Familial Hypercholesterolemia: Under Recognized and Under Treated

Steve Kopecky MD FACC FAHA FACP
Professor of Medicine
Division of Cardiovascular Diseases
Mayo Clinic

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Minnesota Academy of Physician Assistants
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Stephen L Kopecky

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- Prime Therapeutics – Formulary Committee

Board of Directors
- Mayo Clinic Support Services, Texas
- American Society for Preventive Cardiology, IPP
- American Society for Men’s Health
Familial Hypercholesterolemia (FH)

- What is FH?
- What causes FH?
- How do you diagnose FH?
- Once found, should you screen family members with FH?
- How do you treat FH?
Familial hypercholesterolemia (FH)

- **Homo** (2 genes) and **Hetero** (1 gene) -zygous FH
- Severely elevated cholesterol levels - untreated adults >190 mg/dL LDL, children/adolescents >160
- Long-term exposure to high LDL begins in utero
- Cause of premature atherosclerotic heart disease
- Heterozygous FH has the highest prevalence of genetic defects that cause premature mortality (≈1:200 to 1:500 or higher in founder populations)
- Genetic basis – usually impaired functioning of the LDL receptor FH leads to elevated LDL concentrations, with levels in heterozygous.

**LDL** = Low Density Lipoprotein cholesterol

If YOU have FH, your CHILDREN have a 50% chance of inheriting FH

https://thefhfoundation.org
Tier 1 genetic disorder: sufficient evidence for health benefit exists to implement case finding.

3 Autosomal Dominant diseases should be diagnosed more frequently with use of Cascade Screening in order to prevent morbidity and mortality:

- BRCA - BReast CAncer susceptibility gene
- Lynch’s syndrome – colon polyps
- Familial Hypercholesterolemia
Frequency per 1000 births

- Familial Hypercholesterolemia: 2.0
- Sickle Cell Disease: 0.5 (FH is 4x as common)
- Cystic Fibrosis: 0.4 (FH is 5x as common)
Correlation between LDL and Underlying Genetics

Raal et al. JAHA 2013 (r=0.6769; P<0.0001)

(r=0.6769; P<0.0001)
LDL cholesterol levels

<table>
<thead>
<tr>
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<th>FH</th>
<th>Non-FH</th>
</tr>
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<tbody>
<tr>
<td>mean</td>
<td>289</td>
<td>130</td>
</tr>
<tr>
<td>SD</td>
<td>63.0</td>
<td>31.4</td>
</tr>
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</table>

80% probability of FH
False negatives
False positives
Hopkins PN. Clin Lipidol 2010
Did Mona Lisa have Familial Hypercholesterolemia?
True Secondary Dyslipidemia Causes

DM
Excessive alcohol intake
CKD- eGFR (31–60 ml/min)
Antipsychotic medications
Steroids
Proteinuria- UMA (30–299 mg/g)
Immunosuppressive agents
Liver disease- Hi alk phos, Primary biliary cirrhosis
Hypothyroidism
Lupus
Multiple myeloma/gammopathy
Medications - Estrogen : OCP, ERT
Human immunodeficiency virus therapy
Oral retinoids (Isotretinoin)

What causes FH?
3 Genes Affecting LDL Clearance Can Cause FH
1700+ Mutations Identified to Date

APOB (90+ mutations identified) Codes for production of ligand protein, ApoB, which connects LDL particle to receptor.

LDL particle

Liver cell

LDLR (>1000 mutations) codes for LDL receptor which binds to ApoB on LDL particle inducing endocytosis of LDL.

PCSK9 (60+ GOF mutations identified to date) codes for PCSK9 enzyme, which degrades the LDL receptor.

Known mechanisms causing FH linked to LDL receptor (LDLR) function

Gidding et al Circulation. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000297
Prognosis in HeFH

Cumulative risk of fatal and non-fatal CHD

- Men - 50% by age 50 yr
- Women - 30% by age 60 yr
- Pre-statin

HeFH= Heterozygous Familial Hypercholesterolemia
CHD= Coronary Heart Disease

Slack Lancet 1969;ii:1380
Stone et al Circulation 1974;49:476
Prognosis in heterozygous FH

Heiberg & Slack BMJ. 1977;ii:493

—Age at coronary death due to coronary heart disease in affected sib pairs in Norwegian (●) and British (○) series.
Prevalence of CHD in patients with the three different genetic causes of familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CHD+ve/CHD−ve (% CHD+ve)</th>
<th>OR* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>55/101 (35.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>*LDLR (any)</td>
<td>91/145 (38.6)</td>
<td>1.84 (1.10 to 3.06)</td>
<td>0.02</td>
</tr>
<tr>
<td>*APOB (R3500Q)</td>
<td>6/4 (60)</td>
<td>3.40 (0.71 to 16.36)</td>
<td>0.13</td>
</tr>
<tr>
<td>*PCSK9 (D374Y)</td>
<td>6/1 (85.7)</td>
<td>19.96 (1.88 to 211.55)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Significant evidence for an association between gene-mutation group and CHD status (p=0.03).

HoFH: Cholesterol-lowering treatment has been associated with improved outcomes

Cox proportional hazards model with time-varying benefit from statin therapy comparing treated and untreated person-years

HoFH = homozygous familial hypercholesterolemia

Familial Hypercholesterolemia

A striking family history

Key
- Red square: Affected
- Red heart: MI age 40
- Number: Total Chol

Hopkins PN. Clin Lipidol 2010
How do you diagnose FH?
Challenge : Different criteria to Diagnose FH

Dutch criteria : FamHx of hyperlipidemia or CAD, physical exam, LDL, and/or mutation. Score > 8 is ‘definite’

Simon Broome : ‘Definite’<16 yrs TC>268 or LDL >160 or Adult TC >300 or LDL>196 AND : Xanthoma in pt or 1st /2nd OR mutation. ‘Probable’ Same TC/LDL AND FamHx of MI < 50 2nd or <60 1st OR TC >300 in adult 1st/2nd OR TC> 268 if child/sibling < 16 yrs

US MEDPED : uses age-specific and relative specific criteria for TC only; lower TC diagnostic cut-off levels for closer relatives
Familial Hypercholesterolemia: Japanese Criteria

Diagnostic Criteria for adult (≥15 yrs) heterozygous FH

Need 2 out of 3:
1. LDL Pre-Rx ≥ 180 mg/dl
2. Tendon xanthoma or skin nodular xanthoma*
3. Fam Hx in 2nd degree relative of HeFH or premature CAD** (< 55M;65F)

Rule out secondary hyperlipidemia

*Nodular xanthoma of skin does not include palpebral (eyelid) xanthoma.
**Achilles thickening (≥9 mm) on radiography should be regarded as xanthoma. When LDL ≥250 mg/dl, FH should be strongly suspected.

Harada-Shiba et al J Atheroscler Thromb 2012
## Adult FH Diagnostic Categories (Proposed)

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Clinical Criteria</th>
<th>W/ Genetic Testing Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeFH</td>
<td>LDL $\geq 190$</td>
<td>Presence of 1 LDL-raising (LDL receptor, apoB or PCSK9) gene defect.</td>
</tr>
<tr>
<td></td>
<td>AND 1st Deg relative similarly affected</td>
<td>Diagnosed as heterozygous FH if gene-raising defect (even if LDL &lt;160)</td>
</tr>
<tr>
<td></td>
<td>OR With premature CAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR with positive genetic testing*</td>
<td></td>
</tr>
</tbody>
</table>

HeFH = Heterozygous FH  
LDL as mg/dL $= 5$ mmol/L  
*for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)

Gidding et al. *Circulation*. 2015;132:00-00.  
DOI: 10.1161/CIR.0000000000000297
Distance-to-index of different family members

#’s = distance to Index. Broken lines = relatives roughly same age. Theoretical % DNA shared with Index patient: 1-50%; 2-25%; 3-12.5%; 4-6.25%; 5=3.13%; 6-1.62%; 7-0.81%

Besseling et al Atherosclerosis 246; March 2016: 1–6
Cumulative CVD risk by degrees of family membership
HeFH patients identified by genetic cascade screening

Phenotype is determined by molecular defect >>> environment; cascade screening is essential.
Percent of FH Patients Diagnosed*

- Netherlands
- Norway
- Iceland
- UK
- Slovakia
- South Africa
- USA
- Mexico

* Based on 1/500 in population. Eur Heart J, 2013
Once found, should you screen family members FH?
Blue = Legal to marry 1st cousin
**CDC : FH Tier 1 Recommendations**

1.2 Identify people with FH using cascade testing

1.2.2 Offer all with FH referral to an FH specialist for confirmation of diagnosis and cascade testing

1.2.4 Cascade testing using a combination of DNA testing and LDL. Should include at least the 1st and 2nd and, when possible, 3rd degree biological relatives.

1.2.5 If mutation identified, the mutation should be used to identify affected relatives.

1.2.8 Nationwide, family-based, follow-up system recommended for identification of people w/ FH.
MY MOM HAD A HEART ATTACK AT 39... WILL I?
Stop early heart disease in your family.

FH
TheFHfoundation.org
JOIN US and stop family heart disease.

FH, or inherited high cholesterol, leads to early heart disease. Learn how you can help your family.

STAY INFORMED

First Name

Last Name

Email Address

I'm a:

Patient

JOIN NOW

By submitting you agree to the Terms of Service. You will receive emails periodically and can opt-out at any time.

LEARN ➔

If left untreated, familial

CONNECT ➔

If you or a family member are living with

GET INVOLVED ➔

1:200 have FH, yet 90% remain
Do I have FH?

Yes

I don't know

What Now?

What is FH?

Familial Hypercholesterolemia
fa-mil-yal hi-par-ke-les-te-ra-kē-mō-a

F + H = FH
Family History + High Cholesterol

Family History of Heart Disease?

No

Cholesterol over 200?

No

Immediate Family have FH?

No

Yes

Yes

Yes

1 in 500 people have FH
FH is one of the most under diagnosed diseases of the 20th century. FH is a life threatening Disease but its treatable!

Life Style Changes

Like What?

Checkout FH Lifestyle Tips

Find a Lipid Specialist

How?

Look up on FH Referral

Get your Family tested

How?

Fill out a Family Tree & Get Tested

Get involved

- The FH foundation Community
- The FH CASCADE registry - be part of the solution
- Read Stories & Share your own

Find Out More
Katherine Wilemon is the Founder and President of The FH Foundation.

‘After being turned away from the ER several times and having a heart attack at 38, Katherine set out to raise awareness of FH and save lives.’

In the USA there are more than 650,000 people in the USA affected by FH, yet only 10% of them are diagnosed.

fhfoundation.org
Resources for FH Education for Patients and Families

Int: Global genes (globalgenes.org)
International FH Foundation (www.fh-foundation.org)

United States
The FH Foundation (www.thefhfoundation.org)
The Foundation of the National Lipid Association (www.learnyourlipids.com)
National Human Genome Research Institute, NIH (www.genome.gov/25520184)
National Institutes of Health, clinical trials (clinicalstudies.info.nih.gov)
National Organization for Rare Disorders (www.rarediseases.org)
Preventive Cardiovascular Nurses Association (www.pcna.net/patients/familial-hypercholesterolemia)

Gidding et al Circulation. 2015;132:00-00. DOI: 10.1161/CIR.00000000000000297
Cost effectiveness of screening for FH in UK

Interventions: ID & Rx of FH patients w/ screening: universal, opportunistic in primary care, premature MI, or tracing family members. (Screen = lipid profile)

Outcome measure: Cost/life year gained of Screen & Rx

Results: Trace family members most cost effective ($4479/life year gained); Screen 2.6 to identify 1 case at cost of $192/case detected. More cost effective to screen younger people and women.

Conclusions: Screening family members of people with FH most cost effective

CASCADE FH
familial hypercholesterolemia registry

The FH Foundation
raising awareness, saving lives

www.theFHfoundation.org
What are some of the challenges of FH screening?

- Identifying FH patients
  - DNA (gold standard) versus clinical?
  - Who pays?

- There is urgency to finding FH
  - Previously, the Dx usually came after MI
  - Earlier, aggressive Rx → better outcomes
    - Universal screening of teenagers cost-effective
FH and Physical Exam: Is it useful?

Yes!

Extensors- elbows & knees
back & buttocks

Early MI in 2\textsuperscript{nd} & 3\textsuperscript{rd} degree relatives

Xanthoma

Eruptive Xanthoma

Xanthelasma

Achilles thickening > 11mm

Yes !
Achilles Tendon Xanthoma
Corneal Arcus
In FH, Lipoprotein (a) elevation increases CAD Risk

Seed et al NEJM 1990;322:1494-1499
Issues to Address With Families Affected by FH

Individual and family experiences, including CVD events, response to treatment

Genetics and implications of genetic diagnosis
Risk perception (fear of future events)
Med side effects (short, midterm, and lifetime Rx need)
Med adherence
Assessment and Rx of other CV risk factors
Pregnancy
Costs and insurance
Lifestyle behaviors, self-efficacy and lifestyle change

CVD = cardiovascular disease
FH = Familial hypercholesterolemia

Gidding et al Circulation. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000297
How do you treat FH?

**Lifestyle:**
- Omit transfats (partially hydrogenated oils)
- Low saturated animal fat
- Physical activity

**Meds:**
- Statins (atorvastatin & rosuvastatin),
- ezetimibe, +/- bile acid sequestrants,
- +/- apheresis
- PCSK9 Inhibitors – evolocumab SQ Q 2weeks
FH Key Points

• FH is an autosomal dominant disease
• Causes early atherosclerosis morbidity and mortality
• Should be suspected in patients with early CAD
• Remember physical exam!
  Xanthoma, xanthelasma, corneal arcus, bruits
• If suspected, ask about family history for early MI
• Family members should be screened - ‘Cascade’
• Check Lipoprotein a
• fhfoundation.org helpful for patients
• Early (in life) treatment saves lives
Thank you for your attention!

kopecky.stephen@mayo.edu