Case 2: Case of Pregnancy in FCS

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## Pregnancies in FCS

<table>
<thead>
<tr>
<th>Case</th>
<th>Number of pregnancies</th>
<th>Total</th>
<th>Severe hyperTG</th>
<th>Pancreatitis</th>
<th>Post-Partum Pancreatitis</th>
<th>Post-partum death</th>
<th>Alive</th>
<th>Fœtal death</th>
<th>Abortion</th>
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<td><strong>Total</strong></td>
<td><strong>42</strong></td>
<td><strong>28</strong></td>
<td><strong>7</strong></td>
<td><strong>19</strong></td>
<td><strong>2</strong></td>
<td><strong>1</strong></td>
<td><strong>32</strong></td>
<td><strong>2</strong></td>
<td><strong>8</strong></td>
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</tbody>
</table>
### Pregnanacies in FCS

- We reviewed the files of 42 pregnancies in 17 FCS women (homozygotes for null LPL variants p.Pro234Leu or p.Gly215Glu) from 1974 to 2016 (3 additional pregnancies since then, 1 plasmapheresis);

- 21 acute pancreatitis episodes (50% of pregnancies);

- Fetal mortality reached 23%;

- Hospitalization in the third trimester was required in 66% of cases.

- Women with prior history of acute pancreatitis (AP) had a higher risk of hospitalisations or AP during pregnancy;
Fredrickson’s Phenotypes in 145 Relatives\(^1\) (Heterozygotes for the LPL p.Pro234Leu Variant) of 17 FCS (Homozygotes for the Same Mutation)

Observed Frequencies for PHEN UC, LPL
Split By: LPLmut
Cell: P207L
Inclusion criteria: Criteria 11 from Db1 mod juillet

<table>
<thead>
<tr>
<th></th>
<th>HMZ</th>
<th>HTZ</th>
<th>NORMAL</th>
<th>Totals</th>
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<td>Alpha.</td>
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<td>5</td>
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<tr>
<td>Totals</td>
<td>17</td>
<td>145</td>
<td>0</td>
<td>162</td>
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</table>

*: Type V alternates with Type I in 2 HMZ

- 5% of HeLPL relatives presented Type 1
- 17.9% had a normal Phenotype
Lipoprotein Lipase Gene Polymorphisms and FCS or MCM

**Green:** Gain of function or Increased gene expression

**Red:** Null loss of function (LoF)

**Black:** Defective (non-null) LoF or unknown

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**Green:** Gain of function or Increased gene expression

**Red:** Null loss of function (LoF)

**Black:** Defective (non-null) LoF or unknown
Pancreatitis Risk in Variants Having large Size Effect Depends Less on Modifiers

Adapted from Nature 461, 747-753 (2009)

Rare allele causing Mendelian hyperTG disorder

Common variants implicated in common disease by GWAS

High-effect common variants influencing common disease (eg: apoE)

Chylomicronemia and pancreatitis risk depends on Modifiers (eg: HoLPL D9N, HeLPL null)

Chylomicronemia

Pancreatitis risk (eg: HoLPL null)

Effect size

Allele frequency

Very rare

Rare

Intermediate

Common

Low-med frequency variants with variable effect

Modest effect on TG (eg: HeLPL D9N)

LPL

High

Intermediate

Modest

Low

50.0

3.0

1.5

1.1

0.001 0.005 0.05

(eg: HeLPL D9N)

Low-med frequency variants with variable effect

Common variants implicated in common disease by GWAS

Modest effect on TG

Chylomicronemia and pancreatitis risk depends on Modifiers (eg: HoLPL D9N, HeLPL null)

Rare allele causing Mendelian hyperTG disorder

High-effect common variants influencing common disease (eg: apoE)
Familial Chylomicronemia Syndrome (FCS): Disease State Overview
Familial Chylomicronemia Syndrome

- Chylomicronemia syndrome
- Chylomicronemia, familial
- Familial chylomicronemia
- Hyperchylomicronemia familial
- Hyperlipemia idiopathic Burger-Grutz type
- Hyperlipoproteinemia Type I
- Lipase D deficiency
- Lipoprotein lipase deficiency (LPLD)
- Burger-Grutz syndrome
- Endogenous hypertriglyceridemia
- Familial fat-induced hypertriglyceridemia
- Familial hyperchylomicronemia
- Familial LPL deficiency
- Hyperlipidemia Type I (Fredrickson)
- Hyperlipoproteinemia Type IA
- Lipase D deficiency
Familial Chylomicronemia Syndrome

- **Background:**
  - Rare autosomal recessive disorder
  - Severely elevated levels of plasma TGs, generally unresponsive to lipid-lowering therapies\(^1-3\)

- **Clinical expression/risk:**
  - Signs and symptoms:
    - Plasma lactescence and viscosity
    - Lipemia retinalis
    - Abdominal pain
    - Hepatosplenomegaly
    - Eruptive xanthomas
  - Pancreatic insufficiency
  - Recurrent acute pancreatitis/Chronic pancreatitis

FCS pathophysiology

• Chylomicronemia: pathological persistence of chylomicrons in plasma following a fasting period of 10 to 14 hours\textsuperscript{1,2}

• In FCS, chylomicronemia is caused by inherited defects in chylomicron processing\textsuperscript{2}


Abbreviations: FFA, free fatty acid; TG, triglyceride; VLDL, very low-density lipoprotein.

Lipoprotein Lipase

- Breaks down triglycerides from TG rich lipoproteins into FFAs
- Activated by Apo CII
- Inhibited by Apo CIII
- Secreted into the interstitium by adiposites 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
Lipoprotein Lipase Movement to the Capillary Lumen
Role of Apo A-V in Lipoprotein Metabolism

Figure 1: Disminución de triglicéridos mediada por la apolipoproteína A-V. Adaptado de Merkel & Heeren®.
# Genetics: Known mutations responsible for FCS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene product function</th>
<th>Molecular features</th>
<th>% of Monogenic mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPL</strong></td>
<td>Hydrolysis of TGs and peripheral uptake of FFA</td>
<td>Severely reduced or absent LPL enzyme activity</td>
<td>95%</td>
</tr>
<tr>
<td><strong>APOC2</strong></td>
<td>Required cofactor of LPL</td>
<td>Absent or nonfunctional ApoC-II</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>GPIHBP1</strong></td>
<td>Stabilizes the binding of chylomicrons near LPL</td>
<td>Absent or defective GPI-HBP1</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>APOA5</strong></td>
<td>Enhancer of LPL activity</td>
<td>Absent or defective apoA-V</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>LMF1</strong></td>
<td>Chaperone molecule required for proper LPL folding</td>
<td>Absent or defective LMF1</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

Adapted from Brahm, Nat Rev Endocrinol, 2015.

Abbreviations: FFA, free fatty acid; LPL, lipoprotein lipase; TG, triglyceride.


Familial Chylomicronemia Syndrome (FCS): Diagnosis
Familial Chylomicronemia Syndrome – Clinical/Differential Diagnosis

**Potential FCS if any of the following:**
- History of acute pancreatitis
- History of recurrent abdominal pain without other explainable cause
- Confirmation by genetic mutation analysis (i.e. genes for LPL, apoCII, GPIHBP1, ApoA5 or LMF1 and/or other genes shown to modulate LPL)

**Other Causes of HTG:**
- Alcoholism
- Uncontrolled T2DM
- Medications known to HTG*

* e.g. thiazides, beta blockers, estrogen, 2nd generation antipsychotics, Isotretinoin, antiretroviral

**Excluding:**
- Severe HTG (>10 mmol or 880 mg/dL)
- Refractory HTG (not responsive to standard TG therapies)
- Observed > 2x
FCS can be defined via clinical manifestations, and can be due to multiple genetic mutation variants

- **Clinical Manifestations:** Defining FCS through physical manifestations, laboratory testing, and familial history
  - Characterized by the presence of fasting chylomicrons and high triglycerides, usually >880 mg/dL\(^1\)
  - Marked chylomicronemia and hypertriglyceridemia associated with increased pancreatitis risk\(^2\)
  - Consanguinity\(^3\)

- **Genetics:** autosomal recessive inheritance
  - >90% of monogenic chylomicronemia cases are caused by mutations in \(LPL\); however, causative mutations in other genes, such as \(APOC2, APOA5, LMF1,\) and \(GPIHBP1\), have been identified.\(^5\text{-}8\)

Patient profile/natural history literature has remained relatively consistent over the past decades

Presentation during infancy, childhood, during pregnancy, and as adults is described.

- **25% develop symptoms in infancy**,\(^1\) including failure to thrive\(^2\)
- **Some individuals show no symptoms until adulthood**, often presenting with abdominal pain, when this inherited disease may be overlooked\(^3\)
- **Individual variation does not lend itself to clearly defining a phenotype.** Genetic variants are simultaneously inherited, and presentation of FCS will be affected by secondary factors, eg, diet, obesity, diabetes, alcohol. Monogenic forms are more severe than polygenic\(^2,4\)
- **Even though present from birth, FCS may not be discovered until pregnancy**, when elevated TG levels, severe pancreatitis, and chylomicronemia syndrome may emerge\(^5\)

\(\text{BMI} = \text{body mass index}; \text{FCS} = \text{familial chylomicronemia syndrome}; \text{LPL} = \text{lipoprotein lipase.}\)

Familial Chylomicronemia Syndrome (FCS): Management
There are no FDA approved drugs indicated to lower triglycerides in FCS patients

<table>
<thead>
<tr>
<th>Fibrates&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Fish oils&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>Niacin&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Statins&lt;sup&gt;6,7&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Increase lipolysis and elimination of TG-rich particles by activating lipoprotein lipase</td>
<td>Increased β-oxidation of DGAT</td>
<td>Inhibits release of free fatty acids from adipose tissue</td>
<td>Block cholesterol synthesis</td>
</tr>
<tr>
<td>Decrease VLDL-C, increase HDL-C</td>
<td>Increase plasma lipoprotein lipase activity</td>
<td>Increases lipoprotein lipase activity</td>
<td>Increase number of hepatic LDL receptors to enhance uptake and catabolism of LDL</td>
</tr>
<tr>
<td>Decrease hepatic TG synthesis</td>
<td>Decrease hepatic synthesis of VLDL, LDL</td>
<td>Inhibit hepatic synthesis of VLDL and LDL</td>
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</table>

FCS patients are generally unresponsive to lipid-lowering therapies<sup>8</sup>  

*Proposed; exact mechanisms may not be fully delineated.

Abbreviations: DGAT, diacylglycerol acyltransferase; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very low-density lipoprotein; VLDL-C, very low-density lipoprotein cholesterol.


Strict Lifelong Dietary Restriction

Sugar Restriction

Extreme low-fat diet (≤15% of energy)

Complete Avoidance of Alcohol

Although extremely difficult to follow, these mainstays of therapy can improve clinical manifestations\(^1,2,3,4-6\)

- Reduce risk of hepatosplenomegaly
- Reduce abdominal pain
- Reduce risk of xanthomas
- Reduce risk of pancreatitis\(^1,2,3,4,5\)

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Major impact on life/work

- Mental "fog"
- Recurrent hospitalizations and effect on employment
- Relationship issues
- Difficulty in social situations due to diet
- Frustration with lack of diagnosis and treatment.