long QT syndrome	AR	0/1	0/1	0/0

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FCGBP	chr19	A	C	missense variant	rs143773902; COSV108783328;	no clinvar	Crohn's disease;	AR	0/1	0/0	0/0
	chr19	GGGC	G	inframe deletion	rs782081435	no clinvar	Cancers	AR	0/1	0/1	0/0
NEB	chr2	A	G	missense variant	rs2153730770	no clinvar	Nemaline myopathy 2	AR	0/1	0/0	0/0
	chr2	C	T	missense variant	rs876657540	Conflicting		AR	0/1	0/1	0/1
TEX15	chr8	T	C	missense variant	rs144234582	Conflicting	Spermatogenic failure 25	AR	0/1	0/0	0/0
	chr8	ATTG	A	inframe deletion	rs368254330	no clinvar		AR	0/1	0/1	0/0
UMODL1	chr21	G	A	missense variant	rs200089575	VUS	Kallmann syndrome; Down syndrome; Bipolar affective disorder	AR	0/1	0/0	0/1
	chr21	C	A	missense variant	rs144736191; COSV68569427	VUS		AR	0/1	0/1	0/1
De novo											
GDF1	chr19	A	T	missense variant	rs772809060; COSV99439130	VUS	Progressive Myoclonic Epilepsy;	*de novo*	0/0	0/1	0/0
X-linked											
ACTRT1	chrX	G	T	missense variant	rs141145093; COSV64418938	VUS	Acephalic Spermatozoa Syndrome	X-linked	1	1	0/1
ARHGAP4	chrX	G	A	missense variant; splice region variant	rs374827115; COSV100604177	VUS	X-Linked Intellectual Disability; Nephrogenic Diabetes Insipidus	X-linked	1	0	0/0
VCX2	chrX	G	A	missense variant	rs201185727	VUS	Intellectual/Cognitive Disability	X-linked	0/1	0	0/0
VCX3B	chrX	G	A	missense variant	rs376250913; COSV66842319	VUS	Spermatogenesis	X-linked unknown	1	0	0/0
SPANXC	chrX	T	TTGGC	frameshift variant	-	no clinvar	Cancers	X-linked paternal	0/1	0	0/1

* - re-classified variants/flagged submission. AD: autosomal dominant; ALT: alternative; AR: autosomal recessive; CHR: chromosome; REF: reference; rsID: reference sequence ID;

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Table 2 – Common genetic variants in probands

Combinations	Genes
Common to all probands	IL10, GALC, USH2A, AFF3, ATP9A, NEB, UMODL1, HRNR
Common to probands 1 and 3	KMT2C, ATXN2, UMODL1 (compound heterozygous), HLA-DRB1, OR52E1, ZNF45
Common to probands 1 and 2	SLC39A8, ANK2, PODXL
Proband 1 only	SLC12A3, AARS1, ASPM, TTN, DIAPH1, ITCH, SPATA31A3, NEB, TEX15, ARHGAP4, VCX2
Proband 2 only	SLC4A3, GDF1 (*de novo*)

DISCUSSION

In the current study, we recruited a family with multiple neurological conditions. WES did not identify any pathogenic or likely pathogenic variants in genes directly connected to neurological and neurodevelopmental conditions. However, we identified P/LP variants in IL10 (rs1800896), CDKN2B (rs1063192), GALC (rs138577661), and SLC12A3 (rs775765261) genes. Interleukin-10 is an anti-inflammatory agent. Many of its genetic variants are associated with conditions and diseases, including infections, cancers, and premature birth [12-16]. However, Ishizaki et al. reported that an IL10 gene variant was associated with febrile seizures (FS) [17]. Hoshino et al. found an association between IL6 and IL10 polymorphisms and encephalopathy in Japanese patients [18]. Xia et al. reported significant differences in IL10 gene polymorphisms between patients with CP and controls [19]. The -1082 A/G variant of the IL10 gene is in the promoter region, has a minor allele frequency (MAF) of 40%, does not change the protein's amino acid sequence, and affects only expression levels; it was reclassified as benign. CDKN2B gene encodes p15INK4b, a cyclin-dependent kinase inhibitor, a human tumor suppressor gene located on chromosome 9p21.3. A LP variant (rs1063192) of the CDKN2B gene was associated with glioma [20]. However, in the latest criteria update, the rs1063192 variant of the CDKN2B gene was reclassified as benign because it is located in the gene's regulatory region and does not change the protein sequence. GALC gene encodes galactocerebrosidase, and its deficiency causes Krabbe disease, a severe lysosomal neurodegenerative condition. Feo et al. reported a high prevalence of GALC gene variants in adults with neurodegenerative conditions [21]. All three probands and their mother are heterozygous carriers of the rs138577661 missense variant of the GALC gene. To date, no reports link heterozygous GALC alleles to any neurological conditions. SLC12A3 gene encodes the thiazide-sensitive sodium-chloride co-transporter (NCC), a protein responsible for salt reabsorption in the kidneys' distal convoluted tubules and associated with Gitelman syndrome (GS) [22]. In addition, all probands have common heterozygous VUS variants in USH2A, AFF3, ATP9A, NEB, and UMODL1. Variants in these genes are associated with Usher syndrome [23], intellectual disability [24], attention deficit hyperactivity disorder (ADHD) [25], and nemaline myopathy 2 [26], respectively.

Since probands 1 and 3 are diagnosed with ASD, we identified common variants they share that are associated with a neurological background. In addition to the genetic variants shared by all three probands, probands 1 and 3 share common variants in KMT2C, ATXN2, HLA-DRB1, OR52E1, ZNF45, and UMODL1 (compound heterozygous). All variants are heterozygous, except HLA-DRB1. OR52E1 and ZNF45 have no clinical reports of NDs or NDDs. Despite heterozygosity, variants of KMT2C are associated with Kleefstra Syndrome 2, characterized by developmental delay, intellectual disability, seizures, and speech delay [27], and with ASD [28]. ATXN2 gene variants are associated with spinocerebellar ataxia type 2, which is often associated with poor coordination of hands, speech, and eye movements. A review of different clinical features among SCA subtypes was recently published describing the frequency of non-cerebellar features, like Parkinsonism, chorea, pyramidalism, cognitive impairment, peripheral neuropathy, seizures, etc. [29]. Probands 1 and 3 both have a homozygous HLA-DRB1 LoF variant, which leads to a p.Gln125Ter substitution and a premature stop codon. HLA-DRB1 gene encodes a critical major histocompatibility complex (MHC) class II beta chain and is associated with multiple sclerosis susceptibility [30]. However, Lu et al. reported an association between HLA-DRB1 polymorphism and Alzheimer's disease in Chinese patients [31]. Guerini et al. found a significant association of HLA-A, -B, -C and -DRB1 genetic variants with ASD in Italian children [32]. The UMODL1 (Uromodulin-like 1) gene encodes modular proteins containing structural domains such as EGF-like, WAP, and zona pellucida regions, and is located on human chromosome 21q22. Currently, the UMODL1 gene is investigated in relation to neurodevelopmental or psychiatric conditions like Down syndrome and bipolar affective disorder due to its chromosomal location [33].

Probands 1 and 2 are males; they additionally share heterozygous variants in the SLC39A8, ANK2, and PODXL genes. SLC39A8 encodes the ZIP8 protein, a vital metal-ion transporter, and is associated with a rare congenital disorder of glycosylation that can lead to severe developmental delay, low muscle tone, and intellectual disability; it is also associated with ASD [34]. Mutations in the ANK2 gene can cause ankyrin-B syndrome or ANK2-related syndrome, which affects the brain and heart because the encoded ankyrin-B protein helps to stabilize ion channels and support proper neuronal and cardiac cell connections [35]. Affecting the brain can lead to neurodevelopmental conditions such as ASD, developmental delays, intellectual disability, speech impairments, learning difficulties, and epilepsy or seizures [36]. The PODXL gene encodes an anti-adhesive sialomucin in the CD34 family, and its pathogenic variants are linked to certain forms of early-onset Parkinson disease and atypical juvenile parkinsonism [37].

Two out of three siblings have individual variants. Interestingly, proband 3, a girl, has no "personal" variants. Proband 1 has heterozygous VUS in SLC12A3, AARS1, ASPM, TTN, DIAPH1, and ITCH; LoF heterozygous mutations in SPATA31A3, NEB, and TEX15; and X-linked variants in AR-

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HGAP4 and VCX2, which the other 2 siblings don't have. Many of these gene variants are associated with NDs and NDDs, such as developmental and epileptic encephalopathy 29 (AARS1) [38], ASD (SPATA31A3) [39], and X-linked intellectual disability (ARHGAP4) [40].

Proband 2, the only proband diagnosed with epilepsy and with seizures, has only 2 gene variants that were recorded in the ClinVar database. This proband has a heterozygous frameshift variant in SLC4A3, which leads to LoF. The SLC4A3 gene encodes anion exchange protein 3 (AE3), a membrane transporter that regulates intracellular pH and chloride-bicarbonate balance in the heart and brain, and is associated with short QT syndrome 7 (SQT7) and idiopathic generalized epilepsy (IGE) [41]. Additionally, we identified only one *de novo* variant in the family, and it is a heterozygous variant in the GDF1 gene (VUS, c.38T>A; p.Leu13His). GDF1 gene encodes growth differentiation factor 1 and is associated with progressive myoclonic epilepsy 8 (EPM8) [42, 43].

WES of this Kazakhstani family with multiple neurological and neurodevelopmental conditions revealed a complex genetic landscape, with no single pathogenic or likely pathogenic variant in an established neurological or neurodevelopmental disease gene that could explain the phenotypic spectrum observed among the three probands. Instead, we identified multiple variants with different inheritance patterns and potential biological relevance.

The shared variants in several genes among the affected siblings suggest that their phenotypes may reflect a complex genetic background rather than a single monogenic disorder. Of particular interest, probands 1 and 3, both diagnosed with autism spectrum disorder, shared variants in KMT2C, ATXN2, HLA-DRB1, OR52E1, ZNF45, and UMODL1, including a homozygous loss-of-function HLA-DRB1 variant and compound-heterozygous UMODL1 variants. Although some of these genes have previously been implicated in neurological, neurodevelopmental, immune, or psychiatric phenotypes, the identified variants cannot currently be considered causative for ASD without additional segregation and functional evidence.

Proband 2, who presented with epilepsy and seizures, carried a heterozygous loss-of-function variant in SLC4A3, a gene with reported associations with epilepsy and cardiac electrophysiological abnormalities. We also identified a heterozygous *de novo* GDF1 variant in this proband. These findings are of potential interest in relation to the epileptic phenotype but require further evaluation before establishing causality.

CONCLUSION

Overall, our findings demonstrate substantial genetic heterogeneity within a single family presenting with different neurological and neurodevelopmental phenotypes. The results highlight the challenges of interpreting rare and uncertain variants identified by WES and emphasize the importance of integrating variant classification, inheritance patterns, segregation analysis, clinical phenotype, and available gene-disease evidence. Further functional studies and accumulation of additional clinical cases will be required to determine the contribution of the identified candidate variants to autism spectrum disorder, epilepsy, and other neurological manifestations in this family.

AUTHOR CONTRIBUTIONS

Conceptualization – A.G. (Aidana Gabdulkayum), S.A., A.G. (Azhar Giniyat), A.A. (Ainur Akilzhanova), D.Y.; Data Curation – A.G. (Aidana Gabdulkayum), A.D., A.Y., D.Y.; Formal Analysis - A.G. (Aidana Gabdulkayum), Zh.M. (Zhanel Mirmanova), A.D., A.A. (Ainur Akilzhanova), D.Y.; Investigation – A.G. (Aidana Gabdulkayum), Zh.M. (Zhanna Medetbekova), A.K., S.A., A.G.(Azhar Giniyat), D.Y.; Validation - A.G. (Aidana Gabdulkayum), Zh.M. (Zhanel Mirmanova), A.D., Zh.M. (Zhanna Medetbekova)., A.K., S.A., A.G. (Azhar Giniyat), A.Y., A.A. (Akbota Aitkulova), D.Y.; Methodology – A.G.(Aidana Gabdulkayum), S.A., A.G.(Azhar Giniyat), A.A. (Ainur Akilzhanova), D.Y.; Resources – Zh.M. (Zhanna Medetbekova), A.K., S.A., A.G.(Azhar Giniyat), D.Y.; Supervision – A.Y., A.A (Ainur Akilzhanova), D.Y.; Visualization – A.G.(Aidana Gabdulkayum), A.D., D.Y.; Funding Acquisition – D.Y.; Writing – A.G.(Aidana Gabdulkayum), D.Y.; Writing – review & Editing – A.G.(Aidana Gabdulkayum), A.G.(Azhar Giniyat), A.Y., D.Y. All authors read and approved the final version of the manuscript.

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БІРНЕШЕ НЕВРОЛОГИЯЛЫҚ АУРУЛАРЫ БАР ҚАЗАҚСТАНДЫҚ ОТБАСЫНЫҢ ГЕНЕТИКАЛЫҚ ТҮСІНІКТЕРІ: КЛИНИКАЛЫҚ ЖАҒДАЙ

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АҢДАТПА

Кіріспе. Неврологиялық аурулар (НА) орталық жүйке жүйесін (ОЖЖ) және перифериялық жүйке жүйесін (ПЖЖ) зақымдайтын аурулар болып табылады. Неврологиялық аурулардың этиологиясы өте алуан түрлі және генетикалық, қоршаған орта, метаболикалық, инфекциялық, иммундық және жүре пайда болған факторларды қамтуы мүмкін. Эпилепсия, балалардың церебралды сал ауруы (БЦСА) және аутизм спектрінің бұзылыстары (АСБ) — көбінесе балалық шақта көрініс беретін клиникалық және генетикалық тұрғыдан гетерогенді неврологиялық және нейродаму бұзылыстары. Бұл аурулардың негізгі клиникалық белгілері әртүрлі болғанымен, олардың арасында айтарлықтай фенотиптік ұқсастық пен коморбидтілік байқалады, бұл олардың ортақ генетикалық және молекулалық механизмдерінің болуы мүмкін екенін көрсетеді. Әдістер. Отбасын зерттеуге тарту, сұхбат жүргізу, клиникалық деректер мен қан үлгілерін жинау «Ұлттық балаларды оңалту орталығы» КЕАҚ базасында жүргізілді. ДНҚ коммерциялық қолжетімді жинақтардың көмегімен бөлініп алынды. Толық экзомды секвенирлеу (WES) DNA Prep with Exome 2.0 Plus Enrichment Kit жинағын пайдалана отырып, NovaSeq 6000 платформасында жүргізілді. Барлық секвенирлеу ридтері DRAGEN платформасының көмегімен адамның GRCh38 (hg38) референстік геномына карталанды. Генетикалық варианттарды аннотациялау VEP 116.0 нұсқасының көмегімен жүргізілді. Нәтижелер. Зерттеуге бірнеше неврологиялық жағдайлары бар отбасы енгізілді. Ата-аналары — отбасылық анамнезінде неврологиялық немесе нейродаму бұзылыстары жоқ қазақ ұлтынан шыққан ер адам мен әйел. Неке туыстық емес. Отбасында үш пробанд бар, оларға сәйкесінше аутизм спектрінің бұзылысы (АСБ), фокальды симптоматикалық эпилепсия және АСБ мен атаксикалық балалар церебралды сал ауруы (БЦСА) диагноздары қойылған. Биоинформатикалық талдау нәтижесінде *IL10, CDKN2B, GALC* және *SLC12A3* гендерінде патогенді/ықтимал патогенді варианттар анықталды. Сонымен қатар, неврологиялық және нейродаму бұзылыстарымен байланысты көптеген гендерде клиникалық маңызы белгісіз варианттар (VUS), функцияның жоғалуына әкелетін (LoF), компаунд-гетерозиготалы, Х-хромосомамен тіркескен варианттар және бір *de novo* мутация анықталды. Қорытынды. Алынған нәтижелер әртүрлі неврологиялық және нейродаму фенотиптері байқалатын бір отбасы шеңберіндегі айқын генетикалық гетерогенділікті көрсетеді. Нәтижелер толық экзомды секвенирлеу арқылы анықталған сирек және клиникалық маңызы белгісіз варианттарды интерпретациялаудың күрделілігін, сондай-ақ варианттардың жіктелуін, тұқым қуалау сипатын, сегрегациялық талдауды, клиникалық фенотипті және ген–ауру байланысы туралы қолжетімді деректерді кешенді бағалаудың маңыздылығын көрсетеді. Анықталған кандидат варианттардың АСБ, эпилепсия және осы отбасындағы басқа неврологиялық көріністердің дамуына ықтимал үлесін анықтау үшін қосымша функционалдық зерттеулер мен клиникалық жағдайлар туралы деректерді жинақтау қажет.

Түйін сөздер: толық экзомды секвенирлеу; неврологиялық аурулар; церебралды сал ауруы; эпилепсия; аутизм спектрінің бұзылысы.

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ГЕНЕТИЧЕСКОЕ ИССЛЕДОВАНИЕ КАЗАХСТАНСКОЙ СЕМЬИ С МНОЖЕСТВЕННЫМИ НЕВРОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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АННОТАЦИЯ

Введение. Неврологические заболевания (НЗ) представляют собой заболевания, поражающие как центральную нервную систему (ЦНС), так и периферическую нервную систему (ПНС). Этиология неврологических заболеваний чрезвычайно разнообразна и может включать генетические, средовые, метаболические, инфекционные, иммуноопосредованные и приобретенные факторы. Эпилепсия, детский церебральный паралич (ДЦП) и расстройства аутистического спектра (РАС) представляют собой клинически и генетически гетерогенные неврологические заболевания и нарушения нейроразвития, которые часто проявляются в детском возрасте. Несмотря на различия в основных клинических проявлениях, между этими состояниями наблюдаются значительное фенотипическое перекрытие и коморбидность, что предполагает наличие общих генетических и молекулярных механизмов. Методы. Набор семьи для участия в исследовании, проведение интервью, сбор клинических данных и образцов крови осуществлялись на базе НАО «Национальный центр детской реабилитации». ДНК выделяли с использованием коммерчески доступных наборов. Полноэкзомное секвенирование (WES) проводили с использованием набора DNA Prep with Exome 2.0 Plus Enrichment Kit на платформе NovaSeq 6000. Все полученные последовательности были картированы на референсный геном человека GRCh38 (hg38) с использованием платформы DRAGEN. Аннотацию генетических вариантов проводили с помощью VEP версии 116.0. Результаты. В исследование была включена семья с несколькими неврологическими и нейроонтогенетическими состояниями. Родители — мужчина и женщина казахской национальности, не имеющие семейного анамнеза неврологических заболеваний или нарушений нейроразвития. Брак неродственный. В семье трое пробандов, у которых диагностированы соответственно расстройство аутистического спектра (РАС), фокальная симптоматическая эпилепсия, а также РАС в сочетании с атаксической формой детского церебрального паралича (ДЦП). Биоинформатический анализ выявил патогенные/вероятно патогенные варианты в генах IL10, CDKN2B, GALC и SLC12A3. Кроме того, были выявлены варианты неопределенной клинической значимости (VUS), варианты с потерей функции (LoF), компаунд-гетерозиготные и X-сцепленные варианты, а также единичный вариант *de novo* в ряде генов, связанных с неврологическими заболеваниями и нарушениями нейроразвития. Заключение. Полученные результаты демонстрируют выраженную генетическую гетерогенность в пределах одной семьи с различными неврологическими и нейроонтогенетическими фенотипами. Результаты подчеркивают сложность интерпретации редких вариантов и вариантов неопределенной клинической значимости, выявленных методом полноэкзомного секвенирования, а также необходимость комплексной оценки классификации вариантов, характера наследования, сегрегации, клинического фенотипа и имеющихся данных об ассоциации генов с заболеваниями. Для определения вклада выявленных кандидатных вариантов в развитие РАС, эпилепсии и других неврологических проявлений в данной семье необходимы дальнейшие функциональные исследования и накопление дополнительных клинических наблюдений.

Ключевые слова: полноэкзомное секвенирование; неврологические расстройства; детский церебральный паралич; эпилепсия; расстройство аутистического спектра.