JACC: CASE REPORTS VOL. 14, 2023

CASE REPORT

ADVANCED

CLINICAL CASE

A Genetic Etiology Identified for a Form of Familial Polyvalvular Dysplasia

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ABSTRACT

This case presents a family with multiple individuals diagnosed with congenital heart disease (CHD) secondary to a novel TAK1-binding protein 2 pathogenic variant. This case advocates the use of cardiovascular genetic testing in individuals with CHD as part of a comprehensive approach to managing infants with CHD. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2023;14:101837) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An infant born at 39 weeks of gestation to a 32-year-old gravida 3 para 1 mother (who herself has a history of congenital heart disease [CHD]) was prenatally diagnosed with polyvalvular dysplasia involving the tricuspid, mitral, and pulmonary valves, as well as an atrial septal defect. The pregnancy was complicated by a maternal history of partial atrioventricular canal defect (primum atrial septal defect and cleft mitral valve) status postrepair and a dysplastic aortic valve. Postnatal echocardiography for the infant demonstrated similar findings to prenatal echocardiogram with significant polyvalvular dysplasia: coplanar atrioventricular valves with a redundant, thickened tricuspid valve that had moderate insufficiency; a bicuspid, thickened pulmonary valve with mild prolapse and moderate insufficiency; a dysplastic, thickened mitral valve with reduced leaflet excursion; and mild-to-moderate regurgitation through a probable cleft with leaflet prolapse. There was also an atrial septal communication, patent ductus arteriosus, and moderate dilation of the main pulmonary artery. The physical examination was significant for a systolic ejection click at the left upper sternal border but was otherwise normal.

LEARNING OBJECTIVES

- To report a novel pathogenic *TAB2* variant in a case of polyvalvular dysplasia.
- To support the role of cardiogenetic involvement in patients with congenital heart defects.
- To justify the use of cardiac gene panel testing in patients with suspected isolated CHD.
- To illustrate the importance of comprehensive familial evaluations.

INVESTIGATIONS

Medical genetics was consulted given the proband's cardiac findings and maternal history. A detailed family history was obtained (**Figure 1**), and genetic testing via chromosomal microarray was pursued.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 5, 2023; accepted March 27, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.101837

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CHD = congenital heart disease

TAB2 = TAK1-binding protein 2

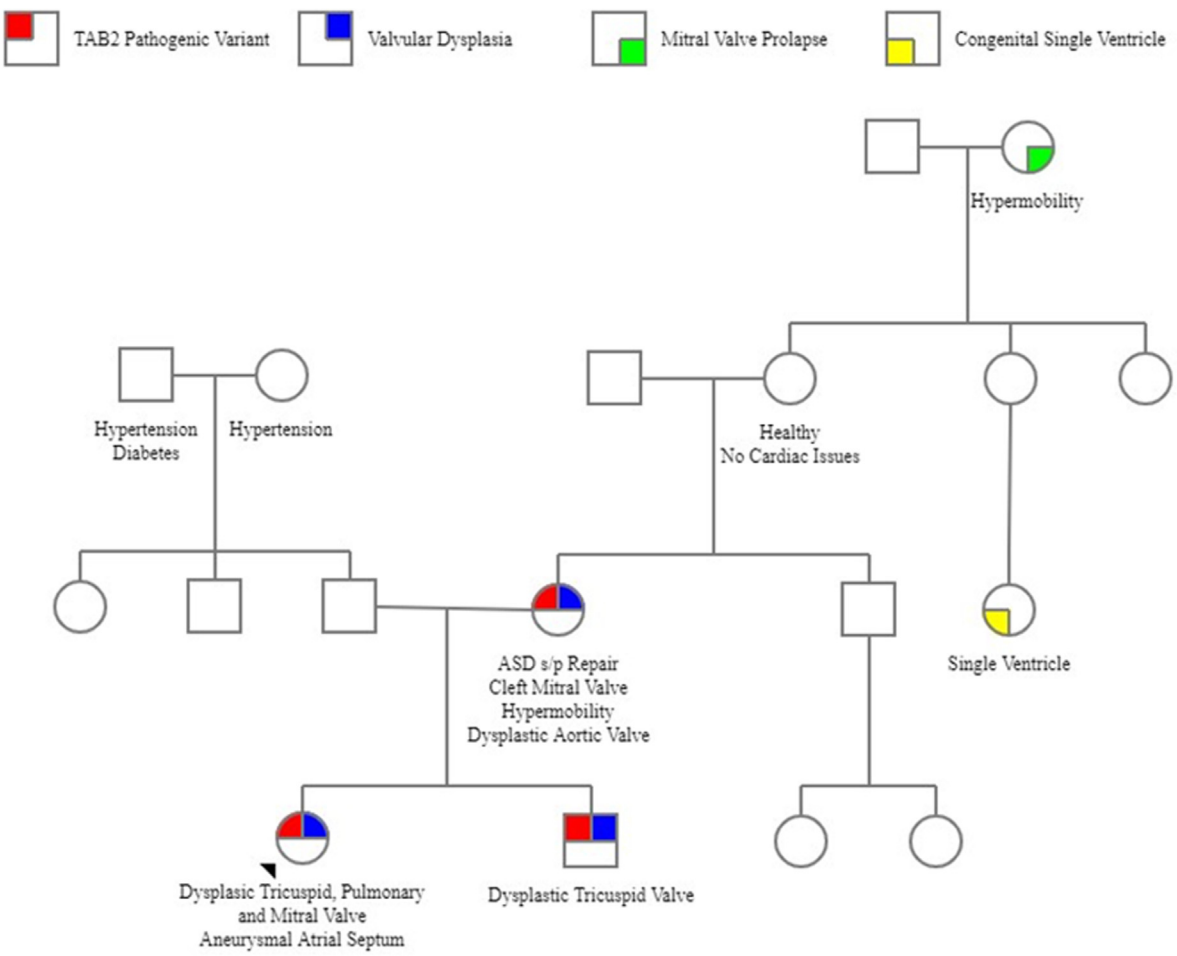
Microarray testing revealed a normal female chromosome complement of 46, XX. After the normal chromosomal microarray, genetic testing through a CHD gene panel was obtained, evaluating 55 genes with known associations with CHD. Testing identified a loss-of-function variant in the TAK1-binding protein 2 (*TAB2*) gene at c.964C>T (p.Arg322*), a pathogenic variant associated with polyvalvular dysplasia, and *TAB2*-related syndrome. *TAB2*-related syndrome (OMIM 614980) is characterized by cardiac valve defects, distinct facial features (broad forehead, low set ears, up/down slanting palpebral fissures, ptosis), short stature and connective tissue abnormalities.

Medical Genetics staff reviewed the gene panel results with the family. The family elected to pursue family variant testing for both the mother and brother. Both individuals tested positive for the same familial variant in the *TAGB2* gene. Although the brother had a normal physical examination, he was referred for echocardiogram, which revealed that he also had a dysplastic mitral valve, mild anterior leaflet prolapse, and anterior leaflet cleft, leading to mild mitral regurgitation. He also had mild tricuspid valve dysplasia with mild insufficiency.

DISCUSSION

TAB2 is a gene located on chromosome 6q25.1 that plays a key role in fetal cardiac development.[1] Loss-of-function variants and deletions in *TAB2* have been associated with congenital heart defects, short stature, hypermobility, and facial features suggestive

FIGURE 1 Pedigree



Pedigree of the proband's family illustrating the autosomal-dominant inheritance and the variable expressivity of the familial *TAB2* pathogenic variant. ASD = atrial septal defect; *TAB2* = TAK1-binding protein 2.

of Noonan syndrome.[2] Cardiac implications associated with *TAB2* gene loss-of-function variants are impacted by variable expressivity as demonstrated by the cardiac phenotypes observed in this family. Conversely, gain of function variants in *TAB2* are reported in patients with frontometaphyseal dysplasia.[1] There have been limited cases of patients with pathogenic variants associated with *TAB2*-related polyvalvular dysplasia documented in the literature.

Congenital heart defects are the most common congenital malformation in newborns, and a leading cause of death in children younger than 1 year of age. The prevalence of CHD in the general population worldwide is approximately 1%, amounting to approximately 40,000 new CHD-affected babies annually in the United States.[3] The etiology of CHD is thought to be multifactorial, with specific genetic etiologies being poorly understood. Growing evidence suggests that many forms of CHD have some genetic basis, however, this is influenced by variable expressivity and incomplete penetrance. Syndromic CHD (CHD with extracardiac involvement) has a well-established genetic basis (eg, structural chromosome, monogenic and copy number variants) but only encompasses up to 30% of CHD cases.[4] Recent data estimates 10% of both syndromic and nonsyndromic CHD cases may be attributed to de novo variants.[4] Although genetic testing is becoming increasingly available, standardized guidelines for pursuing cardiovascular genetic testing lags behind clinical practice patterns.

Genetic testing in individuals with CHD can be a powerful means of identifying genetic mutations responsible for an individual's CHD, informing counseling and education for families, as well as advancing future diagnostic and therapeutic interventions. The American Heart Association (AHA) cites cytogenetic and molecular genetic testing as the 2 most common categories of genetic testing in cardiology. Cytogenetic testing yields information at the chromosomal level using chromosomal microarray or karyotype analysis, whereas molecular testing provides information at the nucleotide level via gene panels with whole exome or genome sequencing. The AHA recommends chromosomal microarray, karyotype, or gene panel testing for patients suspected of having syndromic CHD. The AHA also acknowledges the utility of gene panel testing and exome or genome sequencing for selected patients with isolated CHD.[4]

Along these lines, the AHA recommends 4 main reasons to pursue genetic testing in individuals with CHD: 1) potential involvement of other organ systems; 2) prognostic data for a patient's long-term outcome; 3) reproductive risks for the family; and 4) consideration for broader familial testing.[4-6] In our case, without the proband's findings, it is unlikely genetic testing would have been pursued in the proband's mother or brother, furthermore, the brother would have experienced delay in cardiac evaluation and may have not received a comprehensive genetic or cardiac work-up and appropriate follow-up.

CONCLUSIONS

This case presents a family diagnosed with congenital heart defects secondary to a novel *TAB2* gene loss of function variant. This case advocates the importance of a comprehensive multidisciplinary approach to managing infants with isolated CHD. Specifically, early involvement of both cardiology and medical genetics is vital to assist in guiding genetic testing individualized to the needs of the patient and their family.

ACKNOWLEDGMENTS The authors would like to express our sincere gratitude to the family for their agreement to participate in this report.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS **cardiogenetics, congenital heart defects, genetic counseling, polyvalvular dysplasia, TAK1-binding protein 2**