Diagnostic Yield and Mutation Spectrum of Multi-gene Panel Testing for Hypertrophic Cardiomyopathy

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BACKGROUND & METHODS

- Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease with a worldwide prevalence of 1:500, and is the leading cause of sudden cardiac death in young people. Genetic etiology is suspected in up to 50% of HCM patients. Genetic testing is highly recommended for HCM patients, and for family members following the identification of a causative mutation in the proband.
- To investigate the mutation spectrum of HCM, a retrospective review was conducted on 408 consecutive cases with a clinical suspicion of HCM who underwent multigene panel testing at our laboratory. Detected alterations were classified to five categories by the laboratory as pathogenic, likely pathogenic (VLP), variant of unknown significance (VUS), likely benign (VLB) and benign.

RESULTS & DISCUSSION

Figure 1: Diagnostic rate. A pathogenic mutation was identified in 27% of these individuals. The diagnostic yield is lower than the ~35% reported in the literature[1, 2, 3], which may be explained by:

- The presence of variable phenotypes in individuals.
- Testing of unaffected individuals referred solely due to their family history.
- Differences in testing criteria for research studies compared to those used for clinical testing.
- The lack of clear phenotype information in some cases.
- The strict variant interpretation guidelines used in a clinical diagnostic laboratory.

Patient information	Mutations
52 year old Caucasian female with HCM diagnosed in her 40s. Father, one paternal aunt and paternal grandfather were reported to have cardiac issues.	1. *MYBPC3* c.1928-2A>G 2. *TNNT2* p.R278C c.832C>T
58 year old Caucasian female with diagnosis of HCM. A brother died suddenly in his 30s	1. *MYBPC3* p.R810H c.2429G>A 2. *GLA* p.N215S c.644A>G

Figure 2: Mutation distribution. Eighty-two pathogenic mutations in 15 genes were identified. *MYBPC3, MYH7, TNNT2,* and *MYL3* are the top four most frequently mutated genes. Recurrent mutations were observed in multiple genes.

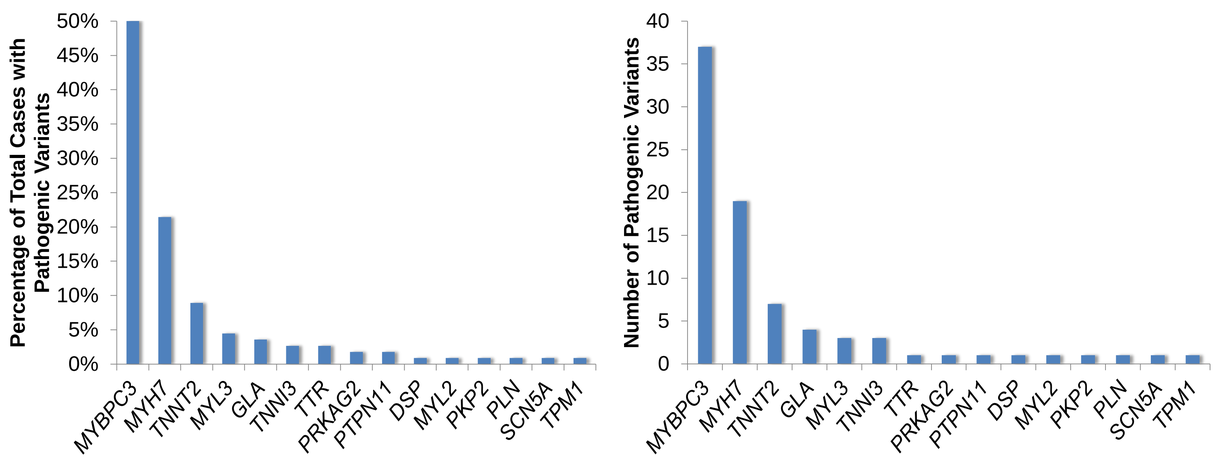


Figure 3: Study of familial mutations.

- 38 individuals from 31 families were positive for the mutation previously identified in their respective probands.
- The median age for mutation-positive individuals reported to have cardiomyopathy was 55.4 years (n=5) vs 20 years (n=21) for unaffected mutation-positive individuals.
- This underscores the great utility of genetic testing in identifying pre-symptomatic at-risk individuals.

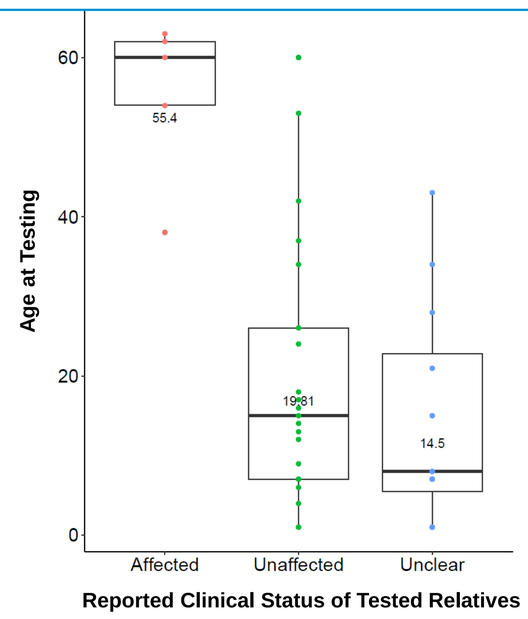
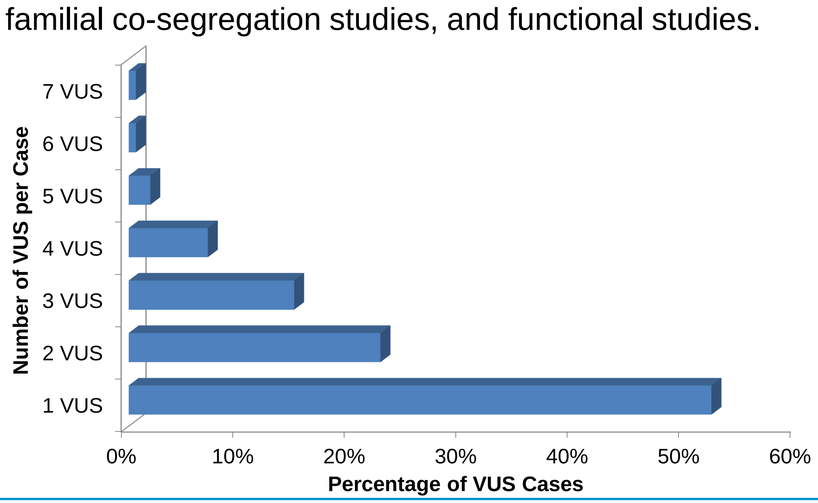
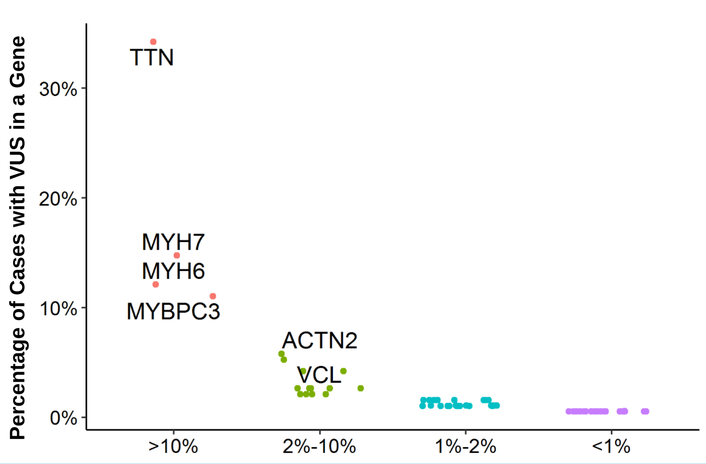
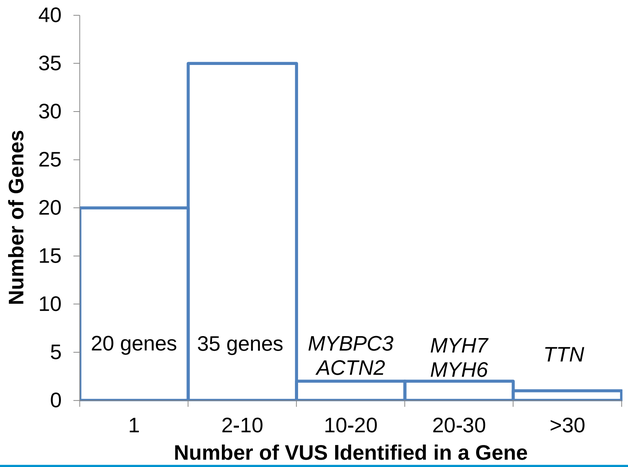


Figure 4: VUS distribution.

- VUS were detected in 46% of the individuals, including 34 probands who had pathogenic mutations.
- About one third of the VUS were in *TTN*, followed by *MYH7, MYH6* and *MYBPC3*.
- The interpretation is challenging and will benefit from continually emerging data, including population frequency estimates in larger and more ethnically diverse populations, familial co-segregation studies, and functional studies.







Take-Home Points

- Hypertrophic cardiomyopathy is a genetically heterogeneous disease with reduced penetrance.
- Young pre-symptomatic mutation carriers may benefit from a personalized plan for surveillance and evaluation.
- VUS were detected in about half of the tested individuals, and present a challenge for clinical correlation.

Reference

1. Gruner C et al. *Circ Cardiovasc Genet*, 2013 Feb;6:19-26
2. Burns C et al. *Circ Cardiovasc Genet*, 2017 Aug;10:
3. Murphy SL et al. *J Cardiovasc Transl Res*, 2016 Apr;9:153-61