



Genetic and ultrasound assessment in recurrent fetal malformations: a case report on *TUBA1A* gene variation

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Abstract

To elucidate the etiology of recurrent fetal brain developmental malformations accompanied by other structural ultrasound anomalies in a Chinese non-consanguineous couple, we performed a comprehensive evaluation of prenatal ultrasound phenotypes across their two consecutive pregnancies. Copy number variation sequencing and exome sequencing were applied to the amniotic fluid sample obtained from the affected pregnancy. One copy number variation and four candidate missense variants in three genes identified in the initial analysis were reassessed and reclassified according to current clinical and genetic evidence. Our results demonstrated that a maternal mosaic c.7G>A(p.Glu3Lys) variant in the tubulin alpha 1a (*TUBA1A*) gene was the underlying cause of the couple's recurrent adverse pregnancy outcomes. These findings enrich the database of pathogenic *TUBA1A* variants, expand the spectrum of associated prenatal ultrasound phenotypes, and provide valuable insights into the underlying pathogenic mechanisms.

INTRODUCTION

Tubulinopathies are a diverse group of neurodevelopmental disorders caused by mutations in tubulin genes, which lead to cortical malformations. The tubulin gene tubulin alpha-1A (*TUBA1A*) was first identified in 2007 in both mice and humans^[1]. Cerebral dysplasia is common in individuals with *TUBA1A* mutations and often results in intellectual disability^[2], cognitive deficits, and epilepsy^[3,4]. Recent research has linked *TUBA1A* to extracerebral anomalies, such as a fetal akinesia deformation sequence (FADS)^[5], and optic nerve abnormalities^[6] associated with *TUBA1A*

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mutations, indicating its role in various developmental processes. Herein, we describe a case involving a Chinese couple with a history of recurrent pregnancies in which fetal ultrasound revealed both intracranial and extracranial anomalies. A heterozygous *TUBA1A* variant (c.7G>A) was detected during the second pregnancy; subsequent validation and reassessment of the variant's pathogenicity confirmed its association with the observed fetal phenotype.

PATIENT AND METHODS

Patient description

This was a healthy, non-consanguineous G2P0 Chinese couple. The first pregnancy was terminated at approximately 23 weeks of gestation due to structural abnormalities detected by prenatal ultrasound, involving the brain, heart, and craniofacial regions. Unfortunately, no autopsy or genetic testing was conducted on the aborted fetus at the hospital where the procedure was performed. In the current (second) pregnancy, neither nuchal translucency (NT) screening nor noninvasive prenatal testing (NIPT) detected any abnormalities. However, a recent second-trimester ultrasonography at 17⁺⁴ weeks of gestation revealed a constellation of fetal structural anomalies highly concordant with those observed in the prior pregnancy. Consequently, prenatal diagnosis was requested, and informed consent was obtained from the couple for further genetic testing, research, and publication. The ethical approval was obtained from the Ethical Review Committee of the Women and Children's Hospital, School of Medicine, Xiamen University, China (No. KY-2024-105-H01), and written informed consent was obtained from all participants. At 18 weeks of gestation, the pregnant woman underwent amniocentesis at the Xiamen Women and Children's Hospital. Following the amniocentesis, the couple elected to terminate the pregnancy due to the multiple abnormal ultrasound findings.

Genetic testing and sequencing parameters

The collected amniotic fluid samples (AFS) were sent to BGI Genomics Co., Ltd. (Shenzhen, China) for singleton copy number variation sequencing (CNV-seq) and exome sequencing (ES). For ES, exome capture and library construction were performed using the NEXome XP Panel v1.0 kit (Cat No. 1001872, Nanodigmbio, Nanjing, China) and the NanoPrep® DNA Library Preparation Kit v2 (Cat No. 1002421, Nanodigmbio, Nanjing, China), respectively. The constructed libraries were subsequently sequenced on the MGISEQ-2000 platform (MGI Tech Co., Ltd., Shenzhen, China) to produce 2 × 150 bp paired-end reads with a minimum sequencing depth of 150×. Candidate variants detected by ES in the AFS were verified by Sanger sequencing. CNV-seq was performed via low-depth whole-genome sequencing on the BGISEQ-2000 platform, with an average sequencing depth of 0.4× and a 100 kb threshold for copy number variation (CNV) calling. Confirmatory ES was conducted on maternal peripheral blood samples by Aegicare Biotechnology Co., Ltd. (Shenzhen, China) using the same protocol as described above, with a minimum sequencing depth of 100×.

Reassessment and reclassification of the variant

Candidate variants are reviewed and reclassified in accordance with the American College of Medical Genetics and Genomics (ACMG)/the Association for Molecular Pathology (AMP) guidelines^[7,8], using the Bayesian classification framework from ClinGen Sequence Variant Interpretation (SVI) Working Group^[9], and its standardized scoring system, wherein each criterion is assigned an integer point ranging from -8 to +8^[10].

RESULTS

Prenatal ultrasound findings

By systematically reviewing the patient's medical records, we retrieved prenatal ultrasound data from both pregnancies [Table 1]. The ultrasound findings showed strong similarities between the two fetuses. Both

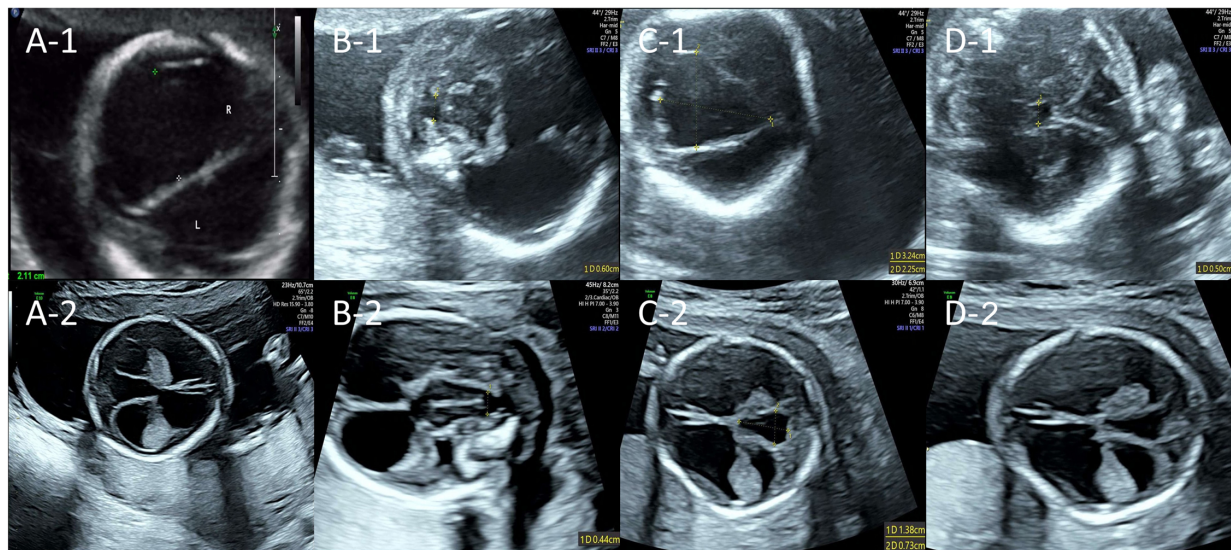


Figure 1. Fetal brain ultrasound findings of two consecutive pregnancies. The upper row shows the prenatal ultrasound from the first pregnancy at 22⁺4 weeks of gestation; the lower row shows that from the second pregnancy at 17⁺4 weeks of gestation. (A-1,2) Ultrasound suggested hydrocephalus; (B-1,2) Ultrasound suggested cerebellar dysplasia with vermian agenesis; (C-1,2) Ultrasound suggested a cystic midline cerebellar lesion (suspected arachnoid cyst); (D-1,2) Ultrasound suggested a complete absence of corpus callosum and cavum septum pellucidum.

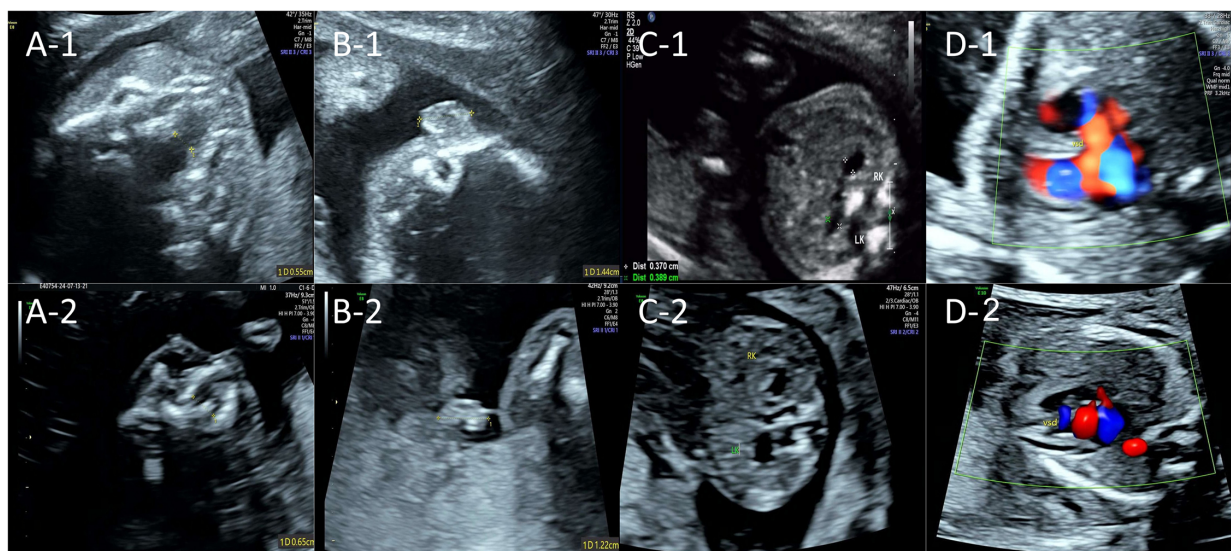


Figure 2. Fetal non-neurological ultrasound findings of two consecutive pregnancies. The upper row shows the prenatal ultrasound from the first pregnancy at 22⁺4 weeks of gestation; the lower row shows that from the second pregnancy at 17⁺4 weeks of gestation. (A-1,2) Ultrasound suggested a cleft palate; (B-1,2) Ultrasound suggested unilateral (right) microtia; (C-1,2) Ultrasound suggested mild bilateral renal pyelectasis; (D-1,2) Ultrasound suggested a ventricular septal defect.

exhibited cerebral dysplasia, featuring hydrocephalus, cerebellar dysplasia with vermian agenesis, cystic midline cerebellar lesions, absent corpus callosum, and cavum septum pellucidum [Figure 1A-D]. Non-neurological anomalies were also present in both cases, including cleft palate, ventricular septal defect, unilateral (right) microtia, and mild bilateral renal pyelectasis [Figure 2A-D].

Genetic test results

CNV-seq analysis detected a 106.79 kb deletion {seq[GRCh37]3p14.1p14.1(68316329_68423116)×1} of

Table 1. Prenatal ultrasound findings of fetuses during two pregnancies

	First pregnancy (GW: 22 ⁺ 4)	Second pregnancy (GW: 17 ⁺ 4)
Prenatal ultrasound findings	Cerebral anomalies: (1) Hydrocephalus (R: 2.11 cm vs. L: 1.97 cm) (2) Cerebellar dysplasia with vermian agenesis (0.6 cm) (3) Cystic midline cerebellar lesion (suspected arachnoid cyst: 3.24 cm * 2.25 cm) (4) Absence of the corpus callosum and cavum septum pellucidum	Cerebral anomalies: (1) Hydrocephalus (R: 1.46 cm vs. L: 1.45 cm) (2) Cerebellar dysplasia with vermian agenesis (0.44 cm) (3) Cystic midline cerebellar lesion (suspected arachnoid cyst: 1.38 cm * 0.73 cm) (4) Absence of the corpus callosum and cavum septum pellucidum
	Non-neurological anomalies: (1) Cleft palate (0.55 cm) (2) Ventricular septal defect (3) Unilateral (R) microtia (R: 1.44 cm vs. L: 1.80cm) (4) Mild bilateral renal pyelectasis	Non-neurological anomalies: (1) Cleft palate (0.65 cm) (2) Ventricular septal defect (0.21 cm) (3) Unilateral (R) microtia (R: 1.22 cm vs. L: 1.35 cm) (4) Mild bilateral renal pyelectasis

GW: Gestational weeks; R: right side; L: left side. Values presented in parentheses correspond to ultrasound measurements, if provided.

unknown origin in the fetus and was categorized as a variant of uncertain significance (VUS) in the report. ES analysis of the AFS identified three candidate single-nucleotide variants (SNVs) potentially associated with the fetal phenotype; however, all were classified as VUS [Table 2]. Sanger sequencing confirmed that the EPH receptor B4 (*EPHB4*): c.2254C>T(p.Leu752Phe) variant in the fetus was paternally inherited, while the two HECT domain and RCC1-like domain 1 (*HERC1*) missense variants were inherited biparentally [Supplementary Figure 1A]. Owing to the ambiguous peak morphology [Supplementary Figure 1B], initial Sanger sequencing failed to determine the parental origin of the *TUBA1A*: c.7G>A(p.Glu3Lys) variant. Subsequent ES analysis confirmed low-level mosaicism (~4.43%) at this locus in the maternal sample [Supplementary Figure 1C]; however, this variant was still classified as VUS in the report, given that the mother was unaffected.

Reclassification of the candidate variants

Given that the etiology of the fetal anomalies remained unidentified in the three initial reports, we performed a comprehensive reanalysis to assess the pathogenicity of the candidate variants. For the copy number loss detected in the fetus, we first mapped the CNV within the *TAFAl* gene using the DECIPHER database [Supplementary Figure 2]. We then applied the Pathogenic Very Strong 1 (PVS1) criterion from the SVI guidelines to reclassify the intragenic CNV^[11,12], as an alternative to the CNV scoring metric system^[13]. Upon querying the ClinGen database (<https://www.clinicalgenome.org>), we confirmed that the gene-disease association remains uncertain to date. Accordingly, the classification of this CNV was maintained as originally reported.

Subsequently, we focused on four candidate SNVs across three genes. For the variant detected in the *EPHB4* gene, although ClinGen has established a gene-disease relationship (*EPHB4*-related vascular malformation spectrum), the clinical presentation in our patient did not align with the phenotype reported in Online Mendelian Inheritance in Man (OMIM) [Supplementary Table 1]. In addition, the variant was inherited from an unaffected parent, further reducing its likelihood of pathogenicity. Thus, it was retained as a variant of VUS, in accordance with the initial classification. Regarding the candidate variants in *HERC1*, while the inheritance pattern documented in OMIM is consistent with the familial pattern observed here, the gene-disease association remains ambiguous. Moreover, the phenotypes recorded in OMIM exhibit minimal overlap with the fetal phenotypes in the present case [Supplementary Table 1]. Given these observations, we conclude that there is inadequate evidence to support upgrading the pathogenicity of these two variants.

In comparison to the two candidate genes mentioned above, the phenotypic spectrum associated with the *TUBA1A* gene demonstrated the strongest concordance with the ultrasonographic phenotypes observed in our cases [Supplementary Table 1]. Consequently, we systematically re-evaluated the original criteria from

Table 2. Detailed information on the candidate SNV variants identified in the fetus

Gene	Gene-disease validity ^a	Transcript	Variant sites and heterozygosity	Origin of variant	Initially reported variant categories (criteria used)	Reclassified variant categories (criteria used)
<i>TUBA1A</i>	Definitive	NM_006009.3	c.7G>A(p.Glu3Lys), het	Maternal (mosaic)	VUS (PM2 + PP2 + PP3)	LP (PM6 + PM2_supporting + PP2 + PP3 + PP4)
<i>EPHB4</i>	Definitive	NM_004444.4	c.2254C>T(p.Leu752Phe), het	Paternity	VUS (PM2 + PP2 + PP3)	VUS (PM2_supporting + PP2 + PP3)
<i>HERC1</i>	NA	NM_003922.3	c.14131C>G(p.Pro4711Ala), het	Paternity	VUS (PM2 + PP2 + PP3)	VUS (PM2_supporting + PP2 + PP3) VUS (PM2_supporting + PP2)
<i>HERC1</i>	NA	NM_003922.3	c.7576A>G(p.Ser2526Glu), het	Maternal	VUS (PM2 + PP2)	

NA: Not available; het: heterozygous; VUS: variant of undetermined significance; LP: likely pathogenic; SNV: single-nucleotide variant. ^a From Clingen (<https://www.clinicalgenome.org/>).

the report and incorporated additional evidence to reclassify the c.7G>A variant as likely pathogenic [Table 2], thereby identifying this variant as the cause of two adverse pregnancy outcomes in the patient.

DISCUSSION

The role of the *TUBA1A* gene in brain development

Previous studies indicate that the *TUBA1A* gene, which encodes the α -tubulin isotype, is essential for microtubule formation and function, and is crucial for neuronal migration, axon guidance, and synapse formation^[14]. Mouse models with *TUBA1A* mutations exhibit impaired neuronal migration and increased branching linked to disrupted microtubule organization and nucleus-centrosome coupling, underscoring its irreplaceable role in neuronal migration and the importance of microtubule flexibility for proper neuronal structure^[15]. Similarly, in humans, *TUBA1A* mutations cause neurodevelopmental disorders known as tubulinopathies - such as lissencephaly and polymicrogyria - highlighting its key role in preserving neuronal integrity and function during brain development^[2,16,17].

Ultrasound phenotypes of fetuses with *TUBA1A* mutation

Compared with postpartum patients, research on the phenotypic characteristics of fetuses with *TUBA1A* mutations is scarce. From 2007 to 2022, multiple studies reported that such fetuses mostly had cerebral developmental abnormalities, including ventricular dilatation, cerebellar hypoplasia, microcephaly, and gyral abnormalities, all carrying *de novo* missense mutations in the *TUBA1A* gene^[3,5,18-27]. The current case had multiple cerebral dysplasias; among them, hydrocephalus, vermian agenesis, and absence of the corpus callosum have been previously reported, but cystic midline cerebellar lesions have not been documented before, which broadens the prenatal cerebral phenotypic spectrum of fetuses with *TUBA1A* mutations.

In addition, previous studies suggested that *TUBA1A* mutations may be associated with extracranial developmental abnormalities (such as ocular abnormalities), but no relevant abnormalities were detected by prenatal imaging^[6,22]. Our study first reported non-neurological ultrasound abnormalities (including cleft palate, ventricular

septal defect, *etc.*) in the prenatal ultrasound phenotypes of such fetuses, which are speculated to be associated with the identified *TUBA1A* mutation, as no other definitive pathogenic CNVs or SNVs related to these manifestations were detected in the proband.

Reclassification of the VUS association of fetal US findings

In 2020, the ACMG proposed ES for fetuses with structural anomalies if karyotyping and microarray analysis were negative^[28], recommending reporting pathogenic (P), likely pathogenic (LP) variants, and phenotype-matched VUS. Recent studies show reanalyzing ES data, especially phenotype-related VUS, can improve diagnostic rates when causes are unclear^[29,30].

In the present case, overlapping prenatal ultrasound findings from two pregnancies prompted a genetic investigation; cerebral dysgenesis indicated a potential association between the *TUBA1A* c.7G>A variant and the disease. Since nearly all previously reported *TUBA1A* variants in probands were *de novo*, we initially sought to determine the parental origin of this variant. Sanger sequencing of the mother revealed background peaks at the *TUBA1A* c.7 locus, suggesting low-level somatic mosaicism, which was subsequently confirmed by ES of maternal peripheral blood. Afterwards, we identified a similar case in which two sisters presented with polymicrogyria due to a *TUBA1A* c.13A>C mutation, with follow-up analysis confirming the same mosaic mutation in peripheral blood samples from their phenotypically unaffected mother^[31]. In accordance with the most recent guidelines issued by the SVI working group^[32], germline variants in offspring resulting from parental mosaicism may be classified using **de novo** criteria - such as Pathogenic Strong 2 (PS2) or Pathogenic Moderate 6 (PM6) - provided that parental origin is confirmed and the phenotypic manifestations are specific. In the present case, the PM6 criterion was applied due to insufficient evidence to confirm consanguinity between the proband's parents.

In addition to the **de novo** criteria, we propose incorporating the Pathogenic Supporting 4 (PP4) criterion to support reclassification of the *TUBA1A* variant. This criterion applies when a patient's phenotype or family history is highly specific for a monogenic disorder^[7]. Two factors warranted its application in this context: the fetal phenotype exhibited a high specificity for *TUBA1A*-related tubulinopathies, and the prenatal findings in the couple's first pregnancy closely mirrored those observed in the second, thereby establishing a pertinent family history. In addition to the newly introduced criteria, the three criteria from the initial ES report were also reassessed. PP2 and PP3 were maintained, whereas Pathogenic Moderate 2 (PM2) was downgraded to a supporting level according to the SVI guideline^[33]. Collectively, *TUBA1A* c.7G>A variant was reclassified using criteria of PM6 (2 points) + PM2_Supporting (1 point) + PP2 (1 point) + PP3 (1 point) + PP4 (1 point), yielding a Bayesian score of six and a "likely pathogenic" interpretation. Based on this conclusion, the couple received comprehensive reproductive guidance.

Limitations of the study

The primary limitation of this study is the lack of *in vitro* experimental validation to functionally support the pathogenicity of the *TUBA1A* c.7G>A variant; these will be explored in future research. In addition, as of the submission of this article, the precise efficacy of the fertility guidance provided remains unclear since the couple has not yet achieved a subsequent pregnancy; thus, long-term follow-up is needed for further observation.

CONCLUSION

This study describes a prenatal case with recurrent fetal brain anomalies and concurrent cardiac, facial, and renal abnormalities. By identifying the variant origin and reclassifying its pathogenicity, we confirmed the proband's phenotype was linked to a maternal mosaic *TUBA1A* variant. This finding enriches the *TUBA1A* pathogenic variant database, expands related prenatal ultrasound manifestations, and provides new insights

into the gene's molecular pathways. However, evidence linking *TUBA1A* variants to extracerebral manifestations is limited, requiring further research to validate our hypothesis.

DECLARATIONS

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Authors' contributions

Conceptualization, writing - review & editing, funding acquisition: Jiang Y

Investigation, funding acquisition: Wu L

Data curation: Du L, Luo Z, Zhao H

Resources: Lu M

Review & editing: Zhang Y

Availability of data and materials

The data that support the findings of this study are available in the China National Center for Bioinformation at <https://bigd.big.ac.cn/gsa-human/browse/HRA012907>, reference number HRA012907.

AI and AI-assisted tools tatement

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval was obtained from the Ethical Review Committee of the Women and Children's Hospital, School of Medicine, Xiamen University (No. KY-2024-105-H01), and written informed consent was obtained from all participants.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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