Hypoplastic Right Ventricle Caused by a Novel *SMAD2* Variant Identified in the First Trimester: A Case Report

Yan-Dong Yang[1,2], Dong-Zhi Li[3]*

[1]Department of Ultrasound, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China, [2]Biomedical Innovation Center, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, China, [3]Department of Prenatal Diagnosis, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China

Dear Editor,

Hypoplastic right ventricle (HRV), also referred as pulmonary atresia with intact ventricular septum, is extremely rare, involving a significant obstruction of the right ventricular outflow tract and interfering with adequate development of the right ventricle.[1] Fetal cardiac anomalies are typically detected by second-trimester anomaly ultrasound performed between 18 and 22 weeks. We here report a fetal case of HRV caused by a *SMAD2* variant, which was identified by ultrasound in the first trimester.

A 32-year-old primigravida woman had a normal genome-wide cell-free DNA aneuploidy screening at 9 weeks' gestation. At 12 + 4 weeks, the routine first-trimester ultrasound revealed a normal nuchal translucency measurement of 1.5 mm, but a single ventricle of the heart [Figure 1a and b]. Chorionic villus sampling was performed, and rapid exome sequencing was used for genetic testing. The Illumina HiSeq2500 Analyzer platform (Illumina, San Diego) was used to obtain a mean sequencing coverage of more than 90×, with more than 98% of the target bases having at least ×20 coverage. At 14 + 4 weeks, a follow-up ultrasound achieved the diagnosis of HRV [Figure 1c-e]. The exome sequencing detected a *de novo* heterozygous variant c.388C>T, p.(Arg130Ter) in the *SMAD2* gene which was not identified in both parents [Figure 1f]. Loss-of-function *SMAD2* variants cause a wide spectrum of autosomal-dominant aortic and arterial aneurysmal disease, complex congenital heart diseases (CHD), and neurodevelopmental disability.[2]

After genetic counseling, the couple opted for pregnancy termination at 15 weeks. Fetal autopsy confirmed the HRV with pulmonary and tricuspid atresia, but with intact ventricular septum. The aortic root, ascending aorta, aortic arch, descending aorta, and the abdominal part of the aorta seemed normal at this fetal stage.

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The involved CHD types associated with *SMAD2* variants include cardiac septal defects, double-outlet right ventricle, unbalanced complete atrioventricular canal, valvular anomalies, dextroposition of the great arteries, anomalous pulmonary venous return, and superior vena cava to the left atrium defect.[3] We first report HRV as the cardiovascular phenotype associated with *SMAD2* pathogenic variants.

In our case, the left ventricle supplies both systemic and pulmonary circulations, the latter reflected by retrograde flow through the ductus arteriosus. We determined the diagnosis of HRV at 14 + 4 weeks' gestation, but it behaved as a univentricular heart on the 12-week ultrasound. In a study of 7167 low-risk cases, Bottelli *et al*.[4] reported that 7/12 fetuses of major CHDs were detected on first-trimester ultrasound (crown-rump length, 50.1–84.0 mm), corresponding to a sensitivity of 58.3%. In a systematic review and meta-analysis, Karim *et al*.[5] reported that first-trimester ultrasound had a pooled sensitivity of 55.80% in 1445 major cardiac anomalies in the nonhigh-risk population, with a sensitivity of 91.7% for hypoplastic right heart syndrome. Therefore, as evidenced by our report, first-trimester ultrasound allows the identification of major cardiac pathology, which gives the time for further genetic investigation and pregnancy management.

Notably, our case had a negative genome-wide cell-free DNA screen before undergoing first-trimester ultrasound. This means that the anomalous fetus had a higher risk for single gene disorders than for chromosomal abnormalities. As a result, we used exome sequencing as the first-tier genetic test rather than microarray. The early use of cell-free DNA screening

Address for correspondence: Dr. Dong-Zhi Li, Department of Prenatal Diagnosis, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, Guangdong, China.
E-mail: drlidongzhi2014@sina.com

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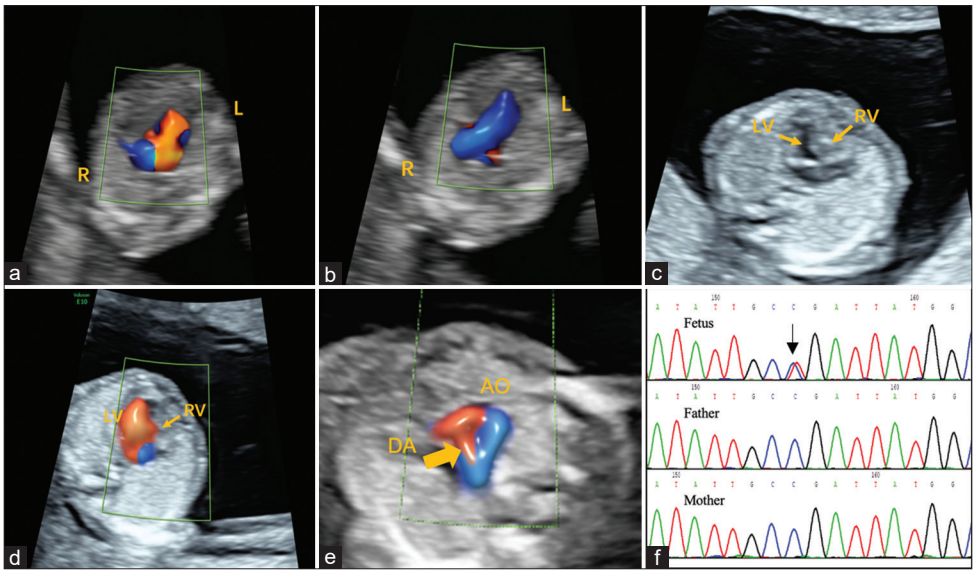

Figure 1: A fetal case of hypoplastic right ventricle caused by a *SMAD2* variant. (a) One set of blood flow through atrioventricular valve in 4-chamber view at 12 + 4 weeks; (b) Only left ventricular outflow tract showed thick blood flow, and the right ventricular outflow tract did not show color Doppler signal at 12 + 4 weeks; (c) A small right ventricular chamber in 4-chamber view at 14 + 4 weeks; (d) Blood flow filling of the left ventricle, but not the right ventricle in 4-chamber view at 14 + 4 weeks; (e) Reverse orientation of the ductus arteriosus in 3-vessel trachea view at 14 + 4 weeks; (f) Schematic diagrams of the variant *SMAD2*: c.388C>T. AO: Aorta, DA: Ductus arteriosus, LV: Left ventricle, RV: Right ventricle

may have an impact on genetic testing strategy in the setting of fetal anomalies.

Ethics statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments.The authors certify that they have obtained all appropriate patient consent form. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Druschel CM, Caggana M, *et al.* Rare copy number variants in a population-based investigation of hypoplastic right heart syndrome. Birth Defects Res 2017;109:8-15.
2. Granadillo JL, Chung WK, Hecht L, Corsten-Janssen N, Wegner D, Nij Bijvank SW, *et al.* Variable cardiovascular phenotypes associated with SMAD2 pathogenic variants. Hum Mutat 2018;39:1875-84.
3. Cannaerts E, Kempers M, Maugeri A, Marcelis C, Gardeitchik T, Richer J, *et al.* Novel pathogenic SMAD2 variants in five families with arterial aneurysm and dissection: Further delineation of the phenotype. J Med Genet 2019;56:220-7.
4. Bottelli L, Franzè V, Tuo G, Buffelli F, Paladini D. Prenatal detection of congenital heart disease at 12-13 gestational weeks: Detailed analysis of false-negative cases. Ultrasound Obstet Gynecol 2023;61:577-86.
5. Karim JN, Bradburn E, Roberts N, Papageorghiou AT, ACCEPTS Study. First-trimester ultrasound detection of fetal heart anomalies: Systematic review and meta-analysis. Ultrasound Obstet Gynecol 2022;59:11-25.