Identifying and Preventing Cardiovascular Disease in individuals with Familial Hypercholesterolemia

Kristin Oehlke, MS, CGC
MCH/CYSHN Geneticist
The Minnesota Department of Health
June 2016
Summary

• FH is characterized by elevated LDL-C levels, is under diagnosed and under treated
• Phenotype includes atherosclerosis and early onset CVD
• Estimated to occur in 1 in 200-500 individuals the population
• Inheritance is autosomal dominant, caused primarily by mutations in 3 genes and identifies families at risk for early CVD
• Optimal health outcomes occur if diagnosis and treatment occur in childhood as soon as diagnosis is made
• Treatment involves lipid-lowering medications, diet and lifestyle interventions
• Once an individual has been diagnosed with FH, up to 50% of relatives may also be affected and most may not know of their risk
Definition of Familial Hypercholesterolemia (FH)

• Autosomal co-dominant high LDL-C
  • Easiest to recognize when examining lipid levels within a family
  • Family history of early-onset CVD (M <55, F <60)
  • Most affected family members have heterozygous FH (HeFH)

• Prevalence of homozygous FH (HoFH) is rare:
  • Estimated to be 1 in 1 million
  • Both parents have HeFH
  • Gene dosage effect ➔ much higher LDL-C and earlier onset of CVD than HeFH
    • Severe vascular disease by mid 20’s
    • Aortic stenosis
    • Xanthomas around eyelids and on tendons of the elbows, hands, knees, and feet

Familial Hypercholesterolemia - GeneReviews® - NCBI Bookshelf, Article found here:
http://www.ncbi.nlm.nih.gov/books/NBK174884/
Diagnosing FH

• Extreme hypercholesterolemia
• Clinical history of premature coronary heart disease (CHD) caused by plaque build-up and subsequent plaque rupture in the coronary arteries [Rosamond et al 2007, Reiner et al 2011].
  • Presentation may include angina pectoris, myocardial infarction, peripheral vascular disease
• Findings on physical examination (xanthomas, corneal arcus)
  • Not always present, especially in young people
• Family medical history of early CVD, especially if suggests autosomal dominant inheritance
• Presence of a pathogenic variant in a gene known to be associated with FH

FH is Underdiagnosed and Undertreated
Frequency of FH in the Population

• Frequency estimated to be 1:500 to 1:200 for HeFH and 1:1,000,000 for HoFH
• Higher frequency is found in some populations (founder effect)
  • Afrikaners, French Canadians, Lebanese,
• 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
Homozygous FH (HoFH)

• Historically the first FH syndrome to be recognized
  • Xanthoma multiplex
    • Irregular yellow patch or nodule on the skin, caused by deposition of lipids.
    • Often found around the eyes, the joints, the neck or the palms, or over tendons
    • May be found through the body

• Dramatic presentation at a young age

• Three genes: LDLR, APOB, PCSK9

• Complete or severe impairment of LDLR activity

• Compound heterozygote most common form
  • Inherit a different LDLR mutation from each parent
  • Parents affected with HeFH

• Double heterozygous LDLR/APOB, LDLR/PCSK9 cases described
  • HoFH phenotype if untreated
  • More responsive to therapy than classical HoFH
Criteria for Diagnosis of HoFH

• Elevated serum total and LDL cholesterol
  • Total Cholesterol 500 to 650 mg/dL or higher
  • LDL-C >400 mg/dL

• Xanthomas in the first decade of life

• Both parents have HeFH

• LDL Receptor mutation or functional deficit
  • True HoFH, compound HeFH, Double HeFH
  • <30% normal LDL uptake by cultured fibroblasts
US MEDPED Diagnostic Criteria for Heterozygous FH

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>First degree relative with FH</th>
<th>Second degree relative with FH</th>
<th>Third degree relative with FH</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (5.7)</td>
<td>230 (5.9)</td>
<td>240 (6.2)</td>
<td>270 (7.0)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>240 (6.2)</td>
<td>250 (6.5)</td>
<td>260 (6.7)</td>
<td>290 (7.5)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>270 (7.0)</td>
<td>280 (7.2)</td>
<td>290 (7.5)</td>
<td>340 (8.8)</td>
</tr>
<tr>
<td>&gt;= 40</td>
<td>290 (7.5)</td>
<td>300 (7.8)</td>
<td>310 (8.0)</td>
<td>360 (9.3)</td>
</tr>
</tbody>
</table>

*The total cholesterol cutpoints for FH is dependent upon the confirmed cases of FH in the family. If FH is not diagnosed in the family, then the cutpoint for diagnosis is as per “general population.”

# UK Simon Broome FH Register Diagnostic Criteria for Heterozygous FH

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>DNA-based diagnosis: mutation in any of the genes that cause HeFH</td>
</tr>
<tr>
<td>B</td>
<td>Tendon xanthomas in the patient or any 1st or 2nd degree relatives</td>
</tr>
<tr>
<td>C</td>
<td>MI by age 50 years in a 2nd degree relative or 60 years in a 1st degree relative</td>
</tr>
<tr>
<td>D</td>
<td>Plasma Total Cholesterol &gt;290 mg/dL in any 1st or 2nd degree relative</td>
</tr>
<tr>
<td>E</td>
<td>Total Cholesterol &gt; 290 mg/dL (adult patient) or &gt;259 mg/dL (child &lt;16 years)</td>
</tr>
<tr>
<td>F</td>
<td>LDL-C &gt; 190 mg/dL (adult patient) or &gt;155 mg/dL (child aged &lt;16 years)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite HeFH</td>
<td>A or B + (E or F)</td>
</tr>
<tr>
<td>Probable HeFH</td>
<td>C + (E or F) or D + (E or F)</td>
</tr>
</tbody>
</table>

# Dutch Lipid Clinic Diagnostic Criteria

<table>
<thead>
<tr>
<th>Family History</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with premature CVD (M &lt;55, F &lt;60)</td>
<td>1</td>
</tr>
<tr>
<td>First degree relative with LDL-C &gt; 95th percentile</td>
<td>1</td>
</tr>
<tr>
<td>First degree relative with tendon xanthomas and/or arcus</td>
<td>2</td>
</tr>
<tr>
<td>Children &lt; 18 with LDL-C &gt; 95th percentile</td>
<td>2</td>
</tr>
<tr>
<td><strong>Personal History of CVD</strong></td>
<td></td>
</tr>
<tr>
<td>Premature CHD (M &lt;55, F &lt;60)</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral or peripheral vascular disease (M 55, F &lt;60)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
</tr>
<tr>
<td>Tendon xanthomas</td>
<td>6</td>
</tr>
<tr>
<td>Arcus senilis in patients &lt;45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>LDL-C level (mg/dL)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;330</td>
<td>8</td>
</tr>
<tr>
<td>250 – 329</td>
<td>5</td>
</tr>
<tr>
<td>190 – 249</td>
<td>3</td>
</tr>
<tr>
<td>155 - 189</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA Analysis</strong></td>
<td></td>
</tr>
<tr>
<td>Functional mutation of LDL receptor gene</td>
<td>8</td>
</tr>
</tbody>
</table>

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

**Definite FH:** >8 points

**Probable FH:** 6 – 8 points

**Possible FH:** 3 – 5 points
Guidelines for Screening Pediatric Populations

• Universal screening between 9 – 11 years & again at 17 – 21 years of age
  • Lipid levels are relatively stable until puberty, then often go down
  • Difference in LDL-C between HeFH and non-FH is most evident
  • Not all ped cardiologists agree on the timing for screening
    • Variability in age, familial and/or ethnic variation in onset of puberty
    • Best plan- consult with referral cardiac specialist

• Screen at age 2 years or later in FH families
  • Rule out hypothyroidism, nephrotic syndrome and liver disease

• Start statin tx at 10 years if LDL stays .190 mg.dL
  • Consider bile acid sequestrant as

• Earlier tx in HoFH

Daniels et al 2011 J Clin Lipidol 5:530
Bamba 2014 J Clin Endocrinol Metab 99:3093
Overlap of clinical and mutation diagnosis of heterozygous FH

Clinical diagnosis without mutation

Patient: treat LDL
Family: monitor LDL and consider treatment

Mutation without clinical diagnosis

Patient: monitor LDL and consider treatment
Family: monitor LDL and consider treatment

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
Power of Prevention: Cumulative Event-Free Survival (%) in FH

Nordestgaard et al. Eur Heart J 2013;34:3478
FH Family Tree

Index case: start of cascade screening

Man

Death 76 yrs No CHD LDL 3.8

Age 50 yrs No CHD LDL 3.3

Woman

Age 78 yrs CHD 58 yrs LDL 7.4

Age 48 yrs CHD 48 yrs LDL 8.3

Age 47 yrs No CHD LDL 2.4 mmol/L

Age 18 yrs LDL 2.2 mmol/L

Age 15 yrs LDL 6.1 mmol/L

Age 8 yrs LDL 5.6 mmol/L

Nordestgaard et al. Eur Heart J 2013;34:3478
All known genes responsible for autosomal dominant FH impair LDL receptor activity
- 50% LDL catabolic rate of normal ➔ 2x increase in LDL in HeFH

LDL Receptor gene: (60% - 80%) of HeFH
- Over 1700 mutations in LDL receptor gene known

ApoB (1% - 5% of HeFH)
- 3 mutations causing FH documented

PCSK9 (0% - 3% of HeFH)
- Gain of function mutations cause FH

Unknown (20% - 40%)

Heterozygous vs. Homozygous FH

Heterozygous FH – one mutation in one allele

True homozygous FH – same mutation in both alleles of the same gene

Compound heterozygous FH – different mutations in two alleles of the same gene

Double heterozygous FH – different mutations in two alleles of different genes
# Summary of Molecular Genetic Testing Used in FH

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of FH Attributed to Pathogenic Variants in This Gene</th>
<th>Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>60%-80%</td>
<td>Sequence analysis ³, ⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis ⁴, ⁵</td>
</tr>
<tr>
<td>APOB</td>
<td>1%-5%</td>
<td>Targeted analysis for pathogenic variants ⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequence analysis ³,⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis ⁵, ⁷</td>
</tr>
<tr>
<td>PCSK9</td>
<td>0%-3%</td>
<td>Targeted analysis for pathogenic variants ⁶</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sequence analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion/duplication analysis ⁵, ⁷</td>
</tr>
<tr>
<td>Unknown</td>
<td>20%-40%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Evaluations Following Initial Diagnosis

- Pre-treatment lipid values and lipoprotein(a) levels when possible
- Exclusion of concurrent illnesses (kidney disease, acute myocardial infarction, infection) that can affect lipid values
- Lipid panel including total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density, lipoprotein cholesterol (HDL-C), and triglycerides
- Consultation with a lipid specialist or clinician with expertise in FH
- Medical genetics consultation
Treatment for Adults with FH

• Cholesterol-lowering drug therapy
• Aggressive management for risk factor reduction
• Regular physical activity, a healthy diet (reduce saturated fat intake, increase intake of soluble fiber to 10-20 g/day), and weight control should be emphasized.
• Blood pressure maintained at 140/90mmHg (or 130/80 mm Hg for diabetics).
• Low-dose aspirin (75-81 mg/day) should be considered in those at high risk for CHD or stroke.
• Consider referral to a lipid specialist with expertise in FH if LDL-C concentrations are not reduced with maximal medical therapy
  • Recommendation generally pertains to LDL-C levels that cannot be reduced by ≥50% with maximal medical therapy over a 6-month period.
• Testing of 1st-degree and 2nd-degree relatives of all individuals with FH

Treatment for Children with FH

• Consultation or referral to a lipid specialist is recommended.
• Management of diet and physical activity is recommended at an early age.
• Statins are the preferred initial pharmacologic treatment in children.
  • Consideration should be given to starting statin treatment at age 8 yrs or older.
  • In children with homozygous FH, drug treatment needs to be initiated < age 8 yrs.
• The goal of lipid lowering therapy in children with FH is ≥50% reduction in LDL-C or LDL-C <130 mg/dL (<3.4 mmol/L)
  • More aggressive lowering of LDL-C levels should be considered for children with additional CHD risk factors (e.g., family history of CHD, high blood pressure, unhealthy diet or exercise behaviors, obesity).

Familial Hypercholesterolemia - GeneReviews® - NCBI Bookshelf, Article found here:
http://www.ncbi.nlm.nih.gov/books/NBK174884/
Agents/Circumstances to Avoid at Any Age

- Smoking
- High intake of saturated and transunsaturated fat
- Excessive intake of cholesterol
- Sedentary lifestyle
- Obesity
- Hypertension
- Diabetes mellitus
Current Recommended Drug Therapies for Adults with FH (1)

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary and Secondary Mechanism of Action</th>
<th>LDL-Lowering Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomitapide (Juxtapid®)</td>
<td>↓ microsomal triglyceride transfer protein activity ($1^O$); inhibition of LDL production ($2^O$)</td>
<td>50% [Cuchel et al 2013]</td>
</tr>
<tr>
<td>Mipomersen (Kynamro™)</td>
<td>Targeted ApoB mRNA degradation (antisense) ($1^O$)</td>
<td>35% [Hair et al 2013]</td>
</tr>
<tr>
<td>Ezetimibe (Zetia®)</td>
<td>↓ Cholesterol absorption in the intestine ($1^O$)</td>
<td>17% [Patel et al 2003]</td>
</tr>
<tr>
<td>Statins</td>
<td>↑ LDLR activity ($1^O$)</td>
<td>&gt;35% $^2$ [Kastelein et al 2008]</td>
</tr>
</tbody>
</table>

### Current Recommended Drug Therapies for Adults with FH (2)

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary and Secondary Mechanism of Action</th>
<th>LDL-Lowering Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants (cholestyramine, colesevelam)</td>
<td>↓ Bile acid re-absorption (1⁰); ↑ LDLR activity (2⁰)</td>
<td>15% ² [Rader et al 2003]</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors (ezetimibe)</td>
<td>↓ Cholesterol absorption (1⁰); ↑ LDLR activity (2⁰)</td>
<td>15% ² [Rader et al 2003]</td>
</tr>
<tr>
<td>Stanol esters</td>
<td>↓ Cholesterol absorption (1⁰); ↑ LDLR activity (2⁰)</td>
<td>10% ² [Rader et al 2003]</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓ VLDL synthesis (1⁰)</td>
<td>20% ² [Rader et al 2003]</td>
</tr>
</tbody>
</table>

LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy.

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
Cascade Screening

• Many individuals with FH identified in families
  • 50% of 1\textsuperscript{st} degree relatives have FH
  • 25% of 2\textsuperscript{nd} degree relatives have FH
  • Estimated at 0.2\% - 0.5\% (1 in 200-500) in the general population

• Most cost-effective means to identify affected relatives of index case

• Infrequently performed in a clinical setting

• Within a FH pedigree, LDL-C level is 90\% - 95\% sensitive and specific as compared to genetic testing

• Find younger FH patients and prevent CVD

Paul Hopkins, MD, MSPH, Cardiovascular Genetics Lab, University of Utah
Cascade Testing Issues in FH (1)

• Notification of relatives at risk of FH should generally not be instituted without the consent of the index case.

• National and local healthcare service protocols concerning disclosure of medical information without consent should be consulted.

• A proactive approach that respects privacy, justice, and autonomy is required.

• All material communicated to relatives and the telephone approach should be comprehensible and not cause alarm.

• Pre-testing counseling should be offered to at risk family members of an index case prior to phenotypic or genetic testing.
Cascade Testing Issues in FH (2)

• If genetic testing detects a causative mutation, a definitive diagnosis of FH can be made, particularly when the phenotype also suggests FH

• If genetic testing does not detect a causative mutation, the diagnosis of FH can be excluded, except when the clinical phenotype is highly suggestive of FH

• If genetic testing detects a causative mutation but the phenotype does not suggest FH, then a definitive diagnosis of FH should not be made
  • the person and family should be monitored every 2–5 years for LDL cholesterol levels

• Genetic testing may have implications for insurance coverage in certain countries

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
### Identifying Relatives of Index Case with FH

<table>
<thead>
<tr>
<th>Age</th>
<th>First Degree</th>
<th>Second Degree</th>
<th>Third Degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (155)</td>
<td>230 (165)</td>
<td>240 (170)</td>
</tr>
<tr>
<td>20-29</td>
<td>240 (170)</td>
<td>250 (180)</td>
<td>260 (185)</td>
</tr>
<tr>
<td>30-39</td>
<td>270 (190)</td>
<td>280 (200)</td>
<td>290 (210)</td>
</tr>
<tr>
<td>40+</td>
<td>290 (205)</td>
<td>300 (215)</td>
<td>310 (225)</td>
</tr>
</tbody>
</table>

Summary

• FH is characterized by elevated LDL-C levels, is under diagnosed and under treated
• Phenotype includes atherosclerosis and early onset CVD
• Estimated to occur in 1 in 200-500 individuals the population
• Inheritance is autosomal dominant, caused primarily by mutations in 3 genes and identifies families at risk for early CVD
• Optimal health outcomes occur if diagnosis and treatment occur in childhood as soon as diagnosis is made
• Treatment involves lipid-lowering medications, diet and lifestyle interventions
• Once an individual has been diagnosed with FH, up to 50% of relatives may also be affected and most may not know of their risk
Selected References


• Nordestgaard et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;34:3478


• Bamba. Update on Screening, Etiology, and Treatment of Dyslipidemia in Children. *J Clin Endocrinol Metab* 2014;99: 3093
