FOXC1 MUTATION AND ITS ASSOCIATION WITH FAMILIAL TRUNCUS ARTERIOSUS

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CASE PRESENTATION

- A 39-1/7 week gestational age male was born via vaginal delivery following a pregnancy complicated by a fetal diagnosis of truncus arteriosus.
- Echocardiogram confirmed type 1 truncus arteriosus with mild-moderate truncal valve stenosis, mild truncal valve insufficiency, and a secundum ASD (Figure 1).
- Physical examination notable for hypertelorism, buphthalmos, and a broad nasal bridge.
- Family history significant for a bicuspid aortic valve in the father and older sister as well as truncus arteriosus is the middle sister and a paternal second cousin (Figure 2).
- Genetics evaluation revealed a likely pathogenic variant of the FOXC1 gene. This variant was also found in both of his sisters. The older and middle sister also had a pathogenic variant in the DSP gene. Genetic testing of the father is pending.

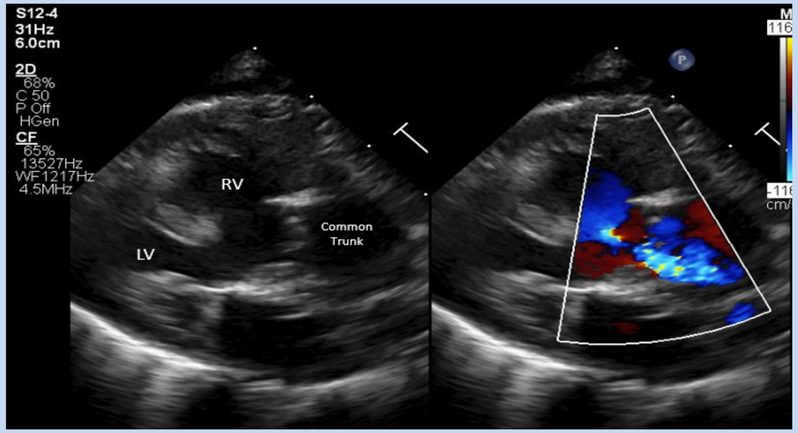

Figure 1: Parasternal long axis view with the right ventricle (RV), left ventricle (LV), a large VSD, and a common arterial trunk.

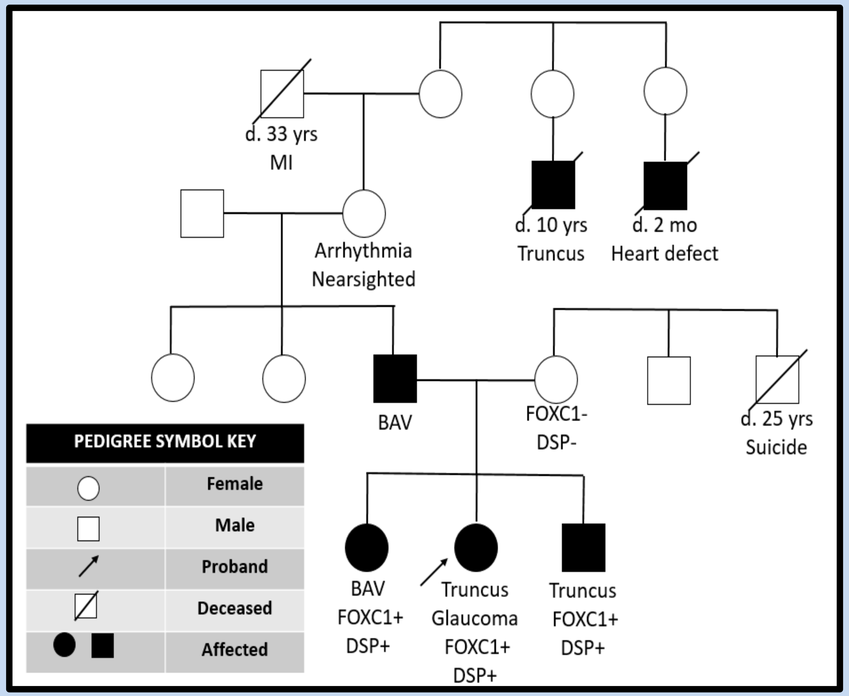

Figure 2: Family pedigree

DISCUSSION

- FOXC1 is a member of the FOX transcription factor family expressed in neural crest cells during cardiac development.
- Defects in the neural crest lineage are associated with multiple congenital heart anomalies including impairment in rotation and septation of the cardiac outflow tract.
- In this case report, all three siblings were found to have a pathologic variant of FOXC1 gene. Two of the siblings carry a diagnosis of truncus arteriosus.
- FOXC1 gene plays a role in conotruncal development and a defect in this gene is likely implicated in the truncus arteriosus diagnoses in this family. It is also associated with ophthalmologic abnormalities such as hypertelorism and infantile glaucoma.
- The DSP gene variant is associated with autosomal dominant and autosomal recessive arrhythmogenic right ventricular cardiomyopathy (ARVC).
- It remains to be seen whether the association with the FOXC1 gene and DSP gene variants is serendipitous in this particular family or a common occurrence.
- At present, all siblings are being followed closely by pediatric cardiology as well as by pediatric ophthalmology. Parents are aware of the need for cardiac and genetic screening with any future pregnancies.

CONCLUSION

- Genetic testing is recommended in patients with conotruncal defects as 22q11 mutations are common.
- FOXC1 gene anomalies should also be considered in patients with conotruncal defects.
- When genetic variants are diagnosed, appropriate follow-up with referral to sub-specialties is important, as directed by the genotypic and phenotypic findings.