Genetics of Familial Hypercholesterolemia

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University of Pennsylvania
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Introduction

• What is Familial hypercholesterolemia (FH)?

• What are the underlying genetic defects that cause FH?

• How does the molecular basis of FH affect lipid lowering treatment?
Familial Hypercholesterolemia (FH)

- Inherited disorder
- Severe hypercholesterolemia with lifelong accumulation of plasma LDL-C
- Premature CVD

Familial Hypercholesterolemia (FH)

- inherited disorder
- severe hypercholesterolemia with lifelong accumulation of plasma LDL-C
- premature CVD

Clinical Manifestations of FH

(A) Extensor tendon xanthomata

(B) Achilles tendon xanthoma

(C) Corneal arcus

(D) Xanthelasmata

Screening for familial hypercholesterolaemia.
Bender, Robert; Bell, Damon; Hooper, Amanda; Edwards, Glenn; van Bockxmeer, Frank; Watts, Gerald; Burnett, John
Pathology. 44(2):122-128, February 2012. DOI: 10.1097/PAT.0b013e32834efa07
FH: very high cholesterol exposure from birth, CHD earlier in life

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

FH - Clinical Diagnosis

• Well defined set of criteria to make the diagnosis of FH.
  – MEDPED (Make Early Diagnosis to Prevent Early Deaths)
  – Simon Broome Registry
  – Dutch Lipid Clinic Network
• All take into consideration a combination of the following:
  – Untreated LDL-C levels (>190 mg/dl; >155 mg/dl if <16yo)
  – Family history (LDL-C↑; premature CHD+)
  – Clinical history (premature CHD+)
  – Physical examination (presence of xanthomas; corneal arcus)
  – DNA analysis
Overlap of Clinical and Mutation Diagnosis of Heterozygous Familial Hypercholesterolemia

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

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Molecular Bases of FH
Why Is It Important to Know Them?

- Understanding of the genetic causes of FH has been instrumental in the development of lipid-lowering drugs
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• Understanding of the genetic causes of FH has been instrumental in the development of lipid-lowering drugs

• Knowledge of the genetic mutation(s) responsible for FH may improve adherence to therapeutic plan

• Knowledge of the genetic mutation(s) facilitate the identification of other family members affected by FH
Estimated % Diagnosed FH in Different Countries, as a Fraction of Those Predicted Based on a Frequency of 1/500 in the General Population

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
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HoFH is Caused by Mutations in Genes Affecting LDL Receptor Functionality

- The impaired LDLR functionality leads to a decreased clearance of LDL particles from plasma

HeFH
LDL-C >190 mg/dl

HoFH
LDL-C > 500 mg/dl
Molecular Causes of FH

**LDLR** (chr 19p13): Primary familial hypercholesterolemia
OMIM: 143890
FH Is Most Frequently Caused by *LDLR* Mutations

- Mutation in *LDLR* are found in ~95% of the confirmed cases of HoFH
- More than 1,000 *LDLR* mutations have been reported
- Based on the mutations patients can be divided in receptor negative (<2% activity) or receptor defective
- The type of mutations affect the LDL-C levels and the response to treatment
Molecular Causes of FH

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

**APOB (chr 2p24):** Familial defective Apo B OMIM: 144010
Molecular Causes of FH

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

**APOB (chr 2p24):** Familial defective Apo B OMIM: 144010

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

~95% due to mutations in LDLR gene
~5% due to other mutations in APOB, PCSK9 and LDLRAP1 (ARH) genes

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

**APOB** (chr 2p24): Familial defective Apo B OMIM: 144010

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

**LDLRAP1** (chr 1p36): Autosomal recessive hypercholesterolemia OMIM: 603813
What Is the Frequency of Mutations Affecting LDLR Functionality?

• Based on early estimates FH frequency is thought to be 1:500 for HeFH and 1,000,000 for HoFH

• Higher frequency is found in some populations (founder effect)

• Systematic genetic characterization of patients and relatives via cascade screening and exome sequencing suggests frequency >1:500 (~1:200)

• Recent advancements have demonstrated the genetic heterogeneity of subjects with clinical diagnosis of HoFH
Heterozygous FH – one mutation in one allele
True 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
Broad Spectrum of LDL-C levels in FH

LDL-C Levels Correlate With Residual LDLR Activity

# Penn HoFH Cohort: LDLR Negative Subjects Have a More Severe Phenotype

<table>
<thead>
<tr>
<th></th>
<th>LDLR negative (n=18)</th>
<th>LDLR defective (n=16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr) at visit 1</td>
<td>11.5 (3.3 - 29)</td>
<td>28.1 (3.3 - 44.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age at 1\textsuperscript{st} xanthomas</td>
<td>2.0 (0.25 - 4)</td>
<td>7.0 (1 - 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr) at FH dx</td>
<td>3.0 (0.5 - 7)</td>
<td>8.0 (2 - 17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dl) at dx</td>
<td>895 (602-1260)</td>
<td>686 (519-900)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (yr) at start of Rx</td>
<td>5.0 (1.2 - 10)</td>
<td>16.0 (2 - 31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (yr) at CAD</td>
<td>12.5 (6 - 16)</td>
<td>22.0 (16 - 37)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Lipid profile at visit 1**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>618 (238)</td>
<td>453 (162)</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>535 (214)</td>
<td>393(159)</td>
<td>0.040</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>388 (142)</td>
<td>293 (92)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Kolansky DM, Am J Cardiol 2008; 102:14-38-43
## LDL-C Levels Correlate With Residual LDLR Activity

<table>
<thead>
<tr>
<th>LDL-R mutation</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
</tr>
<tr>
<td>Receptor defective</td>
<td></td>
</tr>
<tr>
<td>G571E</td>
<td>5.68 ± 0.41</td>
</tr>
<tr>
<td>P664L</td>
<td>6.40 ± 0.35</td>
</tr>
<tr>
<td>V502M</td>
<td>6.19 ± 0.28</td>
</tr>
<tr>
<td>313+1g&gt;a</td>
<td>6.89 ± 0.40</td>
</tr>
<tr>
<td>D200G</td>
<td>6.74 ± 0.16</td>
</tr>
<tr>
<td>Receptor negative</td>
<td></td>
</tr>
<tr>
<td>ΔEx2–12</td>
<td>7.36 ± 0.29</td>
</tr>
<tr>
<td>Fs453</td>
<td>7.48 ± 0.17</td>
</tr>
<tr>
<td>G528D</td>
<td>7.76 ± 0.20</td>
</tr>
<tr>
<td>Fs572</td>
<td>8.24 ± 0.34</td>
</tr>
<tr>
<td>D558Y</td>
<td>8.19 ± 0.28</td>
</tr>
<tr>
<td>E207K</td>
<td>8.65 ± 0.42</td>
</tr>
<tr>
<td>ΔEx13,14</td>
<td>8.62 ± 0.45</td>
</tr>
<tr>
<td>Total</td>
<td>7.35 ± 0.09</td>
</tr>
</tbody>
</table>

Adapted from Table 2 in: Bertolini S et al. Atherosclerosis 2004;174: 57-65
Common Genetic Variants Contribute to the Lipid Phenotype in FH

• Common genetic variants of genes affecting LDL metabolism affect LDL-C levels in FH patients with a known mutation
  • Bertolini et al. 2004 (ApoE, apoB, MTP)
  • Talmud et al. Lancet 2013 (12 variants score)

• Common genetic variants of genes affecting LDL metabolism affect LDL-C levels in FH patients without a known mutation
  • Talmud et al. Lancet 2013 (12 variants score)
LDL-C Burden in Individuals With/Without FH as a Function of the Age of Initiation of Statin Therapy

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273

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Molecular Bases of FH and Drug Target Development

LDLR Synthesis is Tightly Regulated by an Intracellular Cholesterol Pool
LDLR and Cholesterol Synthesis Are Enhanced by Depletion of Intracellular Cholesterol
Statins Up-Regulate the LDLR

Statins → HMG-CoA → HMG-CoA reductase → Mevalonate → Cholesterol ↓ → LDLR ↑

- Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis.
Statins Up-Regulate the LDLR

• Statins are the first line of treatment for all forms of hypercholesterolemia, including HoFH
• Statins are very effective in lowering LDL-C in polygenic hypercholesterolemia and HeFH
• Statins efficacy in HoFH varies from minimal to ~30% reduction in LDL-C
  → LDLR defective patients respond better than LDLR negative patients
• Co-administration of with other lipid lowering treatments is frequently necessary
Most Lipid Lowering Drugs Affect LDL Catabolism By Up-Regulating the LDLR

- statins
- ezetimibe
- bile acid sequestrants
- PCSK9 -inhibitors
PCSK9 Inhibition Prevents the Degradation of The LDLR

Mullard A. Nature Reviews Drug Discovery . 2012.11, 817-819
PCSK9 Inhibition Prevents the Degradation of The LDLR

Mullard A. Nature Reviews Drug Discovery. 2012.11, 817-819
PCSK9 Levels Are Elevated in FH

Raal F et al. J Am Heart Assoc 2013;2:e000028
PCSK9 Inhibition Lower LDL-C in HeFH
Results From a Phase 2 Study
Novel Lipid Lowering Drugs Affect LDL Production by Inhibiting VLDL Secretion
Novel Lipid Lowering Drugs Affect LDL Production by Inhibiting VLDL Secretion

- Mipomersen
- Lomitapide

Diagram:
- Mipomersen inhibits apolipoprotein B (apoB) secretion.
- Lomitapide inhibits MTP (Microsomal triglyceride transfer protein).
- VLDL (very-low-density lipoprotein) production.
- LDL (low-density lipoprotein) and IDL (intermediate-density lipoprotein) metabolism.
Mipomersen Lowers LDL-C in FH

Rall FJ, Lancet 2010. 375: 998 - 1006
Lomitapide Lowers LDL-C in HoFH

Data are mean, 95% CI (n=23)

Cuchel et al, HoFH Phase 3 lomitapide study
Summary

• FH is an inherited disorder characterized by lifelong severe hypercholesterolemia and premature CVD
• FH is underdiagnosed
• FH is caused by mutations on *LDLR, APOB, PCSK9* and *LDLAP1*
• Mutations associated with LDLR negative status results in a more severe phenotype
• Common genetic variants contribute to the LDL-C levels
• Current and novel drugs have been developed based on the understanding of the molecular bases of FH