Familial Hypercholesterolemia: A Prototype for Precision Public Health
20 million high risk individuals on no lipid lowering therapy!

<table>
<thead>
<tr>
<th>Category</th>
<th>E78.01</th>
<th>E78.01 &amp; ASCVD</th>
<th>ASCVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No LLT</td>
<td>42%</td>
<td>23%</td>
<td>49%</td>
</tr>
<tr>
<td>Low/Moderate Statin</td>
<td>50%</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>High Statin</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>MI Statin + ezetimibe</td>
<td>10%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Any Statin + PCSK9i</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Legend:
- Any Statin + PCSK9i
- HI Statin
- HI Statin + ezetimibe
- MI Statin + ezetimibe
- Low/Moderate Statin
- No LLT past 6 years

1/13/20
If precision medicine is about providing the right treatment to the right patient at the right time, precision public health can be simply viewed as providing the right intervention to the right population at the right time.”

State of FH in the US
“I thought I was alone with my FH.

No one in my family talked about or admitted that they had high cholesterol. I found my lipidologist and the FH Foundation after years of uncontrolled levels. Then I started treatment and my LDL hit 126.

I cried for an hour after the news. What a relief that was.”

– Individual with FH
To know where we are going, we need to know where we are
Then (2012)…

• < 1% diagnosed
• No ICD codes for FH
• No FH national registry in the US
• No FH Awareness Day
• No FH support community
• No FH-focused website
• No clear professional FH-specific guidelines
• Incomplete database of FH genetic variants
• Limited treatment options
• No constituency advocating for FH
• Little attention and funding for FH
• No gathering of FH experts
FH Foundation’s Approach

Data + Medical Expertise + Patient Experience
Publications since our last FH Global Summit

2019

Effects of access to prescribed PCSK9 inhibitors on cardiovascular outcome
Circulation: Cardiovascular Quality and Outcomes 2019 | Myers, KD, et al.

Finding missed cases of familial hypercholesterolemia in health systems using machine learning

Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia
Atherosclerosis 2019 | Duell, PB, et al.

2018

Familial hypercholesterolemia patients support groups and advocacy: A multinational perspective
Atherosclerosis 2018 | Payne, J, et al.

Is diet management helpful in familial hypercholesterolemia?
Current Opinion in Clinical Nutrition and Metabolic Care 2018 | Gidding, S.

ClinVar database of global familial hypercholesterolemia-associated DNA variants
Human Mutation 2018 | Iacocca, MA, et al.
What is the State of FH in the US today?
CDC designated FH as Tier-1 health condition for Cascade Screening in 2012

Autosomal dominant condition

Significant public health concern

Effective therapies available today

Family screening saves lives
Treatments for FH Then…Now

**Then**
- Bile Acid Sequestrants
  - August 1973
- September 1987
  - Statins

**Now**
- LDL-Apheresis
  - September 1997
- October 2002
  - Ezetimibe
- Lomitapide
  - December 2012
- July 2015
  - Alirocumab
- August 2015
  - Evolocumab
2018 ACC/AHA Cholesterol Guideline singles out FH for the first time

**CHOLESTEROL CLINICAL PRACTICE GUIDELINES**


A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

**WRITING COMMITTEE MEMBERS**

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Laurence Sperling, MD, FACC, FAHA, FASPC***
Salim S. Virani, MD, PhD, FACC, FAHA∗
Joseph Yeboah, MD, MS, FACC, FAHA†††
FH diagnosis is improving
15% coded with ICD E78.01
More work to do: Undiagnosed “ Likely” FH by state

FH Foundation National Database up to 12/31/2018

#KnowFH #FHSummit19 #FHCantWait
Why is diagnosis still so low?
Primary care awareness is low

“Meeting of the Americas” FH Foundation Survey US Data (N=198)

General Practitioners (N=155)
- Not familiar: 2%
- Somewhat familiar: 15%
- Familiar: 37%
- Very familiar: 46%

Cardiologists (N=20)
- Not familiar: 17%
- Somewhat familiar: 22%
- Familiar: 61%

Other Specialists (N=20)
- Not familiar: 20%
- Somewhat familiar: 35%
- Familiar: 45%
Why is diagnosis still so low? Pediatric screening guideline awareness

Only 26% of pediatricians were knowledgeable about the 2011 NHLBI Guidelines for screening.

CASCADE FH® Registry Network

- > 6,000 enrolled
- > 4,000 longitudinal f/u
  - 60% women
  - 15% non-white
- 5 publications
FH diagnosis often comes too late

CASCADE FH Registry Data Shows Gap in Diagnosis & Treatment from Guidelines

- AAP Guidelines 9-11 years
- FH Diagnosis 48
- 8-10 years Statins Approved
- 21 ACC/AHA Guidelines
- 44 Statin Initiation

CASCADE FH Registry up to 8/31/2019
Many FH patients are living with the consequences of preventable heart disease.

- **Men:**
  - 6% (U.S. NHANES)
  - 47% (U.S. CASCADE FH Registry)

- **Women:**
  - 6% (U.S. NHANES)
  - 29% (U.S. CASCADE FH Registry)

Most people are not genetically tested

505 individuals have had genetic testing

326 tests were confirmatory of 1 or more mutations:
- 9.7% APO-B mutation
- 84.8% LDL-Receptor mutation
- 1.0% PCSK9 mutation
- 4.4% Other mutations
CASCADE FH is longitudinally following adults and children

**HeFH (N=3,443)**
- Adults: 92% (3,169)
- Children: 8% (274)

**HoFH (N=88)**
- Adults: 90% (79)
- Children: 10% (9)

CASCADE FH Registry up to 8/31/2019

#KnowFH  #FHSummit19  #FHCan'tWait
Longitudinal follow-up in CASCADE FH is providing vital insights

Longitudinal low density lipoprotein cholesterol goal achievement and cardiovascular outcomes among adult patients with familial hypercholesterolemia: The CASCADE FH registry

P. Barton Duell\textsuperscript{a}, Samuel S. Gidding\textsuperscript{b,*}, Rolf L. Andersen\textsuperscript{c}, Thomas Knickelbine\textsuperscript{d}, Lars Anderson\textsuperscript{c}, Eugenia Gianos\textsuperscript{e}, Peter Shrader\textsuperscript{f}, Iris Kindt\textsuperscript{b}, Emily C. O’Brien\textsuperscript{f}, Dervilla McCann\textsuperscript{g}, Linda C. Hemphill\textsuperscript{h}, Catherine D. Ahmed\textsuperscript{b}, Seth S. Martin\textsuperscript{i}, John A. Larry\textsuperscript{j}, Zahid S. Ahmad\textsuperscript{k}, Iftikhar J. Kullo\textsuperscript{l}, James A. Underberg\textsuperscript{m}, John Guyton\textsuperscript{n}, Paul Thompson\textsuperscript{o}, Katherine Wilemon\textsuperscript{b}, Matthew T. Roe\textsuperscript{f}, Daniel J. Rader\textsuperscript{p}, Marina Cuchel\textsuperscript{q}, MacRae F. Linton\textsuperscript{r}, Michael D. Shapiro\textsuperscript{a}, Patrick M. Moriarty\textsuperscript{s}, Joshua W. Knowles\textsuperscript{t}
LDL-C levels improve with guideline-recommended specialty care

Average LDL by Therapy (Adults, HeFH)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pre-treatment</th>
<th>Enrollment</th>
<th>Most recent follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low or Moderate Intensity Statin (N=199)</td>
<td>247</td>
<td>240</td>
<td>157</td>
</tr>
<tr>
<td>High Intensity Statin (N=316)</td>
<td>240</td>
<td>141</td>
<td>139</td>
</tr>
<tr>
<td>Statin + Ezetimibe (N=464)</td>
<td>257</td>
<td>144</td>
<td>123</td>
</tr>
<tr>
<td>Statin + PCSK9i (N=92)</td>
<td>285</td>
<td>180</td>
<td>107</td>
</tr>
<tr>
<td>Statin + Ezetimibe + PCSK9i (N=262)</td>
<td>284</td>
<td>145</td>
<td>83</td>
</tr>
</tbody>
</table>

CASCADE FH Registry up to 8/31/2019

#KnowFH #FHSummit19 #FHCantWait
Specialty care also works for HoFH
(Enrollment vs. Follow-up)

HoFH (N=63)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enrollment</th>
<th>Most recent follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>59% (37)</td>
<td>86% (54)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>41% (26)</td>
<td>57% (36)</td>
</tr>
<tr>
<td>PCSK9i</td>
<td>27% (17)</td>
<td>56% (35)</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>16% (10)</td>
<td>24% (15)</td>
</tr>
<tr>
<td>Lipoprotein Apheresis</td>
<td>24% (15)</td>
<td>32% (20)</td>
</tr>
</tbody>
</table>

CASCADE FH Registry up to 8/31/2019
However, LDL-C goal attainment is suboptimal even in specialty care


52% did not achieve LDL-C <100 mg/dL

78% did not achieve LDL-C <70 mg/dL
HeFH cardiovascular event rates are high even at specialty centers

People with FH are worried

How often do you worry that you may have a heart attack or suddenly die? (N=760)

- **6%** Can’t stop worrying
- **21%** Often worry
- **41%** Occasionally worry
- **21%** Rarely worry
- **10%** Never worry

CASCADe FH Registry
Patient Portal

#KnowFH  #FHSummit19  #FHCan'tWait
FH Foundation National Database is a unique resource: Moving beyond FH patients seen at specialty clinics

- 220,926,520 Unique Patients in Dx/Px/Sx Data
- 220,304,041 Unique Patients in Rx Data
- 96,516,511 Patients in Lx Data

FIND FH and FOCUS initiatives

272,854,017 Americans

FH Foundation National Database up to 12/31/2018
Real-world care needs to catch up: FOCUS

Diagnosed FH
- FH Foundation National Database (N=197,479)
- CASCADE FH Registry (N=3,898)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>FH Foundation</th>
<th>CASCADE FH Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 inhibitor</td>
<td>0.8%</td>
<td>30.5%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>6.4%</td>
<td>46.0%</td>
</tr>
<tr>
<td>High Intensity Statin</td>
<td>22.8%</td>
<td>44.3%</td>
</tr>
<tr>
<td>Statin</td>
<td>63.6%</td>
<td>81.0%</td>
</tr>
</tbody>
</table>

FH Foundation National Database up to 12/31/2018; CASCADE FH Registry up to 8/31/2019
Proven therapies are underused in FH (and in ASCVD)

Percent of Population on Lipid Lowering Treatments (all health plans)

- **Diagnosed FH**
- **Undiagnosed Probable FH**
- **Atherosclerotic Cardiovascular Disease (ASCVD)**

**Commercial**
- 56% Diagnosed FH
- 58% Undiagnosed Probable FH
- 42% ASCVD
- 20% Any Statin
- 21% High Intensity Statin
- 18% Any Statin + Ezetimibe
- 4% PCSK9i

**Medicare**
- 67% Diagnosed FH
- 68% Undiagnosed Probable FH
- 60% ASCVD
- 21% Any Statin
- 23% High Intensity Statin
- 23% Any Statin + Ezetimibe
- 3% PCSK9i

**Other**
- 56% Diagnosed FH
- 56% Undiagnosed Probable FH
- 34% ASCVD
- 23% Any Statin
- 21% High Intensity Statin
- 16% Any Statin + Ezetimibe
- 4% PCSK9i

- FOCUS Interactive Dashboard
- Filtered by gender, race and age
- www.thefhfoundation.org/research-circ-ce-data

FH Foundation National Database
1/1/2018 - 12/31/2018
Even in patients with an FH ICD-10 code, there is not a deluge of PCSK9i prescriptions

August 2015 — December 2018

- **249,752** prescriptions for PCSK9i written
- **24,734** individuals have received the medication for a year or more*

- **197,479** individuals have received a diagnosis code for FH (E78.01) - 15%
  - **3.3% (6,542)** of those with ICD-10 E78.01 have been prescribed a PCSK9i
  - **0.5% (1,034)** have actually received the medication for a year or more*

* At least 338 days of therapy within 365 days

FH Foundation National Database up to 12/31/2018
What happens when patients don’t get what their provider prescribed?

Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular Outcomes

Kelly D. Myers, BS*
Niloofar Farboodi, MSc, MPH*
Mkaya Mwamburi, MD, PhD, MA
William Howard, PhD
David Staszak, PhD
Samuel Gidding, MD
Seth J. Baum, MD
Katherine Wilemon, BS
Daniel J. Rader, MD
Patients prescribed PCSK9i are high risk

High rejection rates for PCSK9i


63% prescription rejected by payers for individuals with FH and ASCVD

Increased risk of cardiovascular event within a year if PCSK9i rejected or unfilled


- **Paid vs. Rejected**: 16%
  - increased risk of **heart attacks and strokes** if rejected

- **Paid vs. Unfilled**: 21%
  - increased risk of **heart attacks and strokes** if unfilled
Empowering tools for individuals with FH

What to Expect: Treatment Coverage and Affordability

Cost & Co-pays

Know Your Cost
- Ask if there is a generic version of the medication(s) you are prescribed.
- Shop around for best prices of your medication(s) and lab tests(s).
- Ask your insurance company if your medication(s) and/or test(s) are covered. If it requires a Prior Authorization, what and what you can expect to pay out-of-pocket.
- For PCSK9 inhibitors, make sure your pharmacist is using the lower-priced National Drug Code (NDC).

Co-pay Assistance
- If you are taking a brand name drug, contact the manufacturer to ask if they offer a copay card or a coupon. Co-pay cards are only available to commercial insurance holders (they cannot be used if you have Medicare, Medicaid, or Tricare).
- Pharmaceutical companies may also have assistance programs to cover the cost of the medication(s) for individuals who qualify based on income.

Insurance provided for educational purposes only. Please consult your healthcare provider regarding your specific health needs.

Prior Authorizations & Appeals

Prior Authorizations (PA)
A PA is a review process for insurance approval of certain prescribed medications or procedures. If your medication requires a PA, your healthcare provider (HCP) should submit the PA form and supporting documentation on your behalf. You can help by providing your HCP with additional supporting documentation, such as previous medical reports.

Appealing an Insurance Denial
If your insurance plan denies coverage of a medication prescribed by your HCP, you can appeal that decision. Here’s where to start:

1. Reason for Denial: Check your denial or coverage determination letter to see the reason for the decision.
   - Is the treatment on the “Formulary” (medications covered by your plan)?
   - Does your plan require you to try another medication first (“step therapy”)?
   - Does the plan pay this treatment “not medically necessary”?
   - Does the denial say there is information missing?

2. Work with your HCP: Plan how to address the reasons for denial. Your HCP should submit the appeal and include a letter of medical necessity, but you can help by providing additional documentation or making a call to your insurance plan.
   Even if your HCP is handling your appeal, a phone call from you to your insurance provider can impact your case.

3. Talk to HR: If you have health insurance through your employer, it’s a good idea to keep your company’s HR department in the loop. Your company may be able to provide additional opportunities to escalate any issues you have with coverage and advocate on your behalf with their insurance plan.

4. Get help from the FH Foundation: Remember, you’re not in this alone. Please reach out to the FH Foundation, and we can assist you.

5. We can change this: Our advocacy team is hard at work helping improve access to FH treatments. You can be a part of these efforts, too!

For more information, see the FH Foundation’s Navigating Insurance Guide.

Information provided for educational purposes only. Please consult your healthcare provider regarding your specific health needs.

#KnowFH  #FHSummit19  #FHCan’tWait
Advocating for access and affordability

### PCSK9 Inhibitor Prescription Coverage

<table>
<thead>
<tr>
<th>Total Lives</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>7,508,670</td>
<td>7,433,239</td>
<td>1,238,901</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosed FH Population</th>
<th>Total Number Prescribed a PCSK9/H</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>299</td>
<td>427</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Undiagnosed Probable FH Population</th>
<th>Total Number Prescribed a PCSK9/H</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,144</td>
<td>3,662</td>
<td>103</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>ASCVD Population</th>
<th>Total Number Prescribed a PCSK9/H</th>
<th>Commercial</th>
<th>Medicare</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,077</td>
<td>12,818</td>
<td>473</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Interactive Filters

- **Gender**
  - Female
  - Male

- **Race/Ethnicity**
  - All
  - Black
  - Hispanic
  - White
  - Other
  - Unknown

- **Age Group**
  - All
  - <18
  - 18 - 50
  - 51 - 60
  - 61 - 75
  - >75

- **Health Plan or Other Payer**
  - MVP HEDIS HEALTH SOLUTIONS
  - NEW JERSEY EMPLOYEES SHBP
  - NEW YORK STATE GOVT. EMP.
  - PRIME THERAPEUTICS
  - RITE AID
  - TRICARE MILITARY HFAITH SVC SYS

Use the buttons below to navigate between your changes. The """"button will reset your view.
Advocating for access and affordability

PCSK9 inhibitors no longer eligible for placement on specialty tier in Medicare 2020.
The future is bright for FH: More in the pipeline to address the unmet need

- Bempedoic Acid and Bempedoic Acid plus Ezetimibe
- Inclisiran
- Evinacumab for HoFH
- ARO—ANG3 for HoFH
- Alirocumab and Evolocumab in pediatric trials
- Alirocumab for HoFH
- HDL Acute Lipid Optimization for HoFH
- AAV Gene Therapy for HoFH
- CRISPR Gene Therapy for HoFH?
Advocating for Change
Then (2012)...

- < 1% diagnosed
- No ICD codes for FH
- No FH national registry in the US
- No FH Awareness Day
- No FH support community
- No FH-focused website
- No clear professional guidelines
- No database of FH genetic variants
- Limited treatment options
- No constituency advocating for FH
- Little attention and funding for FH
- No gathering of FH experts

Now (2019)...

- 15% diagnosed with ICD E78.01
- ICD E78.01 and Z83.42 approved in 2016
- 6,000+ enrolled, 5 papers published
- FH Awareness Day is global
  - Reached 15 million in 2019 alone
- A growing community
  - 115 trained FH Advocates in 27 states
- 50,000 + visitors to the website each month
- Genetic testing consensus statement and 2018 ACC/AHA Cholesterol Guideline
- ClinVar
- Innovative treatments available and more in clinical development
- 4 years of FH advocacy on Capitol Hill
- FH is a priority for CDC and NIH
- 7th Annual FH Global Summit
Building the FH Community
We still have a long way to go, but together we will get there.
Variations on the theme of FH variability

Catherine Boileau

Chair of the Department Medical Genetics at Bichat University Hospital
Professor of Genetics Paris Diderot University
Team Leader Inserm U148
Disclosures:

Honoraria /Consultancy from
Amgen, Sanofi/Regeneron, Servier
“Theme & Variation” is a specific form in music.

The piece begins with a theme that is the main melody. That is followed by one or more variations of that melody. A variation is music that is similar to the theme but is also different enough that it does not repeat the melody exactly.

- Bach’s Goldberg variations
- Mozart’s Sets of Variations ("Twinkle, twinkle little star…")
- Beethoven’s Diabelli variations
- Rachmaninov’s Variation on a theme of Paganini
- Elgar’s Enigma variations
From musical variations to phenotype variations

Gouldian finch
Asian ladybug
Britannica.com
FLORIGENE®

John Turner®
Jamie Grill®
Variations on the theme of FH variability

Main points

• What is it due to?
  • How do we detect driver effects?
  • How do we define FH variability?
  • What are the possible drivers?
  • How do we find the drivers?
    • Family studies design
    • Population studies and cross-mapping
Drivers of FH phenotype plasticity

- Environment
  - Epigenetic modifications
  - Gene regulation
- Genetics
  - DNA sequence variations
  - Gene regulation

- Family history
- Intrauterine environment
- Age and sex
- Exercise
- Smoking
- Microbiome
- Infectious agents
- Metabolic modifications

- Nutrients
- Drugs

Arif et al., Hypertension Res, 2019
www.whatisepigenetics.com
Variations on the theme of FH variability

Main points

• What is it due to?

• **How do we detect driver effects?**
  • How do we define FH variability?
  • What are the possible drivers?
  • How do we find the drivers?
    • Family studies design
    • Population studies and cross-mapping
Variability in Chinese FH subjects

Jiang-su province of China

- p.Trp462Stop
- p.Glu207Lys

mean LDL-C: 4.35 ± 1.09 mmol/L*


British Columbia, Canada

mean LDL-C: 7.46 ± 1.29 mmol/L*

Pimstone et al., ATVB 1998;18:309-315

*p<.001
starches like rice or noodles
vegetables
low amounts of meat or fish
fresh fruits
Variability in a single very large FH family

412 descendants with 118 HeFH over 8 generations

[Sijbrands et al., BMJ, 2001 Apr 28;322(7293):1019-23]
Variations in mortality in p.Val408Met carriers

Mortality from FH over time (within generations)

Survival in family branches

Sijbrands et al., BMJ, 2001 Apr 28;322(7293):1019-23
Variations on the theme of FH variability

Main points

• What is it due to?
• How do we detect driver effects?
• **How do we define FH variability?**
• What are the possible drivers?
• How do we find the drivers?
  • Family studies design
  • Population studies and cross-mapping
A molecular picture of PCSK9 today


Adapted from M. Varret
LDL-C Variability in unrelated FH carriers of the same mutation

Adapted from M. Varret and J-P. Rabès
LDL-C Variability in unrelated FH carriers of the same mutation

Adapted from M. Varret and J-P. Rabès
LDL-C Variability in unrelated FH carriers of the same mutation

Adapted from M. Varret and J-P. Rabès
Variations on the theme of FH variability

Main points

• What is it due to?
• How do we detect driver effects?
• How do we define FH variability?
• **What are the possible drivers?**
• How do we find the drivers?
  • Family studies design
  • Population studies and cross-mapping
FH: a cornucopia of possible modifiers

Gene drivers of variable TC and LDL-C

Paththinige et al., Lip Health Dis 2017
FH: a cornucopia of possible modifiers

Gene drivers of atherosclerosis

Normal aorta  Moderate atherosclerosis  Severe atherosclerosis

Human aortas

Healthy aorta  Fatty Streaks (FS)  Fibrolipidic lesion (FLL)

Adapted from J-B. Michel, P. El Khoury and Y. Abou Khalil
FH: a cornucopia of possible modifiers

Gene drivers of atherosclerosis
Variations on the theme of FH variability

Main points

• What is it due to?
• How do we detect driver effects?
• How do we define FH variability?
• What are the possible drivers?

• How do we find the drivers?
  • Family studies design
  • Population studies and cross-mapping
FH drivers of variability: Family studies design

P. family from Puerto Rico

LDLR gene mutation p.Ser156Leu

Incomplete penetrance

Hobbs et al., J Clin Invest. 1989
FH drivers of variability: Family studies design

P. family from Puerto Rico

LDLR gene mutation p.Ser156Leu

Incomplete penetrance and Autosomal Dominant suppressor gene

Hobbs et al., J Clin Invest. 1989
FH drivers of variability: Family studies design

Moslem Arab family in Israel

LDLR gene
p.Tyr807Cys (internalization defective) "J.D. mutation"

Knoblauch et al., Am J Hum Genet 2000

Khachadurian and Kawahara, J Lab Clin Med 1974
Brown and Goldstein, Cell 1976
Davis et al., Cell 1986
Autosomal recessive modifier of TC and LDL-C concentrations

FH-heterozygous persons with values ≤150 mg/dL affected by a cholesterol-lowering trait

Knoblauch et al., Am J Hum Genet 2000
FH drivers of variability: Family studies design

Shared region between family branches and members on chromosome 13

The smallest area of complete sharing
FH drivers of variability: Family studies design

UCSC Genome Browser at 13q
Variations on the theme of FH variability

Main points

• What is it due to?
• How do we detect driver effects?
• How do we define FH variability?
• What are the possible drivers?

• **How do we find the drivers?**
  • Family studies design
  • Population studies and cross-mapping
FH drivers of variability: Extreme Phenotype Sampling (EPS) design

Drivers of Lipid phenotype

Sachdeva et al., Am Heart J, 2009

Zhang et al., Scientific Rep, 2019
Drivers of atherosclerotic plaque phenotype

Coronary Artery Calcium (CAC) scores

Pletcher et al., BMJ Med 2004
Drivers of atherosclerotic plaque phenotype
FH drivers of variability: Extreme Phenotype Sampling (EPS) design

**LDLR mutation carriers**

- Extreme Phenotype Sampling (EPS)
  - Benign group
  - Severe group

- Sibpairs
  - Severe CAC score
  - concordants (C)
  - discordants (D)
  - All same sex:
    - females (C and D)
    - males (C and D)

**Analyses**

- GWAS
- WES
- Linkage Analysis
- Kinship matrix analysis
Drivers of variability: EPS design for Marfan syndrome

1070 FBN1 mutation carriers

Exclusion
- Neonatal MFS
- subjects under 18 y.o.

WES

FBN1 PTC mutation carriers
n = 80 MFS
Skin fibroblasts

Extreme Phenotype Sampling (EPS)
n = 98

Benign group
n = 47

Severe group
n = 51

GWAS

Linkage Analysis

Kinship matrix analysis

Sibpairs
Severe aortic disease
- 8 concordants (C)
- 6 discordants (D)
all same sex:
- 9 females (5C and 4D)
- 5 males (3C and 2D)

Aubart et al., Hum Mol Genet 2015
Aubart et al., Eur J Hum Genet 2018
Drivers of variability: EPS design for Marfan syndrome

Cross-mapping strategy of results

Aubart et al., Hum Mol Genet 2015
Aubart et al., Eur J Hum Genet 2018
Drivers of variability: EPS design for Marfan syndrome

Cross-mapping strategy of results
Drivers of variability: EPS design for Marfan syndrome

Cross-mapping strategy of results

**gMOD-M1**

- At locus 1p36.12
- 3 strategies
- *ECE1* gene*
  *(Endothelin Converting Enzyme)*

*Horowitz et al, Int J Biochem Cell Biol, 2012*
FH drivers of variability: Extreme Phenotype Sampling (EPS) design

**LDLR mutation carriers**

- **Extreme Phenotype Sampling (EPS)**
  - Benign group
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- **Sibpairs**
  - Severe CAC score
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**Analysis**

- GWAS
- WES
- Linkage Analysis
- Kinship matrix analysis
FH genetic drivers of variability

LDLR mutation carriers

Steps of atherogenesis:
- LDL
- Smooth muscle cells
- Macrophages
- Foam cells
- Lymphocytes

Atherogenic driver profiling

Extreme Phenotype Sampling (EPS)
- Benign group
- Severe group

GWAS
WES

Severe CAC score
- concordants (C)
- discordants (D)
- All same sex:
  - females (C and D)
  - males (C and D)
Variations on the theme of FH variability

From FH genetic drivers of variability to personalized care

- LDL
- Smooth muscle cells
- Macrophages
- Foam cells
- Lymphocytes

Steps of atherogenesis:
- Treatment with drugs targeting atherogenic drivers
- Drug R&D

Severe atherosclerosis

Moderate atherosclerosis

Atherogenic driver profiling
Variations on the theme of Mozart’s …