Down the Rabbit Hole: Tales of a Tiered Approach to Genetic Testing for HCM

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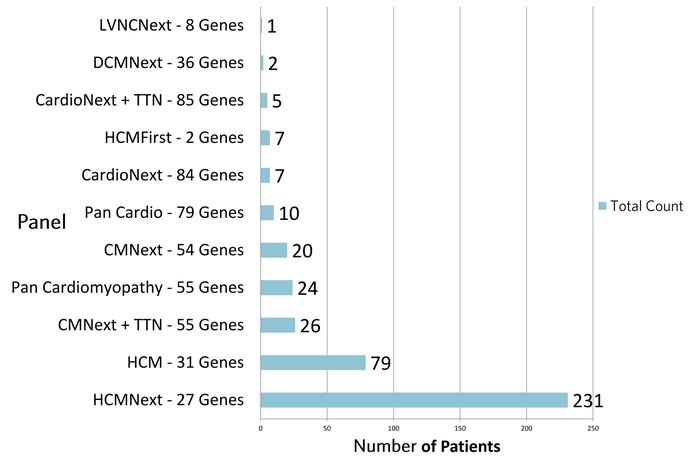
BACKGROUND

- Hypertrophic cardiomyopathy (HCM) has been associated with at least 31 different genes
- The majority of mutations occur in the *MYBPC3* and *MYH7* genes
- Earlier reports suggest that 8% of HCM patients carry more than one mutation
- However, more recent data suggests that the actual number of HCM patients who carry more than one mutation (double mutation carriers) is less than previously suspected (<1%)

Figure 1. Panels Ordered for HCM Patients



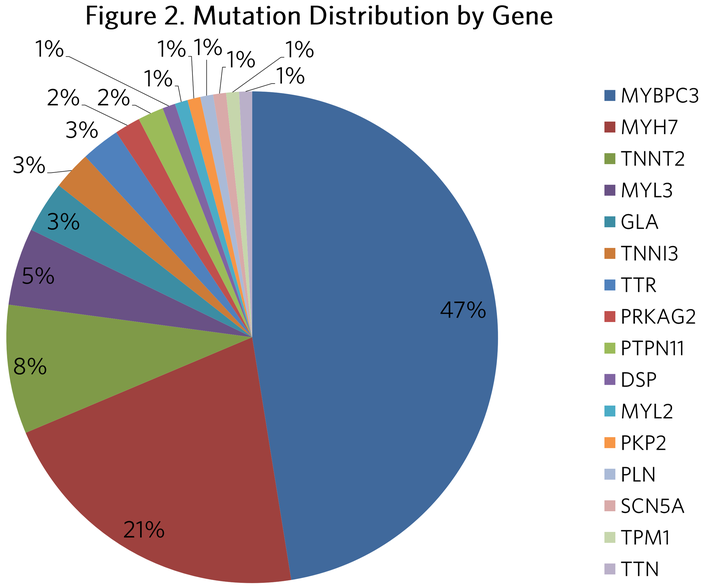
METHODS

- Testing was completed on 412 subjects who had a reported diagnosis of HCM; some subjects had a 2 gene test while others had a comprehensive multi-gene panel
- Demographic and clinical data was obtained from test requisitions, attached clinical records and pedigrees
- Data was reviewed and analyzed retrospectively

RESULTS

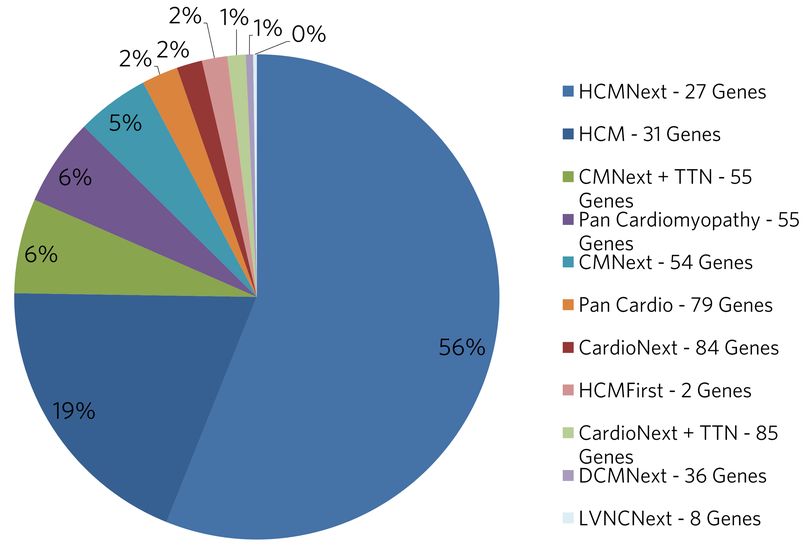
- 118/412 (28.6%) patients tested positive for a pathogenic or likely pathogenic alteration
- 2/118 (1.7%) of total positive patients were found to be double mutation carriers
- In our cohort, age of diagnosis for the two double mutation carriers was 52 and 58 compared to a median age of diagnosis of 39 for heterozygous HCM subjects

Figure 2. Mutation Distribution by Gene



Only 2% of patients were tested for a 2 gene panel, which accounts for 68% of mutations

Figure 3. Distribution of Panels Ordered for HCM Patients



Double Mutation Carrier #1

- 58 year old Caucasian female with HCM
- No mention of Fabry disease or renal disease
- No known family history of HCM
  - Brother with SCD at age 30
- Testing: HCMNext (27 gene panel)
  - *MYBPC3* Variant, Likely Pathogenic: p.R810H (c.2429G>A)
  - *GLA* Pathogenic Mutation: p.N215S (c.644A>G)

Double Mutation Carrier #2

- 52 year old Caucasian female with HCM diagnosed at 47
- History of septal myectomy, ICD
- Family history of HCM was unconfirmed
  - Father died at 72 of unknown heart issue, pacemaker at 70 for Afib
  - Paternal aunt died in late 60s of MI, no autopsy
  - Paternal grandfather died at 50 of heart issues
- Testing: HCMNext (25 gene panel)
  - *MYBPC3* Pathogenic Mutation: c.1928-2A>G
  - *TNNT2* Variant, Likely Pathogenic: p.R278C (c.832C>T)

TAKE-HOME POINTS

- 28.6% of patients with HCM tested positive on a multigene panel
- Mutations in *MYBPC3* and *MYH7* made up the majority of mutations detected (68.7%)
- Double mutation carriers are uncommon: thus a tiered approach to testing, starting with *MYBPC3* and *MYH7*, detects the majority of mutations while minimizing identification of variants of unknown significance
- Double mutation carriers in our cohort did not have a history of significant early-onset of HCM as previously suggested in the literature

REFERENCES

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2. Fourey D et al. Prevalence and Clinical Implication of Double Mutations in Hypertrophic Cardiomyopathy: Revisiting the Gene-Dose Effect. *Circ Cardiovasc Genet*. 2017 Apr;10(2).

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