HoFH-a global perspective

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NLA Scientific Sessions 2016
Presenter Disclosure Information

Financial disclosure:

Aegerion Pharmaceuticals:
Speaker bureau and travel support

Sanofi-Aventis, Regeneron, RegenXBio, CSL Beering:
Research support
HoFH- an European perspective
HoFH- a global perspective
HoFH- a global perspective

• G. Kees Hovingh – The Netherlands
• Frederick Raal and Dirk Blom – South Africa
• Mariko Harada-Shiba – Japan
• Gerald Watts - Australia
Homozygous Familial Hypercholesterolemia

12 Y.O. female
LDL-C=780 mg/dL, xanthomas since age 3, coronary heart disease, cardiac bypass
FH: very high cholesterol exposure from birth, CHD earlier in life

Cumulative exposure (cholesterol yrs) by age: FH vs. unaffected individuals

HoFH is lacking functional LDL receptors

Diagram showing the interaction between hepatic lipase (apoB), LDL receptors (LDLR), TG, B100, and VLDL.
Molecular causes of FH

LDLR (chr 19p13): Primary familial hypercholesterolemia
OMIM: 143890
Molecular causes of FH

**LDLR (chr 19p13):**
Primary familial hypercholesterolemia
OMIM: 143890

**APOB (chr 2p24):**
Fam. defective ApoB
OMIM: 144010

**PCSK9 (chr 1p32):**
Proprotein convertase subtilisin/kexin type 9
OMIM: 603776

**LDLRAP1 (chr 1p36):**
Autosomal recessive hypercholesterolemia
OMIM: 603813
Heterozygous FH: one mutation in one allele
Homozygous FH:
  - Simple homozygous FH – same mutation in both alleles of same gene
  - Compound heterozygous FH – different mutations in the two alleles of the same gene
  - Double heterozygous FH – different mutations in two alleles of different genes
What Is the Prevalence of Mutations Affecting LDLR Functionality?

• **1:500** - historical FH prevalence in the general population
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- **1:500** - historical FH prevalence in the general population
- **Higher prevalence** - known in populations with founder effect

![Diagram showing founder effect with populations: South Africa, Canada, Lebanon, Japan]
What Is the Prevalence of Mutations Affecting LDLR Functionality?

- **1:500** - historical FH prevalence in the general population
- **Higher prevalence** - known in populations with founder effect
- **1:200-1:244** - Recent prevalence estimates
Prevalence of FH is higher than earlier estimates

1. Copenhagen Heart Study

![Graph showing prevalence of FH by age and gender](image)

**DLCN criteria**

Benn M et al Clin Endocrinol Metab. 2012, 97(11):3956 –3964
Prevalence of FH is higher than earlier estimates

2. NHLBI exome sequencing project

LDLR sequence data from >9000 IDs:
In controls: 1 in 217
In CVD cases: 1 in 51
RR 4-13

Do et al Nature 2015
Prevalence of FH is higher than earlier estimates

3. The Netherlands cohort

Sjouke B et al. Eur Heart J 2014;eurheartj.ehu058
Broad range of LDL-C levels in patients with a genetic diagnosis of HoFH

~770 mg/dL

~190 mg/dL

Sjouke B et al. Eur Heart J 2014;eurheartj.ehu058
LDL-C Levels Correlate With Residual LDLR Activity

Genetic variability = Phenotypic variability

Cuchel, Bruckert et al. Eur Heart J, 2014
Broad range of LLTs responses in patients with a genetic diagnosis of HoFH
The broad variability in HoFH is confirmed in a larger cohort

- Age range: 1-75 yo
- uLDL-C 170-1052 mg/dL
- tLDL-C 101-785 mg/dL
- ASCVD+ 38%
- Age at first ASCVD event: 6-63
## Clinical course of classical HoFH patients is still severe

<table>
<thead>
<tr>
<th>Patient, no. (M/F)</th>
<th>Age range on lipoprotein apheresis, years</th>
<th>Follow up of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F)</td>
<td>5–24</td>
<td>No atheromatous change</td>
</tr>
<tr>
<td>2 (F)</td>
<td>4–31</td>
<td>Successful delivery</td>
</tr>
<tr>
<td>3 (F)</td>
<td>9–36</td>
<td>CAD; 1-vessel disease</td>
</tr>
<tr>
<td>4 (M)</td>
<td>6–26</td>
<td>Aortic valve stenosis</td>
</tr>
<tr>
<td>5 (F)</td>
<td>6–36</td>
<td>CAD; 3-vessel disease</td>
</tr>
<tr>
<td>6 (M)</td>
<td>12–38</td>
<td>Aortic valve stenosis; aortic valve replacement</td>
</tr>
<tr>
<td>7 (F)</td>
<td>22–44</td>
<td>CAD; 3 vessel disease; CABG; successful delivery</td>
</tr>
<tr>
<td>8 (M)</td>
<td>27–29</td>
<td>Died of MI at the age of 29</td>
</tr>
<tr>
<td>9 (F)</td>
<td>25–31</td>
<td>Aortic valve stenosis, died of MI at the age of 31</td>
</tr>
<tr>
<td>10 (M)</td>
<td>20–44</td>
<td>CAD; 3-vessel disease, CABG</td>
</tr>
<tr>
<td>11 (F)</td>
<td>22–27</td>
<td>CAD; 3-vessel disease, CABG, Successful delivery twice</td>
</tr>
<tr>
<td>12 (F)</td>
<td>45–46</td>
<td>Multiple coronary artery stenosis</td>
</tr>
<tr>
<td>13 (M)</td>
<td>34–37</td>
<td>Multiple coronary artery stenosis</td>
</tr>
<tr>
<td>14 (M)</td>
<td>30–59</td>
<td>CAD; 2-vessel disease, PCI six times</td>
</tr>
<tr>
<td>15 (F)</td>
<td>36–45</td>
<td>Multiple myositis, died of intestinal perforation</td>
</tr>
</tbody>
</table>

Dr. Harada-Shiba, National Cerebral and Cardiovascular Center - Osaka, Japan
### Serum lipids in HoFH before and after treatment with statins ± ezetimibe

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Taking Modern Lipid-Lowering Therapy</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol, mmol/L</strong></td>
<td>17.3±3.8</td>
<td>13.1±3.3*</td>
<td>-24.3</td>
</tr>
<tr>
<td><strong>Triglycerides, mmol/L</strong></td>
<td>1.28±0.81</td>
<td>1.18±0.63</td>
<td>-7.8</td>
</tr>
<tr>
<td><strong>HDL-C, mmol/L</strong></td>
<td>0.89±0.33</td>
<td>0.91±0.25</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>LDL-C, mmol/L</strong></td>
<td>15.9±3.9</td>
<td>11.7±3.4*</td>
<td>-26.4</td>
</tr>
</tbody>
</table>

* P< 0.0001

Statins ± ezetimibe significantly improve outcome

Cumulative effects of lipid lowering treatments on LDL-C levels in HoFH

EAS guideline for LDL-C goal:
• Children <135 mg/dL
• Adults <100 mg/dL
• Adults with CAD or diabetes <70 mg/dL

Adapted from: Cuchel M et al. Eur Heart J 2014;35:2146-2157
New LLT approached are emerging

Cuchel, Bruckert et al. Eur Heart J, 2014
HoFH- a global perspective

Summary

• Genetic disease
• Prevalence ~ 1:400,000 (1:200 heFH)
• Wide range in phenotypes
• New therapies around the corner
• More insights on prevalence, diagnosis, natural history of HoFH clinical spectrum, prognosis and effect of treatment are needed
The future of FH
FH - research: a shared responsibility

Interactive-web based
Anticipated n >500 HoFH
(130 Japan, 100 South Africa, 100 Canada, 50 Netherlands, 40 Saudi Arabia-Oman, ???US, ....)

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