15q26.3 Deletion in Congenital Heart Disease – A Case of Scimitar Syndrome

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BACKGROUND
Congenital heart disease (CHD) occurs in at least 8 per 1000 live births. Scimitar syndrome is a rare form of CHD characterized by anomalous pulmonary venous return, most commonly partial anomalous pulmonary venous return (PAPVR) of the right pulmonary veins to the inferior vena cava (IVC). This form of PAPVR is often associated with right lung hypoplasia, right sided mediastinal shift, dextrocardia, and pulmonary hypertension in infancy ( Siddiqui 2016).

Single gene mutations can be attributed to 3-5% of CHD, aneuploidies cause 8-10%, and copy number variations cause 3-25% (Cowan 2015). Genetic associations with Scimitar syndrome are not well explored in the literature (Flick 2023). Some cases of total anomalous pulmonary venous return (TAPVR) have been associated with the VEGFR2 and PDGFR2 genes (chromosome 4q12), ANKR1 (chromosome 10q23), SEMA3D (chromosome 7q21), as well as known single gene disorders such as Holt-Oram syndrome (chromosome 1q22), Noonan syndrome (chromosome 12q24), Ivemark syndrome (unknown genetic cause). Still, other cases are associated with chromosomal changes, such as Cat-Eye Syndrome, otherwise known as partial chromosome 22 trisomy or tetrasygy (Abuzaid 2021, Kim 2014, Shi 2018). This case explores the role of 15q copy number variants in relation to Scimitar syndrome and congenital heart disease.

CASE DESCRIPTION
A full term boy was born via normal spontaneous vaginal delivery stable on room air after a largely unremarkable delivery course. Fetal echocardiography suggested complex CHD including ventricular septal defect (VSD), co planar atrioventricular (AV) valve, appearance of bicupid aortic valve, PAPVR (concern for Scimitar syndrome), and dysplastic aortic arch. Postnatal imaging demonstrated the presence of Scimitar syndrome with anomalous drainage of the right pulmonary veins to the IVC, a large VSD, right lung hypoplasia, and pulmonary hypertension (Figure 2). Extracardiac findings included club feet. Chromosome analysis and microarray were significant for a three-way unbalanced translocation resulting in partial trisomy of the long arm of chromosome 2 from band 2q32.3-2qter and partial monosomy of the long arm of chromosome 15 from band 15q26.3-15qter (Figure 1). Of note, no clinically significant duplication or deletion of chromosome 7 material was identified. This translocation was found to be maternally inherited through parental chromosome analysis.

DISCUSSION
Our patient with Scimitar syndrome had a small terminal deletion of the long arm of chromosome 15 (15q26.3). 75% of patients with Scimitar syndrome will have other associated cardiac malformations such as ASD, CoA, VSD, and PDA (Abuzaid 2021). However, there is no reported case of Scimitar syndrome associated with 15q26.3 deletion prior to our patient. A 15q26 deletion syndrome is a rarely described disorder associated with the ISGF3, NR2F2, CHD2 and MEF2A genes (Benbouchta 2021). Of these, MEF2A is present in our patient’s deletion.

MEF2A, also known as myocyte enhancer factor 2A, has been proposed as a novel potential gene important for cardiac development. The transcription factor it encodes is expressed in large quantities in the developing heart and is one of the core cardiac transcription factors, along with GATA4, Nkx2.5, and SRF. Many of these transcription factors co-regulate gene expression. For example, MEF2A and Nkx2.5 co-regulate muscle cell differentiation and cardiac looping pathways. GATA4 and MEF2A co-regulate genes involved in cardiac development and function. In mouse models, most MEF2A knockout mice are not viable. These mice exhibit myofibrillar defects, cardiomegaly, mitochondrial deficiencies, and conduction defects (Desjardins 2016, Thorsson 2015).

In another study, MEF2A knockout leads to primary human coronary artery endothelial cells (HCAEC) senescence (Xiong 2019). Pulmonary vein formation is driven by endothelial cells. The pulmonary veins form by vasculogenesis in the mesenchyme. Around 34 days of gestation, endothelial cells (labeled by CD31) on the ventral surface of the lung buds join to form the pulmonary venous confluence near the left atrial cavity. During the pseudoglandular phase of development at age 38 to 98 days of gestation, capillary beds coalesce to expand the pulmonary veins, and they continue to mature until mid-gestation (Hall 2001). As the MEF2 gene leads to endothelial cell senescence and endothelial cells are important in cardiac and vascular development, abnormalities in the MEF2A gene may play a role in CHD.

There have been multiple described cases of CHD associated with 15q26.3 deletions. In the DECIPHER genetic database, 20 out of 176 patients with a deletion located anywhere within or including the 15q26.3 band were noted to have CHD. When conducting a z-test to compare this single proportion to the population estimate of individuals living in the United States with CHD (Gilboa 2016), the number of individuals with CHD who also have a 15q26.3 deletion is statistically significant (p value of 0, z-value 15.4). The most common forms of CHD in 15q26.3 deletion were VSD (10), ASD (7), PDA (5), and pulmonary stenosis and/or abnormality of the pulmonary artery (3). 15q26 deletions are also associated with left ventricular outflow tract obstructions, including coarctation of the aorta, aortic stenosis and hypoplastic left heart syndrome (Laiana 2014).

CONCLUSION
We highlight the case of a previously undescribed association between Scimitar syndrome and an unbalanced translocation involving deletion of 15q26.3. Deletions of 15q26.3 lead to abnormalities of the MEF2A gene, with a possible association with the formation of CHD. While abnormalities of this gene may have contributed to the formation of Scimitar syndrome, the development of CHD is a complex interplay between genetics, epigenetics, and environmental factors. More research is needed to determine the specific genetic causes of Scimitar syndrome. A meta-analysis of genetic associations with Scimitar syndrome, TAPVR, and PAPVR would be helpful in determining if a true correlation exists between forms of PAPVR and the MEF2A gene.

REFERENCES