Genetic Testing for Patients with Non-Williams Supravalvar Aortic Stenosis: A Preliminary Guide for Clinicians

Tyler Novy MD[1], Sara B. Stephens MPH[2], Benjamin Jacob PA-C[2], Taylor Beecroft MS, CGC[2], Emily Soludczyk MS, CGC[2], Justin Weigand MD[2], Shaine A. Morris MD, MPH[2]

1. Department of Pediatrics, McGovern Medical School, Houston, Texas 2. Section of Pediatric Cardiology, Texas Children's Hospital & Baylor College of Medicine, Houston, Texas

BACKGROUND

- Supravalvar aortic stenosis (SVAS) is commonly associated with Williams syndrome (WS).
- The yield of single gene elastin (*ELN*) testing along with testing for other genetic causes of SVAS when WS is not diagnosed has not been thoroughly investigated.
- Currently, there are no clinical guidelines for genetic testing of patients found to have SVAS once WS has been ruled out.

STUDY AIM

To describe the frequency and yield of genetic testing in a cohort of non-WS SVAS individuals at a tertiary pediatric center

METHODS

- Retrospective cohort design
- Inclusion criteria: Patients evaluated at TCH diagnosed with SVAS between 1991 and 2021.
  - SVAS defined as either (A) a peak supravalvar velocity of >2 meters/second, a sinotubular junction (STJ) or ascending aortic z-score <-2.0, or (B) STJ z-score <-1.5
- Exclusion criteria: WS, complex congenital heart disease, Shone complex, aortic valve disease as primary condition, SVAS as postoperative complication (e.g. TGA)
- Use of descriptive statistics:
  - Frequency of clinical genetic testing (genetic test modality, age at test, genotype) and/or genetic evaluation
  - Results of genetic testing
  - Clinical phenotype corresponding to results

FIGURE 1. Frequency of Variants Among 36 Patients Receiving *ELN* Sequencing

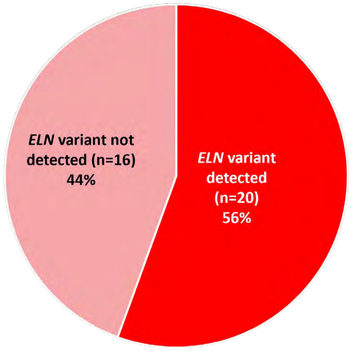


FIGURE 2. Genetic Diagnosis Among 40 SVAS Patients Undergoing Gene Sequencing

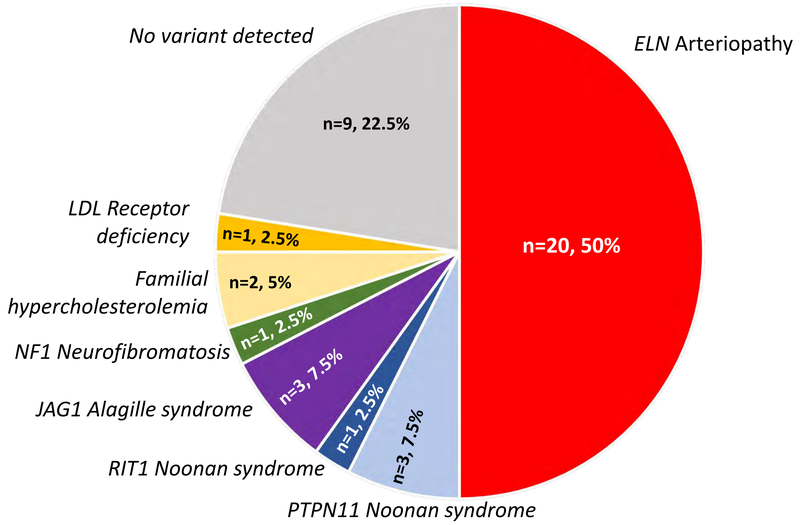
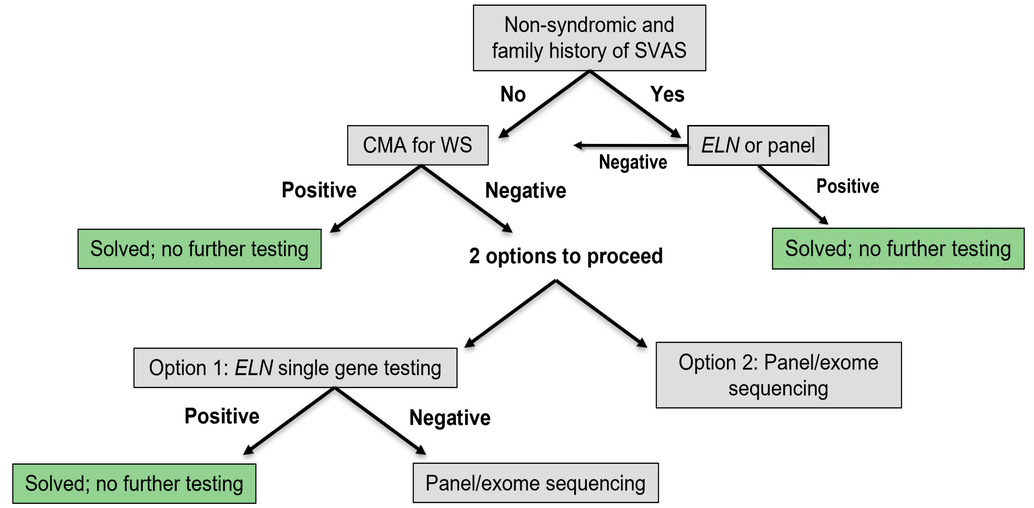


FIGURE 3. Proposed Clinical Algorithm for Approach to non-WS SVAS



LIMITATIONS

- Small sample size, thus limiting ability to perform statistical modeling
- Possible selection bias due to potentially more severe phenotype in children

CONCLUSIONS

- In non-WS SVAS, initial CMA was non-diagnostic (100% in those receiving CMA) but diagnostic yield improved (70%) when gene sequencing was used.
- *ELN* pathogenic variants were most commonly seen among patients with SVAS, but other mutations included variants in *PTPN11*, *RIT1*, *JAG1*, and *NF1*.
- Findings suggest that diagnostic yield is high when further testing for non-WS SVAS includes a panel of these genes.
- Clinical lab testing for hypercholesterolemia may be warranted if clinical suspicion is high.

Author disclosures: SAM serves as a consultant and on the Scientific Advisory Board for Aytu Biopharma clinical trial
Funding: NIH NHILBI Project # 5K23HL127266-03