Two fetuses of hereditary tubulinopathies with TUBB deficiency

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Learning points for clinicians

This report identified two novel missense TUBB variants in two prenatal cases diagnosed with tubulinopathies. This report highlights molecular and MRI diagnosis of tubulinopathies is crucial for diagnosis and genetic counseling of individuals with tubulinopathies.

Case report

Tubulinopathies are a group of clinically heterogeneous neurological disorders 1, caused by pathogenic variants in tubulin genes 1, 2, which is characterized by classic lissencephaly, cerebellar hypoplasia or agenesis of the corpus callosum, centrally predominant pachygyria, microlissencephaly and dysgyria 3. Clinical manifestations mainly include variable of delayed psychomotor development, microcephaly, and facial deformities. However, some cases of tubulinopathies may have no obvious clinical phenotypes, except for imaging abnormalities. We provide two prenatal cases with inherited tubulinopathies in the hope that clinicians will pay more attention to this rare
disease.

The fetus of pedigree 1 presented with right ventricular dilatation (13.4mm) at 30 weeks of intrauterine age, and magnetic resonance imaging (MRI) revealed asymmetrical morphology of bilateral lateral fissures and slight midline deviation (Figure 1A-B). Whole exome sequencing (WES) revealed that the fetus had a heterozygous mutation (c.637C>T, p. R213C) in TUBB, inherited from the mother, who also had a comparable MRI result (Figure 1C-D). She has normal intelligence, no obvious facial deformities, except for slightly slow reactions. The fetus has been born and is currently 8 months old, who grows and develops normally and can pronounce mam and dad.

The fetus of pedigree 2 was incidental finding of TUBB variation by WES due to nuchal translucency (4.7mm) at 11 weeks of intrauterine. No obvious abnormality was found at 16 and 23 weeks of pregnancy in routine ultrasound scan. At 30 weeks of gestation, MRI revealed asymmetrical morphology of bilateral lateral fissures and midline distortion, abnormal sulcation, bilateral frontal lobe asymmetry, and subtle loss of demarcation of the pontomedullary junction (Figure 2A-C). A paternal heterozygous mutation (c.961A>C, p. M321L) in TUBB was found in the fetus by WES. The father had a comparable MRI result (Figure 2D-F), and normal intelligence.

Discussion

TUBB encodes one of the β-tubulin isotypes and widely expressed in various tissues especially in central nervous system. Variant in TUBB can cause cortical...
dysplasia, complex, with other brain malformations 6 (CDCBM6, #MIM 615771), which is characterized by structural brain malformations and microcephaly, and the clinical spectrum is range from severe developmental delay to slightly cognitive impairment and normal motor development 4. However, there are few literatures on the prenatal phenotype contempt of this disease 3. Consequently, molecular diagnosis is crucial for the diagnosis and genetic counseling of individuals with tubulinopathies.

In this study, we identified two novel mutations in TUBB in two fetuses with brain malformations, respectively. We also found a case with abnormal brain morphology, whose phenotype is similar to ours, with TUBB variant (c.961A>G), suggesting that the site is important and indicating the c.961A>C in our study is likely pathogenic.

Most of TUBB variations are de novo, while the variants in our study are inherited from their parents. To better evaluate the fetus’s likely prognosis, MRI were performed on the fetus’s parents, the results were comparable to the fetuses, and the parents had no obvious clinical symptoms, except for the mother of family 1. Therefore, we speculate that asymptomatic tubulinopathies may not be uncommon clinically, when a prenatal tubulinopathies is suspected, molecular testing is advised. Parents' MRI should be improved, if necessary, as this is critical for family counseling.

The imaging phenotype of our cases did not involve dysmorphic basal ganglia so the disease classification may belong to symmetric circumferential skin creases congenital 1 5. As mentioned above, the clinical phenotypes of tubulinopathies vary widely. Most patients have severe to profound intellectual disability, and a few have less severe and less extensive cortical malformations on MRI that allow for near-normal
cognitive abilities. At present, the growth and development milestones of the infants in family 1 were normal, and further follow-up is required.

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Author contributions

Yimo Zeng: Methodology; analysis; writing-original draft; review and editing; visualization. Hongke Ding: Methodology; analysis; review and editing; Yiming Qi: Investigation; Methodology; analysis; Chaoxiang Yang, Lihua Yu, Ling Liu: Qiongmei Li: Analysis and methodology. Aihua Yin: Conceptualization; supervision; review and editing.

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Declarations

This study has been approved by the Institutional Review Board/Medical Ethics Committee of Guangdong Women and Children Hospital (IRB reference number 202301185). Written informed consent was obtained from each participating family.

Registry and the registration: N/A.
Animal studies: N/A.

Conflict of interest

None declared.

Reference


Figure Legends

Figure 1 Clinical and molecular characteristics of case 1. (A-B) Brain MRI of the fetus, (C-D) Brain MRI of the mother. E. Pedigree of family 1; F. Sanger sequencing
of II-1 and control.

**Figure 2** Clinical and molecular characteristics of case 2. (A-C) Brain MRI of the fetus, (D-F) Brain MRI of the father. G. Pedigree of family 2; H. Sanger sequencing of II-1 and control.
Figure 1 Clinical and molecular characteristics of case 1. (A-B) Brain MRI of the fetus, (C-D) Brain MRI of the mother. E. Pedigree of family 1; F. Sanger sequencing of II-1 and control.

290x159mm (300 x 300 DPI)
Figure 2 Clinical and molecular characteristics of case 2. (A-C) Brain MRI of the fetus, (D-F) Brain MRI of the father. G. Pedigree of family 2; H. Sanger sequencing of II-1 and control.