Inherited Atherogenic Disorders of Dyslipidemia

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Familial hypercholesterolemia

- Autosomal dominant genetic disease present in all racial and ethnic groups
- A cause of premature ASCVD; in the prestatin era, median age of onset for first MI was ~50 yrs in men, 60 yrs in women
- Highest prevalence of genetic defects that cause premature mortality (~1/200 to 1/500)
- 3 major genetic defects
  - LDL Receptor
  - Defects in apolipoprotein B binding to LDL-R
  - Gain of function in PCSK9, enhancing LDL-R degredation
- FH leads to elevated LDL levels in untreated adults > 190 mg/dL and untreated children >160 mg/dL
- FH is under-treated and under-recognized. Of the theoretical estimated prevalence of 1/500 for heterozygous FH, <1% are diagnosed in most countries.

1. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease
   Banga G. Nordstierna et al.
   http://dx.doi.org/10.1093/eurheartj/eht273 eht273 First published online: 16 August 2013
Fig. 1. LDL cholesterol (LDL-C) burden in non-FH and FH subjects depending on different age of starting statin therapy (data derived from Starr et al. [38]). For the calculation of the LDL-C burden, the following assumed mean LDL-C values were used: Non-FH sub...

Alpo Vuorio, Kieran F. Docherty, Steve E. Humphries, Jaana Kuoppala, Petri T. Kovanen

Statin treatment of children with familial hypercholesterolemia – Trying to balance incomplete evidence of long-term safety and clinical accountability: Are we approaching a consensus?

Atherosclerosis, Volume 226, Issue 2, 2013, 315–320

doi:10.1136/bmj.a2423
1. MEDPED FH Criteria

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>1st degree relative with FH</th>
<th>2nd degree relative with FH</th>
<th>3rd degree relative with FH</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>5.7</td>
<td>5.9</td>
<td>6.2</td>
<td>7.0</td>
</tr>
<tr>
<td>20–29</td>
<td>6.2</td>
<td>6.5</td>
<td>6.7</td>
<td>7.5</td>
</tr>
<tr>
<td>30–39</td>
<td>7.0</td>
<td>7.2</td>
<td>7.5</td>
<td>8.8</td>
</tr>
<tr>
<td>40+</td>
<td>7.5</td>
<td>7.8</td>
<td>8.0</td>
<td>9.3</td>
</tr>
</tbody>
</table>

A diagnosis of FH is made if the total cholesterol levels (mmol/L) exceed the cut-off points.

2. Simon Broome Criteria

Criterion

a. DNA mutation (either LDL-receptor or apoB gene)
b. Tendon xanthomas in patient or first/second degree relative
c. Family history of myocardial infarction in second degree relative aged <50 years or in first-degree relative aged <60 years
d. Family history of cholesterol >7.5 mmol/L in first or second degree relative
e. Total cholesterol >7.5 mmol/L (adult) or >6.7 mmol/L (age<16 years)
f. LDL-C>4.9 mmol/L (adult) or >4.0 mmol/L (age<16 years)

Diagnosis

Definite FH: criterion a, pr criterion b + (e or f)
Probable FH: criteria c + (e or f), or criteria d + (e or f)
3. Dutch Lipid Clinic Network Diagnostic Criteria

<table>
<thead>
<tr>
<th>Family History</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st degree relative with premature CVD (M&lt;55 yrs, F&lt;65yrs)</td>
<td>1</td>
</tr>
<tr>
<td>1st degree relative with known LDL-C &gt; 5th percentile</td>
<td>2</td>
</tr>
<tr>
<td>1st degree relative with tendonous xanthomas and/or atherosclerosis</td>
<td>2</td>
</tr>
<tr>
<td>Children &lt; 10 years with LDL-C &gt; 5th percentile</td>
<td></td>
</tr>
<tr>
<td>Personal history of CVD</td>
<td>2</td>
</tr>
<tr>
<td>Premature CVD (M&lt;55 yrs, F&lt;65yrs)</td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>Tendonous xanthomas</td>
<td>6</td>
</tr>
<tr>
<td>Arcus sines in patients &lt;45yrs</td>
<td>4</td>
</tr>
<tr>
<td>LDL cholesterol level</td>
<td></td>
</tr>
<tr>
<td>265 mg/dL, 4.5-6.4 mmol/L</td>
<td>8</td>
</tr>
<tr>
<td>5.0-6.4 mmol/L</td>
<td>5</td>
</tr>
<tr>
<td>6.0-8.9 mmol/L</td>
<td>3</td>
</tr>
<tr>
<td>DNA Analysis</td>
<td></td>
</tr>
<tr>
<td>Functional mutation of LDL receptor gene identified</td>
<td>8</td>
</tr>
</tbody>
</table>

Diagnosis

Definite FH: greater than 8 points
Probable FH: 6 to 8 points
Possible FH: 3 to 5 points

Table 4. FH Diagnostic Categories

<table>
<thead>
<tr>
<th>ICD-10 Category</th>
<th>Clinical Criteria</th>
<th>With Genetic Testing Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FH</td>
<td>LDL-C &gt;160 mg/dL (10 mmol/L) for children and &gt;190 mg/dL (5 mmol/L) for adults and with 1st degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C-raising gene defect (ApoB, apoE, or PCSK9)</td>
<td>Presence of 1 abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis as heterozygous FH if gene-raising defect positive and LDL-C &gt;160 mg/dL (10 mmol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasionally, heterozygotes will have LDL-C &gt;160 mg/dL (10 mmol/L); they should be treated similarly to homozygotes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of both abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defects and LDL-C-raising gene variants with (LDL-C &gt;160 mg/dL (10 mmol/L), (2) random-UCLA</td>
</tr>
<tr>
<td>Homozygous FH</td>
<td>LDL-C &gt;260 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C-raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH</td>
<td>Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C-raising (LDL receptor, apoB or PCSK9) gene defects, includes the rare autosomal-recessive type</td>
</tr>
<tr>
<td></td>
<td>If LDL-C &gt;360 mg/dL (14 mmol/L) or LDL-C &gt;400 mg/dL (10 mmol/L) with aortic valve disease or symptoms at &lt;20 yr of age, heterozygous FH highly likely</td>
<td>Occasionally, homozygotes will have LDL-C &lt;160 mg/dL (10 mmol/L), (2) random-UCLA</td>
</tr>
<tr>
<td>Family History of FH</td>
<td>LDL-C level not a criterion; presence of a 1st-degree relative with confirmed FH</td>
<td>Genetic testing not performed</td>
</tr>
</tbody>
</table>

apoB indicates apolipoprotein B; FH, familial hypercholesterolemia; ICD-10, International Classification of Diseases, 10th Revision; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; and PCSK9, proprotein convertase subtilisin/kexin type 9.
Hyper-Lp(a)

- Polymorphic lipoprotein related to LDL
- Contains an additional protein moiety, apolipoprotein(a) (apo(a)).
- Physiologic function is unknown, but support for a causal role for Lp(a) in the development of ASCVD (MI, PAD and calcific AS)
Case

• RC
• 66 yo diagnosed with high cholesterol at age 21. Father had CAD and CABG at age 50. Paternal uncle died suddenly at age 49. Paternal grandmother had an MI in her 40s.
• Management parallels the development of cholesterol treatment
• Took clofibrate, niacin, Questran, mevacor, Lipitor
• Never smoker, lifelong exercise
• Highest LDL 243 on record
• Her brother has had high cholesterol; his highest LDL was 263. His daughter (her niece) was diagnosed with FH at age 5, undergoing genetic testing, which “confirmed” FH

• DLC 6
• Simon Broome probable
• Median LDL since 1999 was 125
• LDL 118 on Crestor 40, Zetia 10 and Welchol 6 tabs
• Beginning Praluent
• We ordered FH genetic testing from Invitae. This testing included evaluation for sequence changes and exonic deletions/duplications in LDLR, APOB, PCSK9, and LDLRAP1.

• The results of RC’s genetic testing showed that:

• RC tested positive for a pathogenic variant in LDLR. Specifically, she has the c.1359-1G>A splice acceptor variant in LDLR.

• This sequence change affects an acceptor splice site in intron 9 of LDLR and is expected to disrupt mRNA splicing and results in an absent or disrupted protein. It is not present in population databases, including ExAC. It has been reported to segregate with FH in several families and has also been observed in numerous unrelated individuals with FH.

• In summary, this positive genetic testing result provides molecular confirmation that RC has Heterozygous FH (HeFH).
• KK
• 38 yo with a h/o high cholesterol since age 15 (diagnosed in the hospital for an MVA), began cholesterol meds at age 20.
• Age 28 underwent CABG and mechanical mitral valve replacement
• Smoked from age 20-25 (5 pack years)
• LDL > 350
• One son age 10 has LDL 209 off of meds, another age 8 has LDL 165 off of meds

• DLC 12
• Evolocumab 420 Qmonth
• Ezetimibe 10
• Niacin 2g
• Rosuvastatin 40
• LDL 122
• Underwent apheresis
• Pre-apheresis LDL 112 → post-apheresis LDL 55
KK tested positive for TWO PATHOGENIC VARIANTS in LDLR.

Specifically, he was found to have both the c.1775G>A (p.Gly592Glu) and c.519C>G (p.Cys173Trp) pathogenic variants in LDLR.

Both of these variants have been reported in the literature. The Gly592Glu variant is a common cause of FH in European ancestry individuals. The Cys173Trp variant has been observed in multiple unrelated individuals with FH.

While the data from this test cannot definitively determine if these variants are on the same (in cis) or opposite (in trans) chromosomes, based on clinical data, we feel it is highly likely that they are in trans and that likely BOTH of his LDLR genes are affected with one each of these two pathogenic variants. Genetic testing in relatives will clarify whether they are traveling together (in cis) or separately (in trans).

If the two LDLR variants are in trans, this confirms a diagnosis of homozygous FH in Kenneth caused by compound heterozygous pathogenic variants (the presence of two different mutant variants at a particular gene locus. In this case LDLR, one on each chromosome of a pair).

Clarifying this has important recurrence risk information for Kenneth’s children, since if his LDLR variants are in trans, all of his children will have inherited one or the other LDLR pathogenic variant. Recommendations for family member cascade genetic testing are below.
24 yo male with no PMH with LDL 173
- Exercise daily, excellent diet
- Patient says his father has high cholesterol but no family history of coronary artery disease
- Patient asked me to call his father:
  - Father said he has very elevated cholesterol and his father had had an MI in his 30s, CABG in his 40s (patient was unaware)

DLC 0 and no FH by Simon Broome
• Genetic testing showed that he has a FH-causing variant: