FAMILIAL HYPERCHOLESTEROLEMIA

Amazingly prevalent and astonishingly diverse

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Monday May 25th
What is the prevalence of hoFH and heFH?
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 G. Schrott, William R. Hazzard, Edwin L. Bierman, and Arno G. Motulsky with the technical assistance of Ellen D. Campbell and Mary Jo Levinski

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

Goldstein et al J Clin Invest. 1973;52:1544-1568
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
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The European numbers

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

The bar chart shows the prevalence of definite or probable FH (familial hypercholesterolemia) by age and gender. The x-axis represents age groups: 20-39, 40-59, 60-79, 80+, and All. The y-axis represents the prevalence in percent (%). The chart distinguishes between women (red bars) and men (blue bars). The prevalence is also shown as a fraction, with the y-axis ranging from 1/400 to 1/100.
The American way...

LETTER

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

A list of authors and their affiliations appears at the end of the paper

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

Discovery exome sequencing

1,027 early-onset MI cases
946 older MI-free controls

Age
Do et al Nature 2015
The European follow up...

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. Meeike Kusters¹, Iris Kindt², Joost Besseling¹, Joep C. Defesche³, Eric J.G. Sijbrands⁴, Jeanine E. Roeters van Lennep⁴, Anton F.H. Stalenhoef⁵, Albert Wiegman⁶, Jacqueline de Graaf⁵, Sigrid W. Fouchier³, John J.P. Kastelein¹,⁷*, 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
HoADH in the Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Homozygotes</th>
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<th>Compound heterozygotes LDLR</th>
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<tbody>
<tr>
<td></td>
<td>LDLR</td>
<td>APOB</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>20</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Age (range)</td>
<td>35.9 (3.3–76.0)</td>
<td>56.5 (33.1–77.5)</td>
<td>35.0 (3.1–65.2)</td>
</tr>
<tr>
<td>Female sex</td>
<td>60%</td>
<td>75%</td>
<td>44%</td>
</tr>
<tr>
<td>Cardiovascular disease* (percentage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>6 (30)</td>
<td>1 (25)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>5 (25)</td>
<td>0 (0)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>PVD</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lipid levels not on LLTb (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 (± 5.8)</td>
<td>7.8</td>
<td>13.4 (± 4.7)</td>
</tr>
<tr>
<td>Lipid levels on LLTb (SD)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>7.3 (± 2.8)</td>
<td>7.2 (± 2.8)</td>
<td>8.2 (± 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>
HoADH in the Netherlands

- 2 null alleles
- 1 null allele, 1 defective
- 2 defective alleles
The Numbers, conclusion

- HoFH: 1:300,000
- heFH: 1:230
FH; “one disease?”

clinical +, mutation -

EAS-consensus

patient: treat LDL-C
family: “monitor LDL-C”

clinical +, mutation +

patient: treat LDL-C
family: mutation test
consider to treat LDLC

clinical -, mutation +

patient: monitor LDL-C
family: monitor LDL-C

Nordestgaard B et al Eur H J 2013;34:3478
Does genetics matter?

Intervention is based on LDL-C, not on genetic result
HoFH: wide range of LDL-C values,
what about heFH?
FH; diversity in LDL-C = diversity CVD risk

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

HoFH
HeFH
Unaffected individuals

Threshold for CHD:
Reached by age 20 in for those with HoFH;
>60 in healthy individuals

HoFH: wide range of LDL-C values; what about heFH?

Besseling, Hovingh, work in progress

![Graph showing LDL-C values per age category](image)

**No. of patients**
- **FH patients**: 2,518, 3,838, 3,271, 4,092, 4,221, 3,596, 2,508, 1,774
- **Unaffected relatives**: 2,253, 4,011, 3,690, 5,121, 6,675, 6,858, 4,984, 3,036

**Age categories (years)**
- 0-9
- 10-19
- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70+
Is this related to the “distance to index”? 
LDL-C (with 95% CI) per distance-to-index

- Heterozygous FH
- Unaffected
heFH; diabetes

Original Investigation

Association Between Familial Hypercholesterolemia and Prevalence of Type 2 Diabetes Mellitus

Joost Besseling, MD; John J. P. Kastelein, MD, PhD; Joep C. Defesche, PhD; Barbara A. Hutten, PhD, MSc; G. Kees Hovingh, MD, PhD

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of Type 2 Diabetes</th>
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<tbody>
<tr>
<td></td>
<td>Familial Hypercholesterolemia</td>
<td>Unaffected Relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. /Total</td>
<td>% (95% CI)</td>
<td>No. /Total</td>
<td>% (95% CI)</td>
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<tr>
<td>Overall comparison</td>
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<tr>
<td>Unadjusted</td>
<td>440/25 137</td>
<td>1.75 (1.59-1.91)</td>
<td>1119/38 183</td>
<td>2.93 (2.76-3.10)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>177/12 300^C</td>
<td>1.44 (1.22-1.69)</td>
<td>812/24 898^C</td>
<td>3.26 (3.04-3.48)</td>
</tr>
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JAMA. 2015 Mar 10;313(10):1029-36
What we do not know...

- CVD risk in statin treated FH patients (prior and after first event)

- whether the new Rx’s (ie Mipo, Lojuxta, CETPi, PCSK9i) do result in additional CVD risk reduction

- the physiological substrate is for the FH-LDL-DM findings
The Power of big data..

big data ... “small” deltas, but potential large impact on understanding of disease....
MISSION STATEMENT FOR FHSC-HICC:
To empower the medical/global community to provide insight in the current status of detection and treatment of homozygous autosomal dominant hypercholesterolemia (hoADH) in order to promoting early diagnosis and more effective treatment of this condition.
Summary FH

• FH: more prevalent than originally thought
• FH: genetics: NGS around the corner
• FH screening: cost effective (cascade screening)