Homozygous Familial Hypercholesterolemia: Genetics, Diagnosis, and Guidelines

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Department of Vascular Medicine AMC Amsterdam

Disclosures

Dr. Kees Hovingh is consultant and speaker for biotechas well as pharmaceutical companies that develop molecules that influence lipoprotein metabolism, including Regeneron, Pfizer, MSD, Sanofi, Kowa, ISIS, Amgen, Roche and Genzyme.

Kees Hovingh is head of the Clinical trial unit AMC, and PI for clinical trials in dyslipidemia conducted with i.e.Amgen, Sanofi, Lilly, Novartis, Kowa, Genzyme, Cerenis, Pfizer, Astra
hoFH is an extremely rare (1:1,000,000,000) non-curable disease, characterized by uniform clinical stigmata, leading to premature cardiovascular disease.

**Age of onset of coronary atherosclerosis in FH heterozygotes (angiography)**

to new insights..

..(ho)FH is a not-so-rare disease, which encompasses a broad spectrum of clinical phenotypes. We can’t cure (yet), but we can redirect the phenotype...

European Perspective

Clinical update

Homozgyous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

What is the prevalence of hoFH?
The initial observations

Hyperlipidemia in Coronary Heart Disease

II. GENETIC ANALYSIS OF LIPID LEVELS IN 176 FAMILIES
AND DELINEATION OF A NEW INHERITED DISORDER,
COMBINED HYPERLIPIDEMIA

Joseph L. Goldstein, Helmut C. Schott, William R. Hazzard,
Edwin L. Rehman, and Aero G. Montalvo with the technical
assistance of Ellen D. Campbell and Mary Jo Levinson.

From the Departments of Medicine (Division of Medical Genetics, University
Hospital, and Division of Metabolism and Gerontology, Veterans Administration
Hospital) and Genetics, University of Washington, Seattle, Washington 98195

Frequency of hyperlipidemia. Although our calculated figures for the frequency of the three monogenic lipid disorders in the general population are indirect and represent conservative estimates, a heterozygote frequency of 0.1–0.2% for familial hypercholesterolemia agrees with the finding of the Framingham study in which about 1 in 850 individuals in the general population were observed with hypercholesterolemic xanthomatosis (31). Until detailed studies are performed on the families of hyperlipidemic individuals selected at random from the general population, the heterozygote frequencies reported here should be considered only as approximate. Assuming, however, that our
The European follow up... #1

**Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication**

Marianne Benn, Gerald F. Watts, Anne Tybjaerg-Hansen, and Børge G. Nordestgaard

Benn M et al Clin Endocrinol Metab. 2012, 97(11):3956 –3964
Copenhagen Heart Study

- Prospective study starting in 2003
- Copenhagen, Denmark
- app 69000 IDs; Caucasian.
- DLCN criteria
Copenhagen Heart Study

<table>
<thead>
<tr>
<th>Cholesterol-lowering medication, off/on</th>
<th>Definite/probable</th>
<th>Diagnostic category of FH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Off</td>
<td>On</td>
</tr>
<tr>
<td>Number</td>
<td>250</td>
<td>242</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/liter)</td>
<td>6.5 (5.1–6.8)^a</td>
<td>4.7 (3.8–5.1)^a</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/liter); metabolic syndrome</td>
<td>6.5 (5.3–6.9)</td>
<td>4.8 (3.9–5.2)</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/liter); diabetes mellitus</td>
<td>5.6 (4.2–6.5)^a</td>
<td>4.7 (4.4–5.2)^a</td>
</tr>
<tr>
<td>Total cholesterol (mmol/liter)</td>
<td>8.6 (7.5–9.4)^a</td>
<td>7.0 (6.3–7.6)^a</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dl)</td>
<td>182 (158–208)^a</td>
<td>148 (127–173)^a</td>
</tr>
<tr>
<td>Triglycerides (mmol/liter)</td>
<td>1.9 (1.3–2.7)</td>
<td>1.8 (1.2–2.6)</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/liter)</td>
<td>1.4 (1.2–1.7)</td>
<td>1.4 (1.2–1.7)</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg/dl)</td>
<td>158 (141–178)</td>
<td>163 (142–182)</td>
</tr>
</tbody>
</table>

The American way...

**LETTER**

Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction

A list of citations and their abbreviations appears at the end of the paper.

**Discovery exome sequencing**

1,027 early-onset MI cases

985 control Mi-free controls

**Age**

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

Do et al Nature 2015
The European follow up... #1 The Dutch Experience

16.8 x 10^6 inhabitants

Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome

Barbara Sjouke1, D. Meelke Kusters1, Iris Kindt2, Joost Besselink1, Joep C. Defesche1, Eric J.G. Sijbrands4, Jeanine E. Roeters van Lennep4, Anton F.H. Stalenhoef5, Albert Wiegman4, Jacqueline de Graaf6, Sigrid W. Foucier7, John J.P. Kastelein6,7, and G. Kees Hovingh1,7*
Methods

Patients in database DNA diagnostics laboratory AMC, Amsterdam
N = 104,682

Double ADH mutation carriers
N = 178

Excluded patients n = 129
Non-pathogenic mutation n = 94
Double heterozygotes n = 25
Reside outside NL n = 9
Died n = 1

N = 49
Collection medical records

HoADH in the Netherlands

- 20 HoFH
- 25 Compound HeFH
- 4 HoFDB patients
  - Ho/CompHeFH (LDLR)
  - HoFDB (APOB)
### HoADH in the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Homozygotes</th>
<th>Compound heterozygotes LDLR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDLR</td>
<td>APOB</td>
</tr>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Age (range)</td>
<td>35.9 (3.3–76.0)</td>
<td>56.5 (33.1–77.5)</td>
</tr>
<tr>
<td>Female sex</td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td>Cardiovascular disease* (percentage)</td>
<td>6 (30%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>CHD</td>
<td>5 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PVD</td>
<td>1 (5)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Lipid levels not on LLT*(SD)

<table>
<thead>
<tr>
<th></th>
<th>LDLR</th>
<th>APOB</th>
<th>LDLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>13.6 (± 5.2)</td>
<td>10.9 (± 1.8)</td>
<td>15.3 (± 4.5)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>12.6 (± 6.4)</td>
<td>7.8</td>
<td>13.4 (± 4.7)</td>
</tr>
</tbody>
</table>

Lipid levels on LLT*(SD)

<table>
<thead>
<tr>
<th></th>
<th>LDLR</th>
<th>APOB</th>
<th>LDLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>7.3 (± 2.8)</td>
<td>7.2 (± 2.8)</td>
<td>8.3 (± 3.5)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>5.7 (± 2.8)</td>
<td>5.0 (± 2.0)</td>
<td>6.6 (± 3.5)</td>
</tr>
</tbody>
</table>

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![Graph showing LDL-C levels before and after LLT](image-url)

- **+** 2 null alleles
- **菱** 1 null allele, 1 defective
- **■** 2 defective alleles

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11/10/2015
# Double Heterozygous Carriers in the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Double Hets</th>
<th>Relatives</th>
<th>Hom/Comp hets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDLR/APOB</td>
<td>LDLR/PCSK9</td>
<td>LDLR</td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Age (range)</td>
<td>46.0 (6-73)</td>
<td>58.7 (51-64)</td>
<td>55.1 (23-89)</td>
</tr>
<tr>
<td>Female sex</td>
<td>55%</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td>CVD (n, %)</td>
<td>7 (32)</td>
<td>1 (33)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Lipids not on LLT†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>10.7 ± 2.9</td>
<td>14.5 ± 3.1</td>
<td>9.5 ± 3.1</td>
</tr>
<tr>
<td>LDL-C</td>
<td>7.8 ± 2.3</td>
<td>12.6 ± 3.2</td>
<td>6.5 ± 2.7</td>
</tr>
<tr>
<td>Lipid on LLT†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>5.4 ± 0.8</td>
<td>5.3 ± 0.7</td>
<td>5.2 ± 1.6</td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.7 ± 0.8</td>
<td>3.7 ± 0.5</td>
<td>3.2 ± 1.5</td>
</tr>
</tbody>
</table>

Sjouke and Hovingh, MS in preparation

# Double heterozygous carriers in the Netherlands

![Graph showing cholesterol levels before and after LLT treatment]
LDL-C Diversity in HoFH

- LDL cholesterol
  - mmol/L
  - mg/dL
- Clinical diagnosis
- Mutation diagnosis
  - Homozygous LDL-receptor negative
  - Homozygous LDL-receptor defective or homozygous LDLRAP1/ARH
  - Homozygous APOB defect/PCSK9 gain of function
  - Compound heterozygous LDL-receptor APOB/PCSK9

hoFH; the diagnosis

- Pedigree analysis
- Genomic analysis
- Normal subject
- FH heterozygote
- FH homozygote
- Normal allele
- FH mutation-bearing allele
hoFH; the diagnosis

hoFH; the diagnosis
hoFH; the diagnosis

- Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus

OR

- untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years
  or
  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH
hoFH; the diagnosis

Photographs kindly provided by Prof. Eric Bruckert and Prof. Frederick Raal.

Cost per genome
Cost per genome

- Cost per Genome
- Moore's Law

1000 USD Genome
NGS

Targeted next-generation sequencing in monogenic dyslipidemias

Robert A. Haggard, Matthew R. Burns, H. Andrew Salle, Adam D. McIntyre, John F. Robinson, and Jian Wang

NGS

48 IDs with SB FH (with tandon xanthomas)
Exome sequencing: Coverage
Mutation detection: 17 LDLR mutations and 3 apoB mutations not detected by standard diagnostic procedure
25 gene panel
430 individuals:
LDL-C above 5 mmol/L: 60% mutations
LDL-C above >9 mmol/L: 100% mutations
“unpublished”

Targeted next-generation sequencing in monogenic dyslipidemias

Robert A. Hegato, Matthew R. Ban, Hennian Cao, Adam D. Molnyra,
John F. Robinson, and Jian Wang

2025?
HoADH Guideline

Homozygous Familial Hypercholesterolaemia
LDL-C targets:
- <2.5 mmol/L
- <3.5 mmol/L
- <1.8 mmol/L

At diagnosis
Lifestyle and Diet + Statin
(most efficacious at highest dose depending on tolerability)

Ezetimibe 10 mg + resins or other drugs
(possibly, nicotinic acid, probucol (use of these additional treatments may be limited by tolerability and drug availability)

New Therapeutic options

Future Therapeutic options
PCSK9 inhibitors
CTP inhibitors
Gene therapy

LDL-Apheresis
As early as possible if available (by 5 years, no later than 8 years)
every 1 or 2 weeks

In selected patients
Liver Transplant

Lomitapide
Approved by FDA, EMA

Hipomersen
Approved by FDA

The future of FH
FH - research: a shared responsibility

Database

Patient and Family

Physician

Interactive-web based
The Power of big data..

big data ... “small” deltas, but potential large impact on understanding of disease....

Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication

Benn et al. JCEM 2012 2012 Nov;97(11):3956-6

Original Investigation

Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus

Josott Besseling, MD, John J. R. Kastelan, MD, PhD, Joep C. Defoche, PhD, Barbara A. Hutter, PhD, MSc, C. Ikens Heusingh, MD, PhD

JAMA. 2015 Mar 10;313(10):1029-36

If you want to go fast,
go alone.
If you want to go far,
go together.

African proverb
HICC
HoADH International Clinical Collaboration

FH; NO BORDERS
hoFH; Conclusion

- Prevalence app 1:400,000
- Genetic disease
- Wide range in phenotypes
- New therapies around the corner

Acknowledgement

All patients and their doctors and special thanks to
Drs. Barbara Sjouke, AMC
Dr. Roeters van Lennep Erasmus University Hospital Rotterdam
Prof. Jacqueline de Graaf, Nijmegen University Hospital