Genetic variants and polygenic risk score associated with the HDL-c response to statin treatment: a GoDARTS study

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Introduction

• Statins mainly act on the reduction of low-density lipoprotein-cholesterol (LDL-c) levels.1
• Studies have shown that statin therapy also helps in improving high-density lipoprotein-cholesterol (HDL-c) levels up to 10-15%.2
• Inter-individual variation in HDL-c response to statins therapy could be partially explained by genetic variation.
• A recent meta analysis suggested only CETP locus for with common genetic variants that influence HDL-c response to statins.3
• Global Lipids Genetics Consortium (GLGC) 2013, has identified 80 genetic variants associated with HDL-c levels.4

Study Objectives

• To investigate genetic variants associated with the HDL-c response to statin treatment in GoDARTS cohorts
• To construct and assess the effect of a polygenic risk score (PRS) for HDL-c response in the study population

Study Methodology

Study population and sample size

• 10,633 statin users in GoDARTS cohorts

Inclusion criteria

• At least, one off treatment HDL-c level and at least one on-treatment level

Exclusion criteria

• Subjects with missing on- or off-treatment measurements

Study outcome

• Change in HDL-c (mmol/L) levels

Study predictor

• Polygenic risk score (Top 22 SNPs for HDL-c from GLGC 2013)

Results

Table 1: Difference between before and after HDL-c value (Paired t test )

<table>
<thead>
<tr>
<th>N</th>
<th>Mean (SD)</th>
<th>Min</th>
<th>Max</th>
<th>t Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,633</td>
<td>-0.27(0.32)</td>
<td>-5.58</td>
<td>1.46</td>
<td>-87.97</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Graph 1 (a & b): Distribution of HDL-c response in the study population

Graph 2: Normal distribution of Polygenic risk score

Table 2: Variants associated with HDL-c response (Adjusted for age, sex, dose, Baseline HDL-c, treatment duration)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>t Value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs247616 (CETP)</td>
<td>0.011</td>
<td>0.003</td>
<td>3.71</td>
<td>0.0002</td>
</tr>
<tr>
<td>rs1532085 (LIPC)</td>
<td>0.011</td>
<td>0.002</td>
<td>-4.08</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Graph 3 (a & b): Regression of Baseline HDL-c (a) and response of HDL-c (b) with Polygenic risk score

Table 3: Effect of PRS on baseline HDL-c (adjusted for age, sex) and HDL-c response (Adjusted for age, sex, dose, baseline HDL-c, treatment duration) (n = 8,271)

<table>
<thead>
<tr>
<th>Outcome parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>P value</th>
<th>Adjusted R square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HDL-c</td>
<td>PRS</td>
<td>0.137</td>
<td>0.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C response</td>
<td>PRS</td>
<td>0.01</td>
<td>0.008</td>
<td>0.0175</td>
</tr>
</tbody>
</table>

Discussion and conclusion

• This study shows statins also helps to improve high-density lipoprotein-cholesterol (HDL-c) levels up to 20% in the study population.
• Individual genetic variants shows significant positive association with the HDL-c response after adjusting for phenotypic traits.
• Overall effect of PRS with HDL-c response is comparatively less than baseline HDL-c. This suggests that some gene variants differentially contribute to baseline HDL-c levels and HDL-c response.

Way forward

• Preliminary data suggested that HDL profile between the two population [Scottish (1.20±0.33) and India (1.04±0.23)] were significantly different (p value <0.001) Hence, genetic differences need to be investigated.
• GWAS using Affymetrix, Illumina, and Broad (genetically adjusted) and meta-analysis will be carried out to find the novel loci in MDRF and GoDARTS data.
• Conditional GWAS will be carried to adjust for variants affecting purely baseline HDL-c levels.
• Discovered novel loci for real pharmacogenetic drug response will be used for polygenic risk score in the study population.

References

5. INSPIRED WP1 – Unpublished data provided by MK Siddiqui

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