Exploring the Yield of RASopathy Variants in Patients with Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common inherited cardiomyopathy and is characterized by left ventricular hypertrophy (LVH) without other systemic or acquired causes of LVH. RASopathy conditions that present with LVH are often diagnosed in childhood, yet their phenotypic heterogeneity and attenuation of noticeable physical features can hinder correct diagnosis in adults presumed to have nonsyndromic HCM. Our work aimed to evaluate the prelevance and importance of including RASopathy genes in genetic testing panels for adults with presumed nonsyndromic HCM.

Methods

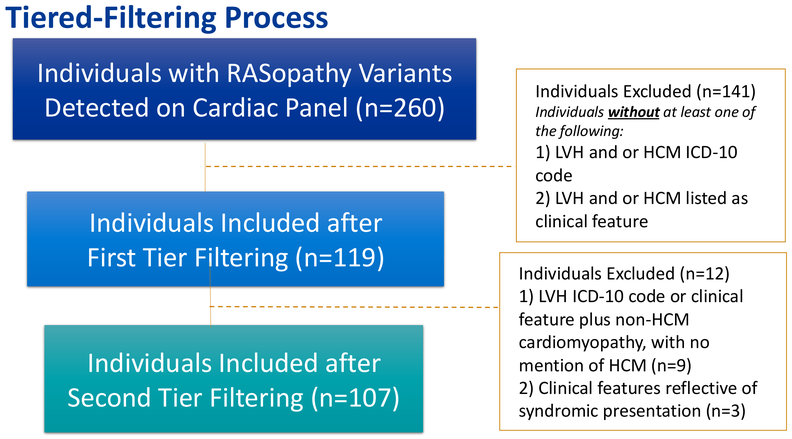
Data Collection:

- Curated and de-identified individual-level data for adults with a Pathogenic (P), Likely Pathogenic (LP), or Variant of Uncertain Significance (VUS) RASopathy variant detected on cardiac panel testing between January 2016 and August 2024 were provided by a commercial laboratory.
- Panels included an HCM-specific panel, a cardiomyopathy-specific panel, a cardiomyopathy and arrhythmia panel, and a customizable cardiology-centric panel.

Data Analysis:

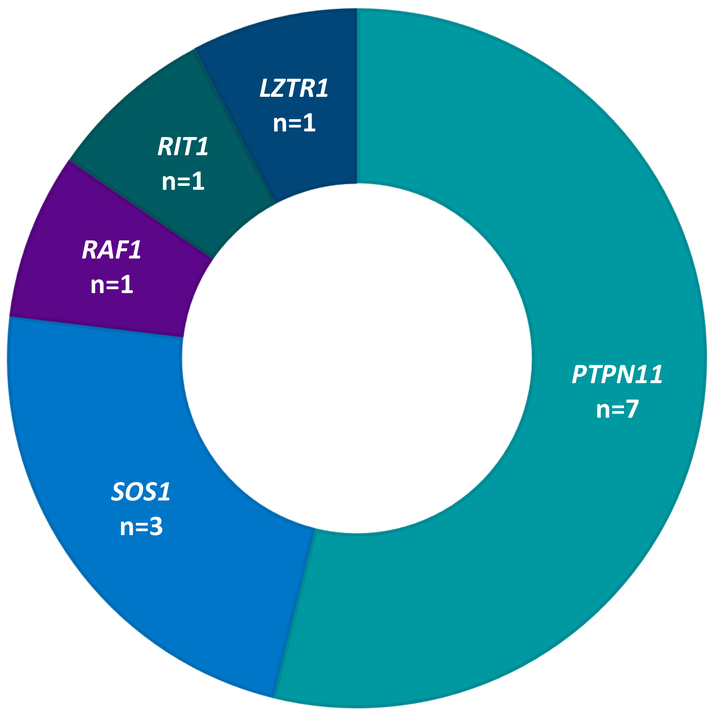
- A tiered-filtering process was used to obtain a nonsyndromic HCM cohort.
- Data were analyzed using quantitative and descriptive statistics.
- Yield was calculated for total cardiac panels and for the HCM-specific panel.

FIGURE 1
Tiered-Filtering Process



Results

FIGURE 2
Pathogenic & Likely Pathogenic RASopathy Variant Distribution



- Thirteen total P/LP variants were detected.
- Most were detected in *PTPN11*, followed by *SOS1.*

TABLE 1
Gene-Specific RASopathy Test Orders and Variant Counts

Gene	Total # of Test Orders	# of P/LP Identified	# of VUS Identified
PTPN11	14,028	7	11
RAF1	14,051	1	30
SOS1	4,512	3	31
RIT1	4,512	1	4
LZTR1	679	1	0
NF1	661	0	1
SPRED1	664	0	1

- Zero variants (P/LP/VUS) were detected in the following genes: *HRAS*, *SOS2*, *SHOC2, BRAF MAP2K1*, *MAP2K2*, *RASA1*, and *CBL.*
- Dataset had no test orders that analyzed *PPP1CB*, *NRAS*, or *KRAS*.
- *SOS1* was the gene with the highest number of reported VUS findings.

TABLE 2
Pathogenic & Likely Pathogenic RASopathy Variant Yield

Test Ordered	Yield of P/LP RASopathy Variants (%)
Total (all cardiac panels)	13/14,097 (0.092%)
HCM-specific Only	10/3,743 (0.267%)

- Most RASopathy variants were detected on the HCM-specific panel.

Discussion

- Small overall yield of 0.092% (total tests) and 0.267% (HCM-specific)
  - RASopathy gene analysis may have limited utility on HCM genetic testing panels for presumed nonsyndromic adult population.
  - However, most nonsyndromic HCM genes also have a small yield (<5%).
    - Yield is only one of many factors that contribute to panel inclusion.
- Most RASopathy gene had zero detected variants.
  - Most genes with P/LP variants detected are already included on HCM guidelines.
  - HCM in most RASopathy genes may be limited to childhood onset with multisystemic features.
  - RASopathies are phenotypically heterogeneous.
- *SOS1* harbored the second-highest number of P/LP variants detected, despite being analyzed in only one-third the number of tests as *PTPN11* and *RAF1.*
  - Growing evidence between RASopathy-associated HCM and *SOS1.*
  - Comparable to *PTPN11,* which has been discussed in clinical guidance.
- *SOS1* was the gene with highest number of reported VUS findings.
- Based on our findings, further consideration about which RASopathy genes are beneficial to include on HCM panels, specifically regarding *SOS1*, is warranted.

References

- Please scan the QR code to view references:

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