Research Square

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Novel Variants in TMEM151A Identified in a Cohort of Patients with Paroxysmal Kinesigenic Dyskinesia

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Abstract

Methods

We recruited 31 sporadic PKD patients and 10 familial pedigrees from the Departments of Neurology at Henan Provincial People's Hospital between June 2023 and April 2025. Whole-exome sequencing (WES) was performed to identify pathogenic variants, followed by Sanger sequencing for validation and segregation analysis. In silico structural modeling and protein stability analyses were conducted for missense variants. A systematic literature review was performed to further characterize *TMEM151A*-related PKD.

Results

Three *TMEM151A* variants were identified in one sporadic case and two familial pedigrees, including two novel missense variants (c.894G > T [p.Trp298Cys] and c.899T > C [p.Leu300Pro]) and one frameshift variant (c.943dup[p.Val315GlyfsTer31]. Notably, in one pedigree, the variant carrier presented with epilepsy without PKD, indicating phenotypic heterogeneity and incomplete penetrance. Structural analyses suggested that missense variants may impair protein stability by altering hydrogen bonding networks. Combined with 74previously reported cases, *TMEM151A*-related PKD typically presents with adolescent onset, brief dystonic episodes, and a favorable response to sodium channel blockers. No significant differences in age at onset or remission were observed between truncating and missense variants, suggesting a shared pathogenic mechanism.

Conclusions

This study expands the mutational spectrum of *TMEM151A* by identifying three previously unreported variants and further refines the clinical characterization of *TMEM151A*-associated PKD. Our findings support that mutation type is not a major determinant of clinical phenotype, implicating a potential common mechanism such as haploinsufficiency.

Introduction

Paroxysmal kinesigenic dyskinesia (PKD) is a rare episodic movement disorder characterized by brief attacks of dystonia or chorea triggered by sudden voluntary movements[1]. PKD is typically inherited in an autosomal dominant manner with incomplete penetrance, although sporadic cases are frequently observed[2]. Among the known causative genes, PRRT2 accounts for the majority of cases[3]. Moreover, other genes potentially linked to paroxysmal movement disorders have also been discovered and documented, such as *SCN8A*, *PNKD*, *KCNMA1*, *SLC2A1*, *KCNA1*, *DEPDC5*, and *CHRNA4*[4, 5]. In 2021, Li et al. initially identified *TMEM151A* gene variations in PRRT2 - negative paroxysmal kinesigenic dyskinesia (PKD) patients via whole - exome sequencing (WES) and verified its pathogenicity[6].

TMEM151A encodes a predicted transmembrane protein localized to the endoplasmic reticulum and highly expressed in the central nervous system. Emerging evidence suggests that it may regulate neuronal excitability, potentially through modulation of intracellular calcium homeostasis[7, 8]. However, the clinical and mutational spectrum of *TMEM151A*-related paroxysmal kinesigenic dyskinesia (PKD) remains incompletely characterized, particularly in sporadic cases[9].

In this study, we analyzed a multicenter cohort of PKD patients, including both sporadic cases and familial pedigrees, and identified three previously unreported TMEM151A variants. By integrating clinical data, in silico analyses, and a comprehensive literature review, we aimed to elucidate genotype–phenotype correlations and provide insights for improved diagnosis and management.

Methods

Participants

Thirty-one sporadic probands with paroxysmal kinesigenic dyskinesia (PKD) and ten familial pedigrees were recruited from the Departments of Neurology at Henan Provincial People's Hospital. All patients were diagnosed with PKD according to the criteria proposed by Cao et al. (2021)[10].Clinical data were systematically reviewed by experienced neurologists, including age at onset, family history, triggering factors, attack characteristics and frequency, laterality, aura symptoms, and treatment response. Patients carrying TMEM151A variants were further analyzed in detail.The study was approved by the institutional ethics committees of hospital(Ethical Committee of Henan Provincial People's Hospital, Ethical Number 2024 LUNSHEN 146), and written informed consent was obtained from all participants or their legal guardians.

Mutation Analysis of the Gene

Mutation Analysis of the *TMEM151A* Gene
Whole-exome sequencing (WES)[3]was performed on 31 sporadic PKD probands and 10 PKD families. Target enrichment was conducted using the xGen® Exome Research Panel v2.0 (Integrated DNA Technologies), and sequencing was performed on the DNBSEQ-T7 platform with 150 bp paired-end reads. The captured region covered approximately 51 Mb, with ≥ 99% of bases achieving sufficient depth. Cross-platform validation was performed using an independent capture system (Agilent) combined with Illumina sequencing technology.

Genomic DNA was extracted from peripheral blood samples using standard procedures. Raw sequencing data were aligned to the GRCh37/hg19 reference genome using BWA-MEM. Variants were identified using GATK[11] and annotated using an online platform (Chigene). Variants with a minor allele frequency < 0.1% were retained based on public databases, including HGMD, ClinVar, and the 1000 Genomes Project.The pathogenicity of candidate variants was evaluated using in silico tools, including PolyPhen-2, PROVEAN, SIFT, REVEL, M-CAP, and MutationTaster[12–14]. Conservation analysis was performed using the UCSC Genome Browser[15].Protein structural analysis was conducted using AlphaFold2 and visualized with PyMOL, while protein stability was assessed using MetaDome[16, 17]. All candidate variants were validated by Sanger sequencing and classified according to ACMG/AMP guidelines[18].

Damaging effect of variants

Damaging effect of *TMEM151A* variants

To evaluate the impact of candidate missense variants on protein structural stability, three-dimensional protein models were generated using the I-TASSER server [19](https://zhanglab.ccmb.med.umich.edu/I-TASSER/). Structural visualization and analysis were performed using PyMOL 1.7 (Schrödinger, LLC).Changes in protein stability were predicted using the I-Mutant 3.0 server[20] (http://folding.biofold.org/i-mutant/i-mutant3.html), which estimates variations in folding free energy (ΔΔG, kcal/mol) induced by amino acid substitutions. Variants with $|\Delta\Delta G| \geq 0.5$ kcal/mol were considered to have a significant impact on protein stability ($\Delta\Delta G > 0.5$ indicating increased stability and $\Delta\Delta G < -0.5$ indicating decreased stability), whereas $|\Delta\Delta G| < 0.5$ kcal/mol was considered neutral.

Excess of variants

Excess of *TMEM151A* variants

The frequency of *TMEM151A* variants was compared with that of benign variants in the Genome Aggregation Database (gnomAD)[21]. To evaluate the association between allele frequency and disease, variant frequencies in the PKD cohort were compared with those in the general population from gnomAD.To assess the significance of compound heterozygous variants, a control cohort comprising 1,942 unaffected parents from trios was included. In this cohort, compound heterozygous variants were inferred based on the transmission of one variant to the offspring. The frequency of compound heterozygous variants was further compared with gnomAD data.

Spatial and temporal expression analysis

To analyze the spatiotemporal expression of *TMEM151A*, expression profiles across tissues and developmental stages were obtained from publicly available databases. Data from the Evolutionary Developmental Mammalian Organ Database were used to assess expression patterns across organs and developmental stages. Expression in adult non-diseased tissues was analyzed using the GTEx database[22], while brain developmental expression profiles were obtained from the BrainSpan database[23].

Single-cell expression of *TMEM151A*

The expression of TMEM151A at different developmental stages was analyzed using single-cell RNA sequencing data from developing brain organoids and adult human brains. Data from undifferentiated brain organoids at 1 and 5 months were obtained from the Human Organoid Single Cell Browser[24]. Single-cell data from adult healthy human brains were retrieved from the ScApeX database (https://bioinf.eva.mpg.de/shiny/sample-apps/scApeX/).

Literature review

A comprehensive literature search was conducted in PubMed using the term "*TMEM151A*". All relevant studies published from database inception to December 31, 2025, were included.

Statistical analysis

All statistical analyses were performed using R software (version 4.0.3). Fisher's exact test was used to compare allele frequencies of *TMEM151A* variants between the PKD cohort and the gnomAD East Asian population, as well as the proportion of individuals carrying any *TMEM151A* variant between groups.For continuous variables, including age at onset and age at remission, normality was assessed prior to analysis. Student's t-test was applied for normally distributed data, while the Mann–Whitney U test was used otherwise. A two-sided p-value < 0.05 was considered statistically significant.

Results

Identification of TMEM151A variants

TMEM151A (NM_153266) was screened for variants in all sporadic patients and probands with PKD. Parental testing was performed in one sporadic case and two familial pedigrees carrying *TMEM151A* variants.The missense variant c.894G>T (p.Trp298Cys) was identified as a de novo mutation (Figure 1A). The missense variant c.899T>C (p.Leu300Pro) was inherited from the father, who also exhibited PKD but experienced spontaneous remission after the age of 25 without treatment (Figure 1B).The frameshift variant c.943dup (p.Val315GlyfsTer31) segregated within a family; notably, the carrier mother presented with focal motor epilepsy but had no PKD (Figure 1C). No *TMEM151A* variants were detected in the remaining patients.

Clinical characteristics of PKD patients with *TMEM151A* variants

One sporadic proband and two individuals from two PKD families were identified as carrying TMEM151A variants. The clinical features of these patients are summarized in Table 1.

Patient 1 (Fig. 1A) was a 12-year-old girl with disease onset at 11 years of age. She presented with recurrent, brief episodes of bilateral limb and facial dystonia occurring 5–10 times per day. Episodes were typically triggered by sudden voluntary movements and lasted approximately 7–10 seconds. Neurological examination, laboratory tests, brain MRI, and EEG were unremarkable. The symptoms were completely controlled with oxcarbazepine. No family history of similar symptoms was reported.

Patient 2 (Fig. 1B) was a 20-year-old male with onset at 10 years of age. He experienced recurrent episodes of exercise-induced limb stiffness with transient loss of motor control, lasting 3–4 seconds. Episodes could be unilateral or bilateral and occasionally preceded by a subjective aura. Previous treatment with sodium valproate, sertraline, and clonazepam was ineffective. Neurological examination, laboratory tests, EEG, and brain MRI were normal. Symptoms were fully controlled after treatment with oxcarbazepine. His father had a similar history of dyskinesia with spontaneous remission after the age of 25.

Patient 3 (Fig. 1C) was a 16-year-old adolescent with onset at 12 years of age. He presented with frequent dystonic episodes (<10 seconds, >10 times per day), predominantly triggered by sudden movements and without loss of consciousness. Neurological examination, MRI, and EEG were normal. Symptoms were well controlled with oxcarbazepine. His mother had a history of focal epilepsy beginning at 13 years of age, which was responsive to phenytoin but relapsed after drug withdrawal and later required retreatment.

In silico prediction of *TMEM151A* variant pathogenicity

In silico prediction tools consistently suggested that the *TMEM151A* variants identified in this study are likely to be deleterious (Table 2). The variant c.894G>T (p.Trp298Cys) was predicted to be damaging by PROVEAN, SIFT, M-CAP, and MutationTaster. Similarly, the variant c.899T>C (p.Leu300Pro) was predicted to be deleterious by PROVEAN, SIFT, REVEL, PolyPhen-2, M-CAP, and MutationTaster. No prediction scores were available for the frameshift variant c.943dup (p.Val315GlyfsTer31).According to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines[18], the missense variants c.894G>T (p.Trp298Cys) and c.899T>C (p.Leu300Pro) were classified as variants of uncertain significance (VUS), whereas the frameshift variant c.943dup (p.Val315GlyfsTer31) was classified as likely pathogenic. Multiple sequence alignment demonstrated that the affected residues Trp298 and Leu300 are highly conserved across vertebrates, including humans, mice, dogs, elephants, chickens, Xenopus tropicalis, and zebrafish (Fig. 1D).

Structural alteration in the *TMEM151A* protein

The *TMEM151A* protein contains a Pfam domain (amino acid residues 26–373) and additional domains predicted by the SMART database[25].Structural analysis showed that the wild-type residue Trp298 forms hydrogen bonds with Ser41, Arg301, and Val302. After substitution, the mutant residue Cys298 retained hydrogen bonds with Arg301 and Val302 but lost interaction with Ser41, suggesting a potential alteration in local structural stability (Fig. 2A).

Similarly, the wild-type residue Leu300 forms hydrogen bonds with Leu296 and Ala304. Following substitution, Pro300 maintained a hydrogen bond only with Ala304, indicating disruption of the original hydrogen bonding network (Fig. 2B). These alterations may affect protein structural stability and function.

Spatial-temporal expression of TMEM151A gene

Spatial–temporal expression analysis showed that *TMEM151A* is widely expressed across multiple tissues (Fig. 3A, B). In the brain, *TMEM151A* expression was observed in several regions, including the cortex, basal ganglia, hippocampus, and thalamus (Fig. 3C). Temporal expression analysis revealed that *TMEM151A* is expressed throughout the lifespan, with two distinct peaks (Fig. 3D–F). The first peak occurred during the fetal to early infancy period and was observed across most developing brain regions. The second peak was detected during adolescence to young adulthood, consistent with the typical age of onset of PKD in this study. The highest expression levels were observed in the cortex and the medial nucleus of the thalamus (Fig. 3F), regions known to be closely associated with PKD[26].

The single-cell expression of *TMEM151A*

Single-cell RNA sequencing analysis of brain organoids revealed that *TMEM151A* exhibits spatiotemporal expression during neural development (Fig. 3G, H). At 1 month, *TMEM151A* expression was primarily observed in early progenitor cells and immature neurons. By 5 months, expression shifted toward more mature neuronal populations, with enrichment in deep and superficial cortical excitatory neurons (EN-CTX-Deep/Superficial) and intermediate neurons in the subventricular zone (IN-LGE), suggesting a role in neuronal maturation and regional specialization. Single-cell clustering and t-SNE analysis demonstrated marked cellular heterogeneity within organoids, distinguishing excitatory neurons, inhibitory neurons, and glial cell populations. Pseudotime trajectory analysis further illustrated the developmental progression of neural cell lineages, indicating that brain organoids recapitulate key spatiotemporal and cellular features of human brain development (Fig. 3I).

Literature review (Genotype–phenotype correlation)

A total of 74previously reported patients with *TMEM151A*-related PKD were included in the analysis (Fig. 4A). The mean age at onset was 12 years, and the mean age at remission was 22 years. Missense variants were occasionally associated with additional clinical features, including epileptic seizures.Comparative analysis between patients with truncating variants (nonsense and frameshift) and those with missense variants revealed no significant differences in age at onset or age at remission (Fig. 4B, C). Most patients showed a favorable response to treatment.

Discussion

TMEM151A was first identified as a gene associated with paroxysmal neurological disorders in 2021[6], and subsequent studies have confirmed its role in PKD and epilepsy[27,28]. *TMEM151A* is predominantly expressed in glutamatergic excitatory neurons and oligodendrocytes and is thought to regulate neuronal network excitability. The mutational spectrum of *TMEM151A* includes missense, nonsense, and frameshift variants, some of which may result in haploinsufficiency.

In the present study, we identified three previously unreported *TMEM151A* variants: c.894G>T (p.Trp298Cys), c.899T>C (p.Leu300Pro), and c.943dup (p.Val315GlyfsTer31). Notably, in one family carrying the frameshift variant, the mother presented with epilepsy without PKD, highlighting marked phenotypic heterogeneity and incomplete penetrance.

PKD (OMIM 128200) is a rare paroxysmal movement disorder characterized by brief, movement-triggered involuntary episodes. Although carbamazepine or oxcarbazepine is generally effective, PKD is frequently misdiagnosed due to its rarity. Compared with *PRRT2*-related PKD, which is typically familial with earlier onset and a higher prevalence of infantile seizures, *TMEM151A*-related PKD tends to present as sporadic cases with later onset (approximately 12 years), shorter attack duration (<10 seconds), and dystonia as the predominant phenotype[6]. Functional studies suggest that *TMEM151A* localizes to the endoplasmic reticulum and may regulate neuronal excitability through calcium signaling or sodium channel modulation[7].

Despite shared clinical features such as movement-triggered episodes and spontaneous remission, *TMEM151A*- and *PRRT2*-related PKD exhibit distinct phenotypic characteristics. Previous studies have reported differences in clinical features, age at onset, and comorbidities[29]. Although most patients respond to sodium channel blockers, the complete remission rate appears to be lower in *TMEM151A*-related PKD compared with *PRRT2*-related PKD (47.1% vs. 85.5%), and some patients may require alternative treatments such as lacosamide. In addition, intrafamilial phenotypic variability is frequently observed, with carriers of the same variant presenting with PKD, epilepsy, or other neurological manifestations, suggesting the involvement of genetic modifiers or environmental factors.

According to ACMG/AMP guidelines[18], the missense variants identified in this study were classified as variants of uncertain significance, whereas the frameshift variant c.943dup (p.Val315GlyfsTer31) was classified as likely pathogenic. Frameshift variants introduce premature termination codons, which may result in truncated proteins or trigger nonsense-mediated mRNA decay (NMD), a key quality-control mechanism for eliminating aberrant transcripts[30]. Similar mechanisms have been described in *PRRT2*-related disorders, where truncating variants lead to loss of function and altered protein localization[3]. These findings suggest that NMD-mediated haploinsufficiency may represent a shared pathogenic mechanism between *TMEM151A*- and *PRRT2*-related PKD.

In our combined analysis of 74previously reported patients, no significant differences were observed in age at onset or remission between truncating and missense variants. This suggests that TMEM151A-related PKD may arise predominantly through a common pathogenic mechanism, such as haploinsufficiency, rather than variant-specific effects. This observation contrasts with PRRT2-related PKD, in which truncating variants are often associated with earlier onset and more severe phenotypes[3], highlighting potential differences in disease mechanisms.

Importantly, most patients in our cohort showed a favorable response to sodium channel blockers, consistent with previous studies[10]. However, considerable phenotypic heterogeneity was observed, even among individuals carrying the same variant, further supporting the role of modifying factors in disease expression. These findings underscore the importance of genetic testing and individualized treatment strategies in patients with PKD.

This study has several limitations. First, the sample size remains relatively small, which may limit the statistical power of genotype–phenotype analyses. Second, functional validation of the identified variants was not performed. Future studies should focus on elucidating the biological function of *TMEM151A*, including its interactions with ion channels and synaptic proteins, and on conducting larger cohort analyses to refine genotype–phenotype correlations.

In conclusion, this study expands the mutational and clinical spectrum of *TMEM151A*-related PKD and provides new insights into its underlying pathogenic mechanisms. These findings have important implications for the genetic diagnosis and personalized management of rare movement disorders.

Conclusions

In summary, this study expands the mutational spectrum of TMEM151A by identifying three previously unreported variants and further delineates the clinical characteristics of TMEM151A-related PKD. Our findings indicate that mutation type is not a major determinant of clinical phenotype, supporting a shared pathogenic mechanism, potentially haploinsufficiency. These results provide valuable insights for the genetic diagnosis and individualized management of PKD.

Declarations

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Author Contribution

Y.C. and M.H. contributed equally to this work and drafted the main manuscript text. L.W. and S.L. were responsible for data collection and clinical data curation. T.Z. and N.W. performed genetic analyses and variant interpretation. J.Y.H. and L.S. conducted bioinformatics analyses and prepared Figures 1–4.

X.H. conceived and supervised the study and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data Availability

Data Availability StatementThe datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

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Tables

Table1 Clinical features of PKD patients with TMEM151A Variants

Family	Patient ID	Age (y)/Sex	AAO (y)	Remission age (y)	Family history	Trigger	Attack duration (s)	Attack frequency	Phenotype	Laterality	Aura	Comorbidity
Sporadic	Patient 1	12/F	11	NA	No	Sudden movement	7–10	3–4/day	Dystonia	Alternating	Yes	No
Family 1	I-1	60/M	12	25	NA	Sudden movement	6–8	5–10/day	Dystonia	Alternating (face)	Yes	No
Family 1	II-2	20/M	10	NA	Yes	Sudden movement	3–4	>10/day	Dystonia	Bilateral (face)	Yes	No
Family 2	I-1	50/F	13	NA	No	NA	NA	NA	NA	NA	NA	Epilepsy
Family 2	II-2	16/M	12	NA	Yes	Sudden movement	<10	>10/day	Dystonia	Bilateral (face)	No	No

ACMG American College of Medical Genetics, AAO age at onset, SM Sudden movement, D dystonia, C chorea, CBZ carbamazepine, F female, M male, NA not available

Table 2 In silico analysis of *TMEM151A* variant

Mutations	Amino acid change	ROVEAN[a]	SIFT[b]	REVEL[c]	Polyphen2[d]	M-CAP[e]	MutationTa
c.894G>T	p.Trp298Cys	deleterious(-12.37)	damaging(0.02)	neutral(0.405)	benign(0.019)	Damaging(0.058051)	disease_ca
c.899T>C	p.Leu300Pro	deleterious(-6.71)	damaging(0.001)	deleterious(0.777)	probably damaging(1.0)	Damaging(0.190479)	disease_ca
c.943dup	p.Val315GlyfsTer31	-	-	-	-	-	-

[a] PROVEAN (http://provean.jcvi.org/protein_batch_submit.php?species=human)

[b] SIFT, Sorting Intolerant From Tolerant (http://sift.jcvi.org/)

[c] REVEL（https://sites.google.com/site/revelgenomics/）

[d] Polyphen-2 (http://genetics.bwh.harvard.edu/pph2/)

[f] MutationTaster (http://www.mutationtaster.org/)

[g] FATHMM-MKL (http://fathmm.biocompute.org.uk/fathmmMKL.htm)

[h] Genomic Evolutionary Rate Profiling (GERP, https://personal.broadinstitute.org/mgarber/GERP/documentation.pdf)

[i] Frequency of variation in the 1000 Genomes database

j Frequency of variation in the total of exome gnomAD (genome Aggregation Database)

k Frequency of variation in the East Asian population of exome gnomAD

Figures

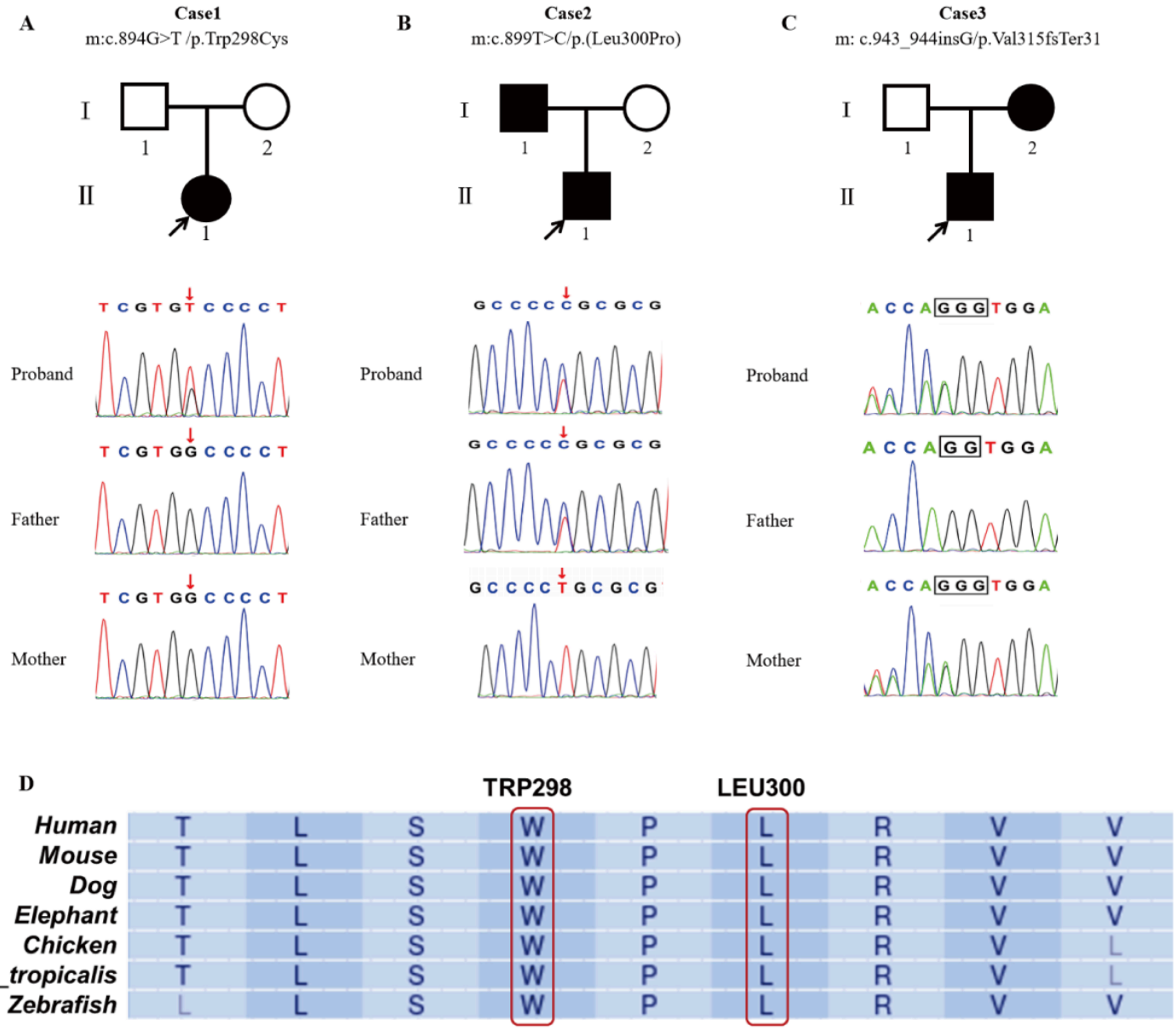

Figure 1

Identification and conservation of TMEM151A variants in patients with PKD.

(A–C) Pedigree analysis and Sanger sequencing validation of three TMEM151A variants. Squares indicate males, circles indicate females, filled symbols indicate affected individuals, and arrows indicate probands. Red arrows denote the variant positions in the chromatograms.Case 1: c.894G>T (p.Trp298Cys); Case 2: c.899T>C (p.Leu300Pro); Case 3: c.943dup (p.Val315GlyfsTer31).(D) Amino acid sequence conservation of TMEM151A across vertebrates. The conserved residues Trp298 and Leu300 are highlighted in red boxes.

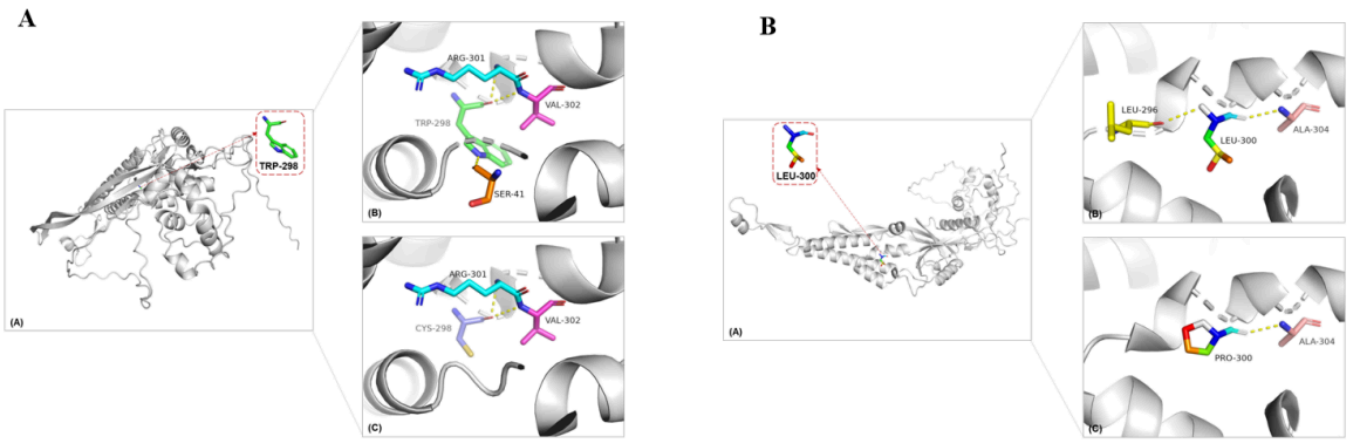

Figure 2

Hydrogen bond alterations of *TMEM151A* variants and their potential impact on protein structure. (A) Structural analysis of the *TMEM151A*p.Trp298Cys variant. The wild-type residue Trp298 forms hydrogen bonds with Ser41, Arg301, and Val302, whereas the mutant residue Cys298 retains interactions with Arg301 and Val302 but loses the bond with Ser41. (B) Structural analysis of the *TMEM151A* p.Leu300Pro variant. The wild-type residue Leu300 forms hydrogen bonds with Leu296 and Ala304, whereas the mutant residue Pro300 retains only the interaction with Ala304. These changes in hydrogen bonding patterns may affect protein structural stability and function.

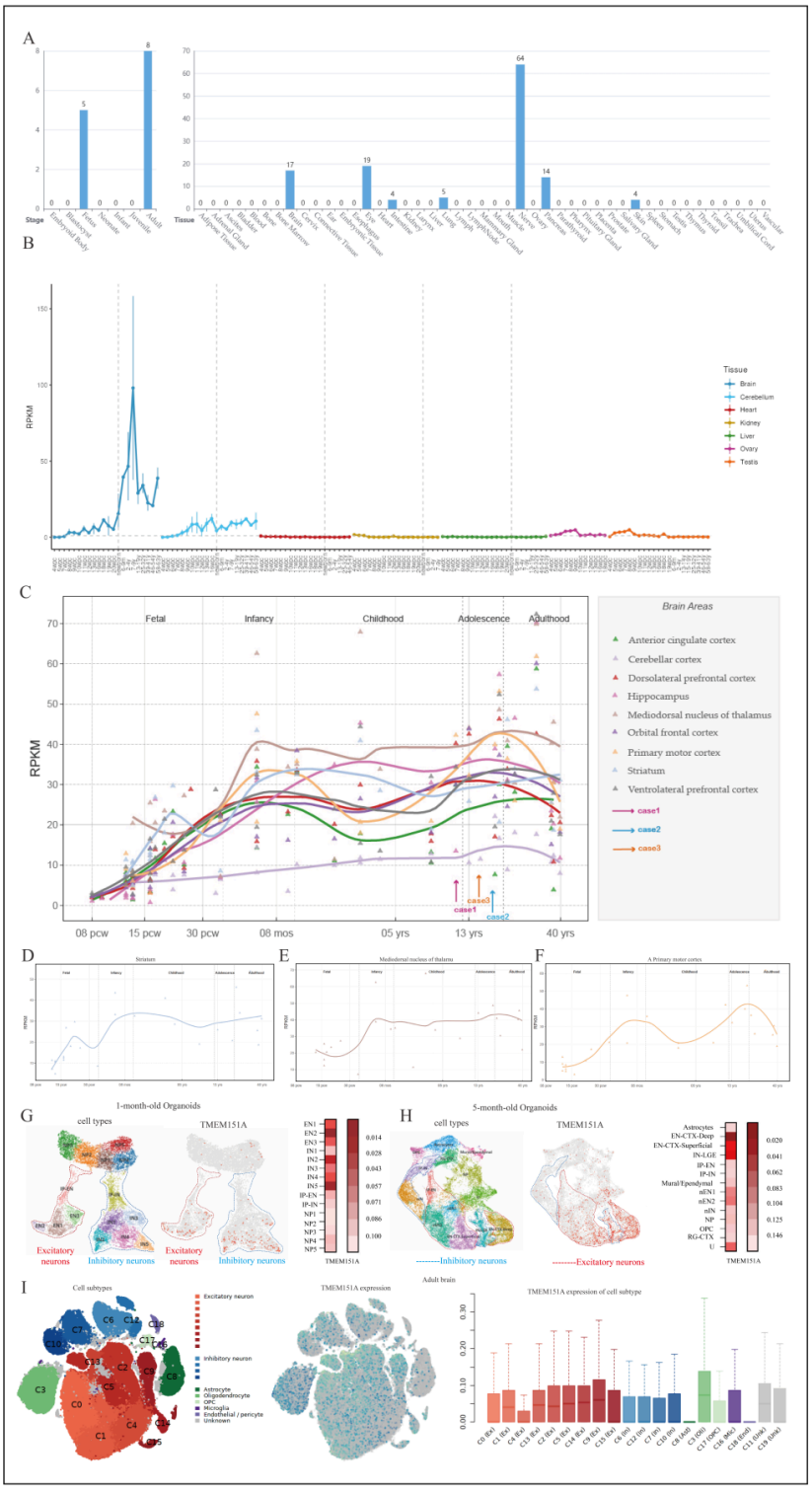

Figure 3

Spatial–temporal expression of TMEM151A.

(A) Expression of TMEM151A across human tissues and brain regions, showing broad expression in multiple brain subregions.

(B) Expression profile of TMEM151A across organs at different developmental stages, with the highest expression observed in the developing brain during adolescence.

(C–F) Temporal expression patterns of TMEM151A in different brain regions, demonstrating expression throughout the lifespan with two distinct peaks.

(G–H) Single-cell expression of TMEM151A in neural rosette-derived cortical organoids at 1 and 5 months.

(I) TMEM151A expression in the adult human brain based on single-nucleus RNA sequencing (snRNA-seq), showing expression in multiple neuronal cell types, including excitatory and inhibitory neurons.

Abbreviations: Ast, astrocyte; CTX, cortex; EN/Ex, excitatory neurons; IN, inhibitory neurons; IP, intermediate neural progenitors; LGE, lateral ganglionic eminence; NP, neural progenitors; Oli, oligodendrocyte; OPC, oligodendrocyte progenitor cell; RG, radial glial cells; RPKM, reads per kilobase per million mapped reads; mos, months; pcw, post-conception weeks; wpc, weeks post-conception; y/yrs, years; Unk, unknown.

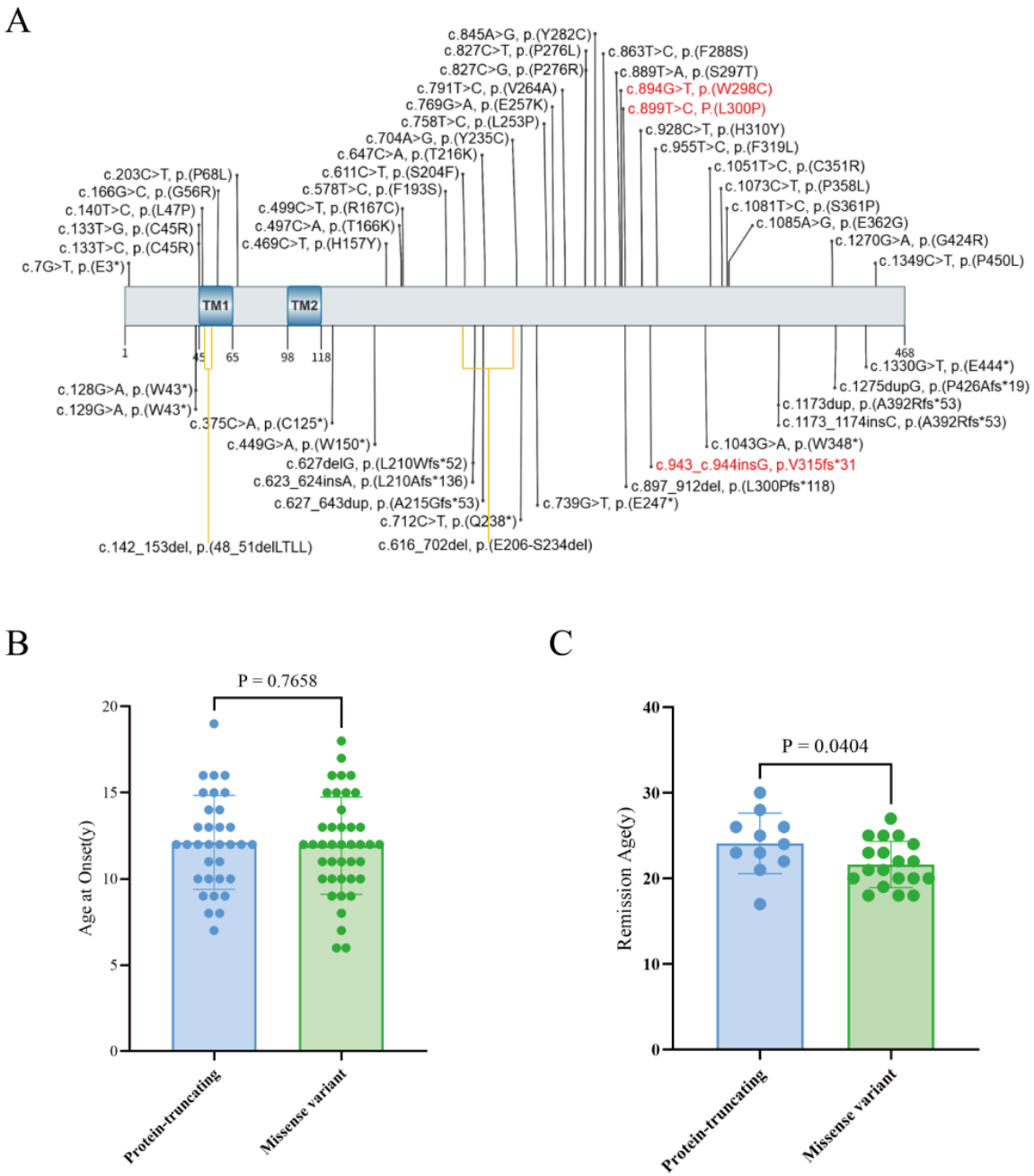

Figure 4

Distribution of *TMEM151A* variants and genotype–phenotype analysis.

(A) Schematic representation of *TMEM151A* protein showing the distribution of reported variants. TM1 and TM2 indicate transmembrane domains. Variants identified in this study are highlighted in red.

(B) Comparison of age at onset between mutation types. No significant difference was observed between patients with protein-truncating variants and those with missense variants (n = 74).

(C) Comparison of age at remission between mutation types. Patients with protein-truncating variants showed a slightly later remission age compared with those with missense variants. After excluding cases with missing data or no remission, 30 patients were included in the analysis (11 with truncating variants and 19 with missense variants).