Genetics of Familial Hypercholesterolemia

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Presenter Disclosure Information

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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
 FH - Clinical Diagnosis

• 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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Why Is It Important to Know Them?

- 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 into 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
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**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 and Homozygous FH

- 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

LDL-CH (mmol/l)

Residual LDL-receptor activity (%)

N=32 HoFH

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 1st 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>
<tr>
<td><strong>Lipid profile at visit 1</strong></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<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>Receptor mutation</th>
<th>LDL-R mutation</th>
<th>LDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Range</td>
</tr>
<tr>
<td>Receptor defective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G571E</td>
<td>5.68 ± 0.41</td>
<td>4.19–7.33</td>
</tr>
<tr>
<td>P664L</td>
<td>6.40 ± 0.35</td>
<td>4.91–10.60</td>
</tr>
<tr>
<td>V502M</td>
<td>6.19 ± 0.28</td>
<td>4.20–8.52</td>
</tr>
<tr>
<td>313+1g&gt;a</td>
<td>6.89 ± 0.40</td>
<td>4.59–9.09</td>
</tr>
<tr>
<td>D200G</td>
<td>6.74 ± 0.16</td>
<td>4.00–11.41</td>
</tr>
<tr>
<td>ΔEx2–12</td>
<td>7.36 ± 0.29</td>
<td>4.78–10.90</td>
</tr>
<tr>
<td>Fs453</td>
<td>7.48 ± 0.17</td>
<td>3.91–12.29</td>
</tr>
<tr>
<td>G528D</td>
<td>7.76 ± 0.20</td>
<td>4.73–11.98</td>
</tr>
<tr>
<td>Fs572</td>
<td>8.24 ± 0.34</td>
<td>4.64–12.16</td>
</tr>
<tr>
<td>D558Y</td>
<td>8.19 ± 0.28</td>
<td>4.90–11.74</td>
</tr>
<tr>
<td>E207K</td>
<td>8.65 ± 0.42</td>
<td>5.09–10.66</td>
</tr>
<tr>
<td>ΔEx13,14</td>
<td>8.62 ± 0.45</td>
<td>7.00–10.04</td>
</tr>
<tr>
<td>Total</td>
<td>7.35 ± 0.09</td>
<td><strong>3.91–12.29</strong></td>
</tr>
</tbody>
</table>

Adapted from Table 2 in: Bertolini S et al. Atherosclerosis 2004;174: 57-65

N=570 HeFH
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

PROBLEM: ↑LDL-C

MECHANISTIC RESEARCH:
clinical, biochemical, cellular, genetic

MECHANISTIC INSIGHT:
LDL receptor clears LDL particles

CLINICAL TRIALS:
statin effects on biochemistry, angiography, CVD endpoints, mortality

MONOGENIC MODEL:
Familial hypercholesterolemia

FUNDAMENTAL DISCOVERY:
LDL receptor and receptor-mediated endocytosis → Nobel prize

DRUG TARGET:
statins to upregulate LDL receptor

IMPACT ON PRACTICE:
statins = standard of care

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 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

Raal F et al. Circulation 2012;126:2408-2417
Novel Lipid Lowering Drugs Affect LDL Production by Inhibiting VLDL Secretion
Novel Lipid Lowering Drugs Affect LDL Production by Inhibiting VLDL Secretion

Mipomersen

Lomitapide
Mipomersen Lowers LDL-C in FH
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 \textit{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