Genotype Positive/ Phenotype Negative: Is It a Disease?

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No disclosures
“What is phenotype negative in HCM?"

• **Guidelines:**
  
  • HCM: wall thickness ≥ 15 mm (unexplained by loading conditions).
  
  • ACC/AHA: 13-14 mm borderline (positive family history!).
  
  • ESC: HCM in first-degree relatives if wall thickness ≥ 13 mm.

• **Phenotype negative = no hypertrophy**

• Cardiac evaluation with ECG and echocardiography is recommended in genotype positive family members.

• Phenotype negative = no disease expression on ECG and echo?

*Gersh et al. J of Thoracic and vascular surgery 2011*
*Elliott et al. Eur Heart J 2014*
“What is the definition of disease?”

WHO 1946: “**Health** is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”

- A **disease** is a particular abnormal condition that affects part or all of an organism and that consists of a **disorder of a structure or function**. Disease is often construed as a **medical condition** associated with specific **symptoms** and **signs**.

- In **humans**, **disease** is often used more broadly to refer to **any condition** that causes **pain**, **dysfunction**, **distress**, **social problems**, **or death** to the person afflicted, or similar problems for those in contact with the person. Diseases can affect people not only physically, but also **emotionally**, as contracting and living with a disease can alter the affected person's perspective on life.

*Wikipedia*
Family screening in HCM

209 probands

- GT performed 196 (94%)
  - Genotype-negative 14 (7%)
  - Genotype-positive 149 (76%)
  - VUS 33 (17%)
- GT not performed 13 (6%)

777 relatives

- GT performed 620 (80%)
  - Genotype-negative 356 (57%)
  - Genotype-positive 264 (43%)
- GT not performed 157 (20%)

Cardiac screening

GT = genetic testing  
Hannah van Velzen, under review
Prevalence of HCM at first screening

421 Relatives
264 Genotype +: HCM in 98 (37%)
157 without genetic testing: HCM in 28 (17%)
Predictors of HCM at initial evaluation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HCM (n=126)</th>
<th>No HCM (n=295)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44±16 (1-75)</td>
<td>34±18 (1-83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men (n,%)</td>
<td>72 (57)</td>
<td>126 (43)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proband age (yr)</td>
<td>37±17</td>
<td>41±18</td>
<td>0.045</td>
</tr>
<tr>
<td>Cardiac symptoms (n,%)</td>
<td>13 (14)</td>
<td>18 (7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Genotype positive (n,%)</td>
<td>98 (78)</td>
<td>166 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MWT (mm)</td>
<td>16±3 (10-25)</td>
<td>9±2 (5-12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>41±6</td>
<td>35±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOT obstruction (mmHg)</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>41 (41)</td>
<td>33 (12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Clinical outcome of relatives with HCM (9 years)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype positive (n=98)</th>
<th>No genetic testing (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality (n,%),</td>
<td>13 (13)</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac mortality (n,%),</td>
<td>7 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Sudden cardiac death (n,%),</td>
<td>3 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Septal reduction therapy (n,%),</td>
<td>6 (6)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Cardiac transplant (n,%),</td>
<td>3 (3)</td>
<td>-</td>
</tr>
<tr>
<td>ICD implantation (n,%),</td>
<td>14 (14)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>12 (12)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>2 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Appropriate ICD shock (n,%),</td>
<td>1 (1)</td>
<td>-</td>
</tr>
</tbody>
</table>
Cumulative HCM incidence

Follow-up 7 years:

HCM in 29 relatives (24 G+)
Mean age 40 years (9-77)
Median wall thickness 14 mm
Rate 0.55 mm/year
Clinical outcome of phenotype negative relatives (8 years)

<table>
<thead>
<tr>
<th></th>
<th>Genotype positive (n=165)</th>
<th>No genetic testing (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality (n,%)</td>
<td>4 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac mortality (n,%)</td>
<td>1 (0.6)</td>
<td>-</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Appropriate ICD shock (n,%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inappropriate ICD shock (n,%)</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
Cardiac events in G+/Ph- relatives

1 Sudden cardiac death:
21-year old MYBPC3 mutation carrier. Autopsy confirmed the absence of HCM. Post mortem analysis revealed a pathogenic mutation (c. 1708G>T, p.Ala570Ser) in the KCNH2 gene associated with long-QT syndrome.

2 ICD’s for primary prevention in G+/Ph-:
53-year old MyBPC3 mutation carrier admitted with symptomatic non-sustained ventricular tachycardia.
43-year old TNNT2 mutation carrier and severe family history of SCD.

3 ICD’s implanted after development of HCM
Survival

- Dutch Population
- G- relatives
- G+ relatives
- Relatives without GT

Cumulative survival (%) vs. Follow-up (y)
Genotype positive/phenotype negative

- ECG
- Functional features
- Morphological features
- Metabolic features
- Pro-fibrotic changes

“You tested positive. But it looks like you’re just a carrier.”
ECG

- ECG is a sensitive, but not specific early marker of disease.
- ECG abnormalities should lead to further phenotyping, including CMR.
- Number and severity of ECG abnormalities correlate to phenotypic expression on CMR.

Charron et al. Int J Cardiol 2003;90:33-38
Delcrè et al. Int J Cardiol 2013
Functional features in G+/LVH-

**TDI/STE/MRI:**
- E’ velocity lower in MYH7 G+/LVH-
  Higher Am velocities in G+/LVH.
- Increased apical counter clockwise rotation, more LV twist.
- Reduced systolic circumferential strain and peak diastolic circumferential strain.

Substantial overlap in values.

But **diastolic abnormalities** present before hypertrophy.

**References:**
Nagueh, Circulation 2000
Ho, Circulation 2002
Michels, JACC Cardiovasc 2009
Germans, J of Cardiov Magnetic Resonance 2010
Mitral valve

172 HCM patients vs controls:
Mitral leaflets elongated in HCM

15 G+/ LVH – subjects:
AML length 21 ± 3 vs 18 ± 3 mm

Elongation: congenital or acquired?

Maron et al. Circulation 2011;124:40-47
Myocardial crypts

- Initial study 13/16 (81%) G+/LVH- subjects crypts.
- 19/31 (61%) G+/LVH – 10/261 (4%) HCM patients.
- Also present in normal population (3.6%).

Germans et al. JACC 2006
Maron et al. Circ Cardiovas. Imaging 2012
Child et al. J of Cardiovas Magnetic Resonance 2014
Crypts in MyBPC3 mice

- Crypts are normal part of development, but resolve at birth.
- Homozygous and heterozygous knockout mice have increased crypt presence, remain present at birth.
- Mitral valve normal in heterozygous mice.

Metabolic features of G+/ LVH - subjects

15 G+/ LVH- subjects vs controls
MRI, $[^{15}\text{O}]$ PET and $[^{11}\text{C}]$ acetate PET.

Myocardial external efficiency (ratio between cardiac work and oxygen consumption) is reduced, before LVH, microvascular dysfunction and contractile dysfunction.

Timmer SAJ, Eur J Heart Failure 2011
Pro-fibrotic changes

• Serum C-terminal propeptide of type I procollagen (PICP) is increased in G+/LVH-.

• Increased extracellular volume (ECV) on T1 MRI.

• “Signal intensity coefficient” a novel echocardiographic assessment of myocardial microstructures correlates with ECV, LV mass, E’ and NT-proBNP.

Ho, N Engl J Med 2010
Ho, Circ Cardiovasc Imaging 2013
Hiremath Circ Heart Failure 2016
Cardiac development? Crypts, Mitral valve?

Metabolic
Pro-fibrotic
Diastolic function
Mitral valve?

Teekakirikul. J of Cell Biology 2012
Conclusions

• Genotype+/phenotype- HCM is a preclinical disease.

• Genetic testing can lead to psychological and socioeconomic consequences – counseling!

• Pre-LVH findings in G+ subjects give valuable insight in the pathophysiology of HCM, hopefully leading to therapeutic options to prevent disease development and progression.

• The prognostic value of “pre-LVH” signs of HCM needs to be defined by long term follow-up studies.
Thank you for your attention