Prenatal diagnosis of feta noncompaction cardiomyopathy with de novo CALM2 mutation

wen zhang[1], xiaohui dai[2], Hanmin Liu[1], Lei Li[1], Shu Zhou[1], Qi Zhu[2], and Jiao Chen[1]

[1]Affiliation not available
[2]West China Second University Hospital,West China Medcical School,Sichuan Univeisity

August 9, 2021

Abstract

We report what apprears to be the first case of fetal noncompaction cardiomyopathy in both ventricles accompanied by a mutation in the calmodulin gene (CALM2): A 25-year-old woman was referred to our hospital at 25+1 weeks of gestation for evaluation of fetal defects. A postnatal echocardiography showed biventricular noncompaction cardiomyopathy. After terminated the pregnancy, fetal noncompaction cardiomyopathy was comfirmed by autopsy and histopathologic examination. And the whole-exome sequencing of genomic DNA demonstrated a de novo heterozygous mutation (c.389A>G;p.D130G) in CALM2, whereas the parents were normal. In this case report, we highlight the gene mutation in noncompaction cardiomyopathy.

Prenatal diagnosis of feta noncompaction cardiomyopathy with de novo *CALM* 2 mutation: first description

Wen Zhang[1,2]#, Xiaohui Dai[1,2]#, Hanmin Liu[2,3], Lei Li[2,4], Shu Zhou[2,5], Qi Zhu[1,2] and Jiao Chen[1,2]*

1. Department of Ultrasonic Medicine, West China Second University Hospital of Sichuan University, Chengdu, Sichuan 610041, China

2. Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan 610041, China

3. Department of Pediatrics, West China Second University Hospital of Sichuan University, Chengdu, Sichuan 610041, China

4. Department of Pathology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan 610041, China

5. Department of Obstetrics, West China Second University Hospital of Sichuan University, Chengdu, Sichuan 610041, China

# These authors contributed equally to this work.

*Correspondence author, Tel/Fax: +86 28 85503744, Email:jiaochen2000@163.com

Abstract

We report what apprears to be the first case of fetal noncompaction cardiomyopathy in both ventricles accompanied by a mutation in the calmodulin gene (*CALM2*): A 25-year-old woman was referred to our hospital at 25^{+1} weeks of gestation for evaluation of fetal defects. A postnatal echocardiography showed biventricular noncompaction cardiomyopathy. After terminated the pregnancy, fetal noncompaction cardiomyopathy was comfirmed by autopsy and histopathologic examination. And the whole-exome sequencing of genomic DNA demonstrated a de novo heterozygous mutation (c.389A>G;p.D130G) in *CALM2* , whereas the parents were normal. In this case report, we highlight the gene mutation in noncompaction cardiomyopathy.

Key words: Prenatal, Noncompaction cardiomyopathy, *CALM2*

1 INTRODUCTION

Noncompaction cardiomyopathy is a rare disorder that frequently manifests as monogenic diseases, especially neuromuscular disorders and chromosomal defects, and was first reported on autopsy in 1969 [1]. The incidence of noncompaction cardiomyopathy in the general population ranges from 0.05% to 0.25%, whereas the incidence in children may reach 9.2% [2]. Noncompaction cardiomyopathy is characterized by increased numbers of prominent trabeculations and deep intertrabecular spaces. With the development of medical imaging techniques, the detection rate of noncompaction cardiomyopathy has increased, and the disorder may even be recognized as early as the fetal period. We herein present the first case of fetal noncompaction cardiomyopathy in both ventricles accompanied by a mutation in the calmodulin gene (*CALM2*) at 25^{+1} weeks of gestation.

2 CASE PRESENTATION

A 25-year-old woman (gravida 1, para 0) was referred to our hospital at 25^{+1} weeks of gestation for evaluation of fetal defects. The patient was allergic to penicillin. Both parents were healthy, and there was no family history of birth defects or exposure to any specific teratogenic agents. A postnatal two-dimensional ultrasonographic investigation (3.0–5.0 MHz) (Voluson E10; GE Healthcare, Chicago, IL, USA) showed biventricular noncompaction cardiomyopathy, slight pericardial effusion, and bradycardia (106 bpm). The ratio of noncompacted to compacted myocardium was about 3 in the left ventricle and about 2 in the right ventricle (Figure 1A). Color Doppler revealed blood perfusion to the intertrabecular recesses (Figure 1B). The cardiovascular profile score was 9. Two weeks later, the fetal heart showed no significant improvement.

The couple decided to terminate the pregnancy by inducing labor with ethacridine lactate (Rivanol®; Fengchen Group Co., Ltd., Qingdao, China). The woman vaginally delivered a stillborn child 2 days later. Genomic DNA was extracted from the muscle of the fetus to perform whole-exome sequencing. The result demonstrated a de novo heterozygous mutation (c.389A>G;p.D130G) in *CALM2*(Figure 2), whereas the sequencing results of the parents were normal. At autopsy, the biventricular wall contained increased numbers of prominent trabeculae and deep intratrabecular recesses (Figure 3). Histopathologic examination confirmed fetal noncompaction cardiomyopathy (Figure 4).

3 DISCUSSION

Noncompaction is a rare cardiomyopathy with various genotypic and phenotypic manifestations. It is categorized as a primary genetic cardiomyopathy by the American Heart Association and as an unclassified cardiomyopathy by the European Society of Cardiology [3]. According to a study by Stöllberger et al. [4], the diagnostic criteria for noncompaction cardiomyopathy by echocardiography in pregnancy are as follows: in the end-diastolic stage, at least four trabeculations protruding apically to the papillary muscle of the left ventricle visible in one imaging plane; a two-layered structure with epicardial compacted and endocardial noncompacted layers and a noncompaction:compaction ratio of [?]2; and in color Doppler, intraventricular blood perfusing the intertrabecular spaces.

The disorder can be familial or sporadic and may be isolated or accompanied by other cardiac diseases. The etiology of noncompaction cardiomyopathy is complex and still unclear. Although at least 40 gene mutations are reportedly associated with noncompaction cardiomyopathy (e.g., *MYH7* and *PRDM16* [5-7]), few case reports of*CALM2* mutation in fetal noncompaction cardiomyopathy have been published. *CALM2* is a Ca^{2+}-signaling gene that encodes for calmodulin and is associated with long QT syndrome (LQTS) phenotypes. In three reported cases, *CALM2* mutation might have contributed to LQTS accompanied by cardiomyopathy (one case of hypertrophic cardiomyopathy and two cases of left ventricular noncompaction cardiomyopathy), indicating the variant positions in *CALM2*(c.396T>G;p.D132E, c.394G>C;p.D132H, and c395A>G;p.D132G) [8-10]. Our case is the first report of a novel *CALM2* mutation (c.389A>G;p.D130G) in fetal noncompaction cardiomyopathy accompanied by bradycardia detected with whole-exome sequencing. Therefore, we highly suspect that *CALM2* is associated with noncompaction cardiomyopathy, particularly in

fetuses with bradycardia. Sinus bradycardia might be a manifestation of LQTS in the fetus [11]. Additionally, with reference to previously reported findings [8-10], we highly suspect that *CALM2* variants might be associated with cardiomyopathy and arrhythmia, especially LQTS. Nonetheless, further research is required to confirm this hypothesis and elucidate the pathogenic mechanism.

CONCLUSION

With the improvement of the ultrasonic resolution, the detection rate of prenatal noncompaction cardiomyopathy was increased, and it is useful to recognize noncompaction cardiomyopathy as early as possible. Meanwhile, this case highlights the importance of genetic testing in the follow-up of prenatal disease, which will provide human databases with more information regarding gene defects, mutation sites, and various phenotypes.

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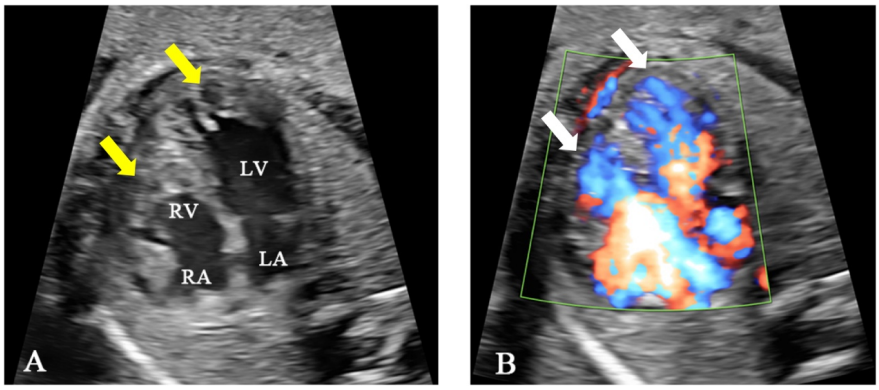

Figure 1. Fetal echocardiography at 25^{+1}weeks of gestation. (A) The two-dimensional ultrasound image shows increased numbers of prominent trabeculations and deep intertrabecular spaces in both ventricles (yellow arrow), especially at the left ventricular apex, with a noncompaction:compaction ratio of 3:1. (B) The color Doppler ultrasound image shows blood perfusing the intertrabecular recesses (white arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

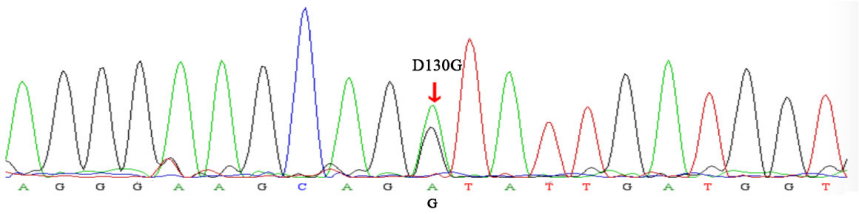

Figure 2. Sanger sequencing electropherogram. The variant (c.389A>G) demonstrated the replacement of a conserved aspartic acid residue at position 130 with glycine (p.D130G) in the*CALM2* gene (red arrow).

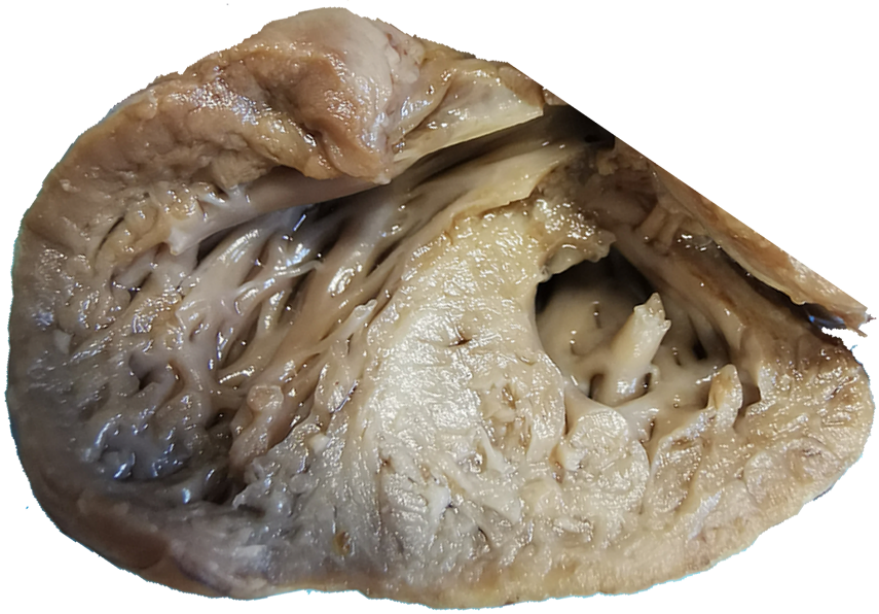

Figure 3. Dissected autopsy specimen. The specimen showed excessive trabeculae and deep intertrabecular recesses within the biventricular myocardium.

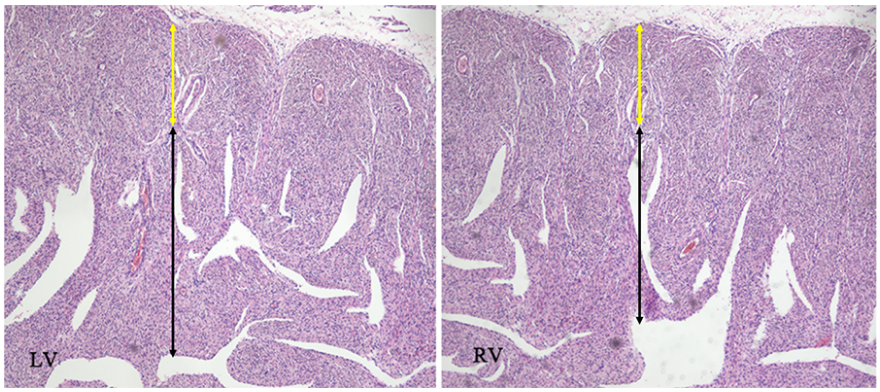

Figure 4. Histopathologic appearance of the myocardium at low magnification (hematoxylin and eosin, ×40). The images were compatible with noncompaction cardiomyopathy, with cardiomyocyte disarray in the noncompacted layer (black arrow) in opposition to regular cardiomyocytes in the compacted layer (yellow arrow).