



OPEN ACCESS

EDITED BY

Alexis Hermida,
Centre Hospitalier Universitaire (CHU)
d'Amiens, France

REVIEWED BY

Luis Alberto Méndez- Rosado,
Centro Nacional de Genética Médica, Cuba
Lihui Jin,
Shanghai Jiao Tong University, China

*CORRESPONDENCE

Rong Xiang,
✉ shirlesmile@csu.edu.cn
Liping Wu,
✉ 33393300@qq.com

RECEIVED 11 July 2025

ACCEPTED 19 September 2025

PUBLISHED 23 October 2025

CITATION

Liu M-W, Dong Y, Xiang R and Wu L (2025) Case
Report: a novel missense variant of *FGD5* in a
family with tetralogy of Fallot.
Front. Genet. 16:1663959.
doi: 10.3389/fgene.2025.1663959

COPYRIGHT

© 2025 Liu, Dong, Xiang and Wu. This is an
open-access article distributed under the terms
of the [Creative Commons Attribution License](#)
(CC BY). The use, distribution or reproduction in
other forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in this
journal is cited, in accordance with accepted
academic practice. No use, distribution or
reproduction is permitted which does not
comply with these terms.

Case Report: a novel missense variant of *FGD5* in a family with tetralogy of Fallot

Meng-Wei Liu^{1,2,3}, Yi Dong³, Rong Xiang^{3*} and Liping Wu^{1*}

¹Longgang District Maternity and Child Healthcare Hospital of Shenzhen City (Affiliated Shenzhen Women and Children's Hospital (Longgang) of Shantou University Medical College), Shenzhen, China, ²College of Basic Medical, Xinjiang Medical University, Urumqi, China, ³School of Life Sciences, Central South University, Changsha, China

Background: Congenital heart disease (CHD) is among the most prevalent birth defects in newborns, with tetralogy of Fallot (TOF) being a classic example. Within weeks to months after birth, infants with TOF often exhibit cyanosis of the skin, lips, or nails and respiratory distress. Early medical intervention is crucial to enhance outcomes and ensure a better long-term prognosis.

Methods and results: A young Chinese couple was referred for prenatal counseling at a gestational age of 26⁺³ weeks for fetal complex CHD, including pulmonary artery stenosis, a widened aorta with overriding, and absence of the ductus arteriosus in their affected fetus, who was later diagnosed with TOF. To determine the genetic basis of the congenital heart defect, whole-exome sequencing and Sanger sequencing were performed to identify potential pathogenic variants. Subsequently, a heterozygous missense variant (c. 3233C>A, p.T1078K) of *FGD5* was identified in both the affected fetus and its unaffected carrier mother, demonstrating an inheritance pattern with irregular dominance. This variant is exceptionally rare in public genomic databases and determined to be the genetic cause of TOF in the proband.

Conclusion: We identified a novel heterozygous missense variant of *FGD5* in a Chinese family with TOF, which expands the genetic spectrum of the disease.

KEYWORDS

tetralogy of Fallot, *FGD5*, genetic variant, whole-exome sequencing, irregular dominance

Introduction

Congenital heart disease (CHD), defined as structural malformations of the heart and major intrathoracic vessels, affects approximately 1% of live births worldwide, making it the most common category of congenital anomalies (Bouma and Mulder, 2017). As a major cyanotic CHD subtype, tetralogy of Fallot (TOF) demonstrates heritable components (Sierant et al., 2025). TOF (OMIM #187500), a complex congenital heart malformation primarily influenced by genetic factors, was first described by French pathologist Étienne-Louis Arthur Fallot in the late 19th century. Fallot defined four core anatomical features: right ventricular outflow tract obstruction (pulmonary stenosis), ventricular septal defect, overriding of the aorta, and hypertrophy of the right ventricle, which emerge as a whole complex deformity that is the main cause of severe cyanosis of the skin and mucous membranes (O'Brien and Marshall, 2014). Several gene variants known to be associated with the development of this genetic disorder include *NKX2.5*, *GATA4*, *GATA6*, *ZFPM2*, and *JAG1* (Goldmuntz et al., 2001; Pizzuti et al., 2003; Zhang et al., 2009; Kola et al., 2011; Huang et al., 2013).

FGD5 (FYVE, RhoGEF, and PH domain containing 5, MIM*614788), a member of the FGD family and located on chromosome 3p25.1, contains 21 exons encoding a protein of 1,462 amino acids. This endothelium-specific gene functions as a guanine nucleotide exchange factor (GEF) in vascular endothelial cells to regulate CDC42 activity and participate in angiogenesis (Cheng et al., 2012; Kurogane et al., 2012). *FGD5* was first associated with TOF in 2019 (Reuter et al., 2019).

In this study, we present the case of a male fetus prenatally diagnosed with TOF exhibiting hallmark features of pulmonary stenosis, ventricular septal defect, and aortic overriding. An *FGD5* missense variant (NM_152536.4: c. 3233C>A, p.T1078K; chr3: 14860469C>A/hg19) was identified in the male fetus, and its pathogenicity was analyzed using three-dimensional protein modeling. This study expands the *FGD5* variant spectrum, demonstrates the pathogenicity of Dbl homology (DH)-domain variants in TOF, and elucidates their role in disrupting cardiovascular development. As TOF has previously been considered a genetic disease with high penetrance (Wang et al., 2022), the discovery of asymptomatic carriers in the family harboring the same p.T1078K variant made the diagnosis challenging.

Materials and methods

Subjects

A fetus (index case II-1) exhibiting ultrasound abnormalities at 22 weeks' gestation and two asymptomatic parents from a Han Chinese family were enrolled. Peripheral blood samples were collected from parents (I-1 and I-2), while the aborted fetus from the proband was obtained for genetic analysis. Whole-exome sequencing (WES) revealed the same missense variant in the proband and the mother. This study received ethical approval from the School of Life Sciences of Central South University in compliance with the Declaration of Helsinki, and written parental consent was obtained.

DNA extraction, whole-exome sequencing, and analysis

Genomic DNA was extracted from whole peripheral blood (EDTA-K₂ anticoagulated) using the QIAamp DNA Blood Mini Kit (QIAGEN, United States). Variants were annotated using MutationTaster, PolyPhen-2, SIFT, CADD, REVEL, and population databases (gnomAD and 1000 Genomes) (Fan et al., 2019).

Variant validation

The *FGD5* variant (NM_001320276.2: exon9: c. 3233C>A: p.T1078K) and its flanking sequences were obtained from NCBI (<https://www.ncbi.nlm.nih.gov/gene/152273>). The PCR primers were designed by the Ensemble genome browser and PrimerQuest to amplify the exon sequences provided by

Sangon Biotech (Shanghai, China). PCR products were approximately 500 bp in length. The primer sequences were as follows: F: 5'-CAAGTGCTCCTCACAGACTATTT-3' and R: 5'-CATAGCGTGGAGATACGAGAGA-3'; for c. 3233C>A, we amplified a 541-bp fragment with an annealing temperature set at 62 °C. *FGD5* protein conservation analysis used NCBI orthologs.

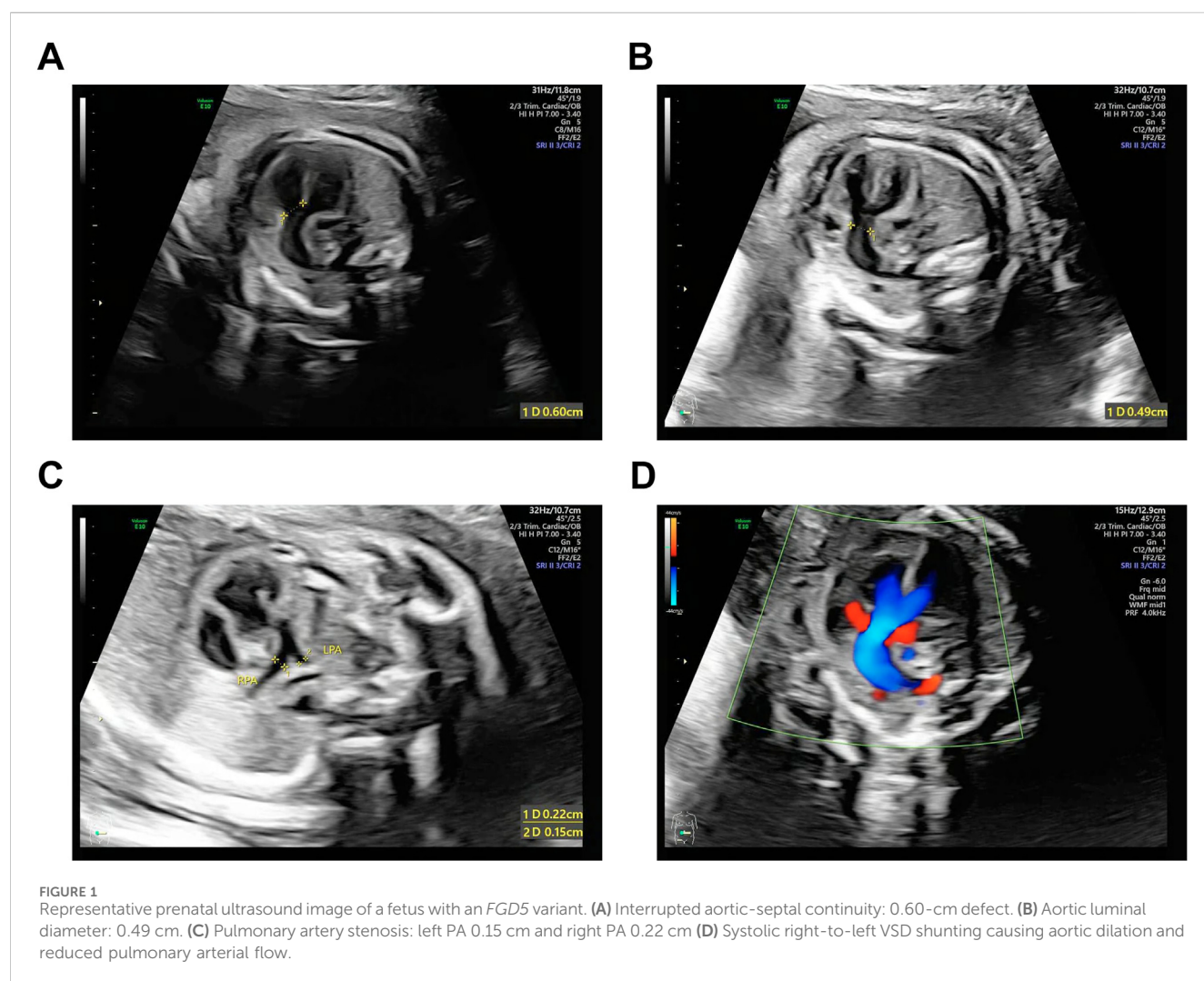
Model build

The three-dimensional model of the *FGD5* protein structure (p.T1078K) was constructed using SWISS-MODEL (<https://swissmodel.expasy.org/>), and the variant tolerance of protein sites was predicted using the MetaDome website (<https://stuart.radboudumc.nl/metadome/>) (Wiel et al., 2019).

Results

Clinical investigation

We enrolled a 26⁺³ weeks' gestation Chinese fetus (II-1) and requested an investigation owing to complex congenital heart malformations (Figure 1). The affected fetus was the only child of non-consanguineous parents. The following physical findings were observed: growth restriction (biparietal diameter, 5.5 cm standard deviation [SD]); head circumference, 21.0 cm (−3.47 SD); and estimated weight, 698 g ± 102 g (−2.84 SD). An ultrasound examination performed at another hospital at 12⁺² weeks' gestation demonstrated a crown–rump length (CRL) of 56 mm and nuchal translucency (NT) of 1.2 mm, both within normal limits for gestational age. At 22⁺⁵ weeks' gestation, an external ultrasound report noted complex CHD with the features of double outlet right ventricle (DORV), ventricular septal defect (VSD), and suspected pulmonary stenosis, accompanied by microcephaly (head circumference, < −2 SD). At 26⁺³ weeks' gestation, comprehensive fetal phenotyping was performed at our hospital, including dedicated fetal echocardiography and genetic counseling, to confirm the cardiac diagnosis and evaluate syndromic associations. A grade III four-dimensional prenatal ultrasound identified that the fetus was in a left sacrotransverse position. Fetal head and face evaluation showed a normal oval-shaped calvarial halo, centered midline intracranial structures, no dilatation of the lateral ventricles bilaterally, and appropriately visualized thalami. The cerebellar morphology appeared unremarkable, with visualization of the vermis and absence of significant posterior cranial fossa cistern widening. No disruption in upper lip skin continuity was identified. Fetal spine assessment confirmed intact alignment with regularly spaced parallel echogenic bands. All four extremities showed appropriate development with the visualization of bilateral humeri, ulnae, radii, femora, tibiae, and fibulae; the hands were maintained in physiologic flexion with closed fists, and both feet were fully visualized. Abdominal viscera were appropriately identified, including the liver, gallbladder, stomach, bilateral kidneys without separation, and bladder. Umbilical cord configuration



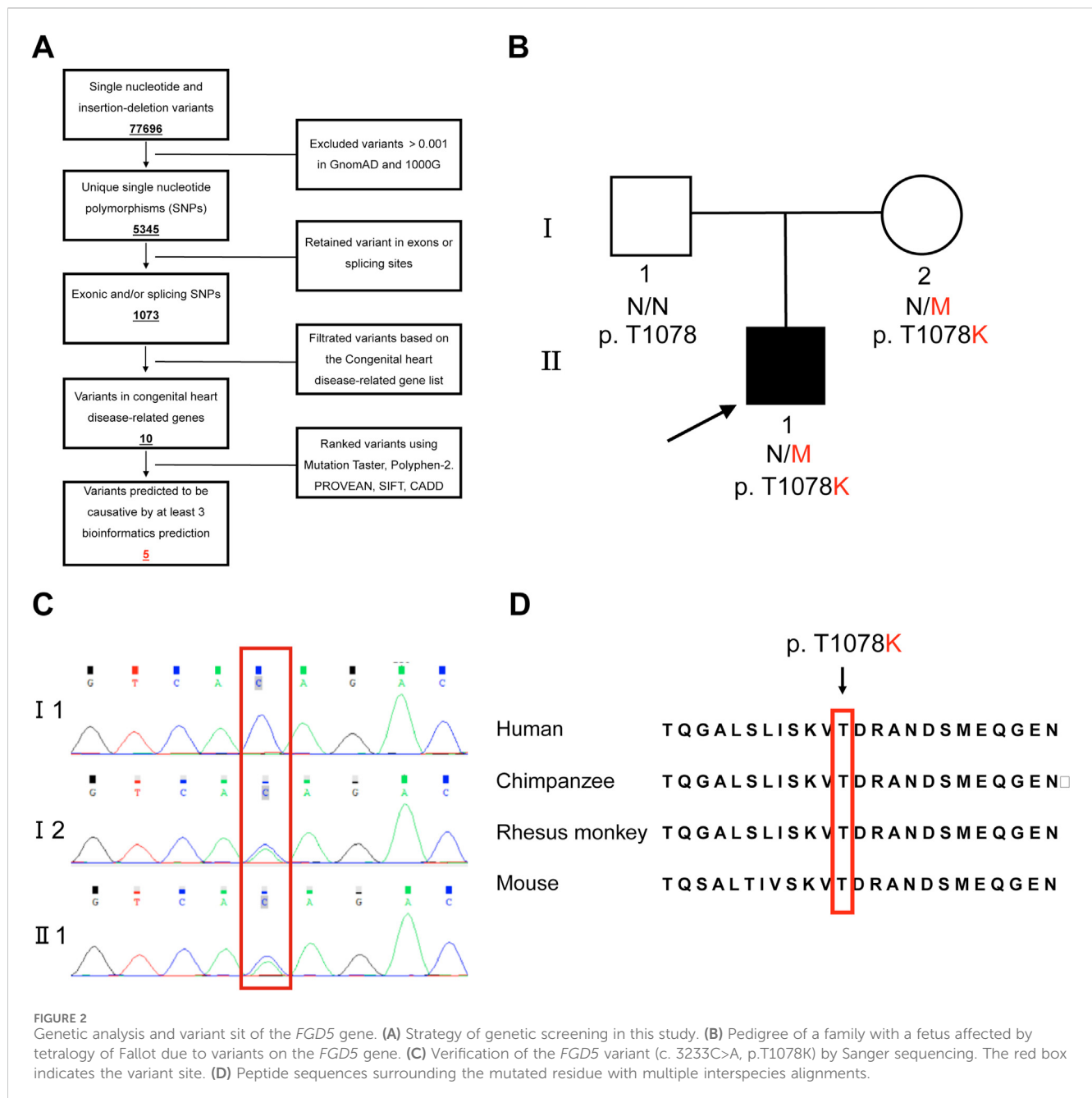
showed two arteries, with no cervical cord indentations noted. The placenta was posteriorly implanted with grade 0 maturity, containing a 3.7 cm × 1.2 cm circumscribed anechoic area exhibiting internal echogenic swirling and no demonstrable flow on color Doppler. Maternal cervical length measured 3.0 cm. Fetal echocardiography highlighted the following findings: (i) four-chamber view with leftward cardiac apex and normal cardiothoracic ratio, concordant atrioventricular connections with a ventricular right-loop configuration, and an intact crux cordis showing normal arteriovenous valve motion without right ventricular hypertrophy; (ii) outflow tract views revealed aortic root dilation (0.49 cm) overriding a 0.6-cm perimembranous ventricular septal defect by 50%, with severe pulmonary stenosis (main PA 0.30 cm, LPA 0.15 cm, and RPA 0.22 cm); (iii) color Doppler showed systolic right-to-left shunting across the ventricular septal defect into the aorta and turbulent accelerated flow through the stenotic pulmonary artery; (iv) venous connections included a single pulmonary vein draining into the left atrium with normal systemic venous return (superior vena cava/inferior vena cava to the right atrium); and (v) a three-vessel-trachea view showed a right-sided aortic arch originating the innominate artery as the first branch, with no detectable

ductus arteriosus. These echocardiographic findings led to a diagnosis of fetal heart malformation (TOF) and growth and developmental delay.

Genetic analysis

Genetic testing was initiated at the parents' request to identify the underlying causes of the proband's symptoms. In total, 77,696 variants were detected in the proband, and five variants in five intellectual developmental disorder-related genes were identified according to the strategy (Figure 2A). Four other variants are also present in Table 1. By analyzing the correlations between these five variants and CHD, the phenotypes of *FGD5* and TOF were more consistent. Sanger sequencing verified that the *FGD5* variant (NM_001320276.2: exon9: c. 3233C>A: p.T1078K) in the affected fetus was inherited from his unaffected mother (Figures 2B, C).

The *FGD5* variant (c. 3233C>A: p.T1078K) was *de novo* (PS2) and absent in gnomAD and 1000 Genomes (PM2). It was predicted to be disease-causing using the following tools: MutationTaster, PolyPhen-2, PROVEAN, SIFT, CADD, and REVEL. Based on the



assessment using these six pathogenicity prediction tools for missense variants, four tools categorized this variant as pathogenic, and the amino acid site p.T1078 was highly conserved evolutionarily (Figure 2D, PP3). Thus, based on the ACMG standards and guidelines (PS2, PM2, and PP3), we determined the variant to be “likely pathogenic” and responsible for the symptoms of the proband.

Based on MetaDome analysis, the variant site was predicted to be neutral, favoring the occurrence of functional genetic variations (Figure 3A). Furthermore, the three-dimensional protein model reveals that the p.T1078K variant is located within an α -helix. This substitution replaces threonine (Thr, T) with lysine (Lys, K), significantly altering the amino acid’s polarity and hydrophobicity—specifically, a shift from threonine to lysine

typically involves decreased hydrophobicity and increased hydrophilicity. These physicochemical changes are predicted to substantially enhance the potential pathogenicity of this point variant (Figure 3B).

Discussion

To date, six members of the FGD protein family (FGD1–FGD6) have been identified, all of which exhibit high structural conservation. These proteins specifically recognize phospholipids such as phosphatidylinositol biphosphate (PIP2) and phosphatidylinositol 3-phosphate (PI3P), along with GTPases, functioning as Rho GEFs to regulate cellular development (Snyder

TABLE 1 Variants identified in the proband by WES in combination with the filtration of intellectual developmental disorder-related genes.

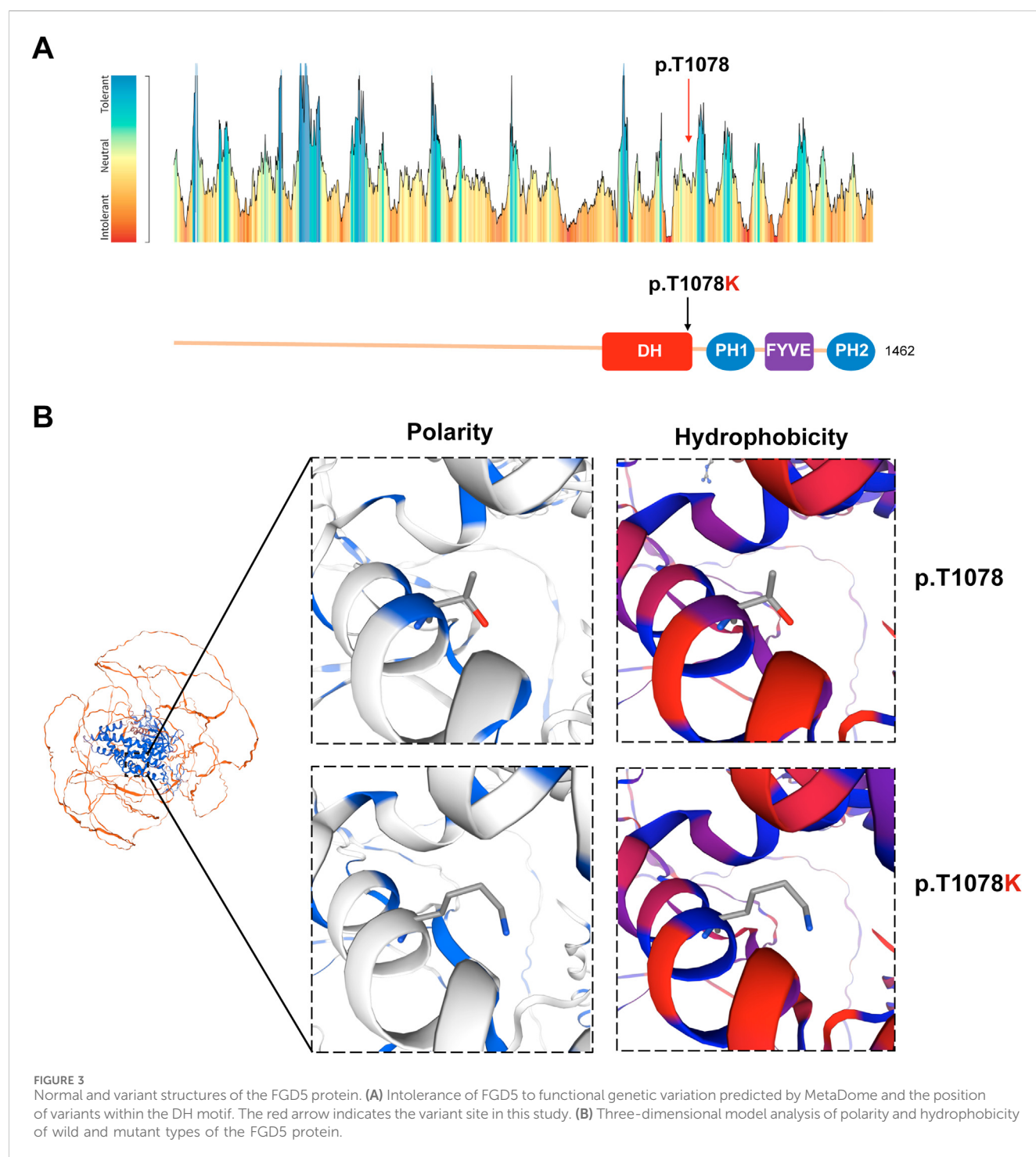
Gene	Variant	Pathogenicity prediction*	GnomAD	1000G	OMIM clinical phenotype
<i>TTN</i>	NM_133378.4: exon53: c.12659G>C: p.G4220A	MutationTaster: D Polyphen-2: B PROVEAN: D SIFT: B CADD: 1.96 (B) REVEL: 0.555 (D)	0.00077	0.00020	AD, dilated cardiomyopathy-1G; AD, hypertrophic cardiomyopathy-9; AD, myofibrillar myopathy-9 with early respiratory failure.
<i>RBM20</i>	NM_001134363.3: exon2: c.325G>A;p.A109T	MutationTaster: D Polyphen-2: D PROVEAN: B SIFT: D CADD: 3.86 (B) REVEL: 0.433 (B)	—	—	AD, dilated cardiomyopathy-1DD.
<i>FLNC</i>	NM_001127487.2: exon2: c.469C>T;p.R157C	MutationTaster: D Polyphen-2: D PROVEAN: D SIFT: D CADD: 3.96 (B) REVEL: 0.487 (B)	0.00019	—	AD, cardiomyopathy of the hypertrophic (CMH26); AD, restrictive (RCM5), AD, dilated (CMD1PP), AD, arrhythmogenic right ventricular (ARVD15).
<i>NTRK3</i>	NM_001007156.3: exon10: c.995C>T;p.T332M	MutationTaster: D Polyphen-2: D PROVEAN: D SIFT: D CADD: 2.94 (B) REVEL: 0.451 (B)	0.00014	0.00020	Congenital heart defects, ventricular septal defect.
<i>FGD5</i>	NM_001320276.2: exon9: c.3233C>A;p.T1078K	MutationTaster: D Polyphen-2: D PROVEAN: D SIFT: D CADD: 3.70 (B) REVEL: 0.292 (B)	—	—	AD, Tetralogy of Fallot

D, disease-causing; B, benign; AD, autosomal dominant.
*, Pathogenicity prediction of CADD and REVEL are based on the paper PMID: 36413997.

et al., 2002). Structurally, FGD proteins contain an N-terminal low-conservation disordered region, followed sequentially by a Dbl homology (DH) domain, two pleckstrin homology (PH) domains (PH1 and PH2), and a C-terminal FYVE domain. The DH and PH1 domains together form a canonical Rho GEF module—the DH domain catalyzes GTP/GDP exchange activity, while PH1 mediates protein localization and activation. Both PH1 and PH2 domains modulate interactions with phosphoinositides (PIs), and the FYVE domain serves as a specific receptor for PI3P. The DH domain adopts a unique “armchair-like” structure composed of six α -helices, with conserved residues in CR1, CR3, and the C-terminal α -helix 6 forming the critical interface for GTPase binding. Amino acid substitutions in these regions significantly impair GEF activity (Liu et al., 1998). In this study, we identified a missense variant (p.T1078K) located within α -helix 6 of the DH domain, which is predicted to severely disrupt FGD5–GTPase interactions. Clinical studies have established strong associations between the FGD family protein variants and human diseases. For example, missense variants in the DH domain of *FGD1* cause Aarskog–Scott syndrome (Orrico et al., 2004; Pérez-Coria et al., 2015), while the DH domain variants in *FGD4* lead to Charcot–Marie–Tooth disease type 4H (CMT4H) (Hyun et al., 2015). These findings underscore the essential role of DH domain conservation in

maintaining proper protein function and preventing genetic disorders.

As hereditary TOF generally manifests as an autosomal irregular dominant disorder, studies consistently report asymptomatic carrier status among substantial numbers of probands’ parents and first-degree relatives (Goldmuntz et al., 2001; Bauer et al., 2010; Baban et al., 2014). In this study, the affected fetus exhibited typical imaging phenotypes of TOF on cardiac ultrasonography, while the mother carrying the variant showed no TOF phenotype. This observation aligns with the characteristic irregular dominance of inherited TOF. Any disruption in the angiogenesis process can lead to vascular abnormalities, resulting in the development of congenital heart disease (Jin et al., 2024). Based on current research findings, the FGD5 protein may regulate vascular pruning by participating in the VEGF (vascular endothelial growth factor) signaling pathway and activating the CDC42 protein, thereby modulating neovascular networks in both physiological conditions and tumor tissues (Farhan et al., 2017; Heldin et al., 2017; Valla et al., 2018). Moreover, evidence indicates that complete deletion of the *FGD5* gene leads to embryonic lethality, accompanied by impaired cardiac and/or vascular development (Cheng et al., 2012; Gazit et al., 2014). Owing to the high penetrance of *FGD5* variants (Reuter et al., 2020),



genetic counseling and prenatal diagnosis should be recommended for the proband's parents, considering subsequent pregnancies.

Conclusion

We detailed the echocardiographic findings of a male fetus at 26⁺³ weeks of gestation. We identified a novel *FGD5* variant

(c. 3233C>A, p.T1078K) in him and analyzed the pathogenicity using three-dimensional protein modeling. Our report provides a perspective on the progress of *FGD5*-related diseases and extends our understandings of *FGD5*-related symptoms. Our identification and compilation expand the pathogenic variant spectrum of *FGD5*, suggest a linkage between *CDC42* and the *FGD5* variant in the DH domain, and contribute to molecular diagnosis and genetic counseling in patients with *FGD5* variants.

Data availability statement

The WES datasets presented in this study can be found in online repositories China National Center for Bioinformation (<https://www.cncb.ac.cn/>), accession number PRJCA047101.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the School of Life Sciences of Central South University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

M-WL: Data curation, Formal Analysis, Writing – original draft. YD: Data curation, Validation, Writing – original draft. RX: Funding acquisition, Project administration, Supervision, Writing – original draft. LW: Resources, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China (grant number 82170598 and 81970403).

References

- Baban, A., Postma, A. V., Marini, M., Trocchio, G., Santilli, A., Pelegrini, M., et al. (2014). Identification of TBX5 mutations in a series of 94 patients with Tetralogy of Fallot. *Am. J. Med. Genet. Part A* 164A (12), 3100–3107. doi:10.1002/ajmg.a.36783
- Bauer, R. C., Laney, A. O., Smith, R., Gerfen, J., Morrissette, J. J. D., Woyciechowski, S., et al. (2010). Jagged1 (JAG1) mutations in patients with tetralogy of Fallot or pulmonic stenosis. *Hum. Mutat.* 31 (5), 594–601. doi:10.1002/humu.21231
- Bouma, B. J., and Mulder, B. J. M. (2017). Changing landscape of congenital heart disease. *Circulation Res.* 120 (6), 908–922. doi:10.1161/CIRCRESAHA.116.309302
- Cheng, C., Haasdijk, R., Tempel, D., van de Kamp, E. H. M., Herpers, R., Bos, F., et al. (2012). Endothelial cell-specific FGD5 involvement in vascular pruning defines neovessel fate in mice. *Circulation* 125 (25), 3142–3158. doi:10.1161/CIRCULATIONAHA.111.064030
- Fan, L. L., Liu, J. S., Huang, H., Du, R., and Xiang, R. (2019). Whole exome sequencing identified a novel mutation (p.Ala1884Pro) of beta-spectrin in a Chinese family with hereditary spherocytosis. *J. Gene Med.* 21 (2–3), e3073. doi:10.1002/jgm.3073
- Farhan, M. A., Azad, A. K., Touret, N., and Murray, A. G. (2017). FGD5 regulates VEGF receptor-2 coupling to PI3 kinase and receptor recycling. *Arteriosclerosis, Thrombosis, Vasc. Biol.* 37 (12), 2301–2310. doi:10.1161/ATVBAHA.117.309978
- Gazit, R., Mandal, P. K., Ebina, W., Ben-Zvi, A., Nombela-Arrieta, C., Silberstein, L. E., et al. (2014). Fgd5 identifies hematopoietic stem cells in the murine bone marrow. *J. Exp. Med.* 211 (7), 1315–1331. doi:10.1084/jem.20130428
- Goldmuntz, E., Geiger, E., and Benson, D. W. (2001). NKX2.5 mutations in patients with tetralogy of fallot. *Circulation* 104 (21), 2565–2568. doi:10.1161/hc4601.098427
- Heldin, J., O'Callaghan, P., Hernández Vera, R., Fuchs, P. F., Gerwins, P., and Kreuger, J. (2017). FGD5 sustains vascular endothelial growth factor A (VEGFA) signaling through inhibition of proteasome-mediated VEGF receptor 2 degradation. *Cell. Signal.* 40, 125–132. doi:10.1016/j.cellsig.2017.09.009
- Huang, R.-T., Xue, S., Xu, Y.-J., and Yang, Y.-Q. (2013). Somatic mutations in the GATA6 gene underlie sporadic tetralogy of Fallot. *Int. J. Mol. Med.* 31 (1), 51–58. doi:10.3892/ijmm.2012.1188
- Hyun, Y. S., Lee, J., Kim, H. J., Hong, Y. B., Koo, H., Smith, A. S. T., et al. (2015). Charcot-marie-tooth disease type 4H resulting from compound heterozygous mutations in FGD4 from nonconsanguineous Korean families. *Ann. Hum. Genet.* 79 (6), 460–469. doi:10.1111/ahg.12134
- Jin, L., Han, Z., Mao, X., Lu, J., Yan, B., Lu, Y., et al. (2024). Genome-wide profiling of angiogenic cis-regulatory elements unravels cis-regulatory SNPs for vascular abnormality. *Sci. Data* 11 (1), 467. doi:10.1038/s41597-024-03272-6
- Kola, S., Koneti, N. R., Golla, J. P., Akka, J., Gundimeda, S. D., and Mundluru, H. P. (2011). Mutational analysis of JAG1 gene in non-syndromic tetralogy of Fallot children. *Clin. Chimica Acta; Int. J. Clin. Chem.* 412 (23–24), 2232–2236. doi:10.1016/j.cca.2011.08.017
- Kurogane, Y., Miyata, M., Kubo, Y., Nagamatsu, Y., Kundu, R. K., Uemura, A., et al. (2012). FGD5 mediates proangiogenic action of vascular endothelial growth factor in human vascular endothelial cells. *Arteriosclerosis, Thrombosis, Vasc. Biol.* 32 (4), 988–996. doi:10.1161/ATVBAHA.111.244004
- Liu, X., Wang, H., Eberstadt, M., Schnuchel, A., Olejniczak, E. T., Meadows, R. P., et al. (1998). NMR structure and mutagenesis of the N-terminal Dbl homology domain of the nucleotide exchange factor Trio. *Cell* 95 (2), 269–277. doi:10.1016/s0092-8674(00)81757-2
- O'Brien, P., and Marshall, A. C. (2014). Cardiology patient page. Tetralogy of Fallot. *Circulation* 130 (4), e26–e29. doi:10.1161/CIRCULATIONAHA.113.005547
- Orrico, A., Galli, L., Cavaliere, M. L., Garavelli, L., Frys, J.-P., Crushell, E., et al. (2004). Phenotypic and molecular characterisation of the Aarskog-Scott syndrome: a survey of the clinical variability in light of FGD1 mutation analysis in 46 patients. *Eur. J. Hum. Genet. EJHG* 12 (1), 16–23. doi:10.1038/sj.ejhg.5201081

Acknowledgments

The authors thank the affected fetus' parents for undergoing clinical examination and blood specimen collection for this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- Pérez-Coria, M., Lugo-Trampe, J. J., Zamudio-Osuna, M., Rodríguez-Sánchez, I. P., Lugo-Trampe, A., de la Fuente-Cortez, B., et al. (2015). Identification of novel mutations in Mexican patients with Aarskog-Scott syndrome. *Mol. Genet. and Genomic Med.* 3 (3), 197–202. doi:10.1002/mgg3.132
- Pizzuti, A., Sarkozy, A., Newton, A. L., Conti, E., Flex, E., Digilio, M. C., et al. (2003). Mutations of ZFPM2/FOG2 gene in sporadic cases of tetralogy of Fallot. *Hum. Mutat.* 22 (5), 372–377. doi:10.1002/humu.10261
- Reuter, M. S., Jobling, R., Chaturvedi, R. R., Manshaei, R., Costain, G., Heung, T., et al. (2019). Haploinsufficiency of vascular endothelial growth factor related signaling genes is associated with tetralogy of Fallot. *Genet. Med. Official J. Am. Coll. Med. Genet.* 21 (4), 1001–1007. doi:10.1038/s41436-018-0260-9
- Reuter, M. S., Chaturvedi, R. R., Liston, E., Manshaei, R., Aul, R. B., Bowdin, S., et al. (2020). The Cardiac Genome Clinic: implementing genome sequencing in pediatric heart disease. *Genet. Med. Official J. Am. Coll. Med. Genet.* 22 (6), 1015–1024. doi:10.1038/s41436-020-0757-x
- Sierant, M. C., Jin, S. C., Bilguvar, K., Morton, S. U., Dong, W., Jiang, W., et al. (2025). Genomic analysis of 11,555 probands identifies 60 dominant congenital heart disease genes. *Proc. Natl. Acad. Sci. U. S. A.* 122 (13), e2420343122. doi:10.1073/pnas.2420343122
- Snyder, J. T., Worthylake, D. K., Rossman, K. L., Betts, L., Pruitt, W. M., Siderovski, D. P., et al. (2002). Structural basis for the selective activation of Rho GTPases by Dbl exchange factors. *Nat. Struct. Biol.* 9 (6), 468–475. doi:10.1038/nsb796
- Valla, M., Mjones, P. G., Engström, M. J., Ytterhus, B., Bordin, D. L., van Loon, B., et al. (2018). Characterization of FGD5 expression in primary breast cancers and lymph node metastases. *J. Histochem. Cytochem. Official J. Histochem. Soc.* 66 (11), 787–799. doi:10.1369/0022155418792032
- Wang, J., Wang, C., Xie, H., Feng, X., Wei, L., Wang, B., et al. (2022). Case report: tetralogy of fallot in a Chinese family caused by a novel missense variant of MYOM2. *Front. Cardiovasc. Med.* 9, 863650. doi:10.3389/fcvm.2022.863650
- Wiel, L., Baakman, C., Gilissen, D., Veltman, J. A., Vriend, G., and Gilissen, C. (2019). MetaDome: pathogenicity analysis of genetic variants through aggregation of homologous human protein domains. *Hum. Mutat.* 40 (8), 1030–1038. doi:10.1002/humu.23798
- Zhang, W.-m., Li, X.-f., Ma, Z.-y., Zhang, J., Zhou, S.-h., Li, T., et al. (2009). GATA4 and NKX2.5 gene analysis in Chinese Uygur patients with congenital heart disease. *Chin. Med. J.* 122 (4), 416–419. doi:10.3760/cma.j.issn.0366-6999.2009.04.0011