What Clinicians Need to Know About Genetic Testing for Patients and Families with HCM

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DISCLOSURE

• Dr. Cresci has no relevant financial interests to disclosure
Should I Offer Genetic Testing to my Patient with HCM ??
Genetic Testing – 2 Categories:

• Diagnostic
  • Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM

• Predictive
  • Focused genetic testing to determine if a family member has a previously identified mutation
    - Pathogenic or Likely pathogenic mutation has been identified in the index family member who has HCM
2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons
Genetic Testing Strategies/Patient Screening—Recommendations

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HCM is Caused by More than 1,400 Individual Mutations in More than 11 Genes

α Tropomyosin
Troponin T

Myosin binding protein C

Myosin heavy chain

β Myosin light chain

Genetic Testing Strategies/Patient Screening—HCM Phenocopies

Metabolic myocardial storage CMs (≤ 1%)

- Regulatory subunit of adenosine monophosphate-activated protein kinase glycogen storage disease
  - (PRKAG2)

- Lysosome-associated membrane protein or Danon disease
  - (LAMP2)
  - X-linked dominant

- Fabry (α-galactosidase A deficiency)
  - (GLA)
  - X-linked recessive
Genetic Testing Strategies/Patient Screening—HCM Phenocopies

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Responds to enzyme replacement therapy
Metabolic myocardial storage CMs (≤ 1%)

- Regulatory subunit of adenosine monophosphate-activated protein kinase glycogen storage disease
  - *(PRKAG2)*

- Lysosome-associated membrane protein or Danon disease
  - *(LAMP2)*
  - X-linked dominant

- Fabry (α-galactosidase A deficiency)
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  - X-linked recessive

Typically rapidly progressive
early consideration for OHT
Genetic Testing Strategies/Patient Screening—HCM Phenocopies

Metabolic myocardial storage CMs (≤ 1%)

- Regulatory subunit of adenosine monophosphate-activated protein kinase glycogen storage disease
  - *(PRKAG2)*

- Lysosome-associated membrane protein or Danon disease
  - *(LAMP2)*
  - X-linked dominant
  - Wolf-Parkinson-White pattern on ECG

- Fabry (α-galactosidase A deficiency)
  - *(GLA)*
  - X-linked recessive
Genetic Testing Strategies/Patient Screening—HCM Phenocopies

Metabolic myocardial storage CMs (≤ 1%)

• Regulatory subunit of adenosine monophosphate-activated protein kinase glycogen storage disease
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• Lysosome-associated membrane protein or Danon disease
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• Fabry (α-galactosidase A deficiency)
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Symmetric LVH and late gadolinium enhancement in posterobasal wall on MRI
Genetic Testing – 2 Categories:

• **Diagnostic**
  - Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM

• **Predictive**
  - Focused genetic testing to determine if a family member has a previously identified mutation
    - Pathogenic or Likely pathogenic mutation has been identified in the index family member who has HCM
Genetic Testing Strategies/Patient Screening—Atypical Presentation of HCM

• Can also help to discriminate between HCM and other causes of LVH, including HTN and “athlete’s heart”
  • Only helpful if pathogenic or likely pathogenic mutation is found
## Proposed Classification System for Sequence Variants Identified by Genetic Testing:

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<th>Class</th>
<th>Description</th>
<th>Probability of being Pathogenic</th>
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<tr>
<td>5</td>
<td>Definitely Pathogenic</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>4</td>
<td>Likely Pathogenic</td>
<td>0.95-0.99</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain (Variant of Unknown Significance; VUS)</td>
<td>0.05-0.949</td>
</tr>
<tr>
<td>2</td>
<td>Likely Not Pathogenic or of Little Clinical Significance</td>
<td>0.001-0.049</td>
</tr>
<tr>
<td>1</td>
<td>Not Pathogenic or of No Clinical Significance</td>
<td>&lt;0.001</td>
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Proposed Classification System for Sequence Variants Identified by Genetic Testing:

- No Mutation Identified in 50%
- Beta myosin heavy chain (15%)
- Myosin binding protein C (15%)
- Troponin T (7%)
- Alpha tropomysin (7%)
- Others (6%)
Can also help to discriminate between HCM and other causes of LVH, including HTN and “athlete’s heart”

- Only helpful if pathogenic or likely pathogenic mutation is found
- No pathogenic mutation or VUS found \(\rightarrow\) can NOT conclude that the patient does not have HCM—still left with clinical impression and uncertain about recommendations for family members
Genetic Testing – 2 Categories:

• **Diagnostic**
  
  • Comprehensive sequence analysis to identify a disease-causing mutation in a patient with HCM

• **Predictive**
  
  • Focused genetic testing to determine if a family member has a previously identified mutation
    
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Clinical Screening with Echocardiography (& 12-Lead ECG) for Detection of HCM

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<th>Age:</th>
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<td>&lt;12 yrs</td>
<td>Optional unless any of the following are present:</td>
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<td>- Family history of early HCM-related death, early development of LVH, or other adverse complications</td>
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<tr>
<td></td>
<td>- Competitive athlete in intense training program</td>
</tr>
<tr>
<td></td>
<td>- Symptoms</td>
</tr>
<tr>
<td></td>
<td>- Other clinical findings that suggest early LVH</td>
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<tr>
<td>12-18 yrs</td>
<td>Every 12-18 months</td>
</tr>
<tr>
<td>&gt;18-21 yrs</td>
<td>Every ≤5 years or w/onset of symptoms or w/change in symptoms</td>
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<td>- More frequently if there is a family history of late-onset LVH or HCM-related-related complications</td>
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Clinical Screening with Echocardiography for Detection of HCM

• Findings consistent with HCM
  • Asymmetric LVH
  • SAM of Mitral Valve
Clinical Screening with Echocardiography for Detection of HCM

- Findings consistent with HCM
  - Asymmetric LVH
  - SAM of Mitral Valve

- Subtle findings
  - Abnormal tissue Doppler pattern for age
  - Abnormal peak systolic strain
  - Crescent shape of LV

E' = 3 cm/s
Genetic Testing Strategies/Family Screening—Recommendations

Identify Family Member with Phenotype (who is willing to be tested)

No Pathogenic variant identified

No Mutation Identified in 50%

- Beta myosin heavy chain (15%)
- Myosin binding protein C (15%)
- Troponin T (7%)
- Alpha tropomysin (7%)
- Others (6%)

Human Molecular Genetics, 2002, Vol. 11, No. 20
Identify Family Member with Phenotype (who is willing to be tested)

- No Pathogenic variant identified
- Variant of Unknown Significance identified

May be reclassified at a later date
Genetic Testing Strategies/Family Screening—Recommendations

1. Identify Family Member with Phenotype (who is willing to be tested)

2. No Pathogenic variant identified
   - Continue to Clinically follow 1st degree family members (repeat echocardiography as previously described)

3. Variant of Unknown Significance identified
   - Continue to Clinically follow 1st degree family members (repeat echocardiography as previously described)
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Genetic Testing Strategies/Family Screening—Recommendations

- Identify Family Member with Phenotype (who is willing to be tested)
  - Likely Pathogenic variant identified
  - Pathogenic variant identified
    - Test 1st degree family members (who wish to be tested) for specific (identified) mutation
      - Present
Genetic Testing Strategies/Family Screening—Recommendations

Normal LVMI:
≤115 in ♀
≤95 in ♂
Genetic Testing Strategies/Family Screening—Issues

- **Incomplete Penetrance**
  - Even if M (+), may always be P (-)
Identify Family Member with Phenotype (who is willing to be tested)

Likely Pathogenic variant identified

Pathogenic variant identified

Test 1st degree family members (who wish to be tested) for specific (identified) mutation

Absent
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Double mutations are present in 5-8% of patients with HCM

Genetic Testing Strategies/Family Screening—Issues

Genetic test (+)

Genetic test (+)

Beta myosin heavy chain (15%)

Myosin binding protein C (15%)

Troponin T (7%)

Alpha tropomysin (7%)

Others (6%)
Genetic Testing Strategies/Family Screening—Issues

No Mutation Identified in 50%

- Beta myosin heavy chain (15%)
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- Others (6%)

P (+) M (+) M (+) M (+) M (+)

Genetic test (+) Genetic test (-)

Human Molecular Genetics, 2002, Vol. 11, No. 20
Genetic Testing Strategies/Family Screening—Issues

• **Incomplete Penetrance**
  • Even if M (+), may always be P (-)

• **Double Mutations**
  • If M (-), there is a minimal, but not 0%, chance of being P (+)
Double or compound sarcomere mutations in hypertrophic cardiomyopathy: A potential link to sudden death in the absence of conventional risk factors

Barry J. Maron, MD,* Martin S. Maron, MD,† Christopher Semssarian, MB, BS, PhD‡

From the *Hypertrophic Cardiomyopathy Center, Tafts Medical Center, Boston, Maryland; and †Agnes F. Molecular Cardiology, Centenary Institute, Sydney Medical School, University of Sydney and Royal Prince Alfred Hospital, Camperdown, Australia.

BACKGROUND Risk stratification strategies employing sarcomere gene mutation analysis have proved imprecise in identifying high-risk patients with hypertrophic cardiomyopathy (HCM). Therefore, additional genetic risk markers that reliably determine which patients are predisposed to sudden death are needed.

OBJECTIVE The objective of this study was to determine whether multiple disease-causing sarcomere mutations can be regarded as markers for sudden death in the absence of other conventional risk factors.

METHODS Databases of 3 HCM centers were accessed, and 18 disease-causing mutations in genes encoding sarcomeric proteins were identified. Patients were followed for a median of 3 years (range, 1 to 11 years). Each patient's personal history and family history were assessed for disease severity and adverse events, and the probability of sudden death was calculated with each cardiac event.

RESULTS The probability of dying from a first cardiac event was significantly greater in those with two or more sarcomere mutations compared with those with one or no sarcomere mutations while controlling for the presence of additional risk factors.

CONCLUSIONS Our findings support the emerging hypothesis that double or compound sarcomere mutations and other risk factors are independently associated with adverse events. The identification of diagnostic and predictive markers for genetic disease susceptibility will ensure successful targeted genetic testing and counselling.

Hypertrophic cardiomyopathy family with double-heterozygous mutations; does disease severity suggest double-heterozygosity?
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Genetic Testing—A Personal Decision

Potential Benefits:
- Targeted clinical surveillance
- ↓ uncertainty
- Opportunity to make realistic life plans

Potential Harm:
- ↑ anxiety if M (+)
- Alteration of self image if M (+)
- Ambiguity if no mutation identified