Ambry Genetics®

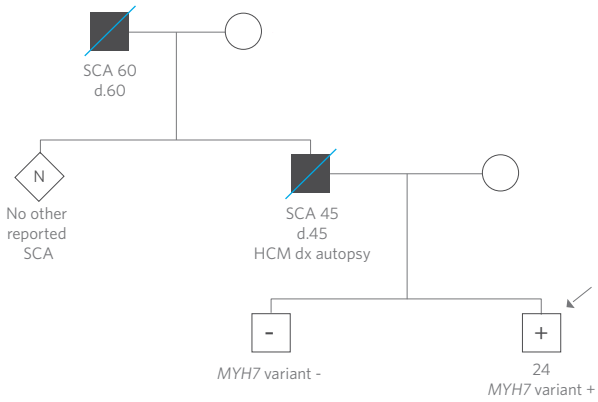
CASE EXAMPLE: Hypertrophic Cardiomyopathy (HCM)

WHO IS THE PATIENT?

- 24 year-old male with no cardiac symptoms; assessed due to family history
- Normal ECG (no left ventricular hypertrophy or conduction disease), cardiac echocardiogram, cardiac MRI
- No prior cardiovascular genetic testing

WHAT IS THE FAMILY HISTORY?

- Family history of sudden cardiac arrest (SCA) and hypertrophic obstructive cardiomyopathy
- Father died at age 45 from SCA: HCM found on requested autopsy report
- Paternal grandfather died at age 60 from SCA
- No prior cardiovascular genetic testing done on family members



WHAT HAPPENED WITH GENETIC TESTING?

- Cardiologist ordered HCMFirst panel (*MYH7* and *MYBPC3* genes) with reflex option on patient (clinical rationale below):
  - Up to 50% of HCM due to a mutation in one of the HCMFirst genes, which represent ~80% of known genetic causes of HCM
  - Tiered approach: HCMFirst panel reflexes to larger HCMNext panel, only if needed
- Positive finding: *MYH7* variant, likely pathogenic: p.G584S
- This alteration is reported in multiple patients with HCM.[1,2,3] *MYH7* mutations account for ~40% of HCM and 5-8% of dilated cardiomyopathy (DCM). *MYH7* mutations can also cause left ventricular non-compaction (LVNC) and skeletal myopathies, with/without cardiac involvement.[4,5]

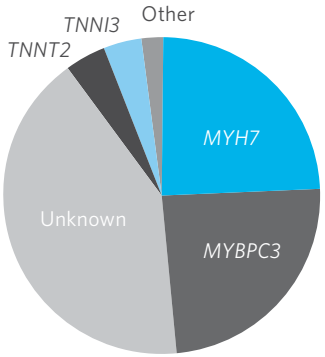
HOW DID GENETIC TESTING HELP THE PATIENT AND FAMILY?

- Confirmed patient to be at risk for HCM and sudden cardiac arrest, despite negative clinical presentation
- Tiered testing allowed quicker results (no need for larger panel)
- Cardiologist referred patient to HCM specialist to develop cardiac surveillance plan
- Patient could tell at-risk family members to speak to physicians about individualized cardiac surveillance
- Patient could tell at-risk family members about targeted genetic testing option
  - -Brother had targeted testing and was negative for *MYH7* variant, confirming no increased risk for HCM in him based on this

WHAT IS HCM?

- Left ventricular hypertrophy, myocyte disarray, and fibrosis
- Severity varies widely, even within the same family
- Can be asymptomatic, sudden death sometimes first and only symptom
- Age of onset childhood to early adulthood
- Occurs in approximately 1 in 500 individuals worldwide
- When inherited, follows autosomal dominant pattern

GENES IMPLICATED IN HCM



- Mutations in 27 genes have been identified in HCM
- *MYBPC3* and *MYH7* account for over 80% of known genetic causes
- "Other" includes the remaining genes in HCMNext

WHO SHOULD HAVE GENETIC TESTING FOR HCM?

- Patients with a clinical diagnosis of HCM
- Patients with autopsy findings consistent with HCM
- Patients with a family history of HCM, based on clinical findings or autopsy

GENETIC TESTING GUIDELINES FROM HEART RHYTHM SOCIETY (HRS) AND EUROPEAN HEART RHYTHM ASSOCIATION (EHRA)

HCM genetic testing is a **Class I recommendation** for all patients with HCM.

Once a pathogenic gene mutation is identified in a family, mutation-specific testing of family members is a **Class I recommendation**.

Adapted from Ackerman MJ, *et al.*, Heart Rhythm., 2011.

WHAT ARE AMBRY'S TESTING OPTIONS FOR HCM?

HCMFirst

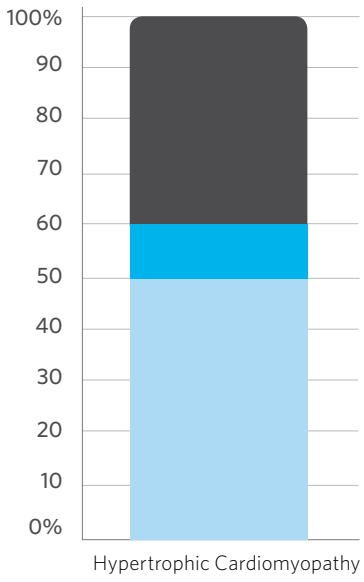
- Next generation sequencing (NGS) and deletion/duplication (del/dup) panel of *MYBPC3* and *MYH7* genes ; TAT is 3-4 weeks

HCMNext

- NGS and del/dup panel of 27 genes implicated in HCM: *ACTC1, ACTN2, ANKRD1, CSRP3, FXN, GLA, JPH2, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, PLN, PRKAG2, PTPN11, RAF1, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL;* TAT is 6-8 weeks (same for reflex option)

Details about our cardiovascular genetic testing options can be found at ambrygen.com/hereditary-cardiovascular-testing

GENETIC TESTING FOR HCM



- Up to 50% of all patients with HCM have a mutation in one of the HCMFirst genes, which represent about 80% of known genetic causes of HCM
- An additional 10% of patients with HCM may have a mutation in one of the HCMNext genes

Our more comprehensive cardiovascular genetics panels (CMNext and CardioNext) may be better for more complicated families, or if HCMFirst/HCMNext testing is uninformative.

REFERENCES

1. Erdmann J, *et al.*, Clin Genet., 2003.
2. Zou Y, *et al.*, Mol Biol Rep., 2013.
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4. Hershberger RE, *et al.*, Circ Heart Fail., 2009.
5. Walsh R, *et al.*, Cardiology., 2010.
6. Ackerman MJ, *et al.*, Heart Rhythm., 2011.