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ORIGINAL ARTICLE

Keipert syndrome beyond classical features: novel *GPC4* variant associated with epilepsy but preserved cognition

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Abstract

Keipert syndrome (OMIM #301026) is a rare X-linked recessive disorder characterized by craniofacial and digital anomalies, variably expressed intellectual disability, and sensorineural hearing loss. Rare variants in the *GPC4* gene have been reported in a limited number of cases. Here, we describe an 11-year-old male presenting with epilepsy and distinctive facial dysmorphism, in whom whole-exome sequencing identified a novel hemizygous missense variant in *GPC4* (NM_001448.3:c.655 C> T; p.Arg219Cys). It was maternally inherited, absent in population databases, and located in a highly conserved region (phyloP100way: 7.716; PhastCons100way: 1.0). Clinically, the patient exhibited a long face, broad forehead, anteverted nares, and broad halluces, without brachydactyly, hearing loss, or cognitive impairment. Neuropsychiatric evaluation confirmed normal intellectual and adaptive functioning. EEG revealed left frontocentrotemporal epileptiform discharges, and brain MRI showed nonspecific subcortical white matter hyperintensities; seizures were controlled following anti seizure medication adjustment. This case expands the phenotypic spectrum of *GPC4*-related Keipert syndrome by demonstrating that epilepsy, EEG abnormalities, and subtle neuroimaging findings may accompany the classical craniofacial phenotype. Importantly, the absence of intellectual disability and hearing loss underscores the variable expressivity of *GPC4* variants and has implications for genetic counseling.

Keywords Keipert syndrome · *GPC4* gene · X-linked disorder · Epilepsy · Rare neurodevelopmental disorder

Introduction

The Glypican 4 (*GPC4)* gene, located at Xq26.2, encodes a member of the heparan sulfate proteoglycans anchored to the cell membrane. The gene product plays critical roles in embryonic development, particularly in signaling, morphogenesis, and tissue organization [1]. Hemizygous variants in *GPC4* have been associated with Keipert syndrome (OMIM #301026).

Keipert syndrome (OMIM #301026) is a rare X-linked recessive disorder. First described by Keipert and colleagues, the syndrome was characterized by distinctive craniofacial features, broad halluces and thumbs, and hearing loss [2]. Since then, only a limited number of cases have been reported in the literature, including affected brother pairs [3], isolated male cases [4–6], and, more rarely, a female patient and her mildly affected father [7].

The typical phenotypic spectrum includes a broad forehead, hypertelorism, prominent nose, wide mouth, Cupid's bow–shaped upper lip, and brachydactyly with widening of the thumbs and halluces ([15]; Amor et al. 2007). Most

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patients present with sensorineural hearing loss, while additional features such as brachycephaly, relative macrocephaly, epileptic seizures, and variable neurodevelopmental manifestations have also been described (Amor et al. 2007; [6]).

The aim of this study is to describe a male patient carrying a novel hemizygous missense variant in *GPC4*, presenting with epilepsy that was initially unresponsive to valproic acid monotherapy and subsequently controlled with levetiracetam and carbamazepine, and to compare his clinical, radiological, laboratory, and molecular findings with those of previously reported cases. By reporting this case, we aim to contribute to the further delineation of the phenotypic and genotypic spectrum of Keipert syndrome.

Materials and methods

Patient

Ethical approval for this study was obtained from the Balıkesir University Ethics Committee on August 08, 2025 (decision no: 2025/290). Written informed consent was obtained from the patient's legal guardians.

The patient, who was being followed in the Pediatric Neurology Clinic with a diagnosis of epilepsy, was referred to our Genetics Clinic for investigation of a possible genetic etiology. The patient's medical records, clinical findings, physical examination results, and family pedigree were evaluated. The clinical assessment was jointly conducted by a clinical geneticist and a pediatric neurologist.

Genetic testing

Genomic DNA was extracted from 200 µL of peripheral venous blood using the Exgene™ Blood SV isolation kit (GeneAll Biotechnology, South Korea), in accordance with the manufacturer's protocol.

Automated genomic DNA isolation was performed using the HiPurA® Pre-filled Clinical Multi-Purpose Nucleic Acid Purification Kit with the HIMEDIA InstaN Mag-96 platform. DNA concentration and purity were assessed using the Qubit® Fluorometer (Thermo Fisher Scientific, USA).

Whole exome sequencing (WES) was conducted using the Roche® KAPA HyperExome 96 reaction kit and sequenced on the MGI DNBSEQ-G400 platform. Raw sequencing data (FASTQ files) were analyzed using Genomize SEQ software, version 8.7.0. Identified variants were interpreted and classified according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria. All detected variants were subsequently validated through Sanger sequencing.

Variant analysis and classification

Raw data were analyzed using the Genomize® (https://seq.genomize.com) data analysis platform based on the human reference genome GRCh38 (hg38). Two main filtering steps were applied to identify pathogenic variants associated with clinical features: (1) After variant calling, synonymous and non-coding variants were filtered out, while nonsense, missense, frameshift, splice-site, and indel variants were retained for further evaluation. (2) Selecting variants with a minor allele frequency <1.0% in population studies (1000 Genomes [1000G], ESP, ExAC, and Genome Aggregation Database [gnomAD]).

The Genome Integrative Viewer was used to visualize sequencing data. Novel variants were queried in the HGMD® and ClinVar (*http://ncbi.nlm.nih.gov/clinvar*) dat abases for validation, and their pathogenicity was assessed using in silico analysis tools (SIFT, DANN, AlphaMissense, REVEL, and CADD).

Variant pathogenicity classification was performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines (Richards et al. 2015). Finally, segregation analysis was conducted using DNA samples obtained from available family members.

Results

An 11-year-old male patient was referred to our clinic from the pediatric neurology department due to epilepsy. He had been followed with a diagnosis of epilepsy and was receiving valproic acid at a dose of 20 mg/kg/day in two divided doses. His past medical history revealed delivery by cesarean section at 37 weeks of gestation with a birth weight of 2250 g (SDS: -2.07). Parental consanguinity was not reported.

On physical examination, the patient's height was 146 cm (SDS: –0.27), weight 41 kg (SDS: 0.08), and head circumference 54 cm (SDS: 0.26), all within normal limits for age. He achieved head control at 2 months, sat without support at 7 months, and walked independently at 18 months. He spoke his first single words at 12 months and two-word phrases at 18 months. Toilet training was completed at 2.5 years of age, and he was able to read and write with good academic performance in light of the normal developmental milestones and preserved academic functioning. Dysmorphic features included a long face, broad and prominent forehead, flat midface, frontal upsweep, hypertelorism, cupped ears with a prominent antihelical root, anteverted nares, downturned corners of the mouth, and a broad hallux. A comprehensive child psychiatry evaluation revealed no evidence of developmental delay or

intellectual disability. Findings from other systemic examinations were unremarkable.

Laboratory investigations demonstrated decreased levels of 25-OH Vitamin D (16.8; reference: 30–70) and ferritin (6.8; reference: 23.9–336.2), while Vitamin B12 was within the low-normal range (241; reference: 180–914). Complete blood count, biochemical, and metabolic parameters were otherwise normal. The seizures, which began at 8 years of age, were characterized by impaired awareness, ocular deviation, bilateral tonic–clonic movements, and postictal confusion, consistent with focal to bilateral tonic–clonic seizures. Electroencephalography (EEG) showed high-voltage 2–4 Hz sharp waves in the left frontocentrotemporal region during both wakefulness and sleep (Figure 1). Cranial magnetic resonance imaging revealed multiple millimetric, non-specific subcortical white matter FLAIR hyperintensities in the bilateral frontal lobes and the left parietal lobe.

During follow-up, due to increased seizure frequency, carbamazepine and levetiracetam were added to the treatment regimen, and valproic acid was gradually discontinued. Following this treatment adjustment, seizure control was achieved after six months, and both awake and sleep EEG recordings were within normal limits.

Consultations with otolaryngology, orthopedics, pediatric cardiology, and ophthalmology revealed no additional pathology.

Genetic result

Whole exome sequencing (WES) analysis revealed a hemizygous missense variant in the *GPC4* gene, designated as NM_001448.3:c.655 C> T (NP_001439.2:p.Arg219Cys). According to the ACMG/AMP criteria, this variant was classified as VUS, fulfilling the PM2 and PP3 criteria. However, in silico predictors (SIFT, DANN, AlphaMissense, REVEL, and CADD) consistently indicated a deleterious effect. Specifically, SIFT (0), CADD (28.8), DANN (0.9995), and AlphaMissense (0.8532) provided pathogenic supporting evidence, while REVEL (0.831) reached a pathogenic moderate threshold, all suggesting a damaging impact on protein function. The variant is not reported in the gnomAD database and is listed in the ClinVar database as a variant of uncertain significance (VUS) in a single individual without phenotype correlation. Evolutionary conservation analysis indicated that the affected region is highly conserved (phyloP100way: 7.716, PhastCons100way: 1.0).

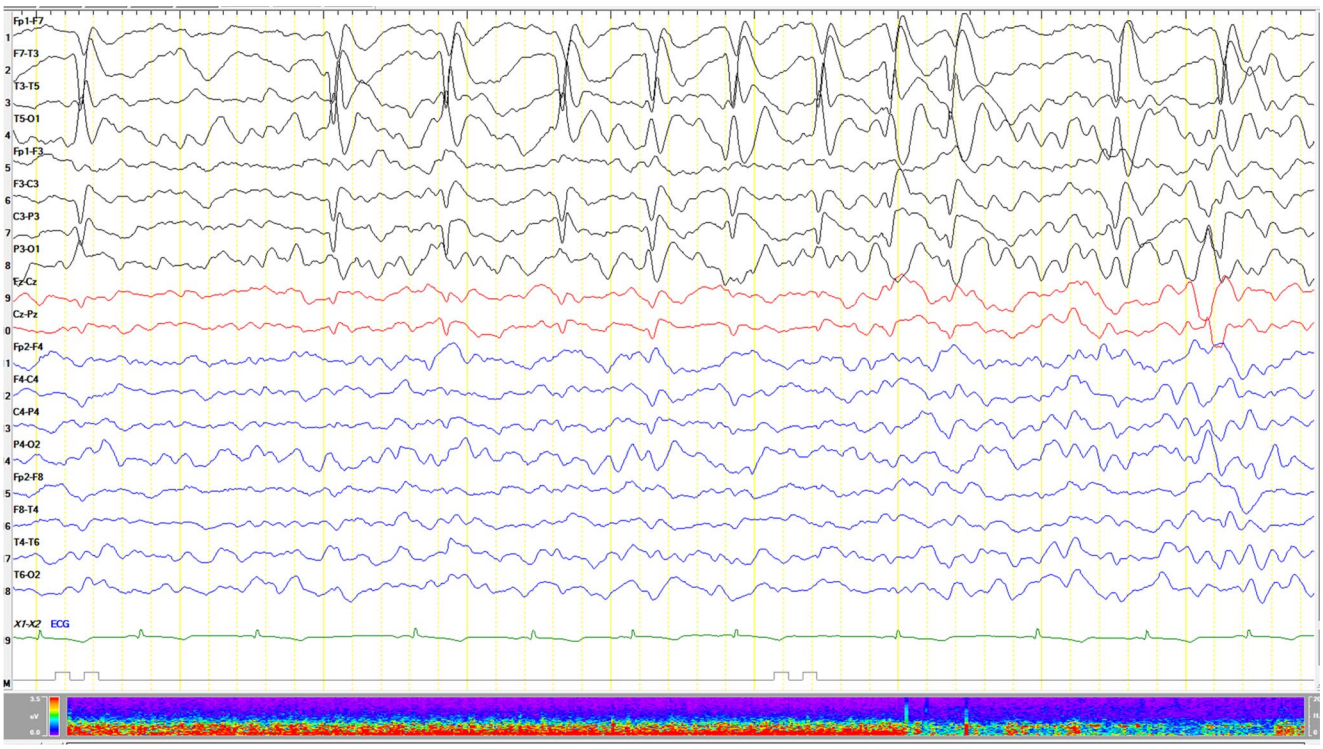

Fig. 1 EEG recording was performed using the international 10–20 electrode placement system. High-voltage sharp wave discharges at a frequency of 2–4 Hz were observed predominantly in the left frontocentrotemporal region during both wakefulness and sleep. The time scale was set to 1 s/div and the voltage scale to 70 µV/div

Segregation analysis within the family revealed that the variant was detected in a heterozygous state in the mother, while it was absent in the father (Fig. 2).

Discussion

Keipert syndrome (OMIM #301026) is a rare X-linked disorder characterized by craniofacial and digital anomalies, variable degrees of intellectual disability, and sensorineural hearing loss (Amor et al. 2007). To date, rare variants in the *GPC4* gene have been identified in a total of 12 patients with Keipert syndrome from eight families [8–10]. However, clinical details were not provided in the report by Lu et al. [10]. In this study, we present the clinical findings of the 13th Keipert syndrome case with a genetically identified *GPC4* variant (Table 1).

Whole-exome sequencing identified a novel hemizygous missense variant in *GPC4*: NM_001448.3:c.655 C> T (p.Arg219Cys). Although this variant is novel and biologically plausible, it remains classified as a variant of uncertain significance (VUS) according to ACMG criteria. Nevertheless, the identification of this variant is consistent with the established association between *GPC4* and Keipert syndrome and contributes to expanding the known molecular spectrum of the disorder. According to the Human Gene Mutation Database (HGMD) Professional 2023.4, a total of 19 distinct variants have been reported in *GPC4* to date, including five missense/nonsense, one splice-site, six small deletions, two small insertions, one regulatory, and four gross insertions. Missense variants constitute a minority of reported alterations, and their phenotypic consequences remain incompletely understood. While the association between *GPC4* and Keipert syndrome is well

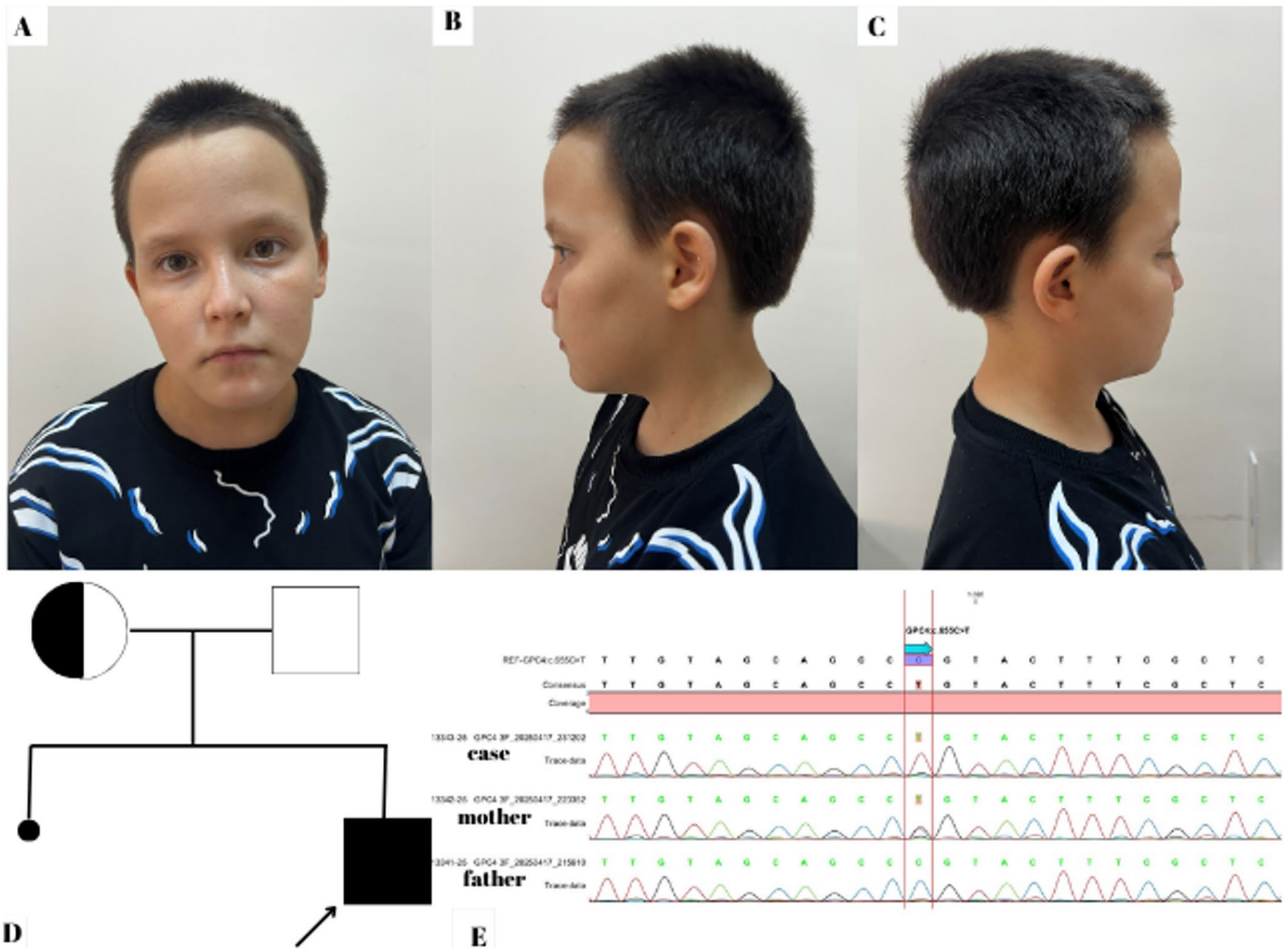

Fig. 2 Clinical photographs illustrating the dysmorphic features of the proband and genetic findings. (**A**) Frontal facial view, (**B**) left lateral view, and (**C**) right lateral view. (**D**) Pedigree of the family. (**E**) Sanger sequencing demonstrating a maternally inherited hemizygous *GPC4* variant identified in the proband: NM_001448.3:c.655 C> T (NP_001439.2:p.Arg219Cys)

Table 1 Overview of clinical characteristics in genetically confirmed *GPC4*-related Keipert syndrome

			Amor et al. [8]	Lu et al. [10]	Kuroda et al. [9]
		Our Case	10 cases from 6 family	1 case	1 case
	Variant		c.1516 C> T c.701dup c.1486G> T c.316delG c.1518_ 1521dup-GTGC c.742delC	c.877 + 1G > A	c.1051 C > T
	ACMG Classification	Likely Patho-genic	Patho-genic	Likely Patho-genic	Patho-genic
Epi-demi-ologi-cal Data	Gender	M	M	M	M
	Current Age	11y	Youngest: 7mo Oldest: 40y	2y	3y
Facial Fea-tures	Macrocephaly	-	7/10	unknown	-
	Prominent forehead	+	7/9	unknown	+
	Flat midface	+	7/9	unknown	+
	Hypertelorism	+	9/9	unknown	-
	Broad nose	-	9/9	unknown	+
	Downturned corners of mouth	+	7/9	unknown	+
	Prominent lip	-	6/9	unknown	+
	Ears simple or low set	+	5/9	unknown	+
Skel-etal sys-tems	Brachydactyly	+	5/9	unknown	+
	Clinodactyly	-	5/9	unknown	-
	Camptodactyly	-	3/9	unknown	-
	Broad thumb	+	5/9	unknown	-
	Broad first toe	+	7/9	unknown	+
	Broad terminal phalanges	-	7/10	unknown	+
Other Sys-tems	Sensorineural hearing loss	-	3/9	unknown	-
	Cognitive impairment	-	8/10	unknown	+
	Autistic features	-	3/10	unknown	+

M male, *y* years, *mo* month

established, the contribution of individual *GPC4* variants, particularly missense substitutions, to specific clinical manifestations requires further investigation.

Facial dysmorphism in Keipert syndrome is variable but typically includes a broad forehead, hypertelorism, a prominent nose, a broad nasal bridge, a wide mouth, and a Cupid's bow shaped upper lip. In adults, mandibular prognathism and a prominent supraorbital ridge have been described and are thought to arise as part of postpubertal craniofacial remodeling ([3, 7, 8]). Our patient exhibited coarse facial features consistent with the syndrome; however, macrocephaly and digital anomalies were absent.

Although sensorineural hearing loss is considered one of the characteristic features of the syndrome, its absence in our case underscores the variable expressivity of the disorder. Similarly, Dumic et al. [7] described affected family members without hearing impairment, suggesting that auditory involvement is not obligatory for diagnosis [7].

Notably, our patient presented with epileptic seizures, persistent EEG abnormalities, and non-specific white matter hyperintensities on brain MRI—features that have not been emphasized in most previously reported cases. Given that seizure control was achieved six months after the introduction of levetiracetam and carbamazepine following failure of valproic acid monotherapy, the clinical course is more consistent with a valproate-unresponsive epilepsy rather than a truly drug-resistant form. Nevertheless, central nervous system abnormalities such as mild developmental delay or unilateral cortical dysplasia have been described in a few patients [4, 6, 7], supporting the notion that epilepsy and EEG abnormalities may represent part of the extended phenotypic spectrum. Importantly, no additional genetic variants potentially contributing to the epileptic phenotype were identified.

No developmental delay or intellectual disability was observed in our patient, whereas these features have been frequently reported in previously described cases. Among the twelve genetically confirmed Keipert syndrome cases reported to date, only two individuals were described as having normal intellectual development [8–10]. Therefore, the absence of cognitive impairment in our patient represents a clinically important observation, further expanding the phenotypic variability associated with *GPC4* variants. This finding also has important implications for genetic counseling, as it indicates that neurodevelopmental outcome in Keipert syndrome may vary and that cognitive involvement is not obligatory. Families should be informed that, although intellectual disability is a recognized feature of the syndrome, preserved cognitive function may be observed in some individuals. Furthermore, the absence of the full spectrum of characteristic features and the overall milder clinical course in our patient may be attributable to the missense nature of the identified variant.

In conclusion, this case broadens the phenotypic spectrum of Keipert syndrome by demonstrating that epilepsy, EEG abnormalities, and non-specific MRI findings may accompany the classical craniofacial phenotype. The absence of both hearing loss and intellectual disability further highlights the variable clinical expressivity of the

condition. Larger case series and functional studies are warranted to better delineate genotype–phenotype correlations and clarify the clinical relevance of novel *GPC4* variants. However, functional studies to assess the effects of the identified variant were not performed in this study, limiting definitive conclusions regarding the molecular pathogenesis and genotype–phenotype correlations.

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Declarations

Ethical approval The study protocol was reviewed and approved by the Balikesir University Clinical Research EthicsCommittee (approval no: 2025/290; Date: August 08, 2025).
Committee (approval no: 2025/290; Date: August 08, 2025).

Conflict of interest The authors declare no conflicts of interest.

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