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Case Report

TNNC1 Gene Mutation in Ebstein's Anomaly and Left Ventricular Hypertrabeculation: A Case Report of a New Causative Mutation?

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Abstract

Background: Ebstein's anomaly (EA) is a rare congenital heart defect characterized by failure of tricuspid valve delamination during embryogenesis. Left ventricular (LV) hypertrabeculation results from incomplete myocardial compaction during fetal development. EA is associated with LV hypertrabeculation in 0.14% of cases, and EA is the most common congenital heart disease in LV hypertrabeculation (up to 29%), suggesting a shared embryogenetic pathway. **Case Report:** We describe a female patient prenatally diagnosed with EA and a large ventricular septal defect. Postnatal echocardiography confirmed EA with moderate regurgitation and revealed previously unnoticed left ventricular excessive trabeculations. Whole exome sequencing revealed a heterozygous never-described variant of unknown significance in the *TNNC1* gene. **Discussion**: The genetic link between EA and LV hypertrabeculation remains unclear, though variants in sarcomeric or cytoskeletal genes like *MYH7*, *TPM1*, and *NKX2.5*—essential for cardiac development—have been implicated. A developmental hypothesis suggests that aberrant contraction during endocardial-to-mesenchymal and epicardial-to-mesenchymal transformation (5th–8th gestational weeks) may affect valve delamination and ventricular compaction via parallel signaling pathways. *TNNC1* encodes troponin C1, a subunit of the troponin complex involved in muscle contraction. Its mutations are known to alter calcium sensitivity and impair cardiac contractility. **Conclusions:** EA and LV hypertrabeculation patients diagnosed in infancy have a greater risk of negative outcomes. Early, especially prenatal, diagnosis is crucial. Genetic analysis can provide fundamental insight into cardiac development. This new and rare variant of *TNNC1* gene supports the hypothesis that early cardiomyocytes dysfunction disrupts both valve delamination and left ventricular compaction and that the two diseases share a common genetic pathway related to cardiomyocyte contraction.

Keywords: left ventricular noncompaction; Ebstein's anomaly; genetic

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1. Introduction

Ebstein's anomaly (EA), first described by Dr William Ebstein in 1866, is a rare congenital heart defect that accounts for 0.3–0.5% of congenital heart defects. The prevalence at birth is approximately 1 in 200,000 live births [1–4]. The malformation consists of apical displacement of the tricuspid valve, resulting in regurgitation and enlargement of the right heart chambers. The specific EA features include attachment of the posterior and septal leaflets to the ventricular septum, apical displacement of the valve, redundant and fenestrated anterior leaflets, atrialization of the part of the right ventricle above the valve, and dilatation of the right ventricle and atrioventricular junction [2]. The pathogenesis is consistent with failure of delamination during embryonic development [2].

Left ventricular (LV) hypertrabeculation is morphologically characterized by prominent myocardial trabeculations and deep intertrabecular recesses, which give the left ventricle a spongy appearance. LV excessive trabeculations is thought to result from failure of the compaction process between the 5th and 8th weeks of embryonic development of the human myocardium [5]. EA can be associated with LV hypertrabeculation with an approximate prevalence of 0.14% [6], and EA is the most common congenital heart disease in LV hypertrabeculation [7]. These findings suggest that there are genetic factors that predispose patients to multiple cardiovascular manifestations [3].

The genetic correlation between EA and LV hypertrabeculation is still not fully understood. The first variant was described by Budde et al., who analyzed the genome of a German family (11 cases of LV hypertrabeculation previously called LV noncompaction, of whom 4 had EA). He described a mutation in the *MYH7* gene (*160760, 14q11.2, AD) encoding the β-myosin heavy chain [8]. After his first description, other significant causative genes, such as *NKX2.5* (*600584, 5q35.1, AD), *GATA4* (*600576, 8p23.1, AD), *TAZ* (*300394, Xq28, XLR), and *TBX20* (*606061, 7p14.2, inheritance not specified) were identified in several cases. Many of these genetic variants affect sarcomeric or cytoskeletal proteins that are crucial for cardiac development and function [9,10]. Other studies have reported mutations in nonsarcomeric proteins such as *SCN5A* (*600163, 3p22.2, AD), *NONO* (*300084, Xq13.1, XL), and *KLHL26* (NM_001345981.1, 19p13.11, AD) in EA/LV hypertrabeculation [11–13]. The diversity of affected loci emphasizes the genetic complexity of tricuspid valve and ventricular development. Cardiogenesis begins with the formation of a heart tube composed of several layers: the outer epicardium, myocardial cells, cardiac jelly, and the endocardial layer. During development, the heart undergoes rightward looping, while the inner layer cells proliferate and differentiate into endocardial cushions, which will later form the cardiac valves. Meanwhile, the myocytes and endocardial cells in the ventricle proliferate to form deep trabeculations. These processes are regulated by common transcription factors (such as *GATA4* and *TBX20*) and signaling pathways (including TGF-β/Smad, Wnt/β-catenin, and Notch), which govern both the formation of the tricuspid valve and the compaction of the LV [2,3].

We report a case of fetal diagnosis of Ebstein's anomaly with a large muscular ventricular septal defect associated with LV hypertrabeculation, in which a new gene variant in a contractility protein was discovered.

2. Case Report

We describe a case of a firstborn baby conceived via intrauterine insemination with a male donor. At 18 + 3 gestational ages, fetal echocardiography revealed Ebstein's anomaly with mild regurgitation associated with a large muscular ventricular septal defect. Both karyotype and array-CGH analyses were normal. The fetal heart remained compensated throughout the pregnancy.

At birth, the baby had normal adaptation (Apgar score of 9 at 1′ and 5′, weight of 3240 g, length of 52 cm, head circumference of 32.5 cm). The first cardiological evaluation confirmed the prenatal diagnosis but revealed increased trabeculation in the LV (Figure 1), a detail that was not clearly identified during pregnancy but was possibly recognizable on a second review of fetal ultrasound images. Abdominal ultrasound, brain ultrasound, and ophthalmological examination were performed, all of which yielded normal results. The baby was discharged on captopril and diuretics due to pulmonary overflow.

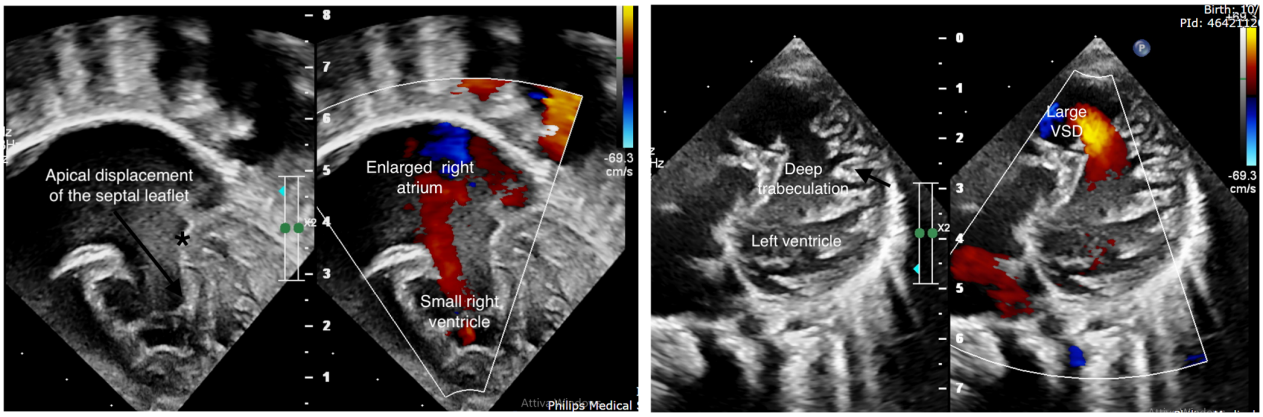

Figure 1. Ebstein's anomaly and left ventricular hypertrabeculation. On the left side, Ebstein's anomaly with displacement of the septal leaflet of the tricuspid valve (black arrow), and the asterisk shows the "normal" insertion of the septal leaflet. On the right side, the image shows the deep trabeculations of the left ventricle lateral wall. From this view, one can also see the large apical ventricular septal defect.

A neonatal cardiac MRI confirmed Ebstein's anomaly with apically and anteriorly rotated septal and posterior leaflets, resulting in atrialization of the basal portions of the right ventricle, a 17 mm ventricular septal defect, and hypertrabeculation of the medium-apical LV, meeting the criteria for noncompaction.

At 1 month of age, a pulmonary banding procedure was needed.

During cardiological follow-up (approximately 17 months), the patient remained in good general condition, and growth was consistent but stable at the lower percentiles. Arrhythmias were never recorded.

Currently, periodic cardiological and cardiosurgical evaluations are ongoing to determine the next therapeutic steps.

Given the association between EA and LV hypertrabeculation, a whole exome analysis was performed. With next-generation sequencing, it is now possible to sequence large amounts of DNA, such as all the regions of an individual's DNA that provide instructions for making proteins (whole exome analysis). These regions, called exons, are estimated to make up about 1 percent of a person's genome.

Patient's analysis revealed a variant of unknown significance, p.Glu66Lys, in the *TNNC1* gene (*191040) that was heterozygous and of nonmaternal origin (Chr3 (GrCh38):g.524521128 (NM_003280.3: c.196G > A) in the exon of the gene *TNNC1*). It describes a substitution of glutamic acid for lysine at position 66 in cTnC. This variant was classified as of unknown significance according to ACMG guideline. The mutation is rare (gnomAD v4.0 MAF0) and it has never been described in the literature, but it is reported in the ClinVar database (ClinVar ID 1024458).

3. Discussion

This case highlights the complex interplay between EA and LV hypertrabeculation, presenting a unique challenge for diagnosis and management.

Patients born with both EA and LV hypertrabeculation diagnosed in infancy have a greater risk of negative outcomes such as heart failure and sudden cardiac death [14,15], along with anatomical variations that pose additional surgical challenges. As in our case, common comorbidities in EA/LV hypertrabeculation patients included septal defects (ASD or VSD) that could complicate the treatment and surgical approach [3,16].

The fetal diagnosis of EA plays a crucial role in predicting outcomes and guiding management, including close monitoring in high-risk pregnancies. This facilitates appropriate parental counseling and proactive planning for potential complications during the neonatal period. Prognostic factors identified in utero include the size of the fossa ovalis, the degree of right atrial dilation, and the presence of tricuspid regurgitation or right ventricular outflow tract obstruction [17,18].

However, the diagnosis of noncompaction cardiomyopathy in fetuses is challenging, and there is no universally accepted standard. According to a study by Stöllberger et al. [19], the echocardiographic criteria for diagnosing fetal ventricular noncompaction include at least four trabeculations protruding apically to the papillary muscle of the LV visible in one imaging plane in end-diastole, a two-layered structure with epicardial compacted (C) and endocardial noncompacted (NC) layers and an N/C ratio of $\geq$2, and perfusion of intraventricular blood into the intertrabecular spaces in color Doppler imaging. As highlighted in our case, fetal diagnosis of LV hypertrabeculation can be missed because of the unique characteristics of the fetal myocardium: the N/C ratio is naturally higher than that in children or adults and approaches 2. This calls for careful attention and close monitoring [20].

EA and LV hypertrabeculation are poorly understood in terms of genetic pathogenesis. The overlap of developmental pathways in the formation of the tricuspid valve and compact myocardium suggests a common morphogenetic origin for both conditions. Both defects are associated with dysfunctions in endocardial-to-mesenchymal transformation and epicardial-to-mesenchymal transition processes during embryogenesis, which are crucial for valve and myocardial structure formation [3,21,22]. In the case of EA, a defect in the delamination of the tricuspid valve causes apical displacement, whereas in LV hypertrabeculation, there is failure of myocardial compaction. Both defects are probably linked to dysfunctions in contraction mechanisms and the maintenance of cardiac structure. Although the clinical manifestations are different, the underlying mechanisms influencing heart morphogenesis and contractile function may overlap [3].

Recent genetic studies suggest that variants in sarcomeric and cytoskeletal genes may be at the root of the pathogenesis of both EA and LV hypertrabeculation. The *MYH7* gene, which encodes the β-myosin heavy chain, is particularly associated with EA, LV hypertrabeculation, and their combination [23]. This variant likely disrupts salt bridge formation, destabilizes the myosin head and impairs myocardial function [5,8].

Our case revealed a new variant in the *TNNC1* gene that was actually classified as being of unknown significance. The *TNNC1* is a sarcomeric gene, it consists of six exons and five introns and encodes the protein troponin C1 (cTnC), one of the three essential subunits of the troponin complex involved in muscle contraction, which is predominantly expressed in cardiomyocytes and skeletal muscular cells [24]. The cTNC serves as a calcium (Ca^{2+}) sensor within the myofilament and plays a key role in regulating cardiac contraction. Its tertiary structure consists of two globular domains, the C-domain and N-domain, connected by a flexible linker. The C-domain binds divalent ions (Ca^{2+} and/or Mg^{2+}) at two helix-loop-helix motifs, which are critical for the structural and functional regulation

of the sarcomere. The N-domain contains a nonfunctional site and a regulatory site that triggers contraction when calcium binds during systole [25].

Mutations in *TNNC1* alter the conformational change of actin (the thin filament of the myocyte) and its transition from a blocked to a closed and then an open state, through a modification of the calcium sensitivity of the cardiac muscle, ultimately impairing the ability of the heart to contract efficiently. However, the precise mechanism by which the many variants influence the calcium binding is still unknown.

Missense mutations in cTnC have been linked to both dilated cardiomyopathy [26] with decrease sensibility to Ca^{2+}, and hypertrophic cardiomyopathies with increased affinity to Ca^{2+}, with or without LV hypertrabeculation [27]. Although rare compared to other sarcomeric mutations in cardiomyopathy, *TNNC1*-associated cardiomyopathies have shown a severe course with earlier onset of the disease and poorer prognosis [28].

Thin contractile filaments, such as cTnC, show a high degree of sequence conservation and have a limited number of described pathogenic mutations, likely related to severe outcomes due to genetic variants not being transmitted to subsequent generations.

However, more than 100 variants of *TNNC1* have been described in the literature, although not all have been studied with functional analysis. In two separate papers, Tadros et al. and Retinoso et al. presented many pathogenic variants supporting the identification of *TNNC1* as a gene associated with cardiomyopathy. Thanks to the use of cryo-electron microscopy they were able to localize each of the functionally studied variants. They found that most of the cardiomyopathy-related variants are located in the alpha-helical regions and in the linkers between NH2 and COOH-terminal regions Among the functionally studied variants that significantly affect the Ca^{2+} binding affinity, we highlight D62N, M81I, E94A, and R102C which are related to LV hypertrabeculation [25,28].

Furthermore, Wu et al. provided evidence of a regulatory role of the cTnC in the nuclear activity, leading to the possibility that thin filaments could also affect nuclear Ca^{2+}-dependent signaling [29].

The major limitation of the study is that our variant currently lacks definitive evidence of pathogenicity, and it requires further characterization and study. However, the main purpose of our article is to describe a novel and rare variant (not previously reported) in a gene known to be associated with cardiomyopathy. Finding a mutation in a contractile protein supports the compelling hypothesis proposed by Thareja et al. [3], which suggests that early cardiomyocyte dysfunction may disrupt both valve delamination and left ventricular compaction, and that these two conditions may share a common genetic pathway related to cardiomyocyte contraction.

Rare variants can contribute to a better understanding of the molecular and cellular mechanisms underlying heart development.

4. Conclusions

The management of patients with a combination of EA and LV hypertrabeculation is extremely complex due to the severity and interaction of these two rare congenital conditions. Early diagnosis, particularly during the fetal period, is crucial for proper patient management, as it allows for closer monitoring and targeted therapeutic planning.

The pathogenesis of both conditions is still under investigation, but it is currently hypothesized that they share a common morphogenesis and a potential shared genetic origin, mostly related to abnormalities in contractility proteins.

A comprehensive, multidisciplinary approach involving gynecologists, pediatric cardiologists, surgeons, and geneticists is crucial to optimize care and effectively address the genetic and structural complexities associated with these conditions.

Author Contributions: S.M. and A.L. analyzed and interpreted the patient data regarding the diagnosis and the clinical follow-up. G.P. and C.C. collected the patient data and images and contributed to the writing of the manuscript. E.C. took care of the genetic analysis and interpretation. V.C. and G.V.Z. contributed to the pediatric care of the patient and contributed to elaborate the manuscript. I.R. made a major contribution to the preparation of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

C	Epicardial compacted layer
Ca^{2+}	Calcium
cTnC	Troponin C1
EA	Ebstein's anomaly
LV	Left ventricle
LVNC	Left ventricular noncompaction
NC	Endocardial noncompacted layer

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