All in the Family: How Family History Affects Diagnostic Yield of Hypertrophic Cardiomyopathy Multigene Panel Testing

Sam Martin[1], Lily Hoang[1], Jill S. Dolinsky[1], Tami Johnston[1], Brittany Dougall[1], Brissa Martin[1], Christian Antolik[1]

[1]Ambry Genetics, Aliso Viejo, CA, 92656

BACKGROUND

- Family history is often a predictor of disease. For hypertrophic cardiomyopathy (HCM), a family history (fhx) is seen in approximately 72% of cases in which a mutation is identified (1).
- To further assess the relationship between family history of HCM and the probability of identifying a pathogenic mutation in an HCM associated gene, the family history of all probands with HCM who underwent multigene panel (MGP) testing were examined.

METHODS

- Patients were included if they had an HCM phenotype and had MGP testing from April 2015 to June 2016.
- Clinical history was collected from test requisition forms, as well as pedigrees and clinical notes submitted with orders.
- Mutation analysis was done on 6 cases tested with 2 genes and 231 cases tested with 27 genes, in which both tests consistently included *MYH7* and *MYBPC3*.
- Family history analysis was limited to those who reported family history information.

RESULTS

Mutation Frequency

- Among 237 patients referred for HCM MGP testing, 32% (n=77) were positive for a mutation; the majority were in *MYBPC3* (n=44, 57%) and *MYH7* (n=13, 17%) (Figure 3).
- Among the 57 HCM probands with positive MGP testing results who reported fhx, 84.2% (n=48) reported 'some cardiac fhx', 36.8%(n=21) reported a fhx of HCM, 28% (n=16) reported a fhx of sudden cardiac arrest (SCA), and 15.8% (n=9) reported no cardiac fhx (Figure 1).
- Probands with mutations in *MYBPC3* had a higher frequency of reporting a fhx of HCM (14/34; 41.2%) or SCA (10/34; 29.4%) compared to probands with *MYH7* mutations, in which fhx of HCM was reported in 22.2% (2/9) of probands and fhx of SCA was reported in 22.2% (2/9) of probands (Figure 2).

Mutation Type

- Approximately half of the *MYBPC3* mutations were either protein truncating, haploinsufficient or splice site mutations (52.2%), while the remainder (47.7%) were missense mutations (Figure 4).
- In contrast, *MYH7* mutations were exclusively missense alterations, consistent with the mechanism of disease for this gene (Figure 4).

Figure 1. Reported Family History Among HCM Probands Positive for a Family History

Figure 2. Reported Family History Among *MYBPC3* and *MYH7* Positive HCM Probands

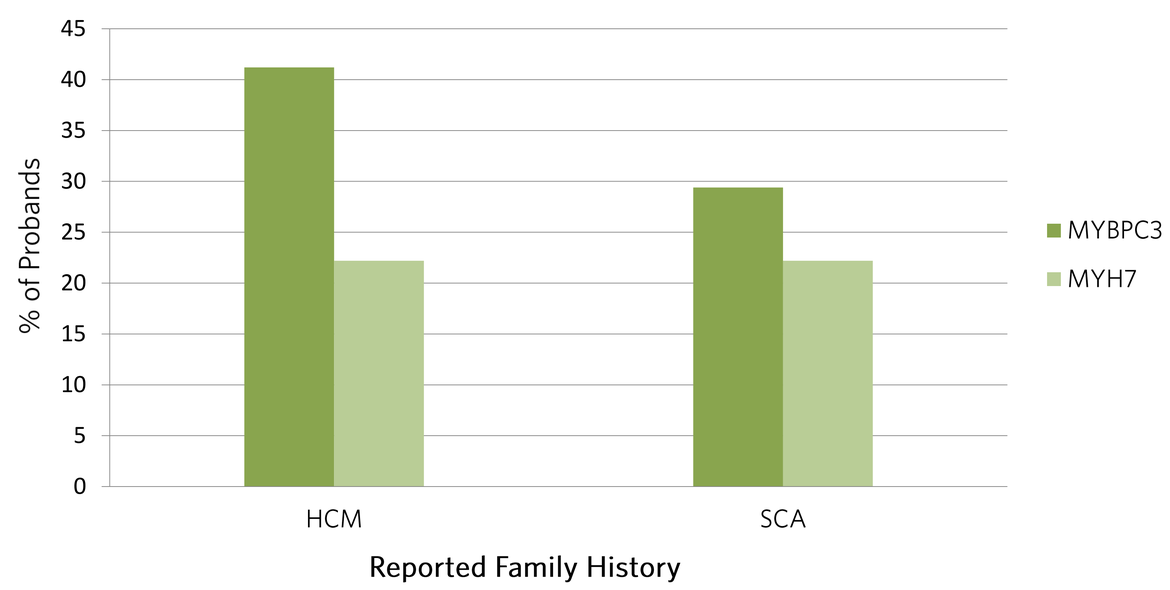


Figure 3. Mutation Distribution by Gene Among Positive Findings

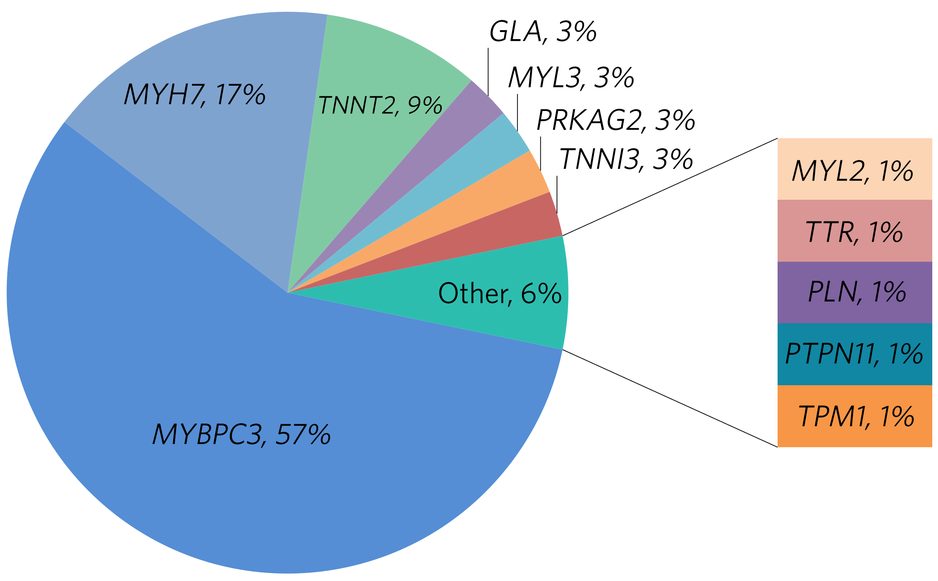
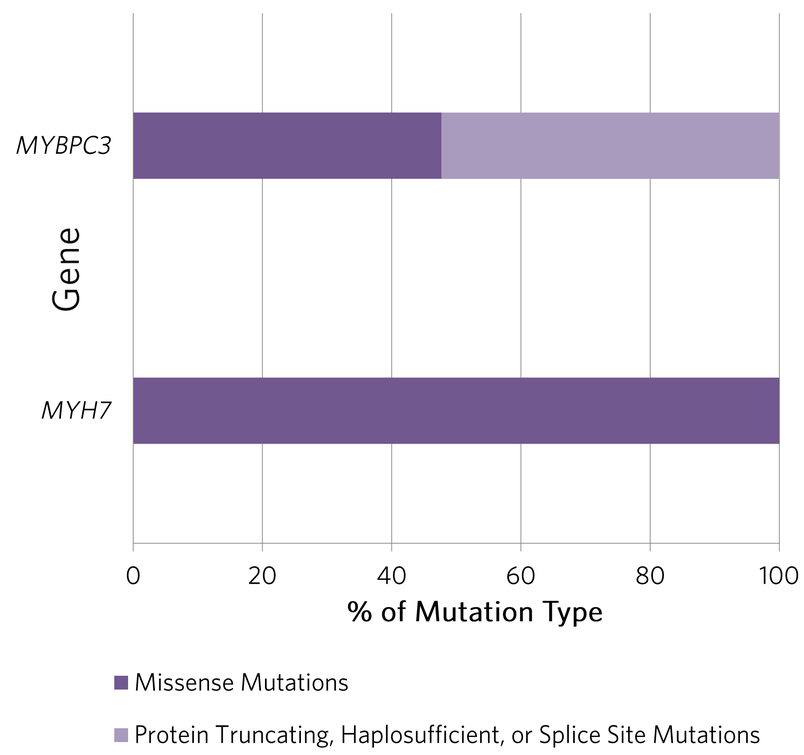


Figure 4. *MYBPC3* and *MYH7* by Mutation Type



TAKE-HOME POINTS

- The prevalence of fhx of HCM (36.8%) and SCA (28%) in our cohort is lower than previously published rates of 72% and 89%, respectively (1).
- This data demonstrates a role for genetic testing among sporadic or familial cases of HCM.
- Further exploration of genotype-phenotype relationships will be valuable for better understanding the predictive value of genetic testing for HCM and may be useful in family risk counseling.

REFERENCES

1. Genet Med. 2013 Dec;15(12):972-7. doi: 10.1038/gim.2013.44. Epub 2013 Apr 18.
2. Circ Cardiovasc Genet. 2013 Feb; 6(1): 118-131.

15 Argonaut, Aliso Viejo, CA 92656 Toll Free 866 262 7943 Fax 949 900 5501 ambrygen.com tjohnston@ambrygen.com