Brief Report

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Prenatal molecularly supported diagnosis of a fetus with urinary malformation caused by novel compound heterozygous variants in the *FAM149B1* gene

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SUMMARY: Biallelic variants in a family with sequence similarity 149 member B1 gene (*FAM149B1*, OMIM #618413) causes a range of abnormal phenotypes associated with Joubert syndrome (JS) in humans. However, the phenotypic spectrum and genetic evidence linking *FAM149B1* to ciliopathies remain limited, with no prenatal cases previously described. Here, we report the first prenatal case from a non-consanguineous Chinese family presenting with isolated right pelvicalyceal and ureteral dilation at 24 weeks of gestation. Notably, the fetus lacked cerebellar malformations or hallmark neuroimaging features such as molar tooth sign (MTS). Trio-whole-exome sequencing (Trio-WES) identified novel compound heterozygous loss-of-function variants in *FAM149B1*: paternal c.279T>A (p.Tyr93*) and maternal c.574dup (p.Ser192Phefs*7). Both variants are predicted to trigger nonsense-mediated mRNA decay (NMD), consistent with a loss-of-function mechanism, and parental segregation confirmed asymptomatic heterozygous carrier status, supporting autosomal recessive inheritance. Gene-disease validity assessment assigned a "Strong" classification to *FAM149B1*-related ciliopathy under ClinGen guidelines, enabling definitive classification of the variants as pathogenic or likely pathogenic. This case expands the phenotypic spectrum of *FAM149B1*-related disorders to include isolated urinary tract malformations in the prenatal period, where neurological manifestations may be absent or subtle. Our findings highlight the utility of prenatal exome sequencing in atypical cases and contribute to the understanding of the expanding genetic and phenotypic landscape of ciliopathies.

Keywords: *FAM149B1* gene, Joubert syndrome, urinary malformation, gene curation, prenatal diagnosis

1. Introduction

Primary cilia are microtubule-based organelles that are essential for mechanosensation, signal transduction, and cellular homeostasis (*1*). Defects in their assembly or function can lead to ciliopathies, a diverse group of genetic disorders characterized by dysfunctional cilia and multi-system involvement, with prominent clinical manifestations in the renal, neurological, and skeletal systems (*2,3*). *FAM149B1*-related disorders encompass a spectrum of genetic conditions associated with variants in the *FAM149B1* gene, which is located on chromosome 10 at the q22.2 region. The protein encoded by this gene, which contains a domain of unknown function 3719 (DUF3719) and a conserved HLR sequence motif, remains incompletely characterized. In 2019, Ranad *et al*. first established the critical role of *FAM149B1* in normal ciliary biology, and identified two distinct phenotypes associated with homozygous loss-of-function variants in *FAM149B1* across four consanguineous families, presenting clinical features analogous to those of Joubert syndrome or oral-facial-digital syndrome type VI (OFD VI) (*4*). In 2021, the Sandy team reported another consanguineous family carrying homozygous *FAM149B1* variants and exhibiting clinical features of JS, although this family also harbored pathogenic variants in two other genes associated with neurologic disorders (*5*). Currently, the paucity of reported cases with *FAM149B1* variants precludes a comprehensive delineation of the associated clinical spectrum. Furthermore, absence of documented prenatal phenotypes related to *FAM149B1* variants represents a significant knowledge gap in the

prenatal diagnosis of JS-related disorders.

Joubert syndrome is a rare and typically autosomal recessive neurodevelopmental ciliopathy, affecting approximately 1 in every 80,000 to 100,000 infants globally each year (*6*). It is characterized by malformations of the posterior midbrain, cerebellar ataxia, oculomotor apraxia, dyspnea, intellectual disability, and varying degrees of developmental delay. Notably, most patients exhibit a specific malformation known as molar tooth sign, including cerebellar vermicosis hypoplasia, featuring prominent, thickened upper cerebellar peduncles, and abnormally deep interpeduncular fossa (*7*). In addition to these core features, most JS patients may also present with multi-organ developmental abnormalities involving the eyes, kidneys, liver, and skeleton. JS demonstrates significant genetic heterogeneity, with over 40 pathogenic genes identified to date, all encoding proteins involved in primary cilia formation or function. In the largest reported cohort, five major genes (*C5ORF42*, *CC2D2A*, *AHI1*, *CEP290* and *TMEM67*) account for 6%-9% of JS cases, three additional genes (*CSPP1*, *TMEM216* and *INPP5E*) each contribute 3%, while the remaining genes each account for JS in few families (*8*). However, approximately 10% of clinically suspected JS-related ciliopathies cases remain genetically unexplained (*9*). Notably, Joubert syndrome has also been reported as a phenotype as part of the spectrum of *FAM149B1*-associated disorders. Yet, existing literature is limited to postnatal manifestations in individuals from consanguineous backgrounds. A systematic literature search was performed in PubMed using the terms "*FAM149B1*", "Joubert syndrome", "ciliopathy", and "prenatal diagnosis" up to May 7th, 2026, and no prenatal cases associated with *FAM149B1* variants were identified.

This study reports, for the first time, a novel compound heterozygous loss-of-function variant in the *FAM149B1* gene in a fetus from a non-consanguineous family, representing the first prenatal case of *FAM149B1*-related disorders. This case broadens the clinical spectrum of *FAM149B1*-related disorders to include early-onset renal anomalies. Notably, the fetus did not exhibit recognizable structural abnormalities characteristic of JS, such as the MTS, highlighting the challenges and complexity of prenatal diagnosis for JS and related disorders.

2. Materials and Methods

2.1. Subjects

A 28-year-old primigravida (Figure 1A, I-2) at 23 weeks of gestation was referred to our institution for genetic counseling and potential prenatal genetics due to suspected fetal urinary system anomalies identified on ultrasound. The pregnant woman, of Chinese descent, and her husband were non-consanguineous and in good health. The husband (Figure 1A, I-1) had a history of smoking but denied exposure to teratogens or other hazardous substances. The pregnant woman reported no medication use before or during pregnancy, and neither partner had a family history of genetic disorders. First-trimester non-invasive prenatal testing (NIPT) indicated low risk, and routine prenatal screenings were unremarkable.

2.2. Ethics approval and consent to participate

The use of human fetal tissue (fetal amniotic fluid cells) in this study was reviewed and approved by the Ethics Committee of International Peace Maternity and Child Health Hospital (GKLW-2022-14), in compliance with the provisions of the Declaration of Helsinki (as revised in 2013). All tissues were obtained with informed consent from donors, independently of any decision regarding pregnancy termination. No financial inducements or payments were made to obtain these materials. Informed consent to participate was obtained from all individuals involved in the study or their legal guardians.

2.3. Prenatal genetic diagnosis

At 24 weeks of gestation, the pregnant woman underwent amniocentesis for prenatal genetic diagnosis. Genomic DNA was extracted from amniotic fluid cells and peripheral blood samples from both parents using the Genomic DNA Extraction Kit (TIANGEN, Beijing, China). Trio-whole exome sequencing (Trio-WES) was performed as previously described (*10*). Sequencing libraries were constructed using the KAPA HyperExome V3 capture kit (Roche, Basel, Switzerland) and sequenced on the MGISEQ-2000 platform (MGI, Shenzhen, China) with 150-bp paired-end reads.

Raw sequencing reads were processed using SOAPnuke (v2.0) to obtain high-confidence clean reads. Clean reads were aligned to the UCSC hg19 human reference genome using the Burrows-Wheeler Aligner (BWA-MEM, v0.7.17). PCR or optical duplicates were marked and removed using Picard Tools (v2.26). Base quality score recalibration, single nucleotide variant (SNV) and small insertion/deletion (INDEL) calling, and genotyping were performed using the Genome Analysis Toolkit (GATK, v4.2) following best practices. All identified variants were annotated in VCF format and analyzed using the BGI-Varanno pipeline for variant interpretation.

In parallel, conventional chromosomal karyotype analysis and chromosomal microarray analysis (CMA) were performed on fetal samples to assess chromosomal abnormalities and genome-wide copy number variations. CMA and Trio-WES were performed as part of standard-of-care diagnostic workup in an accredited clinical laboratory, in accordance with standard medical practice. All testing was ordered by the attending clinicians for

diagnostic purposes, and informed consent was obtained from the parents prior to testing.

2.4. Sanger sequencing validation

Specific PCR primers were designed to validate candidate pathogenic variants in *FAM149B1* (transcript NM_173348.2) identified by trio-WES, using Primer3 software (v. 0.4.0). Primers were synthesized by MAP Biotech (Shanghai, China). For amplification of exon 3 and its flanking exon-intron boundaries, the primer sequences were: forward

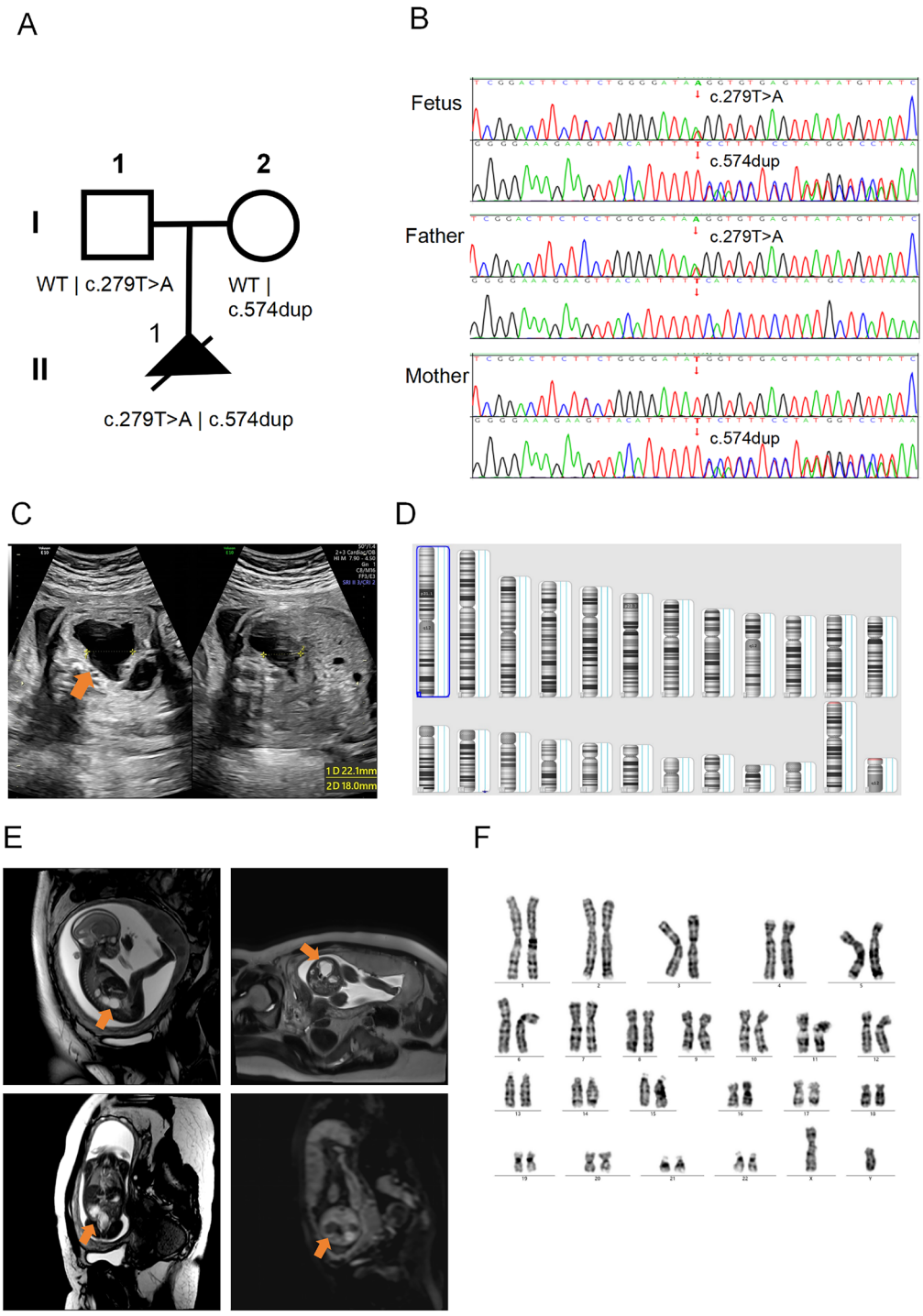

Figure 1. Pedigree, clinical, and molecular characterization of the fetus. (A) Pedigree of the family. Generations are labeled using Roman numerals (I, II). Solid symbols indicate affected individuals. **(B)** DNA sequencing results of the family. Sanger sequencing analysis identified two heterozygous variants associated with the phenotype of the proband in the *FAM149B1* gene, which were inherited from the parents, respectively. Red arrows indicate the variant positions. **(C)** Fetal ultrasound images. The arrow site marks the affected area. **(D)** CMA of the fetus revealed no abnormalities. **(E)** Fetal MRI images. The arrow site marks the affected area. **(F)** Chromosomal karyotype analysis of the fetus revealed no abnormalities.

5′-ATGCCACAGAAAACTTGAGGACA-3′ and reverse 5′-AAACAAAACCATACTCAAAAAGAA-3′. For exon 6 and adjacent splice regions, the primer pair was: forward 5′-ATGTAACTGTGTTTGCATAAGACT-3′ and reverse 5′-AATTCTGGATACCTGAGAAATACAT-3′.

PCR amplification and product purification were performed using the specific primers, followed by sequencing on an ABI 3700 sequencer (Applied Biosystems, Foster City, CA, USA). Sequence data were analyzed using Mutation Surveyor v5.0.2 (SoftGenetics LLC) to confirm presence and zygosity of the variants in the proband and to perform segregation analysis in parental samples.

2.5. Dimensional structure analysis of the FAM149B1 mutant protein

The crystal structure of the wild-type FAM149B1 was obtained from the Uniprot database (*https://www.uniprot.org/uniprotkb/Q96BN6/entry*). Crystal structure of each mutant was then generated using Swiss model (*https://swissmodel.expasy.org/*) and PyMOL (Schrödinger Inc., New York, NY, USA).

3. Results and Discussion

3.1. Clinical and genetic findings

The pregnant woman exhibited no abnormalities in routine laboratory tests prior to pregnancy and during the early stages of gestation. The pregnancy was a spontaneous singleton intrauterine gestation. Ultrasound at 12 weeks of gestation showed that the fetal nuchal translucency measurement was within the normal range. Ultrasound at 17 weeks confirmed fetal growth appropriate for gestational age. At 23 weeks of gestation, ultrasound examination revealed the following fetal biometric measurements: biparietal diameter of 54 mm, head circumference of 194 mm, and femur length of 34 mm. Notably, right pelvicalyceal dilatation was observed, measuring 14.1 mm, accompanied by right ureteral dilation with a maximum diameter of 5.4 mm. An anechoic area measuring 10 × 9 × 7 mm was also identified above the right kidney. At 26 weeks of gestation, ultrasound examination showed right double renal pelvis and 22 mm renipelvic separation of the fetus (Figure 1C). Fetal magnetic resonance imaging confirmed right duplicated renal pelvis with associated pelviectasis and right ureteral dilatation, raising suspicion of a possible ectopic ureteral orifice (Figure 1E). Additionally, a cystic lesion was identified at the upper pole of the right kidney, which appeared consistent with a benign renal cyst, no other fetal structural abnormalities were detected. CMA testing (Figure 1D) and chromosomal karyotype analysis (Figure 1F) revealed no meaningful copy number or chromosomal structural abnormalities in the fetus. To investigate potential genetic cause and provide evidence for the prenatal diagnosis of the fetus, trio-WES was performed. After filtering out low-confidence variants with poor sequencing quality, variants with a population frequency exceeding 1% in the gnomAD database, and those predicted to be benign, the remaining variants were prioritized using "urinary system malformations" as a key phenotypic criterion. This analysis led to the identification of a novel compound heterozygous variant in the *FAM149B1* gene in the fetus: c.279T>A (p.Tyr93*) and c.574dup (p.Ser192Phefs*7), which was subsequently confirmed by Sanger sequencing (Figure 1B). The c.279T>A variant, located in exon 3, was inherited from the father, while the c.574dup variant in exon 6 was maternally inherited.

Prior to this study, only two studies had identified three pathogenic homozygous *FAM149B1* variants in consanguineous families (*4,5*). These frameshift and nonsense variants are severe loss-of-function mutations that lead to truncated protein products. Here, we report the first compound heterozygous variants of the *FAM149B1* gene [c.279T>A (p.Tyr93*) and c.574dup (p.Ser192Phefs*7)] in a Chinese fetal case (Table 1). A systematic literature search identified no previous reports of prenatal cases associated with *FAM149B1* variants, suggesting that this is the first such case described. Both variants are absent from population databases, including gnomAD, underscoring their rarity and novelty. Previous reports of clinical features showed that most patients of *FAM149B1* variants predominantly described with developmental delay accompanied by neurological involvement (*4,5*). Unlike these patients, the fetus in this study presented with isolated right pelvicalyceal and ureteral dilation, detailed ultrasound and MRI assessments revealed no cerebellar malformations or the characteristic MTS. The heterozygous carrier parents exhibited no clinical symptoms, further supporting a recessive inheritance mechanism for *FAM149B1*-related disorders. Phenotypic discrepancy further confirms that *FAM149B1*-related disorders demonstrate significant phenotypic heterogeneity and genotype-phenotype association effects, variations in mutation types and mutation sites may lead to differing degrees of protein functional abnormalities.

3.2. Pathogenicity analysis of the identified *FAM149B1* variants

Given the limited number of reported cases, we first performed gene-disease association curation, according to the framework issued by the Clinical Genome Resource (*11*) before pathogenicity assessment of the *FAM149B1* variants. We conducted a comprehensive literature review using PubMed and identified seven patients with three different *FAM149B1* variants (*4,5*). The fetal case from this study was not included due to insufficient phenotypic information. With 12 points for

Table 1. Clinical characteristics of the patients with *FAM149B1* variants

	Patients in this study (Fetus)	Reported patients (1 female, 6 male)
Ethnicity	Chinese	1 Turkish, 6 Arab
Allelic state	compound heterozygous	homozygous
Variants	1 nonsense (p.Tyr93*) and 1 frameshift (p.Ser192Phefs*7)	3 frameshift (p.Lys119Ilefs*18), 1 nonsense (p.Gln147*), 3 indel-induced frameshift (p.Gln118Hisfs*20)
Developmental delay/Intellectual disability	–	7/7
Molar tooth sign	–	5/6
Ocular motor apraxia/strabismus	–	7/7
Ptosis	–	5/7
Ataxia	–	3/7
Duane Syndrome	–	3/7
Nystagmus	–	3/7
Progressive ophthalmoplegia	–	3/7
Mesoaxial polydactyly	–	5/7
Mild skeletal dysplasia	–	3/7
Macrocephaly	–	3/7
Renal involvement	+	0/7
Cardiac defects	–	1/7
Lateralization defects	–	1/7
Liver involvement	–	0/7

Table 2. Gene-disease association curation for FAM149B1 and autosomal recessive JS-related ciliopathy

		Evidence Type	Case Information Type	Guidelines			Scores	
				Default (per variant)	Range (per variant)	Max	Points (Max)	Tally
Genetic Evidence	Case-Level Data	Variant Evidence	Two variants in trans and at least one de novo or a predicted/proven null variant	2	0–3	12	21 (12)	12
			Two variants (not predicted/proven null) with some evidence of gene impact in trans	1	0–1.5			
		Total Genetic Evidence Points (Maximum 12)						12
	Evidence Category	Evidence Type		Guidelines			Scores	
				Default	Range	Max	Points	Tally
Experimental Evidence	Functional Alteration	Patient cells		1	0–2	2	1	1
		Non-patient cells		0.5	0–1		0	
	Total Experimental Evidence Points (Maximum 6)							1

genetic evidence and 1 point for experimental evidence, the gene-disease relationship between *FAM149B1* and JS related ciliopathy is classified as "Strong" (Table 2). Thus, all evidence criteria outlined in the ACMG/AMP guidelines can be applied (*12,13*). Additionally, in contrast to the three previously reported variants, which are all clustered within the DUF3719 domain, these two variants described in this study are located outside this domain (Figure 2A). The variants p.Tyr93* and p.Ser192Phefs*7 occur in the first third of the FAM149B1 protein sequence, leading to premature termination of translation and severe structural truncation (Figure 2B). These alterations are predicted to result in marked protein instability and are highly likely to trigger nonsense-mediated mRNA decay, consistent with a loss-of-function pathogenic mechanism of *FAM149B1* disorders. Therefore, the p.Tyr93* nonsense variant was classified as likely pathogenic (PVS1+ PM2_supporting), while the p.Ser192Phefs*7 frameshift variant was classified as pathogenic (PVS1+ PM2_supporting+ PM3).

JS has strong clinical heterogeneity, affected individuals may show involvement of other organs to varying degrees classified into multiple clinical subgroups: JS with ocular involvement (JS-O), JS with renal involvement (JS-R), JS with oculorenal involvement (JS-OR), JS with hepatic involvement (JS-H), JS with orofaciodigital involvement (OFDVI syndrome), *etc* (*8,9*). The renal involvement features in JS patients include loss of corticomedullary differentiation and small

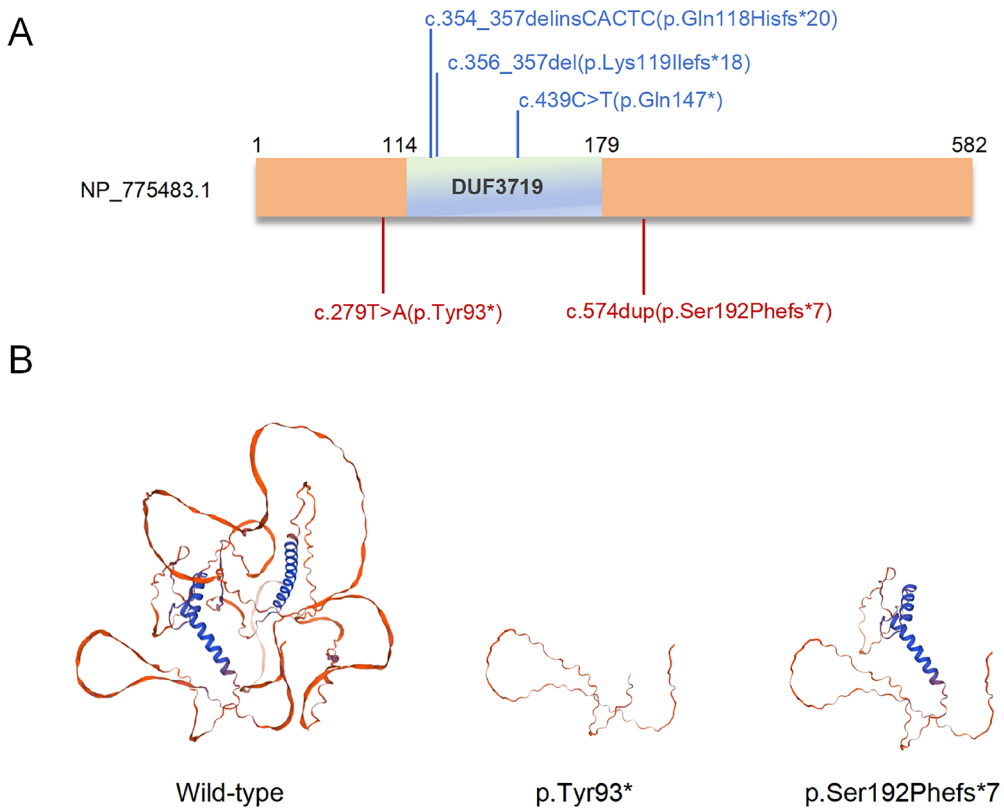

Figure 2. Distribution and structural analysis of the mutants. **(A)** The diagram illustrates the schematic structure of the FAM149B1 protein domain. Variants recorded in previous studies (blue) are annotated above the protein schematic, while the heterozygous frameshift variants identified in this cohort (red) are mapped below and aligned with the corresponding structural context. DUF3719 resemble domain that belongs to DUF families that may be functionally important. **(B)** Crystal structure analysis indicates that, compared to the wild-type FAM149B1 protein, the p.Tyr93* and p.Ser192Phefs* mutants are predicted to cause severe disruption of the protein structure.

cyst formation, most commonly in those with pathogenic variants in *CEP290*, *TMEM67*, *AHI1, NPHP1*, *RPGRIP1L* and *TMEM237* (*14,15*). The absence of the neurological phenotype observed in this fetus as well as its differences from previous cases may be multifactorial. First, this may be due to the limited number of reported patients, resulting in an incomplete understanding and characterization of its phenotypic spectrum. Secondly, the clinical data for this fetal case are primarily derived from assessments during the second trimester, the fetus was still at an early stage of development, and certain extrarenal or neurological features commonly associated with *FAM149B1*-related disorders might not yet have been apparent, the limitations of the evaluation methods for mild neurologic involvement restrict the comprehensive characterization of the phenotype (*16*). Finally, the majority of previously reported patients are from Saudi Arabia, phenotypic heterogeneity related to different ethnic backgrounds also cannot be ruled out. Different residual protein activity and genetic background may contribute to phenotypic heterogeneity.

DUF3719 is a conserved domain found in eukaryotes, comprising approximately 70 amino acids. It features a conserved HLR sequence motif and two fully conserved residues—tryptophan(W) and histidine(H) (*4*). XBX-4, the homologous protein of FAM149B1 protein in nematodes, contains the DUF3719 domain and participates in maintaining ciliary homeostasis through the highly conserved DYF-18/CCRK and DYF-5/MAK kinase cascade (*17*). The non-DUF3719 region of the FAM149B1 protein exhibits high conformational flexibility, may participate in regulating intracellular transport in cilia by interaction with BROMI-CFAP20, and this interaction is enhanced in the presence of CCRK (*18*). Truncating variants that disrupt the structural integrity of proteins may impair these interactions and interfere with normal ciliary assembly and function. Fibroblasts from *FAM149B1*-deficient patients exhibit abnormally elongated cilia, abnormal accumulation of IFT machinery components at the ciliary tips, and significant dysregulation of SHH signaling (*4*). However, whether different *FAM149B1* variants exert differential effects on primary cilia development requires further in-depth research.

3.3. Pregnancy outcome

After clarifying the pathogenicity and clinical significance of the two *FAM149B1* variants, the couple received comprehensive genetic counseling. Considering

severity of the *FAM149B1*-related disorder, they opted to terminate the pregnancy at 28 weeks at other medical institutions. Meanwhile, the family was informed about reproductive options for future pregnancies, including prenatal diagnosis following natural conception and preimplantation genetic testing.

Given the novelty of the fetal phenotype, detailed clinical documentation would have been invaluable for phenotypic correlation. However, the pregnancy was terminated at an external institution, and no autopsy or photographic records of the fetal dysmorphic features were available despite efforts to obtain them. Consequently, the phenotypic characterization is limited to prenatal ultrasound and MRI findings. Owing to absence of relevant experiments covering transcript-level expression analysis, protein function investigation and ciliary functional assessment, we are currently unable to fully clarify the biological effects of the identified variants in depth from mechanistic and biological aspects. Our finding highlights the challenge of diagnosing JS spectrum disorders prenatally when typical neuroimaging features are absent, further suggest the potential association between *FAM149B1* variants and renal abnormalities. More evidence is needed to elucidate the association between variation and fetal phenotype in the future.

In conclusion, we report the first prenatal case carrying pathogenic *FAM149B1* variants with renal manifestations, further expanding the genotypic and phenotypic spectrum associated with *FAM149B1*. It underscores the importance of genetic evaluation following the detection of abnormalities on prenatal imaging and diagnostic value of exome sequencing in fetuses with atypical or isolated structural anomalies.

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