Severe phenotype of a heterozygous with variant on FGFR3 in the second trimester: a case report

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Case Report

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Abstract

Background

Achondroplasia is a congenital skeletal system malformation caused by missense mutation of FGFR3 gene with an incidence of 1 per 20,000–30,000 newborns, which is an autosomal dominant inheritance disease. Despite similar imaging features, the homozygous achondroplasia is absolutely lethal due to thoracic stenosis, whereas heterozygous achondroplasia does not lead to fetal death.

Case presentation

A fetus with progressive rhizomelic short limbs and overt narrow chest was detected by prenatal ultrasound in the second trimester. Gene sequencing results of amniotic uid sample indicated a rare missense variant NM_000142.4: c.1123G > T(p.Gly375Cys), leading to a glusate-to-cysteine substitution. Re-sequencing confirmed that it was a heterozygous mutation, and thoracic stenosis was then confirmed in the corpse by radiological examination.

Conclusions

We identified a wild heterozygous variant of the FGFR3 gene as the rare pathogenic mutation of severe achondroplasia in a fetus. Heterozygous variants of p.Gly375Cys may have a severe phenotype similar to homozygote. It's crucial to combine prenatal ultrasound with genetic examination to differentiate heterozygous from homozygous achondroplasia. The p.Gly375Cys mutation of FGFR3 gene may serve as a vital target for the diagnosis of severe achondroplasia.

Background

Achondroplasia is a congenital skeletal system malformation caused by missense mutation of FGFR3 gene with an incidence of 1 per 20,000–30,000 newborns, which is an autosomal dominant inheritance disease.\cite{1}\cite{2}\cite{3} Mutations in the FGFR3 gene lead to hyperactivation of tyrosine kinase, promoting multiple mitosis, such as carcinogenesis and overgrowth of skin, but inhibiting the proliferation and terminal differentiation of chondrocytes. Therefore, it affects both endochondral and intramembranous ossification.\cite{4}\cite{5}

The phenotypic features of affected individuals include disproportionate short stature, rhizomelic shortening of the arms, a prominent forehead, midface hypoplasia, large skull roof, small skull base and spinal cord compression. Additionally, homozygous achondroplasia is absolutely lethal due to thoracic stenosis. Whereas heterozygous achondroplasia does not lead to fetal death. Radiologic images of the skull, spine, chest, and extremities reveal these characteristic features.\cite{1}\cite{3}\cite{6} In this report, we describe a
case of heterozygous achondroplasia with thoracic stenosis, which was diagnosed in the second trimester based on ultrasound features and genetic testing.

**Case Presentation**

The case is of term female baby delivered by a gravida 2, parity 0 (G2P0) at week 25, who was 29 years old and had an early miscarriage with unknown aetiology. The parents were healthy without family history of genetic diseases or history of infection and medication during the pregnancy. Prenatal ultrasound was firstly performed at 12 + 3w gestational age (GA), the thickness of nuchal translucency was 0.13 cm and the crown-rump length was in accorded with the clinical gestational week. Noninvasive prenatal genetic testing showed a low-risk gestation. At 19w GA, short fetal limbs were found by routine ultrasonography with the femur below − 3SD. The biparental and fetal chromosome examination and whole-exon sequencing were then recommended. Ultrasonographic features at 22w GA indicated obviously short limbs, rhizomelic shortening of the hummers, the femur/abdominal circumference and femur/plantar length, which suggested pathogenic skeletal dysplasia. At 24 + 5w GA, the long bones of fetal limbs were obviously short and the condition was progressively aggravated (Table 1). Narrow chest was found with a ratio of chest/abdominal circumference less than 0.89. The fetus was finally diagnosed with suspected achondroplasia by ultrasonography.

No significant abnormalities were found in biparental and fetal chromosomes. Since heterozygous achondroplasia with a similarly severe phenotype has never been reported previously, we then collected parental blood and fetal amniotic fluid exfoliated cells to perform whole-exon sequencing of FGFR3 gene. As shown in Fig. 3, the sequencing results indicated that a single-base changed from G-to-T at codon 375, which caused a glycine to be replaced by a cysteine.

Given the genetic test reports and ultrasound features (Figs. 1 and 2), this case was finally diagnosed with severe achondroplasia. After prenatal consultation, the couple requested to terminate the pregnancy. The physiological characteristics and radiographic evidence of the corpse (Fig. 4) confirmed the finally diagnosis.

**Discussion**

The FGFR3 (fibroblast growth factor receptor 3) have an extracellular ligand-binding domain, a transmembrane domain and an intracellular domain that contains a split tyrosine kinase subdomain.\(^1\)\(^2\) Heuertz S. suggested that the cysteine residues in the extracellular domain can cause excess disulfide bond formation, leading to a tertiary structure change of FGFR3, further activating tyrosine kinase, resulting in more severe phenotypes\(^7\). This mechanism may be one of the possible causes of the severe phenotype in this case, as the mutation of p.Gly375Cys (indicated by the red star in Fig. 5) also creates additional cysteine residues.
It is well known that 98% of achondroplasia patients are caused by the mutations of p.Gly380Arg in FGFR3, while the remaining 1% is attributed to other mutations. Based on the current reports of achondroplasia, we found none of the heterozygotes showed thoracic stenosis according to the phenotypic analysis. Three cases were reported to be caused by the mutation of p.Gly375Cys, but the phenotype was only described in two of them [8][9][10]. These two patients were diagnosed at two years old and four days after birth respectively. They shared typical imaging features and vertebral flattening, but did not have apparent narrow chests [9][10].

Traditionally, the diagnosis of achondroplasia is based on genetic examination and radiological features [2]. Prenatal ultrasound serve as a routine repeatable imaging method providing additionally valuable information. Although the surviving achondroplasia fetuses have a low life satisfaction due to abnormal appearance and progressive spinal pain [11][12], some families are still willing to accept such children with mild symptoms who are expected to have a nearly normal lifespan with short femurs in the third trimester. Therefore, accurate prenatal diagnosis and risk assessment of achondroplasia are important.

In conclusion, it is crucial to combine prenatal ultrasound with genetic examination to fully evaluate the severe phenotype of heterozygous achondroplasia, and the mutation of p.Gly375Cys may serve as a vital target for the diagnosis.

**Abbreviations**

FGFR3: fibroblast growth factor receptor 3; GA: gestational age; TD : thanatophoric dysplasia type .

**Declarations**

**Ethics approval and consent to participate**

All methods were conducted according to relevant guidelines and regulations, in compliance with the "Regulations on Ethical Review of Biomedical Research Involving Human Subjects" (Order No. 11 of the National Health and Family Planning Commission of the People's Republic of China), the "Quality Management Standards for Clinical Trials of Medical Devices" (Order No. 25 of the State Food and Drug Administration and the National Health and Family Planning Commission of the People's Republic of China), the Helsinki Declaration of the World Medical Association, and the ethical principles of the International Ethical Guidelines for Biomedical Research Involving Human Subjects of CIOMS. The study was approved by the Ethics Committee of The First People's Hospital of Chongqing Liang Jiang New Area. Written informed consent to participate was obtained from the fetal parents.

**Consent for publication**

Written informed consent for publication of identifying images and other personal or clinical details was obtained from the fetal parents. And the copy of the written consent is available for review by the editor of this journal.
Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no conflict of interest.

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Authors’ contributions

PL designed the study and revised the manuscript; SC drafted the manuscript; SC, HD, YL and YZ acquired, analyzed, and interpreted the data. All authors read and approved the final manuscript.

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Tables

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<tr>
<th>GA</th>
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<th>HC</th>
<th>AC</th>
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<td>19w</td>
<td>49(+0.93SD)</td>
<td>179(+0.24SD)</td>
<td>155(+0.50SD)</td>
<td>22.0(-3.55SD)</td>
<td>22.1(-1.81SD)</td>
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<td>22w</td>
<td>57(+1.41SD)</td>
<td>196(-0.47SD)</td>
<td>160(-0.91SD)</td>
<td>27.1(-3.77SD)</td>
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<td>24 + 5w</td>
<td>65(+1.35SD)</td>
<td>231(-0.10SD)</td>
<td>205(+0.13SD)</td>
<td>28.5(-5.70SD)</td>
<td>27.8(-2.82SD)</td>
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<td>145</td>
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<td>0.139</td>
<td>0.63</td>
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Figures
Figure 1

The sagittal image of narrow chest at 24+5w GA.

Figure 2
transverse section of narrow chest and short limbs at 22w GA and 24+5w GA.

Figure 3

Sanger sequencing chromatograms showing a missense variant c.1123G > T in the affected fetus in comparison to her unaffected parents.
Figure 4

Physiological characteristics and radiographic evidence of the corpse. 4a: Physiological characteristics of the corpse: disproportionate shortening of long bones, frontal bossing, midface hypoplasia, and protuberant abdomen, talipes equinovarus in the right side. 4b: X-ray image showing disproportionate shortening of long bones, large skull roof and small skull base. 4c: Computerized tomography 3D bone reconstruction showing narrow thoracic shape as a bell, flat midface and spine. 4d: X-ray image showing narrow chest and flat vertebrae. 4e: the trident hand.

Figure 5
Topology map of FGFR3 with major sites of mutation

ACH = achondroplasia. TD = thanatophoric dysplasia type. HYP = hypochondroplasia.

TKp/d = proximal and distal tyrosine kinase domains. TM = transmembrane.