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A very rare form of autosomal dominant progressive myoclonus epilepsy caused by a novel variant in the PRICKLE1 gene

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ABSTRACT

Purpose: Progressive myoclonus epilepsy (PME) comprises a group of heterogeneous disorders defined by the combination of action myoclonus, epileptic seizures, and progressive neurologic deterioration. Neurologic deterioration may include progressive cognitive decline, ataxia, neuropathy, and myopathy. A number of genes have been identified to cause either isolated PME or diseases that manifest PME. We report a Saudi family with a very rare form of autosomal dominant PME.

Methods: We included two patients from Saudi Arabia with a presumptive clinical diagnosis of PME. The patients were from a family with an affected mother I-2 and two affected siblings proband II-3 and II-4 (a girl and a boy).

Results: Genetic analysis revealed a single variant in the *PRICKLE1* gene NM_153026.2: c.251 G > A (p.Arg84Gln). Segregation study was performed using DNA from the parents and two sisters. The same variant was identified in one affected parent (the mother I-2) and the two unaffected sisters II-1 and II-2 while it was absent from the unaffected father I-1.

Conclusion: This gene was linked to both autosomal dominant and autosomal recessive PME. To our best knowledge, this is the first report that demonstrates a single *PRICKLE1* pathogenic variant segregating with PME in one family. The novel variant identified in this family has never been previously reported as a disease-causing variant. The presence of the same variant in the unaffected individuals may suggest that heterozygous mutations in the *PRICKLE1* gene have incomplete penetrance. Further research is needed to elucidate the penetrance of heterozygous mutations in the *PRICKLE1* gene.

1. Introduction

Progressive myoclonus epilepsy (PME) comprises a group of rare heterogeneous genetic disorders that are generally manifested as a combination of myoclonic and tonic-clonic seizures with cognitive impairment, ataxia and other cerebellar signs, and other neurologic deficits. They are often encompassed under the broader term “catastrophic epilepsies”, which are invariably associated with significant neurological morbidity and often early mortality. This group also include epileptic encephalopathies [1]. Typically, the myoclonus shows a focal or segmental distribution, and is characterized by an arrhythmic, asynchronous, and asymmetric occurrence, which present at rest but activates with posture, action, or stimuli such as noise, light, or touch. The onset of symptoms is usually in late childhood or adolescence. However, they may affect all ages [2].

Several diseases attributed to different etiologies contribute to PME, with Unverricht–Lundborg disease as the most common PME. Less common PME disorders include Lafora disease, neuronal ceroid lipofuscinoses, Gaucher disease, action myoclonus renal failure syndrome, sialidoses, and myoclonic epilepsy with ragged-red fibers syndrome. Many of these have similar clinical presentations yet are genetically heterogeneous, making accurate diagnosis difficult, especially in the early stages of the illness. Other challenges include further problems of management including drug treatment (Table 1) [3].

The majority of genes implicated in PME cause autosomal recessive conditions. However, rare cases show autosomal dominant or

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Table 1
Progressive myoclonus epilepsies.

Entity	MIM	Phenotype	Gene	Inheritance	Ref.
Myoclonic Epilepsy of Unverricht and Lundborg	254800	PME type 1A	CSTB	AR	[3]
Myoclonic Epilepsy of Lafora	254780	PME type 2A	EPM2A	AR	
		PME type 2B	NHLRC1	AR	
Action Myoclonus-Renal Failure Syndrome (AMRF)	254900	PME type 4	SCARB2	AR	
North Sea PME	614018	PME type 6	GOSR2	AR	
Myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK)	616187	PME type 7	KCNC1	AR	
PME type 8	616230	PME type 8	CERS1	AR	
PME type 10	616640	PME type 10	PRDM8	AR	
Neuronal Ceroid-Lipofuscinoses (NCL)	256730	NCL type 1	PPT1	AR	
	204500	NCL type 2	TPP1	AR	
	204200	NCL type 3	CLN3	AR	
	256731	NCL type 5	CLN5	AR	
	601780	NCL type 6	CLN6	AR	
	610951	NCL type 7	MFSD8	AR	
	600143	NCL type 8	CLN8	AR	
	610127	NCL type 10	CTSD	AR	
	162350	NCL type 4B	DNAJC5	AD	
	611726	PME type 3	KCTD7	AR	
Neuraminidase Deficiency	256550	Sialidosis, type I & II	NEU1	AR	
Myoclonic Epilepsy Associated With Ragged-Red Fibers (MERRF)	545000	MERRF	MT-TK	Maternal	
Spinal Muscular Atrophy With Progressive Myoclonic Epilepsy (SMAPME)	159950	SMAPME	ASAH1	AR	
PME type 1B	612437	PME type 1B	PRICKLE1	AR/AD	
Gaucher disease	230800	–	GBA	AR	
PME type 9	616540	PME type 9	LMNB2	AR	[33]
Juvenile Huntington disease	143100	Juvenile Huntington disease	HTT	AD	[34]
Newly identified PME-associated diseases/genes					
Gerstmann-Straussler-Scheinker disease	137440	–	PRNP	AD	[35]
–	–	Childhood-onset progressive myoclonic epilepsy	SERPINI1	AD	[36]
Lipodystrophy, Congenital Generalized, Type 2 (CGL2)	269,700	–	BSCL2	AR	[37]

mitochondrial inheritance. Interestingly, the *PRICKLE1* gene has been linked to both autosomal recessive and autosomal dominant PME [4]. In this article, we report a Saudi family with autosomal dominant PME caused by a novel pathogenic variant in the *PRICKLE1* gene. To the best of our knowledge, this is the first report that describes autosomal dominant PRICKLE1-related PME affecting more than one member in the same family, and it is the second report that describes this very rare form of PME.

2. Methods

We included two patients from Saudi Arabia with a presumptive clinical diagnosis of PME. The patients were from a family with an affected mother I-2 and two affected siblings proband II-3 and II-4 (a girl and a boy). Unfortunately, the proband III-4 died from aspiration pneumonia and status epilepticus at the age of 24 prior to genetic testing (Fig. 1). All family members were examined physically, neurologically, psychiatrically, and questioned about their daily activities. In addition, affected patients had basic blood work, magnetic resonance imaging (MRI) of the brain, and several electroencephalograms (EEGs) with standardized intermittent photic stimulation and hyperventilation.

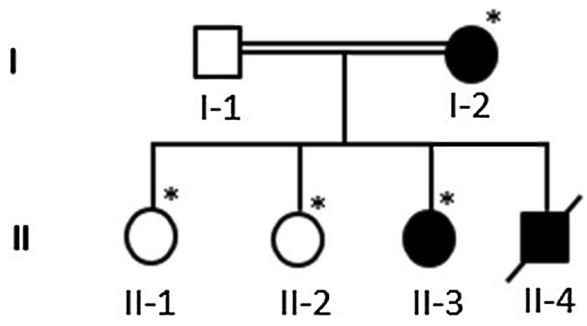

Fig. 1. Pedigree of the members after detailed family history. The variant carriers are marked with an asterisk sign.

The patients were followed-up by a neurologist and treated with different anti-epileptic drug protocol.

The entire family was consented for genetic testing after explanation of pros and cons of such investigations. Genomic DNA was prepared from leukocytes using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. Whole exome sequencing (WES) for the proband was performed using the SureSelect Human All Exon kit (Agilent, Santa Clara, CA) for enrichment, and a HiSeq4000 (Illumina) instrument for the actual sequencing; variants were annotated using Annovar (http://annovar.openbioinformatics.org) and in-house ad hoc bioinformatics tools. Specific attention was paid towards epilepsy-associated genes (comprehensive epilepsy panel). The panel consisted of 194 genes, 2830 exons, 502547 bases, median coverage was 221 and percent > 15X was 99.8. The panel was targeting all protein coding exons and exon-intron boundaries of all target genes. It also covered a number of mutations located outside the coding regions of these genes. This diagnostic tool covers the majority of epilepsy mutations known to date and it is used to detect mutations such as single nucleotide substitutions and small insertions and deletions (INDELs).

The covered genes in the panel were ABCD1, ADAR, ADSL, AFG3L2, AGA, AIMP1, ALDH5A1, ALDH7A1, ALG13, AMACR, AMT, ARG1, ARHGEF9, ARSA, ARX, ASAH1, ASPA, ATP13A2, ATRX, BTD, CACNA1A, CACNA1H, CACNB4, CASK, CASR, CDKL5, CERS1, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN3, CLN5, CLN6, CLN8, CNTNAP2, COL4A1, COX15, CPT2, CSF1R, CSTB, CTSD, CTSF, CUL4B, DARS2, DCX, DEPDC5, DNAJC5, DNM1, DOCK7, DPYD, EARS2, EEF1A2, EFHC1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EPM2A, ETFA, ETFB, ETFDH, FAM126 A, FH, FLNA, FOLR1, FOXG1, FOXRED1, GABRA1, GABRB3, GABRG2, GALC, GAMT, GCDH, GCH1, GFAP, GJC2, GLDC, GNAO1, GNE, GOSR2, GPHN, GRIA3, GRIN2A, GRIN2B, GRN, HCN1, HEPACAM, HNRNPU, HSD17B10, HSPD1, IQSEC2, KCNA1, KCNA2, KCNB1, KCNC1, KCNQ2, KCNQ3, KCNT1, KCTD7, KDM5C, KIF1A, L2HGDH, LGI1, MARS2, MBD5, MECP2, MED12, MEF2C, MFSD8, MLC1, MOCS1, MTHFR, MTOR, NDUFAF5, NECAP1, NEU1, NHLRC1, NOTCH3, NRXN1, OFD1, OPHN1, PCDH19, PGK1,

PHF6, PIGA, PLCB1, PLP1, PNKP, PNPO, POLR3A, POLR3B, PPT1, PRICKLE1, PRICKLE2, PRODH, PRRT2, PSAP, PTS, PURA, QDPR, RAB39B, RELN, RNASEH2A, RNASEH2B, RNASEH2C, RNASET2, SAMHD1, SCARB2, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SERPINI1, SIK1, SLC2A1, SLC6A1, SLC6A8, SLC9A6, SLC12A5, SLC13A5, SLC19A3, SLC25A15, SLC25A22, SLC35A2, SLC46A1, SMS, SNAP25, SOX10, SPTAN1, ST3GAL3, ST3GAL5, STX1B, STXBP1, SUMF1, SUOX, SYN1, SYNGAP1, SZT2, TBC1D24, TCF4, TPP1, TREX1, TSC1, TSC2, TUBB4A, UBE2A, UBE3A, WDR45, WWOX and ZEB2.

Sanger sequencing to confirm variants was carried out on ABI Prism 3500 Genetic Analyzer (Life Technologies, Carlsbad, CA, USA). Identified variants were classified as per the standards and guidelines recommended by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [5]. Any identified variant was described according to the Human Genome Variation Society (HGVS) nomenclature system [6].

2.1. Case report 1

A 50-year-old female I-2 that presented initially as a case of seizures at the age of 12 years with frequent myoclonic jerks and generalized tonic-clonic seizures. Her clinical course was progressive, and her myoclonus was both focal and generalized. She also had a gradually progressive cognitive impairment that started at the age of 35 with ataxia and tremor. At the age of 40, she became wheelchair bound with severe cerebellar deficit including intentional tremor, dysmetria, and dysarthria. She had an MRI of the brain, which was unremarkable. EEG demonstrated frequent bilaterally synchronous polyspike-slow wave epileptiform discharges throughout the record. She was treated with several anti-epileptic drugs and currently she is on valproic acid 500 mg twice daily, levetiracetam 500 mg twice daily, clonazepam 2 mg once daily, and acetazolamide 250 mg once daily. The patient's seizures were controlled with no seizures in the past 8 years.

2.2. Case report 2

A 25-year-old female II-3 that presented initially as a case of seizures at the age of 10 years with frequent myoclonic jerks and generalized tonic-clonic seizures. Her clinical course was progressive, and her myoclonus was both focal and generalized. She had ataxia and tremor in both hands which occur both at rest and action. She had an MRI of the brain, which was unremarkable. EEG demonstrated slow background activity of a moderate degree with frequent episodes of spikes and slow wave discharges (Fig. 2). She was treated with several anti-epileptic drugs and currently she is on valproic acid 400 mg three times daily and levetiracetam 1000 mg twice daily. She is seizure-free for the past 5 years. She also suffers from migraine attacks, which were treated with a nonsteroidal anti-inflammatory drug and beta-blockers.

3. Results

The genetic analysis identified a heterozygous variant in the *PRICKLE1* gene; NM_153026.2: c.251 G > A (p.Arg84Gln) (Fig. 3). This variant affects a highly conserved amino acid (Fig. 4). Prickle contains an N-terminal PET domain and three C-terminal LIM domains. Prickle has been implicated in regulation of cell movement in the planar cell polarity (PCP) pathway which requires the conserved Frizzled/Dishevelled (Dsh); Prickle interacts with Dishevelled, thereby modulating the activity of Frizzled/Dishevelled and the PCP signaling. The mutation lies in the PET domain of Prickle1 protein. It is towards N terminal. The PET domain is a protein-protein interaction domain, usually found in conjunction with the LIM domain, which is also involved in protein-protein interactions. The PET containing proteins serve as adaptors or scaffolds to support the assembly of multimeric protein complexes. Furthermore, this mutation has been predicted to be deleterious by computational in-silico analysis tools such as scale-invariant feature transform (SIFT) algorithm [7], MutationTaster2 [8], and Align-GVGD [9]. In addition, it has been previously identified in only one of 246,094 South Asian chromosomes by the Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org; dbSNP rs766439768) but was absent from other databases including 1000 Genomes Project (http://www.1000genomes.org), the NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), ClinVar database of genotype-phenotype associations (http://www.ncbi.nlm.nih.gov/clinvar), the Leiden Open Variation Database (http://www.lovd.nl), and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk). Deletion/duplication assay using multiplex ligation-dependent probe amplification (MLPA) did not identify neither deletions nor duplications in *PRICKLE1* in the proband. We found a mutation only in *PRICKLE1* gene, and no mutations were found related to any other known epilepsy genes during the data analysis. We did not find any other pathogenic or homozygous variants in genes that may cause the disease. Segregation study was performed using DNA from the parents and two sisters. The same variant was identified in one affected parent (the mother I-2) and the two unaffected sisters II-1 and II-2 while it was absent from the unaffected father I-1 (Fig. 5). One more sibling, a deceased brother, was diagnosed with PME, however, no DNA was available to perform genotyping. Based on the overall data and genotype-phenotype correlation, the identified variant was considered the disease-causing in this family. The presence of the mutation and absence of the disease in the two unaffected sisters suggests that this mutation may have incomplete penetrance.

4. Discussion

The PMEs are a group of inherited disorders characterized by the presence of typically refractory myoclonic and tonic-clonic seizures with progressive cognitive and neurologic deterioration. Most of these epilepsies are caused by a pathogenic mutation inherited as an

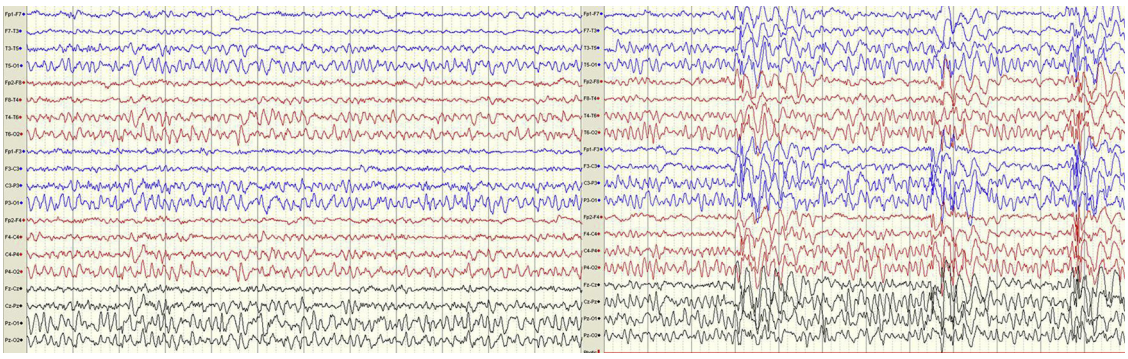

Fig. 2. EEG showing slow background activity of a moderate degree with frequent episodes of spikes and slow wave discharges.

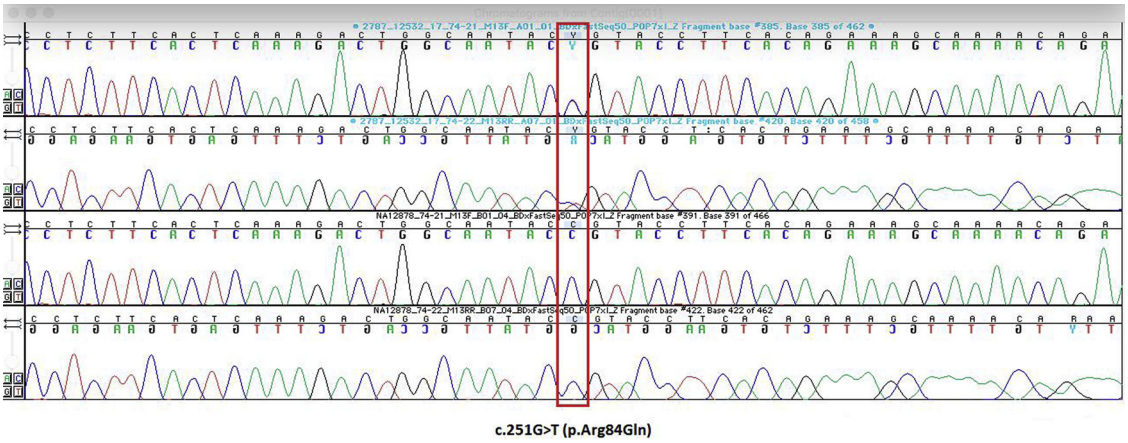

Fig. 3. Representative chromograph of *PRICKLE1* Sanger sequencing read. The red rectangle indicates the affected nucleotide. Genetic analysis identified this variant in both affected females, the proband and her mother. Genotyping was not performed for the deceased affected sibling due to DNA unavailability (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

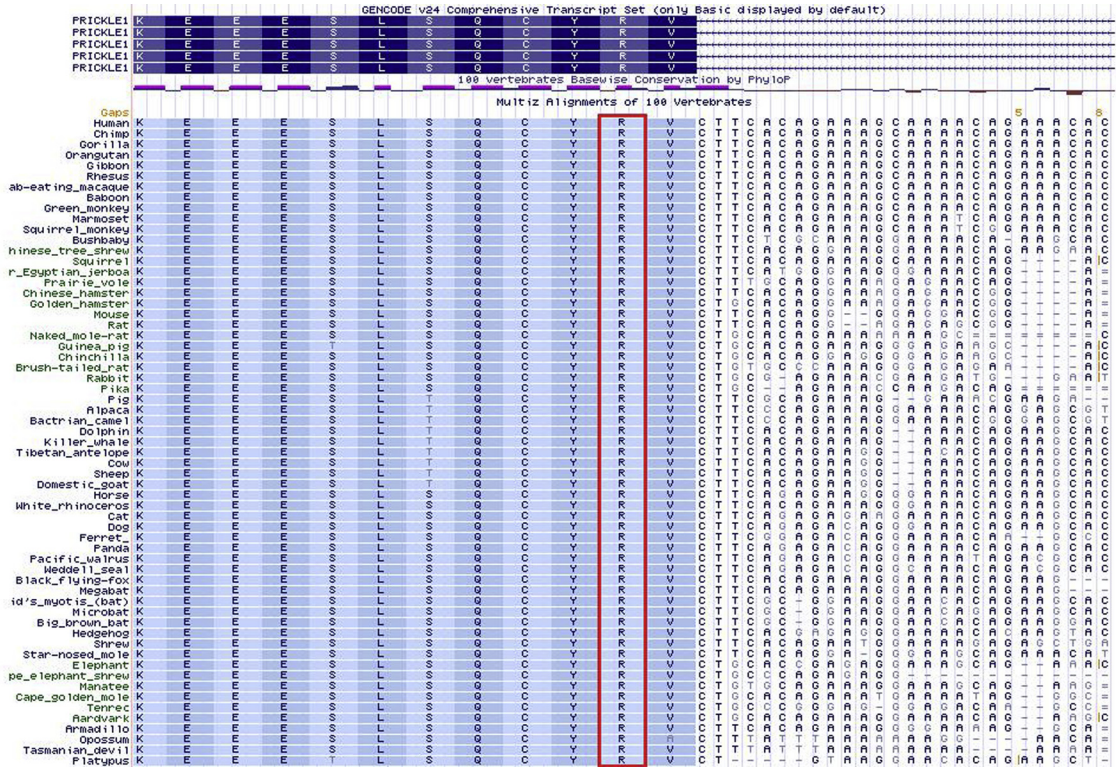

Fig. 4. *Multiple species* protein alignment view for *PRICKLE1* from the University of California, Santa Cruz (UCSC) Genome Browser. The highly conserved amino acid altered in this family (p.Arg84Gln) is indicated by a red rectangle. The high conservation of this amino acid suggests that a change at this position is probably not tolerated and would probably affect protein structure and function (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

autosomal recessive trait. However, few are inherited as an autosomal dominant trait or through mitochondrial inheritance [10]. Most of the known causative diseases in this group are caused by genes that encode lysosomal proteins with few exceptions (ion channels). Despite advances in knowledge of the etiology of PME disorder, the pathogenic mechanism leading to epilepsy and neurological deterioration remain largely unknown. Finding the cause of rare genetic diseases has been tremendously improved and accelerated by next generation-based clinical genetic tests such as WES [11].

PME-ataxia syndrome usually presents at the age of 4–5 years with ataxia and later on develop PME phenotype with mild or absent cognitive decline. Although cognitive decline is severe and generally occur early in many forms of PME, in this disorder, intellect is generally preserved or mildly affected [12]. Cerebellar signs usually occur early in the disease with ataxia, tremor, dysarthria, and difficulty walking. Action myoclonus may affect the limbs, face, or bulbar muscles with worsening on action or exposure to the sun. Seizures can be myoclonic or generalized tonic clonic and generally occur during sleep. MRI of the brain is usually normal. EEG usually reveal generalized epileptiform discharges with spike-wave or polyspike-wave activity [4].

Genetic analysis revealed a single variant in *PRICKLE1* in this patient. Segregation study identified the same variant in one affected parent (the mother) and the two unaffected sisters while it was absent from the unaffected father. The *PRICKLE1* gene (MIM#608,500) is

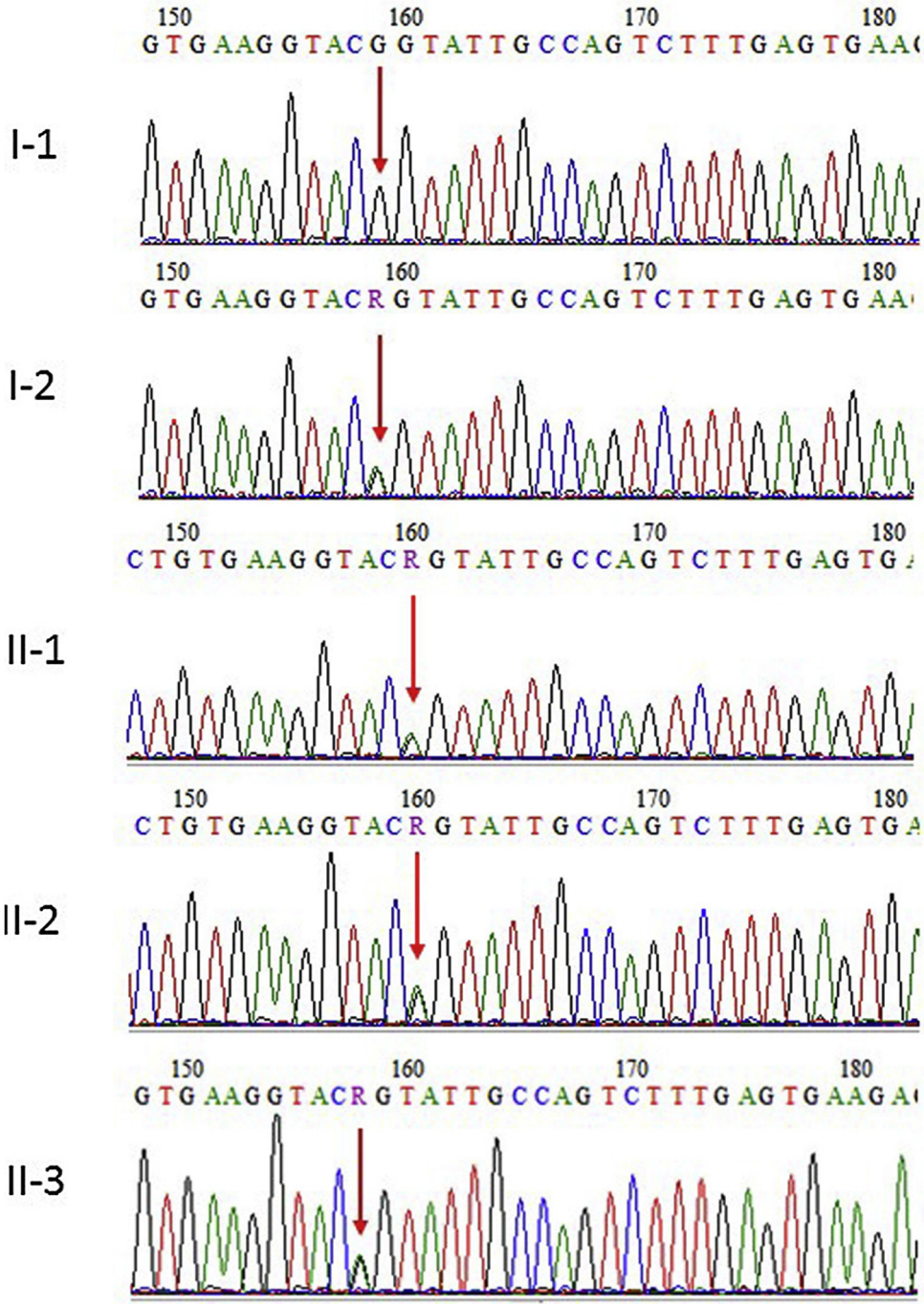

Fig. 5. Representative chromograph of *PRICKLE1* Sanger sequencing read of all family members. Genetic analysis identified this variant in both affected females, the proband II-3 and her mother I-2. In addition, the variant was identified in the two unaffected sisters II-1 and II-2.

located on chromosome 12q12 and encodes the nuclear receptor prickle planar cell polarity protein 1. The Prickle1 protein has multiple protein-protein interaction domains, such as PET (Prickle, Espinas and Testin), LIM (Lin11, Isl-1 and Mec3) and C-terminal PKH (prickle homologous) [13]. Through these domains, *PRICKLE1* is involved in different protein networks and cell signaling pathways [13–15]. In addition, *PRICKLE1* is a well-established member of the planar cell polarity proteins and is involved in establishing cell polarity during embryonic development [16,17], as well as regulating cell morphology and behavior in different processes including neural tube closure and long bone cartilage elongation [18,19]. A recent study suggested that *PRICKLE1* is also involved in myelination of white matter through regulating oligodendrogenesis [20]. In addition, animal model studies showed that throughout mouse embryonic development Prickle1 is expressed in different brain regions including regions implicated in epilepsy, seizures, and ataxia [12,13,21,22].

The *PRICKLE1* gene was linked to different conditions including autosomal recessive and autosomal dominant PME. The mechanism by which mutations in the *PRICKLE1* gene contribute to different phenotypes is not completely understood. However, the findings of *PRICKLE1* functional studies and its different domains-proteins interactions, might suggest that this phenotypic heterogeneity is attributed to the involvement of the *PRICKLE1* domains in multiple cellular networks. In addition, some mutations in Prickle1 were suggested to result in a dominant-negative protein that acts dominant-negatively to inhibit the function of normal Prickle1 protein in neurons [17]. This might explain

Table 2
Summary of reported clinically significant variants in PRICKLE1.

Identified DNA variant	Amino acid change	Variant frequency in the general population*	dbSNP	Reported phenotype	Ref.
c0.1444 G > A	de novo	–	–	Myoclonic Epilepsy and Autism Spectrum Disorder	[31]
c.169 G > C	p.Val57Ile	–	–	Autism Spectrum Disorders	[24]
c.251 G > A	p.Arg84Gln	0.0004% (1/246,094)	rs766439768	Progressive myoclonus epilepsy	This report
c.206 T > C	p.Ile69Thr	0.003% (7/246,154)	rs141795695	Neural tube defects	[27]
c.241 A > C	p.Asn81His	0.002% (5/246,082)	rs796052934	Neural tube defects	[27]
c.311 G > A	p.Arg104Gln	0.002% (5/277,168)	rs113994140	Progressive myoclonus epilepsy-ataxia syndrome	[12]
c.427 T > G	p.Ser143Ala	–	rs796052929	Agenesis of corpus callosum and polymicrogyria	[27]
c.431 G > A	p.Arg144His	0.001% (3/246,166)	rs281865563	Progressive myoclonus epilepsy-ataxia syndrome	[25]
c.553 G > A	p.Glu185Lys	–	–	Autism Spectrum Disorders	[24]
c.820 G > A	p.Ala274Thr	–	–	Early Infantile Epileptic Cncephalopathy	[23]
c.824C > T	p.Thr275Met	0.01% (31/273,982)	rs559947948	Neural tube defects	[28]
c.1138C > T	p.Leu380Phe	–	–	Cleft palate	[29]
c.1414 T > C	p.Tyr472His	–	rs281865564	Progressive myoclonus epilepsy-ataxia syndrome	[25]
c.1648 G > A	p.Val550Met	0.003% (8/237,590)	rs760050261	Neural tube defects	[28]
c.2026C > T	p.Arg676Trp	0.0004% (1/246,238)	rs779314205	Cleft palate	[29]
c.2044C > T	p.Arg682Cys	0.003% (7/277,212)	rs768954477	Neural tube defects	[[28]]
c.2216C > T	p.Ser739Phe	0.08% (211/276,982)	rs138452760	Neural tube defects	[28]
c.2311 G > A	p.Asp771Asn	0.0008% (2/246,172)	rs146670726	Caudal agenesis	[28]

why the presence of a single mutation in *PRICKLE1* is enough to cause an autosomal dominant disease. However, future functional analysis of the effect of the identified variant in this study on *PRICKLE1* functions would further elucidate the molecular mechanism underlying PRICKLE1-associated autosomal dominant PME.

Biallelic pathogenic variants in the *PRICKLE1* gene were reported to cause autosomal recessive PME [12], early infantile epileptic encephalopathy [23], autism spectrum disorders [24]. However, other reports showed that single pathogenic variant and compound heterozygous in this gene could cause PME [25,26], agenesis of corpus callosum and polymicrogyria [27], incomplete penetrant autosomal dominant neural tube defects [28], caudal agenesis [29], and cleft palate [30]. More recently, a novel de novo missense mutation in the *PRICKLE1* has been reported to be associated with epilepsy, autism spectrum disorder, and global developmental delay [31] (Table 2). In addition, in-vivo studies showed that null and missense Prickle1 mutations could cause a wide spectrum of structural birth defects described to phenocopy human Robinow syndrome and velocardiofacial syndromes. [30,32] However, to date, there is no report describes PRICKLE1-associated Robinow syndrome in human.

PRICKLE1-related PME is very rare, and to date, three families of Middle Eastern descent and two other unrelated individuals were reported with this rare form of PME [4,12,25]. Among all the reported *PRICKLE1* disease-causing pathogenic variants, only three were previously reported to cause PME (Table 2). Complete penetrance was observed in the original families studied that had PRICKLE1-related PME inherited in an autosomal recessive manner. Tao et al. [24] reported two heterozygous mutations in the *PRICKLE1* gene in two unrelated individuals with PME. However, no information on the other family members of these patients was provided. In our study, the siblings of the index case were tested and were positive for the same mutation in the *PRICKLE1* gene but were clinically normal although they were older than the index case (29 and 27 years old, respectively), which may indicate that heterozygous mutations in the *PRICKLE1* gene have incomplete penetrance.

5. Conclusion

PME-ataxia syndrome is a rare genetic disorder characterized by ataxia, myoclonic and tonic-clonic seizure, and varying degree of neurological disability. PRICKLE1-related PME is an extremely rare condition, and to date, only three families of Middle Eastern descent and two other unrelated individuals were reported in the literature. To our best knowledge, this is the first report that demonstrates a single *PRICKLE1* pathogenic variant segregating with PME in one family. The novel variant identified in this family has never been previously reported as a disease-causing variant. The presence of the same variant in the unaffected individuals may suggest that heterozygous mutations in the *PRICKLE1* gene have incomplete penetrance. Further research is needed to elucidate the penetrance of heterozygous mutations in the *PRICKLE1* gene.

Conflict of interest

The authors declare that they have no conflicts of interest.

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