Personalized CVD Risk: Yes
Genetic Individualization

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Maui, March 15, 2014
Personalized CVD Risk: No Genetic Individualization

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Disclosures

• uniQure: advisory board
• ISIS: advisory board
• Lexicon Genetics: Consultant
• Norvartis: Grant

Very severe hypertriglyceridemia
Genetic Testing & Therapy

• Familial hypobeta-lipoproteinemia
• Very severe hypertriglycerideridemia
• Very severe hypercholesterolemia
• Very low HDL cholesterol
• High HDL cholesterol and CAD
Familial HypoBeta-Lipoproteinemia

- Defective apoB allele
- Defective PCSK9 allele
- Familial combined hypolipidemia (ANGPTLP3)
- ApoE$_2$E$_2$
- ???
Familial HypoBeta-Lipoproteinemia

- Defective apoB allele: Fatty liver
- Defective PCSK9 allele
- Familial combined hypolipidemia (ANGPTL3)
- ApoE$_2$E$_2$
Familial HypoBeta-Lipoproteinemia

- Defective apoB allele
- Defective PCSK9 allele
- Familial combined hypolipidemia (ANGPTL3)
- ApoE$_2$E$_2$ Potential risk for CAD
B100 Lipoprotein Cascade

Liver → TG (VLDL) → UC, PL, B → Remnant (TG, CE) → HDL, CE (PLTP) → LDL (Apo E, HL)
Defective apoB gene

- Insertion/deletion or premature stop codon
- Half normal hepatic secretion rates for apoB
- 50% reduction in LDL cholesterol
- Decreased premature CAD
- Hepatic steatosis (without cirrhosis?)
Adipose and Muscle Endothelium

HSP

GPIHBP1

Active LPL

VLDL, Chylom.

ApoB

ApoAV

ApoCII

ApoCII

Endothelium

LPL

LMF1

Adipose and Muscle

Deeb & Brunzell
Adipose and Muscle Endothelium

HSP

Active LPL

Inactive LPL

ANGPTL 3

GPIHBP1

LPL

LMF1

Endothelium

Remnant

VLDL, Chylom.

ApoB

ApoAII

ApoAIV
Adipose and Muscle

Inactive LPL

Inactive LPL

Active LPL

VLDL, Chylom.

HSP

GPIHBP1

Remnant

LPL

ANGPTL 3

Adipose and Muscle
Density gradient ultracentrifugation (DGUC) in Normal Subjects

- Insulin Sensitive: (148)
- Insulin resistant: (49)

Cnop 2002

The graph shows the distribution of cholesterol levels across different fraction numbers. The x-axis represents the fraction number, while the y-axis represents cholesterol levels in mg/dl. The graph is divided into regions for different types of lipoproteins: VLDL, LDL, and HDL.
ApoE genotype and cholesterol distribution

Murdoch et al. Athero 2007;192:138
Familial HypoBeta-Lipoproteinemia

- Defective apoB allele
- Defective PCSK9 allele
- Familial combined hypolipidemia (ANGPTL3)
- ApoE$_2$E$_2$ Potential risk for CAD
LDL receptor degradation: PCSK9

Lambert J Lipid Res. 2012; 53:2515
Chylomicronemia Syndrome
Very severe hypertriglyceridemia

• Familial chylomicronemia syndrome ($2/10^6$)
  – Lipoprotein lipase deficiency
  – Other LPL related genetic defects

• Multifactorial chylomicronemia syndrome
  (200 times more common)
  – Three factors present
Familial Chylomicronemia Syndrome

Lipoprotein Lipase Deficiency (2/10^6)

Gene therapy: LPL protein
Postheparin Plasma LPL

- Controls (n=34)
- LPL deficient (n=33)
Chylomicron Triglyceride After Gene Therapy
(alipogene tipavovec: Glybera®)

Gaudet D et al. JCEM 2013; 97:1635
Homozygous Familial Hypercholesterolemia

- LDL receptor
  - Null defect
  - Defective receptor
- Defective apoB (B3500)
MIPOMERSEN THERAPY IN HOMOZYGOUS FH: ApoB Antisence oligonucleotide

Figure 1  Mechanism of action of an antisense oligonucleotide. DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid. © Copyright Antisense Therapeutics Limited, 2012. Accessed at <ce:inter-ref href="http://www.antisense.com.au/technolog...>

Peter P. Toth

Emerging LDL therapies: Mipomersen—antisense oligonucleotide therapy in the management of hypercholesterolemia

Journal of Clinical Lipidology Volume 7, Issue 3, Supplement 2013 S6 - S10

http://dx.doi.org/10.1016/j.jacl.2013.02.004
Figure 2  Change in LDL-C over time with 26 weeks of mipomersen treatment in a phase 3 trial in patients with homozygous FH. Reprinted with permission from Raal et al. LDL, low-density lipoprotein.

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Other drugs for HoFH

• PCSK9 monoclonal antibody
  – Amgen; Regeneron-Sanofi
  – Requires LDL receptor to be present (defective)

• MTTP inhibitor (lomitapide)
  – BMS-Aererion
  – Inhibits the transfer of apoB into ER
  – Hepatic steatosis
  – (Defect in abeta-lipoproteinemia)
HDL genesis and catabolism

• Very low HDL cholesterol
• Very high HDL cholesterol and CAD
• Waldenstrom macroglobulinemia
  (lympho-plasmacytic lymphoma)
Reverse Cholesterol Transport

- HDL2
- HL
- LCAT
- HDL3
- ABCA1 (G1)
- PLTP
- VLDL (LPL)
- AI
- AI/AII
- SR-BI
- Liver
- CETP
- Apo B Lp
- A-I/PL
- CE
- Catabolism
- Biogenesis
- UC
- PL
High HDL cholesterol and CAD

• Hepatic lipase deficiency: 10/12 pCAD
• CETP deficiency (some)
• SRB1 variant?
Reverse Cholesterol Transport

- **HDL2**
- **HL**
- **HDL3**
- **LCAT**
- **ABCA1 (G1)**
- **PLTP**
- **VLDL (LPL)**

**Biogenesis**
- **AI/AII**
- **?**
- **SR-BI**
  - Liver
- **HL**
  - Liver
- **CETP**
  - Apo B Lp

**Catabolism**
- **CE**
- **PL**
- **UC**
- **PL**
- **UC**
SUMMARY

• Very low LDL cholesterol: apoE
• LPL deficiency & gene therapy: LPL protein
• Homozygous FH: Defective receptor
• Very low HDL cholesterol: R/O Waldenstrom
• High HDL & CAD: Defective HDL catabolism?
Premature MI
52 y M

Targeted Risk Reduction

Children
18 – 30 y

Premature MI
52 y M

Children

Siblings
Take-home Message: Genetics

• Personalized genotyping: not ready
• Selected genetic analysis to determine therapies

• Family history premature CAD
  – Lipids involved
  – FHx +: patient at same risk

• Sites for DNA analysis
Thank you