Genetic Causes of Elevated Triglycerides

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Case

- 62 y/o female referred to the Lipid Clinic by nephrologist for elevated TG
- History of resistant HTN on 4 meds for BP, no lipid meds, vitamin D
- BP 162/98 P 56 Exam otherwise unremarkable
- TC 286 HDL 50 LDL 126 TG 550
- All other chemistry is normal except mild elevation in LFT’s
- What is your diagnosis?
Rule out Secondary Causes of Elevated Triglyceride

- Obesity
- Metabolic syndrome/insulin resistance
- DM
- Alcohol
- Estrogen, corticosteroids, protease inhibitors, retinoids, some beta blockers, cyclosporin
- Pregnancy
- Bulemia
Lipid Metabolism

Exogenous

Dietary Fat
Intestine

Dietary Fat

Remnant (LDLr) Receptor

Chylomicron

B-48

Remnant

LPL

TG

FFA

VLDL

B-100

E

C II

HDL

LPL

TG

FFA

IDL

B-100

E

C II

HDL
# Apolipoproteins

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoA-I</td>
<td>HDL structural protein; LCAT (Lecithin cholesterol acyl transferase) activator; Enhances reverse cholesterol transport</td>
</tr>
<tr>
<td>apoA-II</td>
<td>Hepatic lipase activation</td>
</tr>
<tr>
<td>apoA-IV</td>
<td>Triglyceride metabolism; LCAT activator;</td>
</tr>
<tr>
<td>apoB-100</td>
<td>Structural protein of all Lipoproteins except HDL</td>
</tr>
<tr>
<td>apoB-48</td>
<td>Binding to LDL receptor</td>
</tr>
<tr>
<td>apoC-I</td>
<td>Inhibit Lipoprotein binding to LDL Receptor; LCAT activator</td>
</tr>
<tr>
<td>apoC-II</td>
<td>Lipoprotein lipase (LpL) activator</td>
</tr>
<tr>
<td>apoC-III</td>
<td>LpL inhibitor; antagonizes apoE</td>
</tr>
<tr>
<td>apoE</td>
<td>B/E receptor ligand *E2:IDL; *E4: Diet Responsivity</td>
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</tbody>
</table>
Intestinal Absorption of Cholesterol and Bile Acids Influences Lipoprotein Metabolism

Dietary Cholesterol

Ezetimibe

Bile acid sequestrants

NPC1L1

iBAT

Bile

Chol

BA

CM

CMR

BA

LDLR

Blood

Liver

Chol

BA

Rader DJ, Nature Medicine 2001; 7:1282-1284
Exogenous

Dietary Fat

Intestine

Endogenous

Liver

Remnant (LDLr) Receptor

B-48

Remnant

Chylomicron

LPL TG

FFA

VLDL

B-100

E Receptor (LDLr)

LDL

HDL

LPL

HTGL

B-100

C II

IDL

LDL Receptor

B-100

E

C II

HDL

LPL

TG

FFA

E

B-100

C II

IDL

B-100

C II

HDL

LPL

TG

FFA
Lipoprotein Lipase

- Breaks down triglycerides from TG rich lipoproteins into FFAs
- Activated by Apo CII
- Inhibited by Apo CIII
- Secreted into the interstitium by adipocytes and myocytes
- Requires transport to the lumen by GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1)
The role of GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1) in transporting lipoprotein lipase (LpL) into the capillary lumen.

HPSGs = Heparan sulphate Proteoglycans

FA = fatty acid

LpL = Lipoprotein Lipase

Chylo = Chylomicrons
Lipoprotein Lipase Movement to the Capillary Lumen
Lipid Metabolism

Exogenous

Dietary Fat

Intestine

Remnant (LDLr) Receptor

Chylomicron

Remnant

VLDL

LPL

TG

FFA

Endogenous

Liver

LDL Receptor

E Receptor (LDLr)

HDL

LPL

TG

FFA

B-100

C II

E

B-48

E

B-100

C II

E

B-100

C II

E

B-100

C II

E

DGAT = diacylglycerol acyltransferase; PA(P) = phosphatidic acid phosphatase/phosphohydrolase.

Genetic Dyslipidemias

- Disorders affecting LDL
- Disorders affecting Triglycerides
- Low HDL disorders
- Low LDL disorders
- Lp(a)
## Classification of Lipoprotein Disorders (Frederickson / Levy / Lees)

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>TG</th>
<th>Xanthomas</th>
<th>Clinical</th>
<th>Etiology</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>CM</td>
<td>LDL</td>
<td>LPL</td>
<td>FCS</td>
</tr>
<tr>
<td>IIa</td>
<td>N</td>
<td>tendon</td>
<td>CHD</td>
<td>LDLR</td>
<td>FH</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL+VLDL</td>
<td>none</td>
<td>CHD</td>
<td>unknown</td>
<td>± FCH</td>
</tr>
<tr>
<td>III</td>
<td>Remnants</td>
<td>palmar tubero-eruptive</td>
<td>CHD</td>
<td>apoE2</td>
<td>FD</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>none</td>
<td>none</td>
<td>unknown</td>
<td>FEHTG</td>
</tr>
<tr>
<td>V</td>
<td>CM+VLDL</td>
<td>eruptive</td>
<td>pancreatitis</td>
<td>unknown</td>
<td>MHTG</td>
</tr>
</tbody>
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- **CM**: Chylomicron
- **VLDL**: Very Low Density Lipoprotein
- **CHD**: Coronary Heart Disease
- **FH**: Familial Hypercholesterolemia
- **CHD**: Coronary Heart Disease
- **apoE2**: Apolipoprotein E2
- **FD**: Familial Dysbetalipoproteinemia
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<th>Genetic Disorders</th>
<th>Defect</th>
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<td>Hyperchylomicronemia</td>
<td>Lipoprotein Lipase, CII</td>
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<tr>
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<td>Apo B Overproduction</td>
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<td>Apo E2:E2 + FCH</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>Enlarged VLDL</td>
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<tr>
<td>Hypoalphalipoproteinemia</td>
<td>Apo Al, HDL</td>
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<td>Lp (a)</td>
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Genetic Disorders of LDL

• Familial hypercholesterolemia (FH)
  – Heterozygous
  – Homozygous
• Familial defective Apo B-100
• PCSK9 abnormality
• Hereditary Sitosterolemia (Can mimic physical findings of FH)
• Physical findings of
  – Corneal arcus
  – Extensor tendon xanthomas
  – Achilles xanthomas
Genetic Disorders of Triglycerides

• Chylomicronemia
  – Lipoprotein lipase deficiency
  – Apo CII deficiency
• Familial combined dyslipidemia
  – Overproduction of Apo B-100
• Familial hypertriglyceridemia
  – Large VLDL particles
  – Minimal ↑ CAD risk
• Type III dyslipidemia
Clues to Lipid Abnormalities by Serum Examination
Tuberoeruptive Xanthomas in Hypertriglycerideridemia
Tuberoeruptive Xanthomas in Chylomicronemia
Lipemia Retinalis

TG = 8000 mg/dL
Chylomicronemia

Exogenous

Dietary Fat
Intestine
Dietary Fat
Remnant Receptor
Chylomicrons

Endogenous

Liver
LDL Receptor
E Receptor
Remnant
Remnant Receptor
Liver

HDL
LPL
TG
FFA
VLDL
B-100
B-100
C II
C II
LDL
IDL
LDL

Familial Combined Dyslipidemia

Exogenous

- Dietary Fat → Intestine
- Intestine
  - Chylomicron
  - Remnant
  - E Receptor

Endogenous

- Liver
  - LDL Receptor
  - E Receptor
  - TG
  - FFA
  - HDL
  - LPL

- LDL
  - C II
  - B-100
  - Remnant

- HDL
  - C II
  - B-100

- IDL
  - C II
  - B-100

- VLDL
  - E
  - B-100

- HTGL
  - TG
  - FFA

- LPL
  - TG
  - FFA
Familial Combined Hyperlipidemia

- Use Non-HDL cholesterol or Apo B rather than LDL
- Apo B/LDL > 1.0
- Autosomal Dominant/Family Screening/Valuable
- Evaluate Lp (a), homocysteine
Familial Hypertriglyceridemia

**Exogenous**
- Dietary Fat → Intestine
  - Remnant Receptor
  - B-48 → Chylomicron
  - LPL → TG → FFA

**Endogenous**
- LDL Receptor
- E Receptor
- HTGL
- LDL → FFA
- HDL
- LPL → TG → FFA
- Remnant → B-48

Liver

VLDL

HDL
Familial Hypertriglyceridemia

- Family member has hypertriglyceridemia only
- Apo B/LDL < 1.0
- HDL usually low
- CHD risk only slightly above average
Type III Dyslipidemia

- Extremely rare (1:10,000)
- Combination of familial combined dyslipidemia and Apo E2/E2 phenotype
- ↑ risk for CAD
- Extremely diet sensitive
- Orange palmar creases
- Palmar xanthomas
Type III Dyslipidemia

Exogenous

Dietary Fat → Intestine → Remnant

Endogenous

Liver → LDL Receptor → LDL → LDL Receptor

E Receptor

HDL → LPL → HDL

B-100

C II

Remnant

B-48

Chylomicron

VLDL

HDL

LPL

TG

FFA
Apo-E Isoforms and Type III Hyperlipidemia

Features of Apo-E2 Homozygosity

1% incidence in population
Total cholesterol and LDL cholesterol
VLDL Cholesterol
1:50 people homozygous for Apo-E2 develop type III hyperlipidemia
Coincident second defect in lipoprotein metabolism required for Type III Hyperlipidemia to develop
Hypothyroidism, obesity, estrogen deficiency or glucose intolerance may result in expression of Type III Hyperlipidemia
Orange Palmar Creases in Type III
Tubero-Eruptive Xanthomata-Dysbetalipoproteinemia
Palmar xanthomas in Type III
Palmar Xanthomas in Type III (Dysbetalipoproteinemia)
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