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Original Article

Genetic Etiologies of an Epilepsy Outpatient Clinic: Single-center Experience

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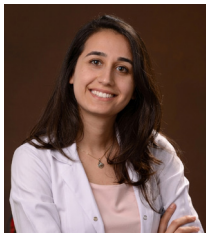

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Abstract

Objective: We aim to documented genetic etiology of epilepsy at a single-center epilepsy outpatient clinic in state hospital.

Methods: The patients' demographic data, clinical and electrophysiologic features, and gene analysis were re-evaluated from medical records of patients with epilepsies between August 2021 and January 2024. The detected variants were searched in gnomAD, ClinVar, DECIPHER, and PubMed databases. The common and distinct features of the phenotype of patients were compared with the literature.

Results: The medical records of 354 patients with epilepsy were reviewed. Forty (11.2%) patients were diagnosed with genetic generalized epilepsy. Among them, 37 patients (10.4%) were diagnosed with idiopathic generalized epilepsy, and 3 patients (0.8%) were diagnosed with epilepsy with eyelid myoclonia. We included patients with epilepsy and confirmed genetic etiology at diagnosis. Nine (2.5%) patients with epilepsy and confirmed genetic etiology were included; seven (1.9%) patients had rare monogenic variants in (*ZNF142, ZMYND11, DLG4, PEX11B, SCARB2* and *GRM-1*) genes and two (0.5%) had chromosomal abnormalities (1p36 deletion and 15q15.1deletion).

Conclusion: This study reported genetic etiologies of epilepsy were determined in single-center state hospital. The reported families demonstrate that similar genotypic variations can lead to different phenotypic outcomes. Indeed, similar phenotypic features may result from two distinct genotypic alterations. Specifying the variants and their phenotypic features with diagnostic tools in every single-center are important starting to investigate across the country.

Keywords: *DLG4*, genetic etiology of epilepsy, genotype, gonadal mosaicism, *SCARB2*, phenotype, *CAPN10-ZMYND11, ZNF142*, 15q15.1

INTRODUCTION

Epilepsy affects almost 4% of the general population over a lifetime.[1] The primary goal of physicians should be to determine the underlying etiology of epilepsy. According to 2017 International League Against Epilepsy (ILAE) classification, one of etiological categories of epilepsy is genetic.[2] Idiopathic generalized epilepsy (IGE) makes up around 25% of all epilepsies.[3] In focal epilepsies, twin studies have shown higher concordance rates of mesial temporal lobe epilepsy in monozygotic twins compared to dizygotic twins.[4] Population studies have shown a 2.5-fold increased risk of focal epilepsy in first-degree relatives of patients with focal epilepsy compared to the general population.[5]

Since the first gene was identified in 1995,[6] thousands of genes have been found to be associated with monogenic epilepsy.[7] In contrast to traditional Sanger sequencing, next-generation sequencing (NGS) technologies enable an entire genome to be sequenced in a single experiment. This technology has transformed the approach to diagnostic testing, allowing multiple genes to be tested simultaneously rather

than one at a time. However, these technologies also increase the likelihood of uncertain results when rare sequence variants are detected in one or more genes.[8] The ILAE genetic literacy series-2 proposed three key questions during the evaluation of patients: 1) Is the gene in question an established genetic etiology for epilepsy? 2) Is the variant in this particular gene pathogenic by established variant interpretation criteria? 3) Is the variant considered causative in the clinical context?[8] This pathway is recommended to assist epileptologists and physicians in interpreting the reported variants.

Identifying the responsible genes which are lead to genetic epileptic etiology can help understanding which genes are common in area and following projects may lead to determine frequency of responsible variants. Detection of responsible variants give direction on diagnostic test protocols, panels and opening new doors for patients treatments. Nowadays, in state hospital there are some of genetic analyses are covered by health insurance. Although, clinical exomes analyses may be accessible with insurance in some areas, moreover disease-related gene panels are used for monogenic disease investigation. The creation of disease-related gene panels or clinical exome sequences based by literatures. This study aimed to document responsible genetic disease and rates of patients with epilepsy whom are genetic etiology at a single-center epilepsy outpatient clinic in a state hospital to get started reporting in across country. Secondly, common and distinct genotype-phenotype correlations were identified based on aforementioned questions.

METHODS

Patients and Procedures

Medical records of patients followed at the epilepsy outpatient clinic at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital were reviewed from August 2021 to January 2024. Epilepsy etiology was classified according to the ILAE classification.[2,9,10] Treatment responses were categorized as seizure-free and drug-resistant epilepsy.[11]

Patients who were diagnosed with genetic etiology during follow-up were included in the study. Systemic and neurological features; age at seizure onset; seizure types; seizure triggers; electroencephalographic and neuro-imaging findings; treatment responses; and family history were recorded from medical records. Patients with a previous diagnosed were excluded. Patients in whom a genetic etiology could not be identified were excluded.

Scalp electroencephalography (EEG) was performed during routine wakefulness and/or sleep recordings in patients with epilepsy. Electrode placement followed the international 10-20 system, using both monopolar and bipolar montages (Fp1, Fp2, F3, F4, T3, T4, P3, P4, O1, O2, Fz, Cz, Pz). Cranial magnetic resonance imaging (MRI) or brain computed tomography (CT) was performed to evaluate brain anatomy, depending on the patient's level of cooperation and cognitive function.

The patients and/or their caregivers were informed that anonymized medical data might be used for academic purposes, and all provided their approval. Written informed consent was obtained from each patient and/or their caregiver. The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (decision no: 2025-323, date: 03.09.2025).

Genetic Analyses

The patients were examined in detailed by corresponding author (Dilara Mermi Dibek), suspected gene was stated if it was determined and they were consulted to medical genetic. The patients with dysmorphism, mental retardation, or presence of history of maternal miscarriage were analyzed for chromosomal abnormalities first.

Array comparative genomic hybridization (CGH) was used to detect chromosomal abnormalities when karyotyping results were normal. The Agilent GeneSure Cyto 8x60K CGH Microarrays system was employed, and results were analyzed using the Agilent CitoGenomics software (v5.2.0.20).

Clinical exome sequencing (CES), whole-exome sequencing (WES), and clinic-specific gene panels were utilized to identify single nucleotide variants.

The "twist CES kit" was used to examine the exon and exon-intron splice regions of panel genes. These regions were amplified using polymerase chain reaction (PCR) and sequenced on a DNBSEQ-G400 (MGI Tech) genetic sequencer via NGS in a patient presenting with congenital cataracts, spontaneous nystagmus, polyneuropathy, and seizure. Sequencing coverage was at least 99.80% at 5x and at least 99.50% at 20x.

For WES, the "TWIST 36Mb capture" kit was used to sequence exon and exon-intron splice regions of panel genes, also amplified by PCR and analyzed on the MGI DNBSEQ-G400 via NGS. Sequencing coverage was at least 99.55% at 5x and at least 99.18% at 20x. One of patients with progressive myoclonia underwent CES targeting a 342-gene panel associated with myoclonic disorders. For a patient with suspected spinocerebellar ataxia, a clinic-specific gene comprising 43 genes was analyzed (Supplementary File 1). Identified variants were reviewed using PubMed, gnomAD, ClinVar, and DECIPHER databases (https://gnomad.broadinstitute.org, https://www.ncbi.nlm.nih.gov/clinvar/, https://www.deciphergenomics.org).

Statistical Analysis

IBM SPSS version 26.0 were used for statistical analysis. The distribution of epilepsy syndrome classifications were calculated with descriptive statistics, and were presented number and percentage (%).

MAIN POINTS

- Establishing a link between a gene variant and the genetic etiology of epilepsy requires an assessment of genotype-phenotype correlation.
- Patients can be affected by mutations in two genes, where as their relatives may carry a mutation in only one gene and present with a different phenotype.
- If variants of uncertain significance are identified, further investigations such as family segregation analyses and in vivo or in vitro functional studies should be conducted.
- Detection and reporting of patients with genetic epilepsy in each epilepsy clinic is important to adjust the diagnostic test protocols and treatment options across the country.

RESULTS

The medical records of 354 patients with epilepsy were reviewed. Forty (11.2%) patients were diagnosed with genetic generalized epilepsy (GGE). Among them, 37 patients (10.4%) were diagnosed with IGE and 3 patients (0.8%) were diagnosed with epilepsy with eyelid myoclonia. Forty-one patients with epilepsy (11.5%) had autism spectrum disorders or/and intellectual disability.

Eight patients with epilepsy (2.2%) who had been previously diagnosed at another epilepsy center before commencing follow-up at our center were excluded. Three patients (0.8%) were diagnosed with neuro-cutaneous syndromes (linear nevus syndrome, n=1; tuberous sclerosis, n=2). Four patients (1.1%) were diagnosed with neuro-metabolic syndromes (galactosemia, n=2; mucopolysaccharidosis, n=2). One (0.2%) patient was diagnosed with Bardet-Biedl syndrome.

Ultimately, we included nine patients with epilepsy (2.5%) in whom an identifiable genetic etiology was established. Of these, seven (1.9%) had rare monogenic variants [zinc finger protein 142 *(ZNF142)*, zinc finger MYND-type containing 11 *(ZMYND11)*, discs large MAGUK scaffold protein 4 *(DLG4)*, peroxisomal biogenesis factor 11 beta *(PEX11B)*, scavenger receptor class B member 2 *(SCARB2)*, and glutamate receptor metabotropic 1 *(GRM-1)*] and two (0.5%) had chromosomal abnormalities (1p36 deletion and 15q15.1 deletion).

Rare monogenic variants in *ZNF142*, *ZMYND11*, *DLG4*, and *SCARB2* were detected using WES. A monogenic variant in *PEX11B* was identified through CES, and a variant in *GRM1* was detected using a locus-specific gene panel for spinocerebellar ataxia.

A 24-year-old male patient presented to the epilepsy outpatient clinic. No significant perinatal history was reported. His parents are consanguineous, and his older brother (currently 35 years old) has a progressive speech disorder. However, the brother has no history of epilepsy, except for a single febrile seizure at the age of 2. The family pedigree is shown in Figure 1A. The patient experienced febrile seizures until the age of 8. After discontinuation of antiseizure medication (ASM), he developed motor convulsive status epilepticus with coma at the age of 20. Since then, he has been seizure-free under treatment with valproic acid (1000 mg/day). He is able to walk independently, but he exhibits cognitive decline and progressive speech disorder, although he had acquired speech by the age of 4. He also presents with renal agenesis, without evidence of renal failure. Notably, no hyperkinetic or hypokinetic movement disorders have been observed up to the age of 24. EEG during wakefulness showed background activity characterized by diffuse theta and delta frequencies (Figure 2A). Sleep graphoelements appeared synchronous and symmetric during stage II non-rapid eye movement (NREM) sleep. Cranial MRI was normal. The chromosomal microarray analysis revealed normal results: -arr[hg38] (1-22)x2, (X,Y)x1. WES identified a homozygous pathogenic variant in the *ZNF142* gene [(NM_001105537.4: c.3175 C>T), (NP_001099007.1:p.Arg1059Ter)], located at chr2:219508064 (patient no. 1 in Table 1).

A 23-year-old female patient (patient no. 2 in Table 1) was first evaluated in the EEG laboratory during an episode of non-convulsive status epilepticus (NCSE) with coma, following a bilateral tonic clonic motor seizure triggered by a respiratory infection (pneumonia), and accompanied by severe hyponatremia (Na:113 mEq/L). After treatment of the metabolic disturbance and infection, the NCSE resolved, and she recovered without sequelae. She had hypoxic birth and was hospitalized for one week in the neonatal intensive care unit. There is no biological relationship between her parents. Her younger brother has similar dysmorphism and has a history of seizures. The patient demonstrates cognitive decline and significant speech impairment, with a vocabulary limited to 5-10 words without evidence of progressive loss. Dysmorphic features include ocular hypotelorism, low posterior hairline, flat nasal bridge, and short stature. She began walking at age 4, although she had Achilles tendon contractures. She is ambulatory with support. She has been diagnosed with diabetes mellitus, hypothyroidism and hypergonadotropic hypogonadism. Seizures began at the age of 1 year. Infections and metabolic disturbances are primary seizure triggers. Seizures typically present as status epilepticus. In the absence of t metabolic imbalance or infection, she remains seizure-free under treatment with valproic acid (800 mg/day). Brain CT showed no gross pathology. EEG revealed slow background activity with bifrontal or left frontal spike and wave discharges, sometimes recorded as bilateral hypersynchronous. Less frequently, occipital spike-and-wave were recorded. (Figure 3A, B). Her younger brother, aged 15 (patient no.3 in Table 1), had no significant perinatal complications. He has

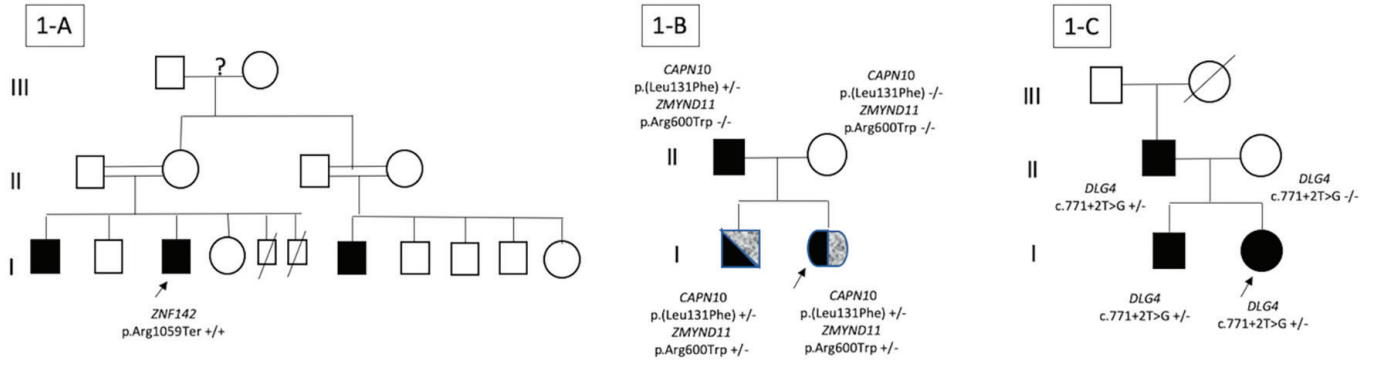

Figure 1. The pedigrees of the selected patients. Circles and squares indicate females and males, respectively. Solid symbols indicate affected individuals. +/+: Homozygous, +/−: +/−, heterozygous variant; −/−, homozygous reference. 1-A. The pedigree of patients with *ZNF142* homozygotes mutation (patient no.1 in Table 1). 1-B. The pedigree of patients with *CAPN10* with and without *ZYMND11* gene heterozygotes mutations (patient no.2 and no.3 in Table 1). 1-C. The pedigree of patients with *DLG4* heterozygotes mutation (patient no.4 in Table 1)

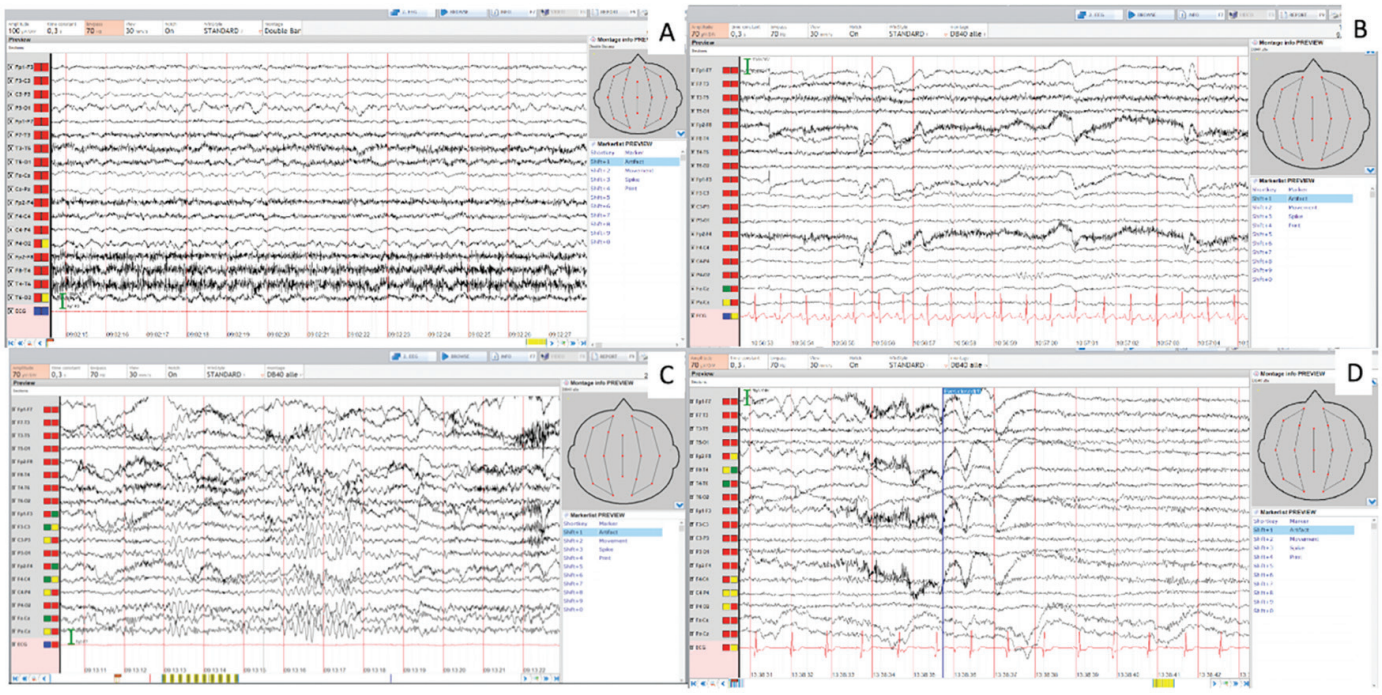

Figure 2. The EEG captures of the patients with changes on background activity. A. Slow background activity without epileptiform abnormality on EEG at the patients with *ZNF142* mutation (patient no.1 in Table 1). B. Slow background activity without epileptiform abnormality on EEG at the patients with *DLG4* mutation (patient no.4 in Table 1). C. Paroxysmal theta activity with higher amplitude on slow background activity on EEG at the patients with *PEX11B* mutation (patient no.5 in Table 1). D. Fast frequency and low amplitude in background activity on EEG at the patients with *GRM1* mutation (patient no.7 in Table 1)
EEG: Electroencephalography

a history of occasional seizures, typically triggered by metabolic disturbances or infections, but no history of status epilepticus. He exhibits similar dysmorphic features, including a depressed nasal bridge, ocular hypotelorism, low posterior headline, and short stature, but he does not have Achilles tendon contractures. He is ambulatory. He has cognitive decline. Although his speech is impaired, he can form sentences, with communication ability better than his sister's. He has also been diagnosed with diabetes mellitus and hypothyroidism. His EEG demonstrated slow background activity with bilateral fronto-centro-parietal sharp and spike-and-wave discharges, and bilateral hypersynchrony during NREM sleep without normal sleep graphoelements (Figure 3C, D). The mother has no notable phenotypic abnormalities. The father has diabetes mellitus but normal cognitive and motor development, and no history of seizures. His EEG during wakefulness was normal. During stage II NREM sleep, sleep graphoelements were synchronous and symmetric, though a transient left frontocentral asymmetric theta sharp contoured-slowing was observed (Figure 3E, F). Three family members- the father, daughter (patient no.2 in Table 1), son (patient no.3 in Table 1) have a calpain 10 (*CAPN10*) gene variation, while the mother did not. Chromosomal microarray analysis of patient no.2 normal: arr(1-22,X)x2. Additionally, WES revealed a heterozygous pathogenic variant in the *ZMYND11* gene [(NM_001370100.5 c.1798C>T), (NP_001357029.1:p.(Arg600Trp)] in both patient no.2 and patient no.3, but not in either parent. The family pedigree is shown in Figure 1B.

An 18-year-old female patient presented to the epilepsy outpatient clinic, there is no known consanguinity between her parents. Her mother, aged 40, had epilepsy during childhood but has remained seizure-free without ASM treatment since the age of 11. Her father, aged 43, has mild intellectual disability and mild dysphasia, he can speak comprehensively but has no history of seizures or musculoskeletal, cardiac, or gastrointestinal system disorders. Her 14-year-old brother has a intellectual disability and his speech more developed than his sister's but less developed than his father's. He also has long, thin, and elastic fingers, consistent with digital deformity. He does not present with seizures or other systemic abnormalities. The pedigree is shown in Figure 1C. The patient demonstrates cognitive decline and restricted-but non-progressive-speech ability. She required incubator care during the first week of life due to neonatal jaundice. Her first afebrile seizure, a bilateral tonic seizure, occurred in the neonatal period. After a seizure-free interval, she experienced a unknown onset bilateral tonic clonic motor seizure at age 7. She was initially treated with valproic acid, and seizures occured once or twice per month. No specific seizure triggers were identified. She has remained seizure-free for the past 3 years with on carbamazepine monotherapy. Neurological examination revealed limited left horizontal gaze, while other gaze directions were preserved. Motor development was normal, though she exhibited a mildly ataxic gait. Both Hoffman and Babinski reflexes were positive. She also had a history of patent ductus arteriosus and gastroesophageal reflux. EEG during wakefulness showed normal background activity (Figure 2B); however, poor morphology of sleep graphoelements was noted during stage II NREM sleep. Cranial MRI showed no gross abnormalities. Chromosomal microarray analysis was normal: arr[hg19] (1-22,X) x2 in the index case. WES identified a heterozygous pathogenic variant in the *DLG4* gene [(NM_001365.4: c.771+2T>G)] in the index patient, her father and her younger brother. The variant was not detected in her mother (patient no.4 in Table 1).

Table 1. Clinical and genetic features of the patients with monogenic variants and epilepsy

No, age (years), sex	Seizure onset	Seizure type	Other system symptomes	EEG	MRI/CT	Response of ASMs	Genetic analysis	Gene variants	Disease
No.1 24, M	2y febrile seizure 19y status epilepticus	Unknown onset bilateral tonic-clonic motor	CD, progressive speech disorders, renal agenesis	Slow background activity, Poor morphological changes in sleep grapho elements	Normal	Seizure free with VPA 1000 mg/day	NGS-WES	*ZNF142* Chr2 c.3175 C>T (p.Arg1059Ter) Homozygotes	Neurodevelopmental disorder with impaired speech and hyperkinetic movements
No.2 23, F	1y	Status or nonconvulsive status epilepticus triggered by infection or metabolic disturbances, unknown onset bilateral tonic-clonic motor	MMR, short stature, microcephaly typical face: ocular hypotelorism, low nape, flat nose, achilles contracture, hypogonodothropic hypogonadism hypothyroidism, DM	Slow background activity, diffuse slow and sharp waves	Normal	Seizure free with VPA 800 mg/day	CAPN10 gene analysis, NGS-WES	*CAPN10* c.391C>T, p.Leu131Phe Heterozygotes *ZMYND11* c1798C>T p.(Arg600Trp) Heterozygotes	Kalpain 10- Intellectual developmental disorder, autosomal dominant
No.3 15, M	4y	Unknown onset bilateral tonic-clonic motor	MMR, Short stature, microcephaly, typical face: ocular hypotelorism, low nape, flat nose, hypothyroidism, DM	Slow background activity, diffuse slow and sharp waves	NA	Low drug compliance, Refuse the usage of ASMs	CAPN10 gene analysis, NGS- WES	*CAPN10* c.391C>T, p.Leu131Phe Heterozygotes *ZMYND11* c1798C>T p.(Arg600Trp) Heterozygotes	Kalpain 10- Intellectual developmental disorder, autosomal dominant
No.4 18, F	1y	Unknown onset bilateral tonic-clonic motor	CD, partial ophtalmoparesis, ataxia, patent ductus arteriosus, gastro eusofageal reflux	Fast atenuated rhythm on background activity	Normal, coinsidental septum pellusidum	Seizure free with CBZ 800 mg/day	NGS- WES	*DLG4* c.771+2T>g Heterozygotes	Intellectual developmental disorder, autosomal dominant 62 wes
No.5 34, M	3y-11y febril and afebril seizures 32y afebril bilateral tonic-clonic seizures	Unknown onset bilateral tonic-clonic motor	MMR, Infantil cataract operation, spontanous nystagmus, sensorial neuropathy	Slow background activity with sharp contured high amplitüde paroxysmal sinusoidal transients	Cortical athrophy	Seizure free with LEV 1250 mg/day	NGS-CES	*PEX11B* chr1 c.595C>T Homozygotes	Peroksizom biogenesis disorders PBD14B
No.6 53, M	47y	Myoclonia triggered with photic stimulations, positive and negative myoclonia	Progressive tremor and myoclonia, parkynsonism	Slow bacground activity with generalized polyspikes, eye closed sensitivity with bioccipital spikes and waves photosensitivity: extremity myoclonia in IPS	Normal	DRE: progressive myoclonia despite of CLZ 4 mg/day, TPM 200 mg/day	342 genes related to myoclonia in WES	*SCARB2* chr4 c.1113+6T>A Homozygotes	Epilepsy progressive myoclonus 4 w/wo RF- EPM4C
No.7 20, M	3 months-infantil	Tonic, unknown onset bilateral tonic-clonic motor	MMR, dysphonic speech, spontanous rotatuar nystagmus, bilateral dysmetri, dystonic tremor, hipothyroidism	Fast atenuated rhythm on background activity	Cerebellar athrophy	DRE: 3-4 in a years with VPA 1000 mg/day, OXC 750 mg/day	NGS- 43 genes related to spinocerebellar ataxia panel	*GRM-1* (SCA-44) c.1610G>A p.(Arg537Gln) missense heterozygotes	Spinoserebellar ataksi-44

ASMs : Antiseizure medications, F: Female, M: Male, *CAPN10*: Calpain 10, CBZ: Carbamazepine, CES: Clinical exome sequencing, CLZ: Clonazepam, CD: Cognitive decline, *DLG4*: Discs large MAGUK scaffold protein 4, DM: Diabetes mellitus, DRE: Drug-resistant epilepsy, *GRM-1*: Glutamate receptor metabotropic 1, LEV: Levetiracetam, MMR: Mental-motor retardation, NA: Not applicable, NGS: New genome sequencing, OXC: Oxcarbazepine, *SCARB2*: Scavenger receptor class B member 2, *PEX11B*: Peroxismal biogenesis factor 11 beta, TPM: Topiramate, WES: Whole exome sequencing, VPA: Valproic acid, *ZMYND11*: Zinc finger MYND-type containing 11, *ZNF142*: Zync finger protein 142, EPM: Epilepsy, progressive myoclonus 4C, MRI/CT: Magnetic resonance imaging/computed tomography

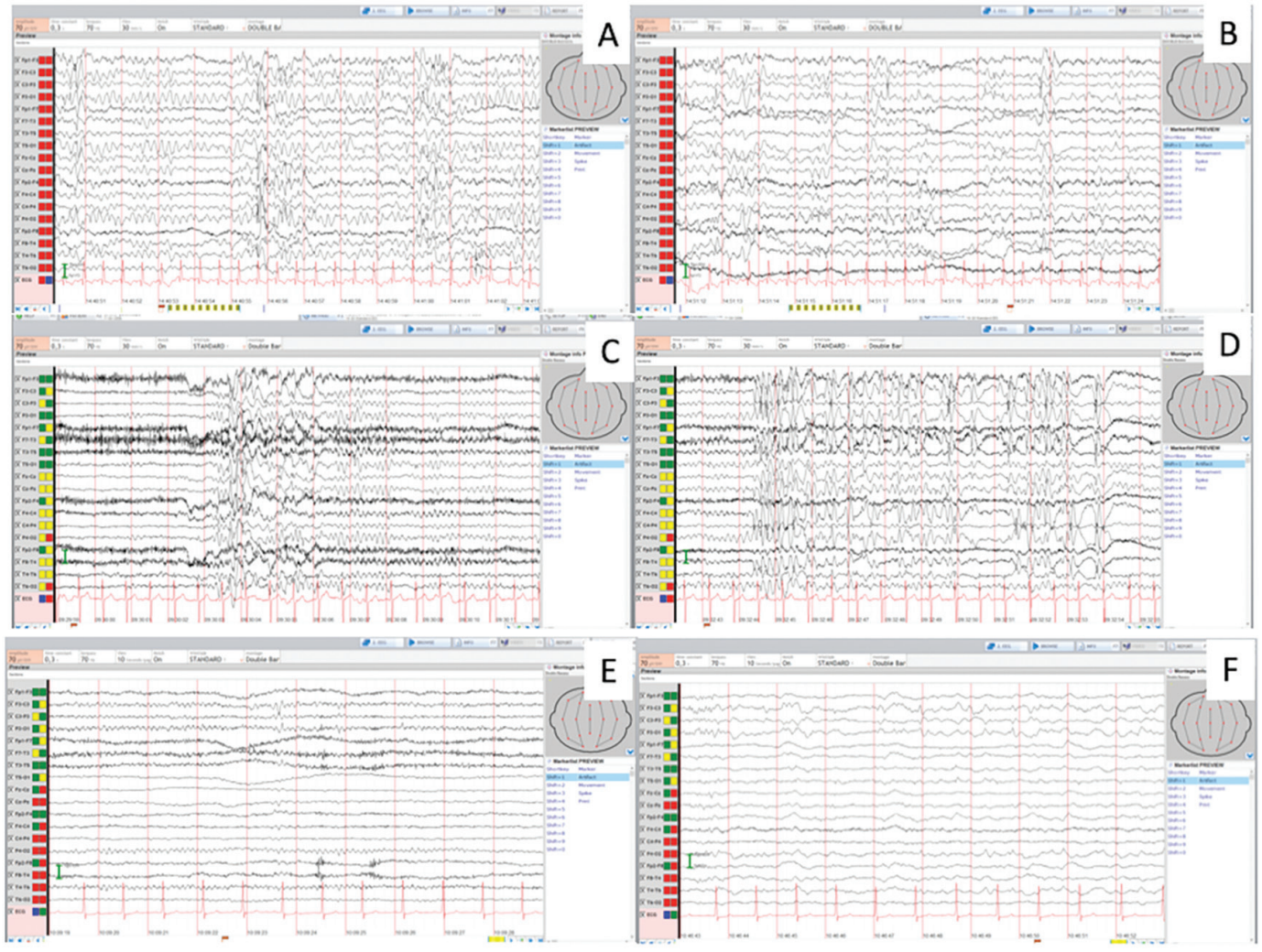

Figure 3. The EEG captures of the family members with mutation in *CAPN10* whit or without *ZMYND11*. A. Slow background activity and bilateral centroparietal sharp wave during wakefulness under 1000 mg/day VPA treatment; B. Left frontal spike and waves during NREM sleep stage at patient with mutation at *ZMYND11* and *CAPN10* (patient no.2 in Table 1); C. Left fronto-centroparietal predominant bilateral spike and sharp waves during wakefulness without treatment. D. Bilateral fronto-centroparietal predominant generalized sharp and waves during NREM sleep stage at patient with *ZMYND11* and *CAPN10* mutation (patient no.3 in Table 1). E. Normal background activity. F. Left centroparietal asymmetry and sharp waves during NREM II sleep stage at father of (patient no.2 and 3 in Table 1), who has *CAPN10* mutation without *ZMYND11* mutation
EEG: Electroencephalography, NREM: Non-rapid eye movement

A 34-year-old male patient presented to the epilepsy outpatient clinic with history of cognitive decline and motor retardation. He is ambulatory with the assistance of a wheelchair. His parents are consanguineous, he had no siblings, and there is no significant family history of neurological disorders. The patient experienced febrile seizures beginning at the age of 3 and was treated with valproic acid until age 11. Following a seizure-free period, ASM was gradually tapered and discontinued. At the age of 32, he experienced a unknown onset bilateral tonic clonic seizure without an identifiable trigger, after which levetiracetam was initiated. Since ten, he has had fewer than one seizure per year, typically occurring in the context of respiratory infections. He underwent bilateral cataract surgery at the age of 2 years and demonstrated spontaneous nystagmus and restricted horizontal gaze to the right. Although, he did not exhibit overt ataxia, sensorial polyneuropathy was identified via electroneuromyography. He also had a history occasional micturition syncope. EEG during wakefulness revealed background activity consisting of 5-6 Hz theta frequency. Additionally, paroxysmal sinusoidal activity with sharp contours and higher amplitude than background were observed at 7-7.5 Hz (Figure 2C). Cranial MRI showed mild to moderate cerebral cortical atrophy. CES identified a homozygous pathogenic variant in the *PEX11B* gene [(NM_003846.3: c.595C>T), NP_003837.1:(p. Arg199Ter)] located at chr1:145522734. Both parents were found to be heterozygous carriers of the same variant (patient no.5 in Table 1).

A 53-year-old male patient initially presented to EEG laboratory. His perinatal and family history were unremarkable. He was a retired insurance agent. His symptoms began six years prior to presentation, initially with fine hand jerks and low-amplitude tremors. Despite two years of treatment with primidone and propranolol, postural and kinetic tremors progressed, and sudden jerky hand movements emerged. Over time, he developed

progressively slow movements and speech. Eventually, he experienced falls without loss of consciousness, attributed to sudden myoclonic jerks. Neurologic examination revealed bradyphrenia, bradymimia, monotonous speech with hypophonia, bradykinesia predominantly affecting the left hand, and mild bilateral dysmetria without postural instability. Zonisamide and clonazepam were prescribed for myoclonus but yielded limited benefit. EEG performed during wakefulness showed background activity consisting of slow 5-6 Hz theta frequency. Bi-occipital predominance spike-and-wave discharges were observed with eyes closed (eye closed sensitivity). Additionally, photic stimulaton elicited photosensitivity and myoclonic activity in the upper extremities, coinciding with generalized polyspikes-and-wave discharges (Figure 4D-F). Cranial MRI showed no gross structural abnormalities. Clinically combination of symptoms and EEG findings was consistent with mild parkinsonism and progressive myoclonus. CES of 342 genes associated with myoclonus revealed a homozygous variant of uncertain significance in the *SCARB2* gene, NM_005506.4: c.1113+6T>A, located at chr4:77091014. This gene is implicated in progressive myoclonic epilepsy type 4 (PME4), with or without renal involvement. A full list of the analyzed genes is provided in Supplementary File 1 (patient no.6 in Table 1).

A 20-year-old male patient presented to the epilepsy outpatient clinic. There was no known biological relationship between his parents. He had an older brother and mother who were alive; his father was deceased. The family history was otherwise unremarkable. The patient experienced focal clonic and focal to bilateral tonic-clonic seizures. While receiving treatment with oxcarbazepine and valproic acid, seizure frequency was reduced to 3-4 times per year. In addition to cognitive decline, neurological examination revealed spontaneous rotatory nystagmus, bilateral asymmetry, an ataxic gait, and mild dystonic tremor. Cranial MRI demonstrated cerebellar atrophy (Figure $5A_{1,2,3}$). EEG revealed fast frequency, low amplitude background activity (Figure 1D).

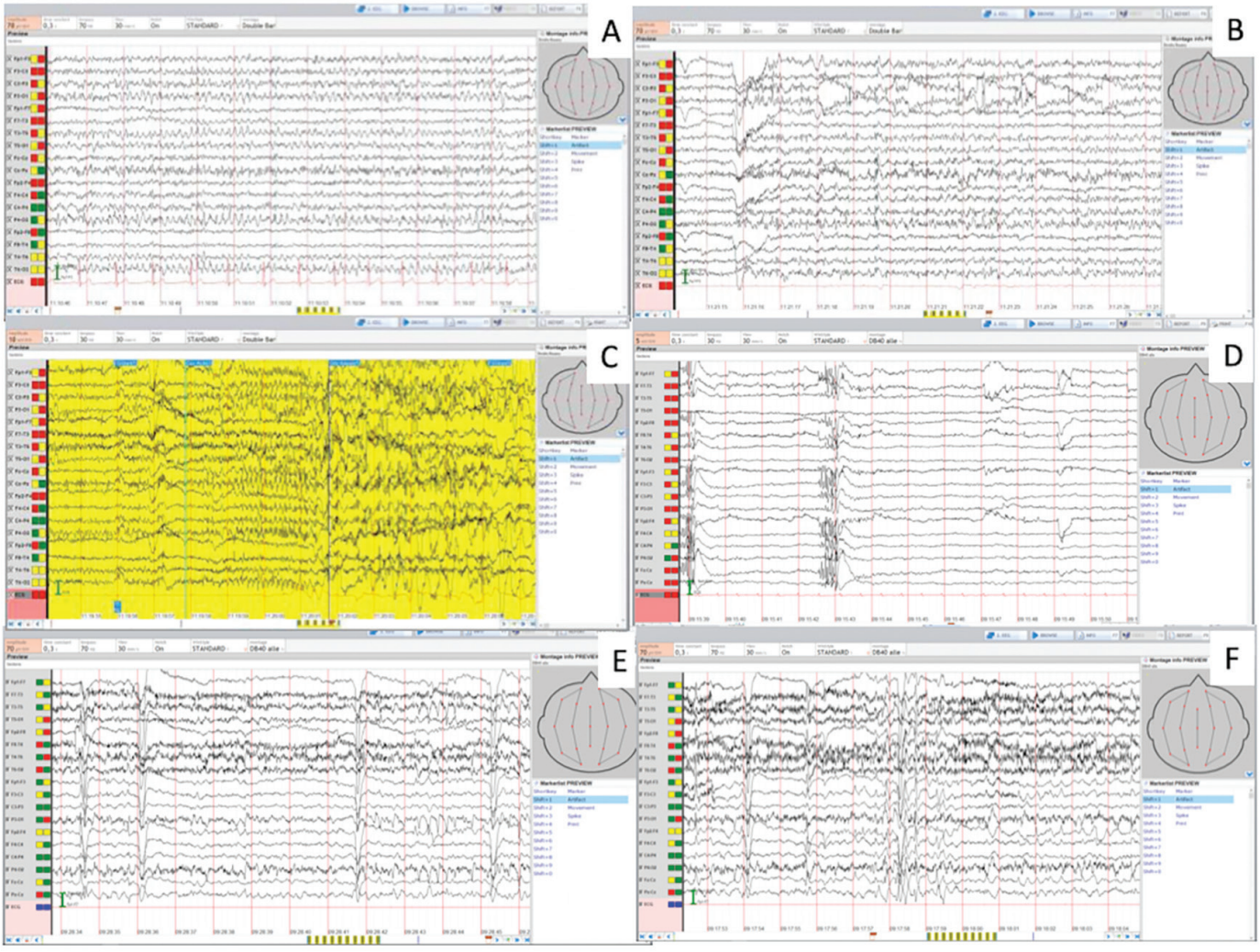

Figure 4. The EEG captures of the patients with special EEG features. A. Slow background activity during wakefulness, B. Eye closed sensitivity with bi-occipital spikes, and C. Generalized poly-spikes and waves with bilateral upper extremity myoclonia at 15 Hz frequency intermittent photic stimulation at patients with *SCARB2* gene mutation (patient no.6 in Table 1). C. Slow and attenuated background activity with generalized poly-spike train on EEG at patient with 1p36 deletion (patient no.1 in Table 2). D, E. Slow background activity with synchronous or asynchronous bi-occipital sharps waves, secondary bilateral hypersynchrony on EEG at patient with 15q15 deletion (patient no.2 in Table 2)
EEG: Electroencephalography

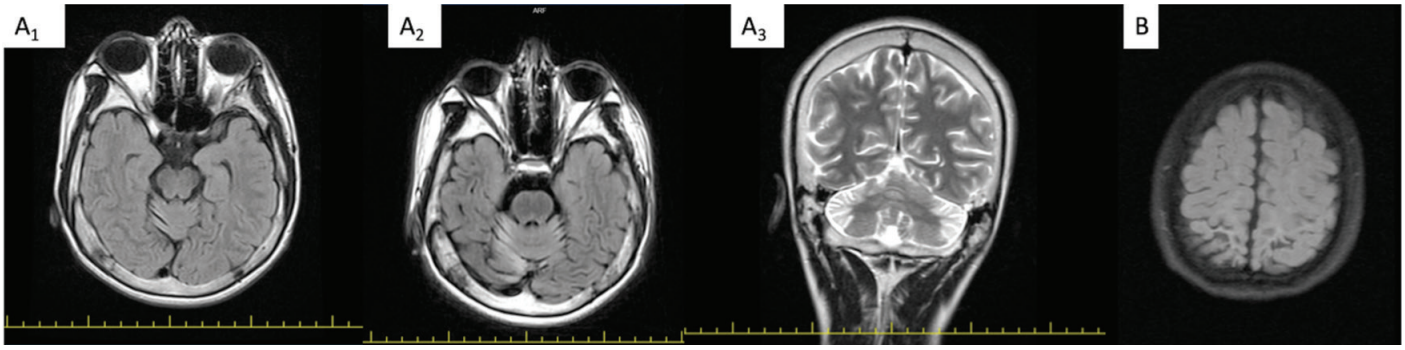

Figure 5. The brain MRI captures of the patients with structural changes. A_{1-3}. Cerebellar atrophy in cranial MRI in patients with mutation at *GRM1* (patient no.6 in Table 1). B. Bilaterally parietooccipital encephalomalacia in patients with deletion at 15q15.1 (patient no.2 in Table 2)
MRI: Magnetic resonance imaging

During NREM stage II sleep, synchronous and symmetric sleep graphoelements were recorded, without any epileptiform discharges. Genetic analysis using a disease-specific panel for spinocerebellar ataxia identified a heterozygous variant of uncertain significance in the *GRM1* gene [(NM_001278064.2: c.1610G>A), (NP_001264993.1:p.(Arg537Gln)]. This gene associated with autosomal dominant spinocerebellar ataxia 44 (patient no.7 in Table 1).

A 19-year-old female patient presented to epilepsy outpatient clinic. Her parents were consanguineous. She was a twin in utero; however, her co-twin died intrapartum. The patient had been experiencing atypical absence seizures 1 -2 times per month while on treatment with levetiracetam and topiramate. She has been present since the neonatal period. She exhibited cognitive decline and motor retardation. Dysmorphic features included short stature, a thick neck, ocular hypotelorism, and short fingers and feet. She was wheelchair-bound and unable to ambulate independently. Additionally, she had insulin intolerance and hypothyroidism. EEG revealed attenuated, slow background activity and frequent generalized poly-spikes discharges, also referred to as a generalized poly-spike train (GPT) were recorded (Figure 4C). Cranial MRI showed no gross abnormalities. Array-CGH identified a 1p36.33 deletion (patient no.1 in Table 2).

A 19-year-old male patient presented to epilepsy outpatient clinic. There was no known biological relationship between his parents. He had 2 male siblings, and there was no significant family history. He was born three weeks prematurely and required postnatal incubation. Seizures began at three months of age and were characterized by eye deviation occurring several times per day, often triggered by infections. He exhibited cognitive decline, spontaneous nystagmus, and ocular gaze deficits. EEG showed a background rhythm of 4-6 Hz theta activity. In addition, both synchronous and asynchronous occipital spikes and bilateral hypersynchronous sharp waves were recorded (Figure 4E, F). Cranial MRI revealed bilateral parieto-occipital encephalomalacia (Figure 5B). Karyotype analysis was normal. Array- CGH identified a heterozygous 15q15.1 deletion encompassing 52 genes over a 1.789 Mb region (Supplementary File 1). Parental array results were normal (patient no.2 in Table 2).

The patients' demographic characteristics, phenotypic features, responses to ASM, EEG and neuroimaging findings, as well as genetic analyses, are summarized in Tables 1 and 2.

DISCUSSION

In this study, we reported the 9 distinct genetic causes of epilepsy identified during follow-up at the epilepsy outpatient clinic of a state hospital. All patients exhibited cognitive impairment accompanied by neurological and/or other systemic findings. Four patients (44.4%) had a history of seizures triggered by metabolic imbalance or infections; in one patient, the seizure presented as status epilepticus. Four patients (44.4%) remained seizure-free without identifiable triggers, while another four (44.4%) had drug-resistant epilepsy. Notably, both patients with chromosomal abnormality had drug-resistant epilepsy. EEG revealed slow background activity in seven patients (77.7%). One patient with PME exhibited both eye closure sensitivity and photosensitivity. Cranial MRI showed cortical atrophy in two patients (22.2%) and cerebellar atrophy in one of patients (11.1%).

The *ZNF142* gene encodes the zinc finger protein 142, a member of the zinc finger protein superfamily-one of the largest groups of mammalian transcription factors.[12] Pathogenic variants in these proteins have been associated with various neurodevelopmental disorders.[13] To date, 42 patients have been reported in the literature with heterozygous *ZNF142* variants, typically presenting with neurodevelopmental disorder with impaired speech and hyperkinetic movements.[14,15] In the present study, we described a patient carrying a *ZNF142* variant who exhibited with a progressive speech impairment without hyperkinetic movements, dystonia, ataxia, or typical dysmorphic features. His seizures were well-controlled with ASMs, and he remained seizure-free for three years during follow-up. However, a relapse presenting as status epilepticus occurred upon ASM discontinuation. Given his positive family history and progressive speech difficulties, a genetic etiology was investigated.

The *ZMYND11* is a critical gene associated with the 10p15.3 microdeletion syndrome, which is characterized by developmental delay or intellectual disability, behavioral abnormalities, dysmorphic features, hypotonia, and seizures. To date, approximately 20 patients have been described in the literature with this condition.[16] In our study, two siblings were identified with mental and motor retardation, along with characteristic facial dysmorphism. Both, carried the same pathogenic variant in *ZMYND11*. However, the clinical severity differed: the sister exhibited severe symptoms, including status epilepticus triggered by infections or metabolic disturbances, whereas the brother had infrequent unknown onset

Table 2. Clinical and genetic features of the patients with chromosomal abnormality and epilepsy

No, age (years), sex	Seizure onset	Seizure type	Other system symptomes	EEG	MRI/CT	Response of ASMs	Genetic analysis	Chromosomal abnormality
No.1 19, F	New-born	Atypical absance, tonic atonic	MMR Short, ocular hypotelorism, nasal flattened, immobilise, bilateral Babinski sign	Atenuated slow background activity with generalized poly-spike trains	Normal	DRE: 1 in 2 months atypical absance with LEV 2000 mg/day, TPM 200 mg/day	Array-CGH	1p36 deletion
No.2 19, M	3 months-infant	Focal motor seizure with ocular deviation and rare focal onset bilateral tonic clonic motor	CD, autism spectrum disorders, steretypical movements, restricted eyes horizontal gaze	Slow background activity with asyncronous and syncronous bi-occipital spikes and frequent secondary bilateral hypersynchrony	Bilateral parietooccipital encephalomalasia	DRE: 1-2 seizures in a week with VPA 1000 mg/day, LEV 2000 mg/day, LCM 400 mg/day, LTG 300 mg/day, CLZ 2 mg/day	Array-CGH	15q15.1 heterozygotes deletion

ASMs: Antiseizure medications, F: Female, M: Male, CBZ: Carbamazepine, CD: Cognitive decline, LEV: Levetiracetam, CLZ: Clonazepam, LCM: Lacosamide, LTG: Lamotrigine, CGH: Comparative genomic hybridization, TPM: Topiramate, VPA: Valproic acid, MMR: Mental-motor retardation, MRI/CT: Magnetic resonance imaging/computed tomography, DRE: Drug-resistant epilepsy

bilateral tonic-clonic seizure. EEG findings also varied. The sister showed frequent frontal asynchronous sharp waves and bilateral hypersynchronous sharp waves, while the brother's EEG demonstrated longer-lasting bilateral hypersynchronous diffuse sharp-and-waves discharges. The sister was treated with valproic acid, whereas the brother declined ASM. These EEG differences may, in part, be attributable to the effect of valproic acid treatment. Additionally, both siblings and their father were diagnosed with diabetes mellitus and carried a variant in the *CAPN10* gene, which has been implicated in susceptibility to type 2 diabetes mellitus.[17] The father had no history of seizure and exhibited normal cognitive and motor development. His EEG was unremarkable except for transient theta slowing in the left centroparietal region during NREM sleep, which was considered clinically insignificant. The mother did not carry either the *ZMYND11* or *CAPN10* variants. Given that both siblings harbored the *ZMYND11* variant while neither parent carried it, gonadal mosaicism is the most plausible explanation. This family thus demonstrates combined phenotypic features resulting from pathogenic variant in two different genes- *ZMYND11* and *CAPN10*.

The *DLG4* (discs large MAGUK scaffold protein 4) encodes postsynaptic density protein 95, which is expressed in various tissues, including the brain. Pathogenic variants in *DLG4* have been associated *DLG4*-related synaptopathy, a neurodevelopmental disorder characterized by intellectual disability, autism spectrum disorders, muscular hypotonia, abnormal movements, epilepsy, ophthalmologic abnormalities, and marfanoid features. In the literature, approximately 54 patients with *DLG4*- related disorders have been described.[18,19] In the present study, a novel heterozygous splice-site variant [(NM_001365.4: c.771+2T>G)] in *DLG4* was identified in three family members. The index patient's younger brother, who carried the same variants, had intellectual disability, but spoke better than his sister, though not as fluently as their father. He had marfanoid joint deformities but no history of seizure or other systemic abnormalities. Their father, who carried same variants, had mild intellectual disabilities but otherwise systemically intact, enabling him to maintain employment. Interestingly, none of the three individuals with the *DLG4* variant exhibited dystonia. This family illustrates infrafamilial phenotypic variability associated with the same pathogenic variant. The inheritance pattern appeared to be autosomal dominant in the siblings, with a *de novo* origin in the father, suggesting this variant is novel in familial context.

The *PEX11B* encodes a peroxisomal membrane protein that is predicted to contain two transmembrane domains.[20] Homozygous variants in this gene have been associated with congenital cataracts, progressive deafness, polyneuropathy, gastrointestinal issues, and intellectual disability.[21] To date, seven patients with mutations have been reported in the literature.[22] Our patient carried a homozygous variant in the *PEX11B* gene. His parents, who were consanguineous, were both heterozygous carries. The patient presented with intellectual disability, speech impairment, spontaneous nystagmus, sensorial neuropathy, and epilepsy which remained seizure-free under monotherapy. EEG revealed slow background activity with high-amplitude sharply contoured paroxysms. Unlike previously reported cases our patient did not exhibit hearing loss.

The *SCARB2* encodes lysosomal integral membrane protein type-2 (*LIMP-2*).[23] Mutations that impair *LIMP2* function disrupt the biogenesis and maintenance of the lysosomal and endosomal compartments, leading to PME.[24] If the clinical history, examination findings, EEG, and MRI results suggest PME, genetic testing should be performed in accordance with recommendations from the ILAE regarding progressive myoclonic epilepsies.[25] Rubboli et al.[26] reported a patient with PME due to *SCARB2* mutation without renal failure. Similar to our case, their patient exhibited photic- and eye closure-induced myoclonus; however, their patient background EEG activity was normal.[26] While their patient was under 30 years old, ours was 53 years old. The slower EEG background in our patient may be attributable to age-related changes in brain activity, as background rhythms are known to slow over time. Previous studies have described 62 patients with *SCARB2*-related disorders, presenting with spectrum that includes action myoclonus renal failure syndrome, REM sleep behavior disorders, parkinsonism, PME with or without renal failure.[24,25,27] Our patients exhibited progressive myoclonus, tremor, and parkinsonism, but did not show REM sleep behavior disorders and renal failure. Further research is warranted to clarify the relationship between *SCARB2* variants of uncertain significance and these phenotypes.

The *GRM1* encodes metabotropic glutamate receptor 1, which plays a crucial role in slow excitatory postsynaptic transmission, synapse formation, synaptic plasticity, and motor control. The *GRM1* gene shows its highest expression in the cerebellum, beginning in early development and continuing throughout ontogenesis.[28,29] Mutations in this gene have been associated with autosomal dominant or recessive cerebellar atrophy, intellectual disabilities, cerebellar atrophy without cognitive impairment, late-onset mild symptoms, short sleep duration and efficiency, autism spectrum disorders, and schizophrenia in total of 12 reported individuals.[30-33] Our patient presented with intellectual disability, autism spectrum disorders, dysphasia with dysphonia, spontaneous nystagmus, dystonic tremor, and seizure. A missense heterozygous variant of uncertain significance was identified. The phenotypic features were consistent with those previously described in the literature. However, *in vivo* or *in vitro* functional studies, as well as parental segregation analyses, are necessary to confirm genotype-phenotype correlation.

1p36 deletion syndrome (del1p36) is characterized by developmental delay, behavioral abnormalities, hypotonia, seizures, brain abnormalities, visual impairment, orofacial cleft, congenital heart defects, cardiomyopathy, renal anomalies, short stature, and a distinctive gait.[34] Phenotypic differences between distal and proximal deletion have been described: distal deletions are more associated with microcephaly, whereas proximal deletions more frequently involve brain malformations, epilepsy and cardiomyopathy.[35] Epilepsy with patient eith del1p36 is often accompanied by cranial abnormalities.[35] Our patient had a distal del1p36 and presented mental and motor retardation, typical facial features, short stature, and drug-resistant epilepsy. EEG showed GPT, though her neuroimaging was normal. GPT has been described in patients with GGE associated with drug resistance epilepsy.[36] Our patient similarly exhibited drug resistance epilepsy.

A 15q15.1 deletion has been reported in association with limb girdle muscular dystrophies.[37] However, our patient did not show any myopathic features. He had a perinatal asphyxia and exhibited bilateral parieto-occipital encephalomalacia on MRI. Clinically, he presented with intellectual disabilities, aphasia, restricted eye gaze, stereotypical movements, and focal motor seizures characterized by forced conjugated lateral gaze. Although the deletion encompasses several genes related to epilepsy, the presence of encephalomalacia from perinatal asphyxia may also contribute to the phenotype. The absence of phenotypic abnormalities and chromosomal deletions in both parents suggests that the chromosomal anomaly detected in the patient is de novo and likely contributes to the observed phenotype. Nevertheless, the severity and complexity of his clinical features go beyond what would typically be expected from asphyxia alone, underscoring the importance of conducting genetic analysis in such cases.

Study Limitations

We reported the genetic etiology of patients with epilepsy followed in a single-center outpatient clinic. Patients who had been previously diagnosed at another center were excluded to avoid duplication in the literature. One of the main limitations of this study is retrospective design that all the reported genetic etiologies were based solely on clinical work-up which is lead to selection bias, and patients whose genetic investigations are still ongoing were not included. These factors contributed to small sample size which is major limitations of the study. Secondly, genetic testing was selected individually based on each patient's phenotypic findings, leading to variability in the genetic tests performed. For instance, among 41 patients with cognitive decline followed in the epilepsy outpatient clinic, a definitive genetic diagnosis was reached in only nine cases during 2.5 years follow-up period. This low diagnostic yield represents another key limitation of the study. Further research is needed to identify epilepsy-related variants, possibly through the use of comprehensive genetic epilepsy panels. Despite these limitations, our data included two notable findings: (1) two patients were affected by mutations in different genes due to inherited gonadal mosaicism; and (2) variable phenotypic features related to the same gene were observed within a single family. All reported patients and their parents were examined in detail and their findings were thoroughly documented. Finally, our study highlights the importance of conducting *in vivo* or *in vitro* functional studies to clarify the pathogenicity of variant uncertain significance.

CONCLUSION

In conclusion, when cognitive decline, autism spectrum disorders, dysmorphic features, or multisystem involvement are presented in patients with epilepsy, we should consider genetic etiology. Selecting appropriate genetic tests based on these clinical findings is essential for identifying the underlying genetic etiology. Reporting the patients with genetic epilepsy etiology from each epilepsy center to across the country will be improved the diagnostic tools and treatment options.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (decision no: 2025-323, date: 03.09.2025).

Informed Consent: Written informed consent form was obtained by each patient and/or their caregivers.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.M.D., A.G., B.U., L.Ş., Concept: D.M.D., İ.Ö., B.B, S.C., Design: D.M.D., İ.Ö., B.B, S.C., Data Collection or Processing: D.M.D., S.C., Analysis or Interpretation: D.M.D., A.G., B.U., L.Ş., İ.Ö., B.B, S.C., Literature Search: D.M.D., Writing: D.M.D., A.G., B.U., L.Ş., İ.Ö., B.B, S.C.

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Supplementary File 1. https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/ddec7c26-cbee-43b4-85ed-3dbda4deba2e.pdf

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