Elucidating the Genetic Etiology of a Familial Case of Supravalvar Aortic Stenosis and Peripheral Pulmonary Arterial Stenosis

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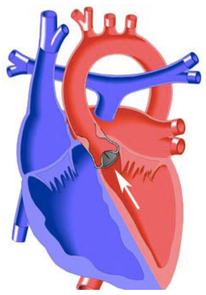
BACKGROUND

Supravalvar Aortic Stenosis (SVAS)



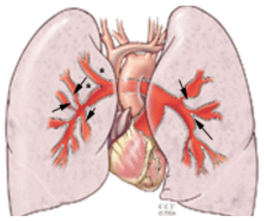
Narrowing of the aortic media and intima just above the aortic valve with two presentations:

- Narrowing at the sinotubular junction
- Narrowing of a long segment of the ascending aorta.

Presentation: Chest pain and shortness of breath
Risks: Left ventricular hypertrophy, elevated systolic pressure in aortic root
Treatment: Patch repair of aorta

Peripheral Pulmonary Arterial Stenosis (PPAS)

Narrowing of one or more of the branches of the pulmonary artery. It can occur in isolation or as part of other congenital cardiovascular defects.



Presentation: Chest pain, shortness of breath, fluttering of heart
Risks: RV hypertrophy, systolic/diastolic dysfunction, ventricular failure (9)
Treatment: Balloon angioplasty

INTRODUCTION

- SVAS is a congenital heart defect (CHD) accounting for 0.5% of CHD and 5% of congenital aortic stenosis cases (1).
- More than half of patients diagnosed with SVAS have accompanied PPAS (2).
- SVAS and PPAS have been described in sporadic cases but are more common in patients with Williams Syndrome (Incidence between 45%-70%) (1).
- Investigating the genetic etiology of a multigenerational familial case affected by SVAS and PPAS can help us elucidate the genetic origins of this CHD.
- Our study describes a search for candidate variants in a family with 5 out of 11 family members having both SVAS and PPAS.

METHODS AND MATERIALS

- Clinical phenotyping of the family was done through chart review, MRI, and echocardiography data (pedigree pictured above).
- Exomes of three phenotypically similar members and one unaffected member were analyzed using VarSeq genetic software.
- Variants were filtered using quality measures, an allele frequency of x < 0.2%, a CADD PHRED scaled score of 25, and a count alleles algorithm.
- Literature review of candidate variants was completed.

FAMILIAL CASE

- Family of Middle Eastern descent
- No history of consanguinity
- No history of Williams Syndrome
- Non-syndromic phenotype
- Five out of 11 members affected with SVAS/PPAS

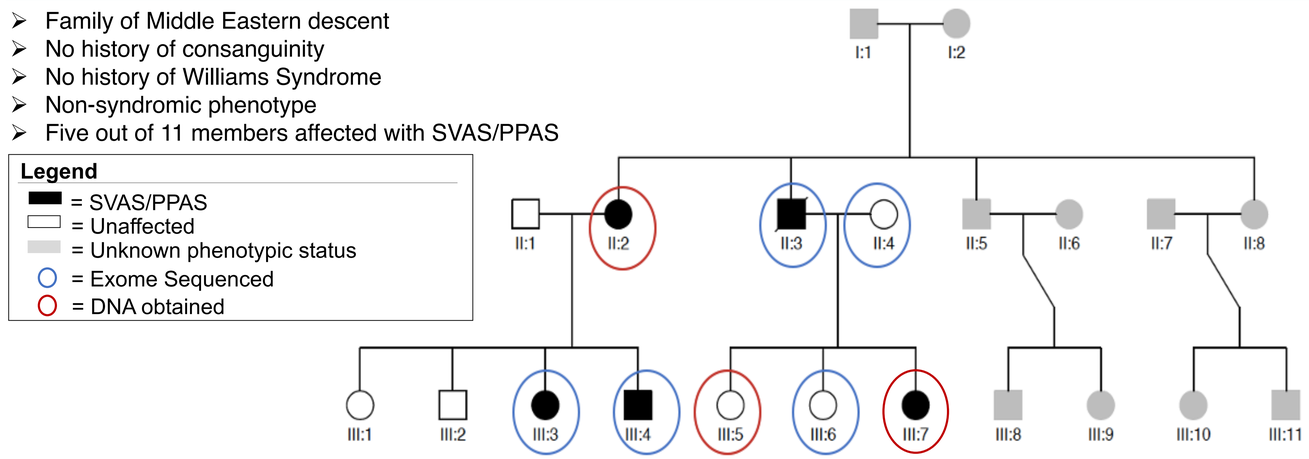
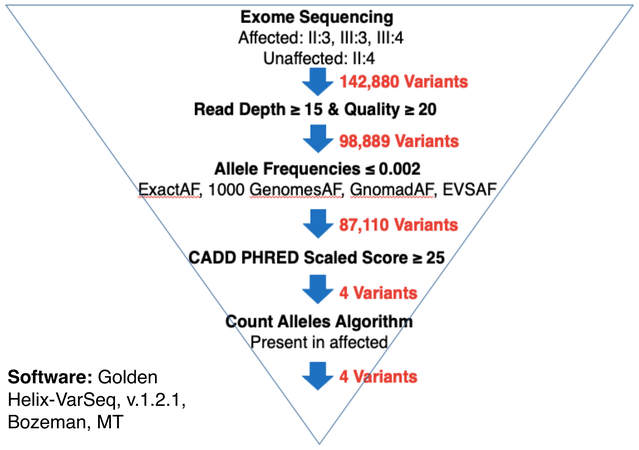


Figure 1: *The familial pedigree indicates high penetrance and an autosomal dominant inheritance pattern of SVAS and PPAS. We obtained DNA from all those circled in red. Those in blue have been exome sequenced.*

II:1	Normal heart
II:2	SVAS, PPAS, No surgery
III:1	Normal heart
III:2	Normal heart
III:3	SVAS, Mild PPAS, Balloon angioplasty
III:4	SVAS, Mild PPAS
II:3	SVAS, PPAS, Left HF, Aortic stenting
II:4	Normal heart
III:5	Normal heart
III:6	Mild SVAS that resolved
III:7	SVAS, Severe PPAS, No response to balloon angioplasty

Table 1: *Phenotype of family members with corresponding pedigree ID. Listed is affected status (SVAS/PPAS) and whether patient underwent treatment.*

EXOME SEQUENCE VARIANT FILTERING



Software: Golden Helix-VarSeq, v.1.2.1, Bozeman, MT

Figure 2: *Using phenotypically similar affected members and one unaffected control, we filtered exome sequences and identified four candidate variants outlined below.*

1. Read Depth and Quality: Used to remove genes that are only partially read during the exome sequencing process.

2. Allele Frequency: How often an allele is found in a population. An allele frequency of 0.2% was used and allows for a broad variant search.

3. CADD PHRED Scaled Score: A score of 30 indicates the variant is in the top 0.1% of damaging variants. A score of 20 is in the top 1% and a score of 10 is in the top 10%.

4. Count Alleles Algorithm: Cross checks our variant list and double checks that variants are found in affected individuals, not in unaffected individuals.

Gene Name	Description	Relevance to Familial Case	Sequence Ontology	Position and Ref Allele	CADD Phred Scaled score
1. (*BSCL2*): Berardinelli-Seip congenital lipodystrophy 2	Codes for a protein called Seipin. Found in the endoplasmic reticulum, it aids in intracellular lipid droplet creation.	Mutations of BSCL2 have been reported in people of Middle Eastern origin. Additionally, BSCL2 variants have been associated with hypertrophic cardiomyopathy (4).	Missense p.Arg392His	11q12.3 (C/T)	27.3
2. (*SNIP1*): SMAD Nuclear Interacting Protein 1	Acts as a transcriptional co-repressor in the TGF-Beta and NF-kB pathways.	SNIP1 deficiency was found to exacerbate cardiac hypertrophy, hypertension, and fibrosis (6). Knockout studies of SNIP1 have shown up-regulation of ECM proteins (12).	Missense p.Arg122Trp	1p34.3 (G/A)	27.9
3. (*SLC9A4*): Solute Carrier Family 9 Member A4	Codes for a Na^+/H^+ exchanger. Involved in pH regulation and signal transduction	Suggested to play a role in the chemical homeostasis of vascular smooth muscle cells (5).	Missense p.Arg430Gln	2q12.1 (G/A)	34
4. (*TINAGL1*): Tubulointerstitial Nephritis Antigen 1	An extracellular matrix (ECM) protein that interacts with other ECM proteins and is a ligand for integrin receptors.	TINGAL1 has been shown as an inhibitor of the epidermal growth factor receptor (8).	Missense p.Arg41Gln	1p35.2 (G/A)	27.2

Table 2: *Completed literature review of the candidate variants yielded information on how the variants may contribute to the familial SVAS/PPAS*

CONCLUSIONS

- We were able to phenotype family members using clinical data.
- In this case of familial SVAS/PPAS, members are affected in an autosomal dominant inheritance pattern.
- Exome sequencing followed by analysis using VarSeq, identified the following candidate variants: *BSCL2, SNIP1, SLC9A4,* and *TINAGL1.*

FUTURE DIRECTIONS

- Sanger sequencing will be used as a confirmatory method for all identified variants of those exome sequenced and the additional family members circled in red on the pedigree.
- Quantitative disease phenotyping will be done using echocardiography data.
- Future functional studies for candidate variants can ascertain which variant may be responsible for disease.

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