

ORIGINAL ARTICLE

Genetic Counseling for Fetal Growth Restriction Associated with Rare Pathogenic Variants in TCF20 and TMEM151A Genes

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ABSTRACT

Background: This study aimed to analyze the pathogenic variant sites in the TCF20 and TMEM151A genes in a kindred presenting with developmental delay with variable intellectual impairment and behavioral abnormalities (DDVIBA) and paroxysmal kinesigenic dyskinesia (PKD), thereby facilitating genetic counseling and prenatal diagnosis for the family.

Methods: With the pregnant woman as the proband, peripheral blood samples were collected from the proband, her husband, and her parents, along with amniotic fluid from the fetus. Genomic DNA was extracted from these samples. Relevant gene sequences were analyzed using next-generation sequencing (NGS), and the suspected pathogenic variants were verified by Sanger sequencing.

Results: Genetic sequencing identified two autosomal dominant pathogenic variants: a TCF20 variant (c.5430_5431insA; p.Ala1811Serfs*4) in exon 1, and a TMEM151A variant (c.375C>A; p.Cys125*) in exon 2. Both variants were detected in the proband and fetus but were absent in the proband's parents and spouse.

Conclusions: The TCF20 and TMEM151A variants are associated with the proband's intellectual disability, motor incoordination, and fetal growth restriction (FGR). This study enabled prenatal genetic diagnosis and informed genetic counseling for the family, guiding their future reproductive planning.

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KEYWORDS

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INTRODUCTION

Developmental delay with variable intellectual impairment and behavioral abnormalities (DDVIBA) is a rare autosomal dominant neurodevelopmental disorder caused by pathogenic variants in the TCF20 gene located on chromosome 22q13, with an estimated preva-

lence of approximately 1 - 3% [1]. DDVIBA encompasses a broad spectrum of clinical phenotypes and etiologies, among which intellectual disability and attention-deficit hyperactivity disorder (ADHD) are frequently observed. Paroxysmal kinesigenic dyskinesia (PKD) is the most common form of paroxysmal movement disorders [2]. It is characterized by movement-induced involuntary movements, including chorea and dystonia. Due to its episodic nature, PKD is often misdiagnosed as epilepsy or other paroxysmal movement disorders, underscoring the need for accurate clinical differentiation. PKD is categorized into primary and secondary forms. Clinically, the vast majority of cases are primary PKD, typically exhibiting autosomal dominant inheritance. Two major pathogenicity genes - PRRT2 and TMEM151A - have been identified [3,4]. In rare cases, variants in KCNA1 and SLC2A1 may also lead to PKD phenotypes [5,6], often with incomplete penetrance. Carbamazepine has shown favorable therapeutic efficacy in affected individuals. Early identification of whether neurodevelopmental disorders originate from genetic variants facilitates symptom-targeted treatment, thereby reducing unnecessary medication and associated adverse drug reactions. In this study, we performed variant analysis of the TCF20 and TMEM151A genes in a kindred presenting with co-occurring DDVIBA and PKD phenotypes. The objective was to characterize the mutation types and patterns, thereby providing a scientific basis for prenatal diagnosis and genetic counseling.

MATERIALS AND METHODS

Subjects

The proband was a 25-year-old pregnant woman (Figure 1), gravida 1 para 0, with a primary school education level and an intelligence quotient (IQ) score of 89. According to her parents, she was delivered at term with a birth weight of 2.4 kg, presenting with a depressed nasal bridge and thick lips. Since childhood, she exhibited motor incoordination, communication difficulties, stuttering, anxiety, and mild restlessness. A brain MRI scan performed in early childhood revealed no obvious abnormalities. Her two elder brothers and one elder sister had normal intelligence. Her husband graduated from high school and was cognitively normal. Neither the proband nor her spouse had a family history of hereditary diseases, and the couple were non-consanguineous. This pregnancy was conceived with the assistance of traditional Chinese medicine (TCM). The last menstrual period was on October 22, 2024; the estimated due date was on July 29, 2025. On February 20, 2025 (gestational age 17 + 4 weeks), Doppler ultrasonography indicated that all fetal biometric parameters were smaller than expected, although none were below -2 standard deviations (SD): biparietal diameter (BPD) 37 mm (-0.647 SD), head circumference (HC) 136 mm (-0.882 SD), abdominal circumference (AC) 110 mm (-1.601 SD),

femur length (FL) 22 mm (-0.985 SD), and estimated fetal weight (EFW) 167 g (-1.399 SD). Gestational age was confirmed as accurate. Despite biometric parameters remaining not exceeding -2 SD, fetal growth restriction (FGR) could not be ruled out due to the early gestational age. In addition, because the proband has intellectual and developmental disability with motor incoordination, she met the indications for invasive prenatal diagnosis. Following informed consent from the proband's parents and her husband by the institutional Ethics Committee (approval nos. 2020025 [peripheral blood], 2020029 [amniotic fluid]), on February 25, 2025, an ultrasound-guided amniocentesis was performed. Fetal amniotic fluid and peripheral blood samples from the proband and her spouse were collected for chromosomal karyotyping, CNV-seq, and family-based whole-exome sequencing (WES). The pregnant proband was designated as the index case, while her parents underwent testing only for validation of the pathogenic variant sites. The procedure was uneventful, and the post-procedural course was unremarkable.

Chromosome karyotype analysis

Karyotyping procedures were performed on amniotic fluid and peripheral blood samples, including cell culture, harvesting, slide preparation, G-banding, and chromosome karyotype analysis. Results were interpreted according to the International Nomenclature System for Human Cytogenomic Nomenclature 2020 (ISCN 2020) [7].

The instruments and reagents used in this study included a cell incubator (Thermo Fisher Scientific, USA), a chromosome analyzer (Zeiss, Germany), amniotic fluid culture medium (Irvine Scientific, USA), Ikaros Karyotype Analysis Software (Metasystems, Germany), colchicine and Giemsa stain (Guangzhou Dahui Biotechnology Company, China), an MGISEQ-2000 high-throughput sequencing platform (BGI Genomics, Shenzhen, China), and a MagPure Buffy Coat DNA Midi KF Kit (MAGEN, Guangzhou, China).

Culture, harvesting, slide preparation, and banding of fetal amniotic fluid cells

Two 8 mL aliquots of amniotic fluid were centrifuged and subjected to sequential procedures: Centrifugation, inoculation, primary culture, subculture, harvest, secondary culture, trypsin digestion, cell collection, hypotonic treatment, prefixation, fixation, dripping, aging, trypsin digestion, and Giemsa staining. Following G-banding, at least 20 cells exhibiting clear chromosome banding patterns were selected for chromosome karyotype analysis.

Culture, harvesting, slide preparation, and banding of parental peripheral blood lymphocytes

Peripheral venous blood (3 mL each) was collected from the proband's parents and from the proband and her spouse, using heparin as an anticoagulant. After centrifugation, lymphocytes were inoculated into cul-

ture medium and incubated at 37°C for 68 hours. Subsequently, 0.1 mL of 40 µg/mL colchicine was added. The supernatant was removed. Cells underwent standard protocols: hypotonic treatment, prefixation, fixation, slide preparation, and Giemsa staining (4 minutes) followed by tap water rinsing and air-drying. Chromosome karyotypes were then selected and photographed using an automated chromosome scanning system, with 20 - 30 metaphases counted microscopically (doubled for abnormal karyotypes). A minimum of 5 karyotypes were analyzed.

Genomic DNA extraction

Peripheral venous blood (3 mL each) from the proband's parents and from the proband and her spouse, as well as 8 mL of fetal amniotic fluid, were collected in EDTA anticoagulation tubes. DNA was extracted following standard protocols using the MagPure Buffy Coat DNA Midi KF Kit (MAGEN, Guangzhou). The purity of the extracted DNA was assessed using Nano-drop 8000 (Thermo Fisher) with an A260/280 ratio of 1.8 - 2.0. Quantification was performed with Qubit 4.0 (Thermo Fisher) to ensure concentrations ≥ 20 ng/µL. DNA integrity was further evaluated using the MGI-Care LabChip GX system (BGI), and samples with DV200 $\geq 30\%$ were considered qualified.

CNV-array analysis

Genomic libraries were prepared using the MGIEasy Universal DNA Library Prep Set (BGI). The specific workflow included fragmenting 50 - 100 ng of DNA using BGI's MGIEasy Fragment Enzyme at 37°C for 15 minutes, followed by end repair and dA-tailing. This was then ligated with BGI-specific adapters (containing an 8-bp double-ended index) and amplified through eight cycles of PCR. Library quality was assessed using MGI Care LabChip GX (fragment peak at 280 ± 20 bp). Low-depth whole-genome sequencing was performed on the DNBSEQ-T7 platforms (2×100 bp). Each sample generated approximately 5 million effective reads ($0.1 \times$ genome coverage). MPS chemistry (CoolMPS™) was applied to enhance data quality. Clean reads were aligned to the GRCh38 reference genome using BWA-MEM (v0.7.17), with optimized alignment performed via SOAPaligner (v2.21). CNVs were identified and annotated through the Enliven® Variants Annotation Interpretation System. The results were compared with multiple databases, including the internal Chinese CNV database, OMIM (<https://www.omim.org/>), DGV (<http://dgv.tcag.ca/dgv/app/home>), DECIPHER (<https://www.deciphergenomics.org/>), and ClinGen (<https://clinicalgenome.org/>), to assess the pathogenicity of the detected CNVs.

Library construction and whole-exome sequencing (WES)

Sample pretreatment employed a combined enzymatic digestion and mechanical shearing technique to fragment DNA. Following end repair to form blunt ends,

dATP tailing reactions were performed to prepare TA cloning adapters. The fragment selection of ligation products was accomplished using a magnetic bead screening system. The library concentration was optimized through a pre-amplification process to construct standardized sequencing libraries. Targeted capture employed the KAPA HyperExome customized probe pool for liquid-phase hybridization, with specific probe binding enabling efficient enrichment of exonic regions. Library quality was verified using the CaliperGX_1000 chip-based electrophoresis system in conjunction with a BMG microplate reader. Qualified libraries were screened using preset parameters for subsequent pooled library construction. Sequencing was performed on the MGISEQ-2000 platform in paired-end mode (PE100 + 10). Raw data underwent basic quality control with SOAPnuke to filter out low-quality reads. Qualified reads were aligned to the human reference genome HG19 using BWA, and SNVs and InDels were identified following the GATK Best Practice. The variant annotation system integrates multi-dimensional databases, including population genetics databases (1000 Genomes Project, ESP6500, Chinese Healthy Population Database), the database for nonsynonymous SNPs' functional predictions (dbNSFP), and clinical association databases (ClinVar, OMIM, HGMD). The pathogenic classification of genomic variants was achieved through the BGI-Varanno self-developed algorithm, strictly following ACMG guidelines for clinical interpretation. Exon-level CNV analysis relied on the ExomeDepth, while large CNVs (≥ 1 Mb) were evaluated using CNVkit. ExpansionHunter was employed for tandem repeat expansion analysis of dynamic mutations. Ultimately, we systematically analyzed pathogenic variants by integrating genetic characteristics with clinical manifestations to establish molecular diagnostic conclusions through genotype-phenotype association modeling. Standardized quality-control checkpoints were implemented throughout to ensure that results met clinical diagnostic requirements.

Sanger sequencing

Variants detected by whole-exome sequencing (WES) in the proband were validated by Sanger sequencing; the same variant sites were also tested in the proband's parents, husband, and the fetus. Specific primers for amplifying exon 1 of the TCF20 gene and its adjacent introns, and exon 2 of the TMEM151A gene and its adjacent introns (Table 1), were designed using Primer3.0. For TCF20 c.5430_5431insA (p.Ala1811Serfs*4), the upstream primer sequence was GCCCAGAGAATAC-AACCCTCAT and the downstream primer sequence was ATCCCCAAGATTATGCAGCCAC; for TMEM151A c.375C>A (p.Cys125*), the upstream primer sequence was ACCTTCCTCAGCCGGGTAAAGC and the downstream primer sequence was TGTCAGCGCG-CTCATGGTACAC. PCR conditions were as follows: pre-denaturation at 95°C for 5 minutes; denaturation at 95°C for 30 seconds, annealing at 60°C for 30 seconds,

Table 1. Primer sequences for the TCF20 and TMEM151A genes.

Primer	Sequence (5, -3)	Product size (bp)
TCF20 c.5430_5431insA Exon 1-F	GCCCAGAGAATACAACCCTCAT	412
TCF20 c.5430_5431insA Exon 1-R	ATCCCCAAGATTATGCAGCCAC	412
TMEM151A c.375C>A Exon 2-F	ACCTTCCTCAGCCGGGTTAAGC	567
TMEM151A c.375C>A Exon 2-R	TGTCAGCGCGCTCATGGTACAC	567



Figure 1. The proband has distinctive facial features.

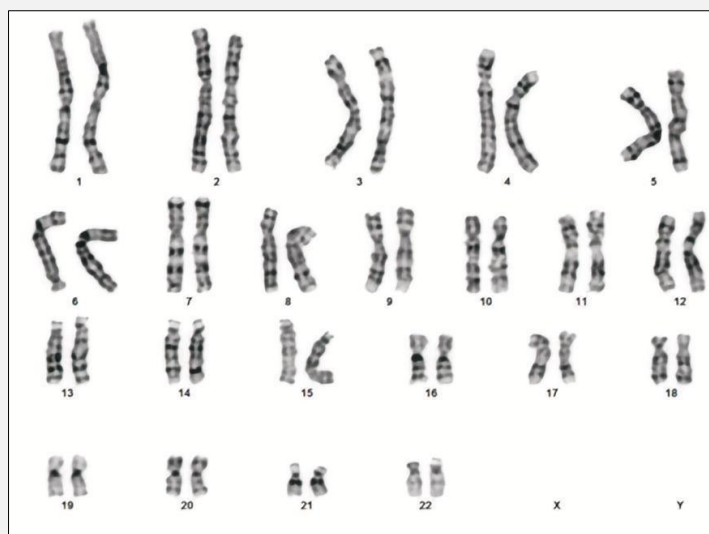


Figure 2. The fetal chromosome karyotype is 46, X?.

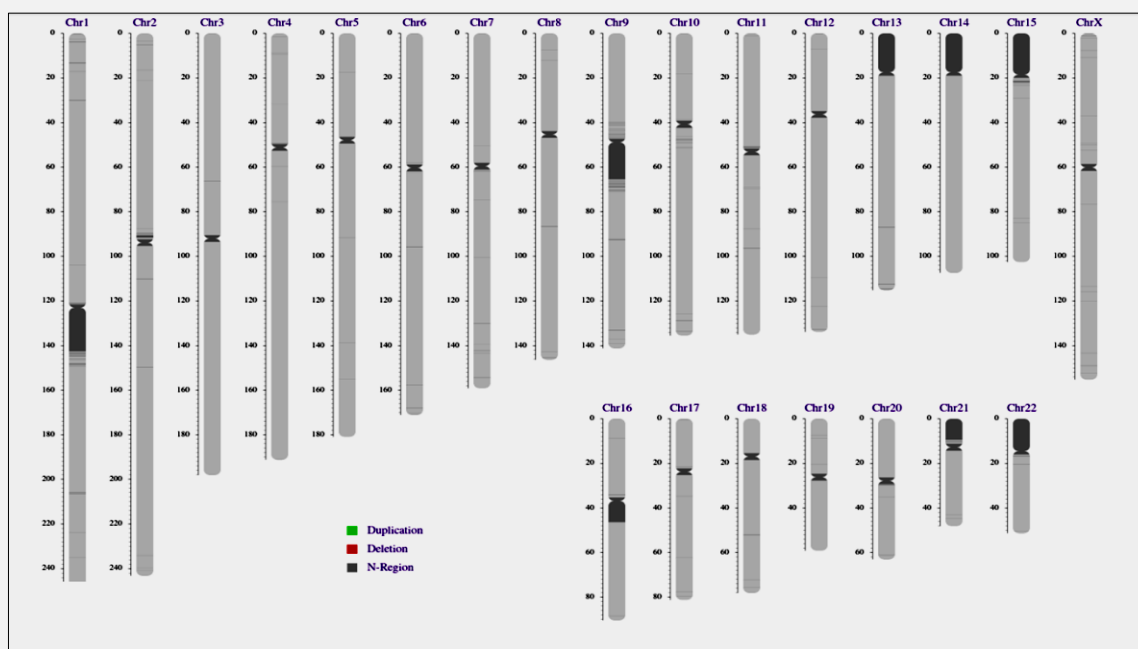


Figure 3. The CNV-seq results of the proband showed no pathogenic copy number variations.

and extension at 72°C for 30 seconds, for 35 cycles; followed by a final extension at 72°C for 5 minutes. The amplified DNA products were verified using 2% agarose gel electrophoresis. The sequencing products were purified by sodium acetate-ethanol precipitation and then sequenced. Data analysis was performed using BaseCaller software for base calling, and the sequencing results were ultimately compared with the standard sequences from GenBank using PolyPhred software to identify variant sites.

RESULTS

Chromosome karyotype analysis

Nine days after amniocentesis, on March 6, 2025, the fetal karyotype was 46, X? (Figure 2). The proband's husband had a karyotype of 46, XY, and the proband had 46, XX.

CNV-seq results

Seven days after amniocentesis, on March 4, 2025, no copy number variants were detected by CNV-seq in the fetal amniotic fluid (Figure 3) or in peripheral blood from the proband and her spouse; all CNV-seq results were interpreted as normal.

Family-based WES

Thirty-six days after amniocentesis, on April 12, 2025, family-based WES (including the proband's parents, the proband and her husband, and the fetus) identified a TCF20 exon 1 variant c.5430_5431insA (p.Ala1811-Serfs*4) in both the proband and the fetus (Figure 4), resulting in a frameshift at amino acid Ala1811. A TMEM151A exon 2 variant c.375C>A (p.Cys125*) that was likewise identified in the proband and the fetus (Figure 5), producing a nonsense change at Cys125. According to American College of Medical Genetics and Genomics (ACMG) guidelines [8], the TCF20 gene exon 1 c.5430_5431insA variant is indicated as a pathogenic mutation site, with evidence for pathogenicity classified as "PVS1+PM2+PM6_Supporting".

The TMEM151A gene exon 2 c. 375C>A is a likely pathogenic mutation site, with evidence for pathogenicity rated as "PVS1_Strong+PS4_Supporting+PP1".

After searching the China-specific Shen Zhou Genome data Cloud, the reference population database 1000 Genomes Project (1000 Genomes), the Exome Aggregation Consortium (ExAC) database, the Genome Aggregation Database (gnomAD), and relevant literature [4,9,10], these two genetic variants were identified as previously unreported pathogenic variants in fetuses. Both parents of the proband and the proband's husband are not carriers of these two pathogenic genetic variants. The results suggest that the proband's genetic variant is

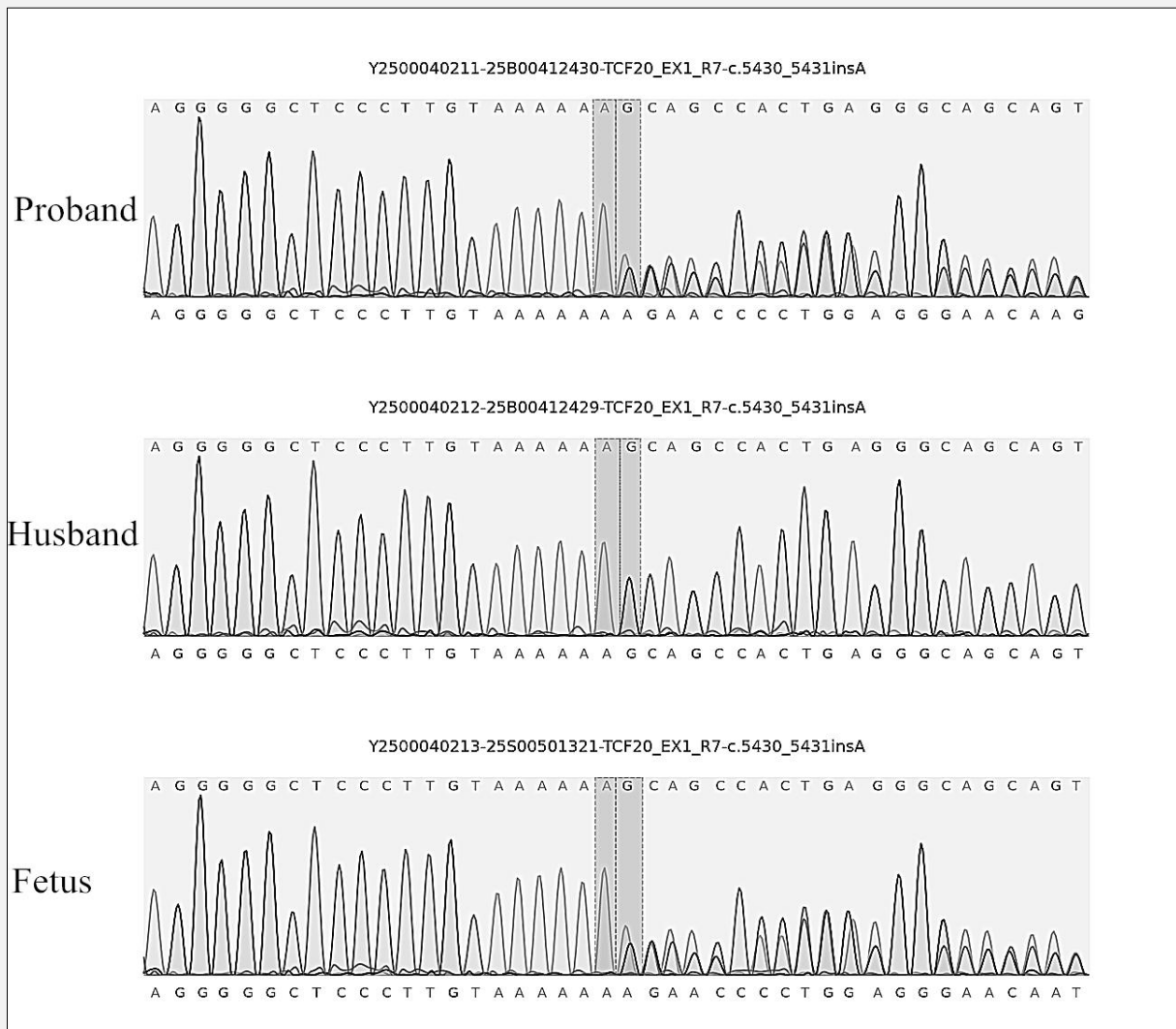


Figure 4. The Sanger sequencing of the TCF20 gene in the proband's family identified the variant c.5430_5431insA (p.Ala1811-Serfs*4).

de novo, while the fetus's genetic variant was inherited from the proband.

Pregnancy outcome

On March 15, 2025, an ultrasound performed at 20⁺⁴ weeks of gestation at an external hospital indicated the fetus was small for gestational age (AUA: 18w4d). All biometric parameters were small with a worsening trend: Biparietal diameter: 46 mm (-0.657 SD), head circumference: 164 mm (-1.74SD), abdominal circumference: 142 mm (-1.718 SD), femur length: 29 mm (-1.539SD), estimated fetal weight: 280 g (-2.065 SD). Fetal growth restriction (FGR) was considered. Com-

bined with family WES results, genetic variants in fetal TCF20 and TMEM151A genes were identified as the cause of fetal FGR. The parents made an informed choice to discontinue the pregnancy. In this case, post termination examination confirmed a female fetus (gestational age: 22 weeks) with the following measurements: Head circumference: 178 mm (-2.048 SD), weight: 342 g (-2.489 SD). These findings corroborated the prenatal ultrasound diagnosis of FGR.

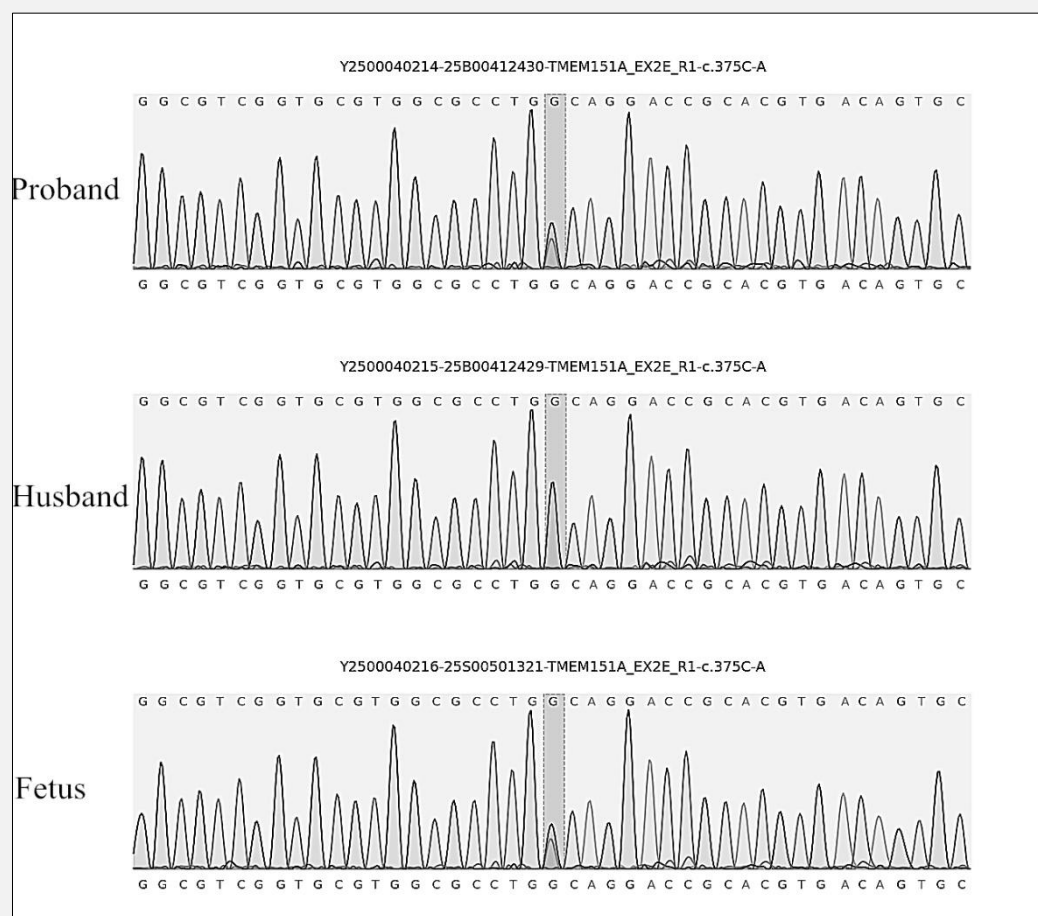


Figure 5. The Sanger sequencing results of the TMEM151A gene in the proband's family identified the variant c.375C>A (p.Cys125*).

DISCUSSION

TCF20, also known as stromelysin-1 platelet-derived growth factor-responsive element-binding protein (SPBP) [11], is located at 22q13.2 (chr22:42,160,013-42,343,537). It comprises six exons and encodes a protein of more than 1,900 amino acids. It encodes two open reading frames generated by alternative splicing. Isoform 1 is expressed in the brain, heart, and testis tissues, with predominant expression in the liver and kidney, whereas isoform 2 is mainly expressed in the lung [12] (<http://genome.ucsc.edu/cgi-bin>). The TCF20 gene contains multiple functional domains and is nuclear-localized. It shows relatively high expression in the brain, with the hippocampus and cerebellum exhibiting the highest levels [13]. It also interacts with estrogen receptor- α (ER α) [14]. TCF20 functions as a coactivator that can bind to target sequences within promoters or en-

hancers of numerous transcription factors with completely distinct structures and functions, such as c-Jun, Ets, Spl, and Pax6 [9]. It is expressed in most tissues of the body except the ovary and prostate [15]. The DNA demethylation factor TDG is a downstream target of TCF20. TDG regulates the DNA methylation levels in the promoter region of T-cell factor 4 (TCF-4), thereby influencing TCF-4 expression and modulating neural differentiation. Studies have shown that TCF20 deficiency in neural stem cells of mouse embryos affects neurogenesis. It reduces neuronal numbers and consequently leads to abnormal brain function [16]. Lévy J et al. [17] summarized 71 reported TCF20 variants, comprising frameshift mutations (n = 41), nonsense mutations (n = 19), missense mutations (n = 7), and canonical splice-site variants (n = 1), as well as three structural variations on chromosome 22 (one pericentric inversion and two deletions). Most mutations were de novo, indi-

cating a high incidence and pathogenicity. Schäfer et al. [18] found that inactivating variants of TCF20 are associated with individuals exhibiting autism spectrum disorder, intellectual disability, and postnatal overgrowth. In addition, Topa et al. [19] identified TCF20 variants in families with craniosynostosis. Studies have also determined that TCF20 gene variants or microdeletions are associated with premenstrual syndrome (PMS), as TCF20 functions via estrogen receptors (ER) and androgen receptors (AR) to regulate circadian rhythms. TCF20 variants may lead to disruptions in the circadian rhythm [9]. Recent studies have shown that TCF20 variants are also associated with peripheral liver fibrosis and immune system dysfunction [20]. Mechanistically, TCF20 can regulate immune cell proliferation and differentiation, as well as the activity of transcription factors governing innate and adaptive immune responses. Loss of TCF20 function alters the expression of hepatic proteins involved in fibrotic remodeling and may underlie immune diseases such as autoimmune hepatitis and hyper-IgE syndromes [21], underscoring that TCF20 functions extend beyond the central nervous system. In 2022, Svorenova et al. [22] reported 69 individuals with TCF20 variants presenting developmental delay with variable intellectual impairment and behavioural abnormalities (DDVIBA) - including ASD and attention-deficit hyperactivity disorder (ADHD) - together with neurological features including intellectual disability, proportionate overgrowth, motor delays, ataxia, reduced muscle strength, speech impairments, seizures, and structural brain abnormalities. In addition, some patients exhibited non-neurological phenotypes, including overgrowth (e.g., obesity), abnormal head circumference, distinctive craniofacial appearance (e.g., distinctive facial features), and genitourinary abnormalities (e.g., abnormal testicular descent or cryptorchidism) [17,21]. Rare immune system manifestations have been observed, including elevated IgE levels, immune thrombocytopenic purpura, cow's milk protein allergy, and wheezing bronchitis [15]. In longitudinal studies of cognitive characteristics and functions [23], TCF20 variants exhibit epigenetic effects closely linked to environmental factors. Common features include developmental delay/intellectual disability (DD/ID) (100%), autism spectrum disorder or autistic traits (69%), attention deficit or hyperactivity (67%), additional neurobehavioral disorders (85%), hypotonia (63%), other neurological or muscular problems (85%), and minor abnormalities detected during physical examinations (74%). Ninety-three percent of patients reported other features affecting various organ systems [21].

The first causative gene identified for paroxysmal kinesigenic dyskinesia (PKD) is PRRT2. TMEM151A (ENST00000327259.5_4) is the second causative gene for PKD, with a penetrance of approximately 53.8%. It is located at 11q13.2 (chr11:66,059,365-66,064) and consists of two exons. Li et al. [4] reported that most variants cluster in the C-terminal extra-membranous domains, suggesting a hotspot region. The TMEM151A

protein comprises 468 amino acids and harbors two putative transmembrane domains (aa 45 - 65 and 98 - 118) [10]. As a transmembrane protein it localizes to the endoplasmic reticulum (the intracellular Ca²⁺ storage) and may participate in the regulation of calcium signalling. The TMEM151A gene mutation does not affect protein localization but significantly reduces protein expression, suggesting a potential loss-of-function mechanism leading to paroxysmal kinesigenic dyskinesia (PKD). As of 2023, more than 50 TMEM151A mutation sites have been identified in PKD cases, including truncating mutations, missense mutations, and non-frameshift deletions [24].

The TMEM151A gene mRNA is highly expressed specifically in the central nervous system (including the brain and spinal cord), with elevated expression levels observed in the cerebral cortex, hippocampus, spinal cord, brainstem, and thalamus [25]. Real-time PCR and in situ hybridization show widespread expression in the murine CNS, with high levels in the cortex, hippocampus, spinal cord, brainstem, and thalamus (<http://genome.ucsc.edu/cgi-bin>). In the cerebellum, TMEM151A is expressed mainly in the white matter and not in the granule cell or Purkinje cell layers, with secondary expression in the flocculonodular system. PKD often begins in childhood or early adolescence, with many patients experiencing a reduction in attacks after reaching adulthood. Male patients significantly outnumber female patients, with a ratio of 2 - 4:1 [24]. In the general population, the prevalence is estimated at 1:150,000. The most common symptoms are autism spectrum disorder (ASD), with most patients exhibiting impaired intellectual development accompanied by speech disorders, behavioral abnormalities, and attention deficits and/or hyperactivity. Although there is no specific pattern, many patients exhibit dysmorphic features. Additional variable features include hypotonia, somatic overgrowth with macrocephaly, mild distal skeletal anomalies, sleep disturbances, movement disorders, and gastrointestinal problems such as constipation. Overall, the clinical phenotype is highly variable. The TMEM151A gene expression is low during embryogenesis, increases after birth, peaks around day 14, and declines in adulthood, aligning with the natural course of PKD [24]. It is hypothesized that the abnormal function may change with age and disappear in adult PKD patients. Therefore, even if TMEM151A variants cause loss of function, they may not lead to PKD in adulthood.

The TMEM151A gene knockout mouse models were constructed [24], exhibiting movement-induced dyskinesia lasting 10 - 37 seconds, which resembles the clinical phenotypes of PKD. Compared with PRRT2-related PKD, TMEM151A is expressed primarily in white matter rather than cerebellar cortex. Therefore, PKD patients carrying TMEM151A variants exhibit shorter attack durations and are more prone to developing dystonia [26].

With advances in molecular genetic testing, whole-exome sequencing (WES) enables the analysis of genetic

variations at the nucleotide level, particularly for identifying potential genetic etiologies in fetuses with normal karyotypes and chromosomal microarray analysis (CMA) [27]. Research data indicate that prenatal WES can provide an additional diagnostic yield of 12.7% to 24.0% beyond conventional karyotyping and CMA [28]. When FGR is accompanied by structural abnormalities, CMA can detect an additional 10% of pathogenic CNVs; when FGR is not accompanied by structural abnormalities, CMA yields an additional 4% of pathogenic CNVs [29]. In summary, this case employed a combination of multiple genetic testing techniques, ultimately identifying a family with developmental delay, intellectual disability, and behavioral abnormalities (DDVIBA) combined with paroxysmal kinesigenic dyskinesia (PKD) through whole-exome sequencing. The study confirmed that pathogenic variants in the TCF20 and TMEM151A genes constitute the genetic etiology of this family's condition. Although the TCF20 gene variant c.5430_5431insA(p.Ala1811Serfs*4) in exon 1 and the TMEM151A gene variant c.375C>A(p.Cys125*) in exon 2 have been previously reported in adults [4,9,10], this represents the first discovery and report of these mutations during the fetal period, both domestically and internationally. Furthermore, this study provides the first documentation of these two gene variants causing fetal growth restriction (FGR), thereby expanding the spectrum of known fetal genetic variations and offering relevant genetic counseling services for the proband's family. These findings offer a new theoretical basis for prenatal genetic diagnosis, prognostic assessment, and exploration of the pathogenic mechanisms of FGR. By integrating genotype-phenotype analysis in the fetus, this study deepens the understanding of the relationship between FGR genetics and clinical presentation, thereby enhancing prenatal genetic diagnosis capability. Based on the inheritance patterns, primary prevention strategies can be implemented, including screening and intervention for high-risk populations, to reduce the prevalence of TCF20 and TMEM151A gene variants in the population, thereby achieving the goal of eugenics and improved birth outcomes.

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The authors declare that no generative AI was used in the preparation of this manuscript.

Ethical Approval Statement:

All study methods were approved by the Ethics Committee of the Affiliated Hospital of Putian University, and all subjects gave their written formal consent.

Declaration of Interest:

All authors declare that there are no potential conflicts of interest.

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