GENE EXPRESSION SIGNATURE OF RECURRENT ACUTE PANCREATITIS RISK IN LPL DEFICIENCY AND SEVERE HYPERTRIGLYCERIDEMIA

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Background
Fasting triglyceride levels > 10 mmol/L (886 mg/dL) is a sign of chylomicronemia (CM) and increased risk of acute pancreatitis (AP) [1]. The risk of pancreatitis is however higher in presence of complete LPL deficiency (LPLD) or familial CM syndrome (FCS) compared to multifactorial causes of CM (MCM) [1, 2, 3]. Whatever the underlying cause, there are important inter-individual variations in AP incidence and severity [4]; some patients will experience recurrent AP (RAP) while others will either have no episodes or only one or a few throughout their lifetime. Mechanisms of RAP are still not well characterized. The aim of this study was to investigate gene expression profiles of RAP in patients with CM and to identify possible biomarkers that could play a role in the physiopathology of AP or RAP.

Methods
From a total of 400 adults with history of CM (60 FCS and 340 MCM), a sample of 47 who consented to participate in this study were included. CM patients were divided into three groups covering a wide spectrum of occurrence of pancreatitis crisis: 0 (n=21), 1-3 (n=10) or ≥ 4 (n=16) AP episodes (Table 1). Whole blood gene expression profiles were compared to 15 controls using Affymetrix® Human Gene ST 2.0 microarrays (Santa Clara, CA, USA). RNA was applied to raw intensities [5]. Differential expression moderated T-tests between studied groups were performed using a linear model of the Bioconductor package Limma. False discovery rate (FDR) was controlled using the Benjamini-Hochberg procedure [6]. Data were analyzed using QIAGEN’s Ingenuity® Pathway Analysis (IPA®, Redwood City, CA, USA).

Table 1: Summary of characteristics of study participants

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Controls (n = 15)</th>
<th>CM without pancreatitis (n = 21)</th>
<th>CM with 1 to 3 pancreatitis (n = 10)</th>
<th>CM with ≥ 4 pancreatitis (n = 16)</th>
<th>p-value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women</td>
<td>8.7</td>
<td>14.7</td>
<td>5.5</td>
<td>6.10</td>
<td>NS</td>
</tr>
<tr>
<td>Body Mass Index, Kg/m²</td>
<td>24.8 (0.8)</td>
<td>29.7 (0.9) ¹</td>
<td>25.6 (1.8)</td>
<td>22.4 (0.9) ²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol Abstinence, n(%)</td>
<td>1 (6.7)</td>
<td>4 (19.0)</td>
<td>5 (50.0)</td>
<td>5 (31.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ex or Current Smoker, n(%)</td>
<td>9 (60.0)</td>
<td>11 (58.9)</td>
<td>6 (60.0)</td>
<td>11 (68.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Total Triglycerides, mmol/L a</td>
<td>1.1 (0.1)</td>
<td>6.2 (0.6) ¹</td>
<td>10.8 (2.8)</td>
<td>22.3 (3.5) 1.2, 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-Cholesterol, mmol/L</td>
<td>1.3 (0.1)</td>
<td>0.8 (0.1)</td>
<td>0.8 (0.1) ¹</td>
<td>0.4 (0.1) 1.2, 3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are geometric mean (SE), unless otherwise stated. CM = Chylomicronemia; HDL = High-Density Lipoprotein.

Table 2: Differential expression analysis results

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Nb of probes * at p &lt; 0.01 and 5% FDR</th>
<th>Nb of probes * at p &lt; 0.01 and FDR</th>
<th>Up ▲</th>
<th>Down ▼</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM without pancreatitis vs CTL</td>
<td>3,110</td>
<td>41</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>CM 1 to 3 pancreatitis vs CTL</td>
<td>2,527</td>
<td>92</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>CM ≥ 4 pancreatitis vs CTL</td>
<td>4,503</td>
<td>94</td>
<td>58</td>
<td>36</td>
</tr>
</tbody>
</table>

CM = Chylomicronemia; CTL = Controls; FC = Fold change; FDR = False discovery rate.

Figure 2: IPA® diseases and bio functions (A) and upstream regulators (B) analyses. Heatmaps present a comparison of each chylomicronemia (CM) recurrent acute pancreatitis studied groups: z-scores in blue indicate a predicted inhibition and those in orange a predicted activation.

Figure 1: Venn diagram representing differentially expressed biomarkers among chylomicronemia (CM) recurrent acute pancreatitis studied groups (FC ≥ 2). CM without pancreatitis group (A), CM with 1 to 3 pancreatitis group (B), and CM with ≥ 4 pancreatitis group (C) include 0.0%, 50.0% and 87.5% of FCS subjects respectively.

References

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