Familial Hypercholesterolemia in Public Health & Clinical Practice
APHA Genomics Forum Webinar
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Genetics, Epidemiology, & Public Health Implications of FH

Claudia Mikail, MD, MPH
Center for Preventive Care & Genetics
Woodland Hills, CA
Instructor, Health Policy & Management, UCLA Extension
Objectives for this segment

- Defining FH, its genetics, and epidemiology
- Sharing general guidelines for cholesterol screening
- Introducing how FH is diagnosed and managed
- Reviewing the concept of cascade screening and its public health implications
- Summarizing Tier 1 Recommendations
What is familial hypercholesterolemia (FH)?

- A common hereditary form of hyperlipidemia characterized by severely elevated LDL cholesterol (LDL-C) levels
- Cholesterol levels in FH patients are significantly higher than those typically seen in patients with high cholesterol
- FH patients at substantially increased risk for coronary heart disease (CHD) at an early age
- Disease caused by one or more mutations in genes that affect LDL-C levels in the blood

Two forms of FH

- **Heterozygous (HeFH)**
  - ~60-80% of cases due to a mutation in one of three genes:
    - LDLR
    - APOB
    - PCSK9
    - More genes identified

- **Homozygous (HoFH)**
  - two mutations present
    - two in same gene or one in two different FH genes (compound heterozygote)

http://www.fhfoundation.org
Epidemiology

- **Prevalence**
  - HeFH (more common): 1:200 to 1:500 people
  - HoFH (rarer, more severe): 1:160,000 to 1:1,000,000
  - Some ethnic groups at higher risk

- **Morbidity/mortality**
  - If untreated, 20-fold increased risk for CHD, typically presenting as angina or MI
    - Males: 50% risk for a coronary event by age 50
    - Females: 30% risk for a coronary event by age 60
  - In HoFH, morbidity and mortality appears as early as childhood or adolescence, with most patients having advanced CHD by their mid-20s

- **Underdiagnosed**
  - Only small percentage of Americans with FH are diagnosed, so may not receive adequate treatment (Chen & Hay, 2015)
Inheritance pattern

- Autosomal dominant; *de novo* mutations very rare
- Practically all FH patients inherited the disease from a parent(s)
- HoFH patients transmit FH to all offspring
- Patients with HeFH have a 50% chance of transmitting it to each of their offspring
- If *both* parents have HeFH, there is a 75% chance for each child to have some form of FH

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Power of family history

Once FH is diagnosed in a patient, the likelihood of discovering it in close relatives is very high.
First step: Detecting hypercholesterolemia in individual patients

The USPSTF currently recommends screening men aged 35 or older for lipid disorders and screening men and women aged 20 and up for lipid disorders if they are at increased risk for coronary heart disease (e.g., due to family history of premature heart disease)

Should kids be tested too?:
AAP and NHLBI guidelines

- American Academy of Pediatrics (AAP) recommends that *if there is a family history of heart disease in men before age 55 or in women before age 65, children in that family undergo cholesterol testing as early as age two, and before age 10*

- The National Heart, Lung, and Blood Institute (NHLBI) and AAP recommend *universal cholesterol testing for all children between the ages of 9 and 11 (and again between the ages of 17 and 21)*

http://www.thefhfoundation.org/common-familial-hypercholesterolemia/
Recognizing and diagnosing FH

- Family history of premature CHD
- Physical signs suggestive of FH
  - Xanthomas (cholesterol deposits in tendons)
  - Xanthelasma (cholesterol deposits around eyes)
  - Corneal arcus (especially if present before age 45)
- Lipid panel indicating high likelihood of FH
  - Adults with LDL-C >190 mg/dL or total cholesterol >310 mg/dL
  - Children or adolescents with LDL-C >160 mg/dL or total cholesterol levels >230 mg/dL
- Presence of FH mutation(s)
Treatment needs to be more aggressive than in non-FH hypercholesterolemia

- **Lifestyle changes**
  - Controlling fat intake
  - Increasing fiber intake
  - Promoting physical activity
  - Smoking cessation
  - Limiting alcohol consumption

- **Pharmacotherapy**
  - Statins
  - Ezetimibe
  - Other antihyperlipidemics
  - Alirocumab (newly FDA-approved PCSK9 inhibitor)

- **LDL apheresis, liver transplant in more severe cases**

Once we’ve diagnosed FH in an individual patient is our job done?

- Not from a genetic standpoint
- Like other hereditary disorders, we need to start thinking about potentially affected family members
- Identifying an index case (proband) leads us to additional possible cases, giving us the opportunity to prevent CHD in more patients through early detection and treatment
- Rationale behind cascade screening for FH
Public health benefits of cascade screening

- **Cost effective method for CHD prevention**
  - Ademi et al (2014) found cascade screening for FH, via a combination of genetic testing and LDL-C measurement and treatment of affected patients with statins, to be a cost-effective means for preventing CHD in families at risk for FH

- **Reduced morbidity and mortality with treatment**
  - Versmissen et al (2008) showed an 80% reduction of morbidity due to CHD in FH patients treated with statins
  - Neil et al (2008) showed a 37% reduction of mortality due to CHD in FH patients treated with statins
By targeting individuals with high risk for CHD cascade screening and treatment for FH supports several Healthy People 2020 objectives

- **HDS-2** Reduce coronary heart disease deaths
- **HDS-6** Increase the proportion of adults who have had their blood cholesterol checked within the preceding 5 years
- **HDS-7** Reduce the proportion of adults with high total blood cholesterol levels
- **HDS-8** Reduce the mean total blood cholesterol levels among adults
Approach to cascade screening: NICE/CDC Tier 1 recommendations

- Once FH has been diagnosed in an index case, cascade testing of relatives is recommended to identify affected family members.
- Healthcare professionals should offer all people with FH a referral to a specialist for confirmation of diagnosis and initiation of cascade testing.
- Healthcare professionals with expertise in FH should explain cascade testing and its implications to all FH patients.
Cascade testing using a combination of DNA testing and LDL-C levels is recommended to identify affected family members, including 1\textsuperscript{st}, 2\textsuperscript{nd}, and, if possible, 3\textsuperscript{rd} degree relatives of the index case.

- In families with a known mutation, the mutation and not LDL-C level should be used to identify affected relatives.
- In the absence of a DNA diagnosis, cascade testing using LDL-C levels should be undertaken.
(continued)

- Use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH
- Healthcare professionals should be aware of the latest guidance on data protection when undertaking cascade testing
  - Privacy and confidentiality

http://www.cdc.gov/genomics/implementation/toolkit/FH_1.htm
State efforts: Big steps, little steps

- **West Virginia:** West Virginia DHHS and CARDIAC-FH Program at West Virginia University provide blood testing, LDL receptor analysis, and family history analysis to identify relatives with FH and to establish a state-wide registry of FH patients.

- **Connecticut:** In 2013, the Connecticut Department of Public Health added questions relating to FH to their Behavioral Risk Factor Surveillance System (BRFSS).

- **How might we implement similar initiatives in other states?**

http://www.cdc.gov/genomics/implementation/toolkit/FH_2.htm
References

Up next...

The next segments of this webinar will provide greater details on:

- **Clinical diagnosis and management of FH**
- **Genetic counseling perspectives**
- **West Virginia’s FH program**