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Expanding the prenatal phenotype and mutant spectrum associated with *THOC6* variants

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ABSTRACT. Objective: We present the first case of *THOC6* variant with a prenatal clinical phenotype of double-outlet right ventricle.
Case report: The fetus in this case presented with double-outlet right ventricle.Two compound heterozygous variations for the *THOC6* gene (NM_024339.5), neither of which has been reported, (exon12: c.826C>T:p.Q276* and exon3:c.178G>T:p.E60*), were identified by exome sequencing in the pre-documented individuals.
Conclusion: This case extends the variant spectrum and clinical characteristics of the *THOC6* gene. It suggests that the double-outlet right ventricle may be a prenatal clinical feature caused by this gene variant. Fetal cardiac ultrasound can be used as an early screening method for these diseases, and it highlights the importance of prenatal whole - exome sequencing technology in elucidating prenatal diagnosis and prognosis.

Key words: *THOC6*; Congenital heart disease; Gene variant.

INTRODUCTION

THOC6 (THO complex subunit 6, OMIM:615403) represents a component of the THO complex responsible for organizing the processing and export of mRNA, the THO complex communicates with other parts to compose the larger TREX complex, a conserved eukaryotic complex that plays an essential part in gene expression (Beaulieu CL, 2013). Beaulieu-Boycott Innes syndrome (BBIS, OMIM:613680) is an autosomal recessive disorder that has been linked to mutations in the *THOC6* gene (Anazi S, 2016). The core clinical features of BBIS include mental retardation, growth retardation, and facial anomalies, while other clinical features. However, there are only few cases in the world, the clinical characteristics as well as mutation spectrum brought on by this gene mutation have not yet been thoroughly identified owing to the absence of medical data.

We report a case of *THOC6* mutation in a prenatal fetus that presented only with congenital heart disease (CHD), with fetal cardiac ultrasound findings of double outlet right ventricle (DORV). Through the instances in this paper and the literature review, we propose that DORV is a clinical prenatal hallmark of *THOC6* abnormalities. Our case broadens the range of *THOC6* gene mutations and clinical features.

CASE PRESENTATION

A 26-year-old pregnant woman, G1P0, in good health, not taking any medication during her pregnancy, was unrelated to her husband. At 24 weeks of gestation, the abnormal ultrasound examination of fetal heart showed an interruption of the ventricular septum of approximately 4 mm and two large arteries originating from the right ventricle (Figure 1). Color Doppler showed RV blood flow to the two arteries (Supplementary Video 1) and the two arteries ran in parallel (Supplementary Video 2). Based on these findings, DORV was diagnosed. The couple decided to terminate the pregnancy and undergo genomic sequencing but declined an autopsy.

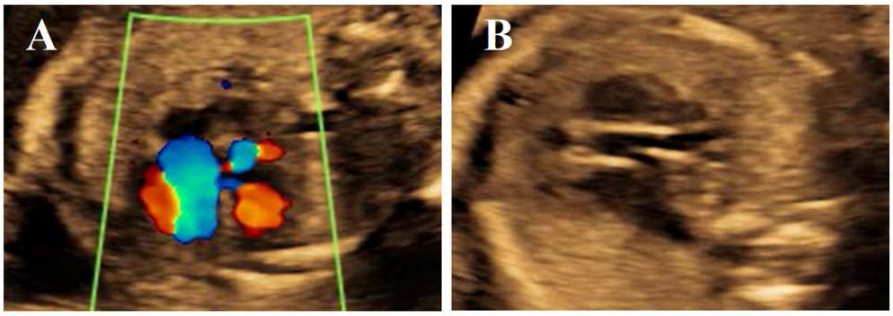

Figure 1. The echocardiography of the fetus identified congenital double outlet right ventricle of the heart.

Using the techniques previously reported, we performed a trio (fetus and the parents) exome sequencing (WES) and copy number variation sequencing (CNV). Following ACMG guidelines (Sun H, et al., 2020b; Richards S, 2015), pathogenic variants were regarded as confirmed genetic outcomes and Sanger sequencing was used for validation.

In the identified CHD genes, we did not find any chromosomal abnormalities or harmful variants, however we did find two variants in the *THOC6* gene (variant 1: exon12: c.826C>T:

p.Q276* from the mother; variant 2: exon3: c.178G>T: p.E60* from the father) forming compound heterozygous variants were detected (Figure 2).The reference population's Thousand Genomes (1000G), Shenzhou Genome Database, Human Exome Database (ExAC), as well as Population Genome Mutation Frequency Database (gnomAD) did not contain the variant loci. With the knowledge that both variants would lead to the relevant codon changing to a stop codon and altering how proteins function, the variant had been classified as a pathogenic variant.

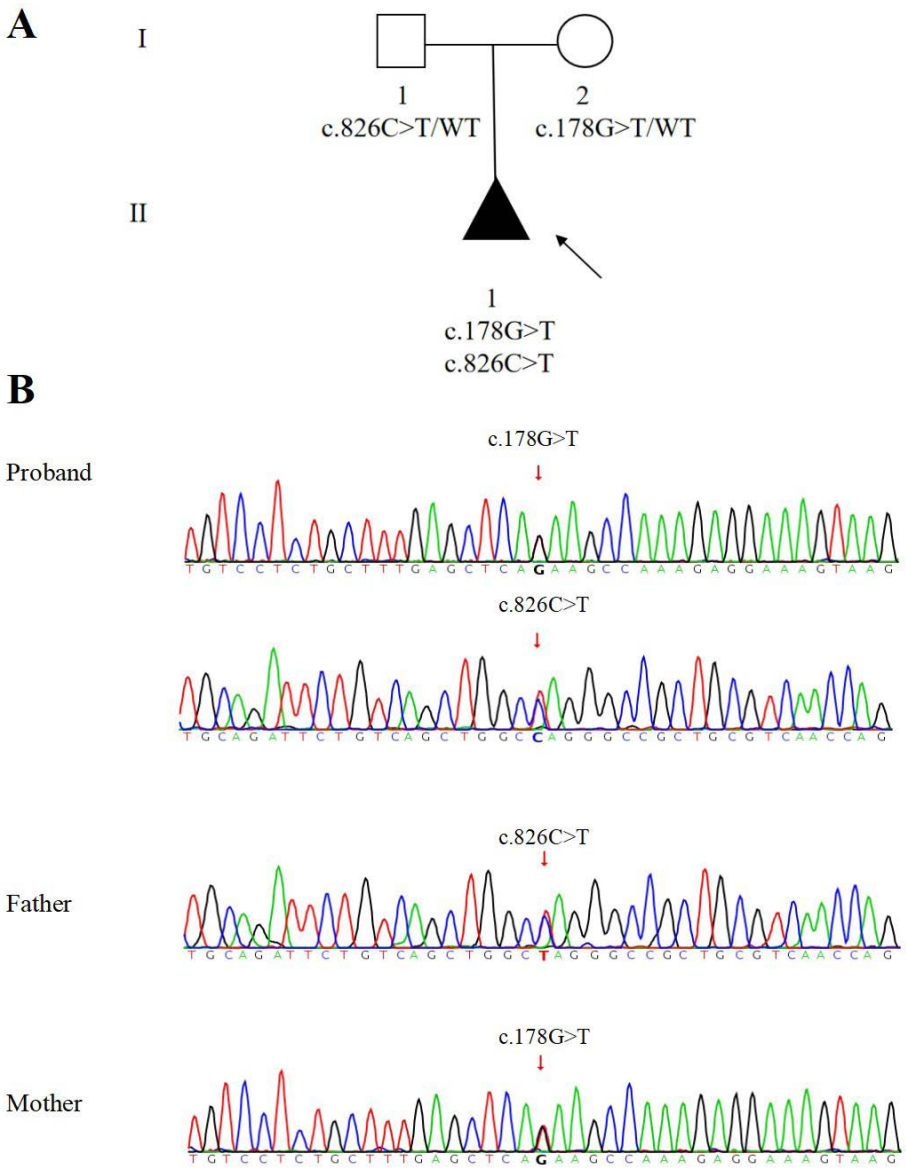

Figure 2. (A) Patient's family pedigree. (B) Sanger sequencing image of the two variants in the *THOC6* gene (exon3: c.178G>T: p.E60* and exon12: c.826C>T: p.Q276*) in the proband, two variants were inherited from the mother and father.

DISCUSSION

We provide a case of prenatal fetal *THOC6* mutation at two previously unknown loci, which broadens the range of *THOC6* gene mutations and further relates congenital cardiac right ventricular double outlet to the phenotype of BBIS.

THOC6 mutation can lead to the development of BBIS, which is a rare autosomal recessive syndrome-type genetic disease that affects the development of the human nervous system, so timely diagnosis of this disease is crucial.

We searched all cases up to January 2025 using PubMed database. Keywords included *THOC6*, BBIS. An extensive exploration of both literature and public repositories was undertaken to accumulate insights on prior clinical instances related to *THOC6* mutations (Table 1). The core clinical characteristics include: intellectual disability, distinctive facial features, microcephaly, teeth anomalies, etc. But most cases are not detected until after birth, our report expands the understanding of BBIS, suggesting that DORT may be one of the emerging prenatal clinical phenotypes of BBIS.

An element of the TREX complex implicated through the coupling for mRNA transcription, processing, as well as nuclear export of spliced mRNA is encoded by the THO complex 6 gene (*THOC6*), which is localized in the nucleus. In HeLa cells, *THOC6* was knocked down to see an increase in apoptosis. It has been discovered that mutations in *THOC6* result in an aberrant location in the cytoplasm, preventing the protein from completing its usual function. Meanwhile, Francesca et al. found that *THOC6* mutation not only leads to nuclear localization, but also affects the interactions with THOD protein chaperones (Jukam D, 2019). Previous studies have shown that a number of signaling molecules as well as transcription variables are regulated by RNA splicing throughout cardiac development, and the THO complex can play a bridging role in the RNA splicing process by controlling the splicing selection of transcription factors and signaling molecules (Xue Y, 2015). It is possible for the THO complex to function abnormally, which could result in abnormal RNA splicing during cardiac development and interfere with the heart's normal development. Together, these findings raise the possibility that the *THOC6* gene may play a pathogenic part in congenital cardiac disease. But there have been no studies on the mechanisms by which *THOC6* controls the growth and functioning of the heart. Considering that *THOC6* may act as the causative gene of fetal CHD in this case is of great significance in exploring how *THOC6* regulates cardiac development, and it also provides a new way of thinking for the further study and treatment of these diseases.

The prenatal clinical phenotype of this case was only DORT, and no other exocardiac malformations were found. Although DORT is a complex congenital heart disease, it can be treated by surgical intervention after birth. The mutation of *THOC6*, the presumed pathogenic gene in this case, has been identified as the genetic cause of a neurodevelopmental disorder, and the pathogenic mutation of this gene will seriously affect the survival period and quality of life of the patient. As a result, if the case is not genetically tested, a faulty prognosis for the fetus may be determined based only on cardiac ultrasound results. Prenatal whole exome sequencing technology can serve as the foundation for proper counseling, which is of utmost importance for elucidating prenatal diagnosis and prognosis.

It is important to note that even while ultrasound did not reveal any visible extracardiac anomalies, it is still challenging to determine whether the congenital heart disease of the fetus is isolated or syndromic. Because the pregnancy was terminated, it is unknown whether other phenotypic characteristics of BISS may manifest in the future. On the one hand, some phenotypes,

Table 1. Comparison of the Clinical Features Observed by previous study and in our case.

Clinical feature	Our patient (n=1)	Boycott et al. (2013) (n=4) (Beaulieu CL, 2013).	Alkuraya et al. al.(2016) (n=1) (Anazi S, 2016).	Boycott et al. (2016) (n=3) (Boycott KM, 2017).	Capra et al. (2018) (n=1) (Capra V, 2018).	Amelie et al. (2018) (n=2) (Mattioli F, 2019).
Age at last examination	fetus	varied	4 years	varied	17 years	varied
Congenital heart defects	+	+	+	+	-	+
Intellectual disability	NA	+	+	+	+	+
Development delayed	NA	+	+	+	+	+
Facial Dysmorphism	NA	+	+	+	+	+
Microcephaly	NA	-	-	+	-	+
Teeth anomalies	NA	+	-	-	+	+
Renal malformations	NA	+	-	-	-	-
Occult spina bifida	NA	-	-	-	-	-
Finger anomalies	NA	-	-	-	+	+
Cystic hygroma	NA	-	-	-	-	-
Abnormal vision	NA	+	-	-	-	+
Anus anomalies	NA	-	+	-	+	-
Cerebellar hypoplasia	NA	-	-	-	+	-
Gynaecological problems,	NA	-	-	-	+	-

Clinical feature	Seber et al. (2021) (n=1) (Kiraz A, 2022).	Hughes et al. (2016) (n=1) (Casey J, 2016).	Attie-Bitach et al. (2022) (n=2) (Ruaud L, 2022).	Abasi et al. (2020) (n=2) (Hassanvand Amouzadeh M, 2020).	Kabra et al. (2019) (n=2) (Kabra M, 2020).
Age at last examination	16 months	14 years	varied	varied	varied
Congenital heart defects	+	-	+	+	
Intellectual disability	+	+	+	+	+
Development delayed	+	+	+	+	+
Facial Dysmorphism	+	+	+	+	+
Microcephaly	-	-	-	-	+
Teeth anomalies	+	+	-	+	-
Renal malformations	+	+	-	+	+
Occult spina bifida	+	-	-	-	-
Finger anomalies	+	-	+	-	+
Cystic hygroma	-	-	+	-	-
Abnormal vision	-	-	-	-	-
Anus anomalies	-	-	-	-	-
Cerebellar hypoplasia	-	-	-	-	-
Gynaecological problems	-	-	-	-	-

+, positive; -, negative; NA, not available

particularly neurodevelopmental diseases, are difficult to detect within the prenatal context.

We report a case of a prenatal *THOC6* mutant fetus presenting with congenital right ventricular double outlet, and this example broadens the mutational landscape and clinical characteristics associated with the *THOC6* gene, suggesting that right ventricular double outlet may be a characteristic prenatal clinical phenotype due to mutations in this gene. The pathophysiologic mechanisms by which *THOC6* mutations lead to CHD need to be investigated. Additionally, our report suggests that when abnormal results are found in prenatal fetal cardiac ultrasound, further genetic testing should be conducted to determine whether there is a disease-causing gene mutation, so as to rule out whether it may lead to other phylogenetic abnormalities and conduct early intervention to improve outcomes.

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AVAILABILITY OF DATA AND MATERIALS

The raw data obtained from whole-exome sequencing of the family in this study cannot be publicly accessed due to the need to protect participant confidentiality. Furthermore, in accordance with the regulations of the People's Republic of China on the management of human Genetic Resources, the original data of genetic resources involving clinical patients cannot be disclosed without approval. However, re-analysis of the whole-exome sequencing data can be made available upon reasonable request, and interested parties can contact Prof. Yihua He (Email: heyihuaecho@hotmail.com) at the Department of Echocardiography in Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

INFORMED CONSENT

The present research secured approval from the Beijing Anzhen Hospital's Ethics Committee, affiliated with Capital Medical University. The parents have provided informed written consent for publication.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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