Familial Chylomicronemia Syndrome: Distinguishing the Rare Among the Common in Adults for Appropriate Management


University of Pennsylvania, Corporal Michael J. Crescenz VAMC, Philadelphia, PA

**Background**

- Hypertriglyceridemia (HTG) is a common dyslipidemia and mostly polygenic, often associated with other metabolic abnormalities
- Familial chylomicronemia (FCS) is a rare and monogenic condition with an estimated prevalence of one in 1 million
- FCS is associated with chylomicronemia with TG levels often over 2,000 mg/dL
- Lipoprotein lipase (LPL) deficiency due to bi-allelic loss-of-function (LOF) mutations in the LPL gene (OMIM 238000) is the best-known cause of FCS

**Materials and Methods**

- Fraternal twins and their older brother were recruited into an IRB-approved study of dyslipidemia at the University of Pennsylvania
- The post-heparin lipase activity (PHLA) was measured in the flash frozen plasma samples as described (Di Filippo et al., 2014)
- Molecular analysis was performed using LipidSeq next-generation sequencing (Johansen et al., 2014), especially focusing on the FCS-related genes, particularly the LPL gene, and Sanger sequencing was used to confirm the findings

**Case Presentation**

- 52-year-old fraternal twins and their 54-year-old brother without any other significant medical history presented with severe hypertriglyceridemia (HTG), and recurrent acute episodes of pancreatitis
- No other family members had severe HTG
- All were on low-carbohydrate diet prior to presentation

**Comparison of Three Siblings**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Female Twin</th>
<th>Male Twin</th>
<th>Older Brother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported age of symptom onset</td>
<td>13 years old</td>
<td>17 years old</td>
<td>18 years old</td>
</tr>
<tr>
<td>Pancreatitis episodes (maximum)</td>
<td>4 times/year</td>
<td>4 times/year</td>
<td>2 times / lifetime</td>
</tr>
<tr>
<td>Eruptive Xanthoma</td>
<td>Never</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Lipemia Retinalis</td>
<td>Yes, reported</td>
<td>Yes, reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maximum Reported TG (mg/dL)</td>
<td>7,200</td>
<td>5,000</td>
<td>6,000</td>
</tr>
<tr>
<td>Minimum Reported TG (mg/dL)</td>
<td>700</td>
<td>774</td>
<td>321</td>
</tr>
<tr>
<td>Maximum TG:TC Ratio (calc. mg/dL)</td>
<td>14:1</td>
<td>20:1</td>
<td>11:1</td>
</tr>
<tr>
<td>Maximum TG:ApoB Ratio (calc. mg/dL)</td>
<td>&gt;59:1</td>
<td>&gt;96:1</td>
<td>&gt;47:1</td>
</tr>
<tr>
<td>Minimum ApoB (mg/dL)</td>
<td>&lt;40</td>
<td>&lt;40</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

**Triglyceride-Rich Lipoprotein Metabolism**

A – Exogenous pathway: dietary fats absorbed in the intestine, are packaged into CMs, released by triglycerides. LPL hydrolyzes CMs into TG remnant particles or IDLs. Further lipolysis converts those into LDL particles, that are taken up by the peripheral tissues or the liver by LDLR.

B – Endogenous pathway: VLDLs packaged in the liver, are released into the circulation; then some TGs go through lipoprotein, releasing free fatty acids and monoglycerides, leaving VLDL remnant particles or IDLs. Further lipolysis converts those into LDL particles, that are taken up by the peripheral tissues or the liver by LDLR.

**Lipid Profile**

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>Female Twin</th>
<th>Male Twin</th>
<th>Older Brother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>250</td>
<td>414</td>
<td>381</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>1336</td>
<td>3265</td>
<td>503</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>17</td>
<td>15</td>
<td>63</td>
</tr>
<tr>
<td>Direct LDL-C (mg/dL)</td>
<td>NA</td>
<td>18</td>
<td>39</td>
</tr>
</tbody>
</table>

**FCS (Monogenic) vs. Polygenic Chylomicronemia**

- Former Designation (Electrophoresis)
  - Type I: Hyperlipoproteinemia
  - Type V: Hyperlipoproteinemia
- Major Lipoproteins
  - Chylomicron
  - Chylomicron and VLDL
- Genetics
  - Monogenic (autosomal recessive, bi-allelic)
  - Polygenic, familial clustering
- Prevalence
  - 1 in 100,000 to 1,000,000
  - Approximately 1 in 600
- Disease onset
  - Childhood/adolescence
  - Mostly adulthood
- Features of Chylomicronemia
  - TG > 1,000 mg/dL
  - TG > 1,000 mg/dL
  - TG > 8.8
  - TG > 8.8
  - Apolipoprotein B (apoB)
  - < 75 mg/dL
  - ≥ 75 mg/dL
- Serious Clinical Consequence
  - Pancreatitis
  - Pancreatitis (~10%)
- Dermatological Finding
  - Eruptive xanthomas
  - Eruptive xanthomas (rare)
- Ophthalmological Finding
  - Lipemia retinalis
  - Lipemia retinalis (rare)
- Physical Finding
  - Hepatosplenomegaly
  - None to marginal response
  - Robust response
- Association with Cardiovascular disease
  - None to minimal risk
  - Evidence of increased risk

- The clinical characteristics of the siblings are consistent with the clinical diagnosis of FCS
- Among the siblings, the male twin has had the most severe clinical course.
The Family Pedigree

Family history was significant for a consanguinity in the parents who are first cousins

LPL Functional Analyses

Clinical Features  | Female Twin  | Male Twin | Older Brother |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid PIs</td>
<td>4.8 (13.8%)</td>
<td>2.5</td>
<td>NA</td>
</tr>
<tr>
<td>Activity, Method 1: normal</td>
<td>34.8 mmol/l/min, Range 22.47.6% (% of Reference)</td>
<td>3.4</td>
<td>146.08 (36.7%)</td>
</tr>
<tr>
<td>Activity, Method 2: normal</td>
<td>37.8 mmol/l/min, Range 22.47.6% (% of Reference)</td>
<td>NA</td>
<td>134.99</td>
</tr>
<tr>
<td>Activity, Method 3: normal</td>
<td>0% (% of Reference)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>LPL Mass, ng/ml (% of Reference)</td>
<td>NA</td>
<td>112</td>
<td>87.9</td>
</tr>
</tbody>
</table>

LPL-Associated Proteins and FCS genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Note in LPL-dependent Lpolyus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL</td>
<td>Glycoprotein found on the luminal surface of endothelial cells that catalyzes the hydrolysis of the TG in CMs and VLDL lipoproteins, releasing non-esterified FAs and 2-3MG for tissue utilization</td>
</tr>
<tr>
<td>LMF1</td>
<td>Chaperone protein of LPL, required for maturation and transport</td>
</tr>
<tr>
<td>GPIHB1</td>
<td>Protein important in LPL anchoring, dimerization, and stabilization to the endothelium</td>
</tr>
<tr>
<td>APOC2</td>
<td>Activating co-factor of LPL</td>
</tr>
<tr>
<td>APOA5</td>
<td>Stabilizing co-factor of LPL and apoc-II, and also a modulator of hepatic TG metabolism</td>
</tr>
<tr>
<td>APOC3</td>
<td>Attenuator of LPL activity</td>
</tr>
</tbody>
</table>

Genetic Analyses

- Lipid-Seq of FCS-associated genes (LPL, APOC2, LMF1, GPIHB1, and APOA5) was performed identified a variant in the LPL gene
- LPL gene (bp213) with 10 exons
- GTA -> GCA (c.617 T>C) in exon 5 (Valine to Alanine, p.V636A)
- The variant has never been reported in the homozygous state
- The variant was not listed in GnomAD website (only p.V206V is listed, but not p.V636A)
- Apo Protein E genotype (3/3)

TG Polygenic Score

<table>
<thead>
<tr>
<th>Chr</th>
<th>SNP</th>
<th>Gene</th>
<th>Change</th>
<th>Locus and Type</th>
<th>Pedicel Twin</th>
<th>Male Twin</th>
<th>Other Brother</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>rs10568253</td>
<td>ANGPTL7</td>
<td>A&gt;C</td>
<td>Intron variant</td>
<td>GG</td>
<td>AA</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>rs1267919</td>
<td>APOB</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>CC</td>
<td>CC</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>rs10568253</td>
<td>GCNR</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>CC</td>
<td>CC</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>rs714052</td>
<td>MLN6</td>
<td>A&gt;G</td>
<td>Intron variant</td>
<td>GG</td>
<td>GG</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>rs7819412</td>
<td>KLR5</td>
<td>A&gt;G</td>
<td>Intron variant</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>rs78238</td>
<td>LPL</td>
<td>A&gt;G</td>
<td>Stop gain</td>
<td>DD</td>
<td>DD</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>rs1267919</td>
<td>APOE</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>rs78238</td>
<td>LPL</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>AA</td>
<td>AA</td>
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<tr>
<td>9</td>
<td>11</td>
<td>rs174547</td>
<td>APOB</td>
<td>A&gt;G</td>
<td>Intron variant</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>rs1041546</td>
<td>ZNF182</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>CC</td>
<td>CC</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>rs235596</td>
<td>APOE</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>GG</td>
<td>GG</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>rs827972</td>
<td>APOE</td>
<td>A&gt;G</td>
<td>2-missense variant</td>
<td>AA</td>
<td>AA</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>rs7216652</td>
<td>LPL</td>
<td>A&gt;G</td>
<td>Intron variant</td>
<td>CC</td>
<td>CC</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>rs7879</td>
<td>LPL</td>
<td>A&gt;G</td>
<td>Missense variant</td>
<td>CC</td>
<td>CC</td>
</tr>
</tbody>
</table>

Risk Score: 15/28

Conclusion and Discussion

- HTG conditions are heterogenous
- Making an accurate diagnosis can determine the most appropriate therapy (considering a rare disease is important even in adults)
- In FCS, preventing pancreatitis is the main goal of therapy
- At present, medical nutrition therapy is the mainstay of management
- Novel therapies may become available for patients with FCS in the future
- Referral to a lipid specialist and an experienced dietitian should be considered

Method 1: Di Felice et al., J. Lipid Res. 2014;55(12):2491-4306
Method 2: Di Felice et al., J. Lipid Res. 2014;55(12):2491-4306
No standardization of LPL functional analysis methods provides variable results. Thus, genetic analysis is according a bioassay approach.
Familial Chylomicronemia Syndrome: Appropriate Management

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**Predicted LPL 3-D Protein Structure V206A**

- Tail region
- Head
- Catalytic site
- V23 (V206A)
- U3 (V206A)

Rotated (180 degree) Image for better view of the tail region (N-terminus)

- The tail region is shifted on the protein, which is important for:
  - LPL chemistry
  - TG substrate proximity to the enzyme's active site

**FCS Management**

- No FDA-approved drugs for FCS
- Prevention of acute pancreatitis: TG to be lowered to the individual's threshold, ideally <500 mg/dL, but at least <1,000 mg/dL
- Medical nutrition therapy: low-fat diet (less than 15% of total calories as fat, <15 to 20 g per day), including essential fatty acids, especially in children
- Medium-chain triglycerides (MCT): caloric supplementation if necessary
- Avoid TG-raising medications: oral estrogens, diuretics, isoretinoin, glucocorticoids, SSRIs, and beta-adrenergic blocking agents, (OTC fish oil supplements may raise FFA)
- Avoid alcohol
- Adjunct TG-lowering medications: (not very effective, but may aid in VLDL-lowering)

**Experimental APOC3 ASO in Female-Twin**

- APOC3 antisense oligonucleotide (ASO, 5’-AGCTTCTTTGTCAGCTTTAT-3’), Volanesorsen, against APOC3 mRNA, 16 doses (300 mg/dose) SQ qw & q2w

**LPL Molecular Dynamics**

- Experimental Novel Biologics

- An experimental APOC3 ASO lowered her TG level from 3,447 to 201 mg/dL (i.e., ~94%) within 3 months
- The patient result was similar to the previously published FCS cases with different LPL mutations in Gaudet DJ et al., NEJM 371:23 Dec 4, 2013 (LPL: p.G188E, and p.P207L)
- APOC3 inhibition might have enhanced the residual LPL function and also might facilitate a better interaction between LPL and ApoC-III
- The effectiveness of APOC3 inhibition may depend on the type and location of FCS-causal LPL mutations

**Mechanism of Action**

- Enhanced residual LPL activity by reducing APOC3-mediated LPL inhibition
- Variability in efficacy expected, depending on the baseline LPL activity and unknown long-term effect
- Reduction
- Same improvement

**Mechanism of Action**

- Enhanced residual LPL activity by reducing ANGPTL3-mediated LPL inhibition
- Variability in efficacy expected, depending on the baseline LPL activity and unknown long-term effect
- Reduction

2. Gaudet DJ et al., NEJM 373:3 July 30, 2015
3. Graham MJ et al., NEJM 377:3 July 20, 2017
4. Doney PG et al., NEJM 377:3 July 20, 2017