Genome-Wide Screen for Metabolic Syndrome Loci

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Disclosures

Research support, travel expenses
(Orion-Farmos research and development foundation)
Metabolic syndrome

The International Diabetes Federation (IDF)

Waist Circumference (European ancestry):
≥ 94 cm (men)
≥ 80 cm (women)

Plus any two of the following criteria:

Triglycerides ≥ 1.7 mmol/L or specific treatment for this lipid abnormality

HDL-cholesterol ≤ 1.03 mmol/L (men) or ≤ 1.29 mmol/L (women) or specific treatment for this lipid abnormality

Blood pressure ≥ 130/85 mmHg or treatment of hypertension

Fasting plasma glucose ≥ 5.6 mmol/L or diagnosis of type 2 diabetes

Phenotypes in our genetic study:

• MetS case-control status

• MetS component traits:
  • Waist circumference
  • Triglycerides
  • HDL-cholesterol
  • Diastolic/systolic blood pressure
  • Plasma glucose
Study samples

GenMets - The Genetic Background and Molecular Pathogenesis of Metabolic Syndrome and Its Component Risk Factor Traits

Study samples:

- Health 2000 Study (sub-sample of MetS cases and controls)
- NFBC 1966 Study
- Helsinki Birth Cohort Study (“IDEFIX-study”)
- LASERI, The Cardiovascular Risk in Young Finns Study

<table>
<thead>
<tr>
<th></th>
<th>H2000</th>
<th>NFBC66</th>
<th>HBCS</th>
<th>LASERI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2124</td>
<td>5373</td>
<td>1676</td>
<td>2443</td>
</tr>
<tr>
<td>Age, y</td>
<td>51 ± 11</td>
<td>31 ± 0</td>
<td>61 ± 3</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>Men, %</td>
<td>49</td>
<td>48</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>MetS case %</td>
<td>48</td>
<td>10</td>
<td>38</td>
<td>18</td>
</tr>
</tbody>
</table>

In total 2,637 cases and 7,927 controls
Genetic markers for analysis

Single nucleotide polymorphism (SNP)
- A single nucleotide in the DNA sequence differs between genomes

Copy number variation (CNV)
- A segment of DNA for which copy-number differences have been found by comparison of two or more genomes (diallelic deletions and duplications or complex, multiallelic, CNPs)
Study outline

Genome-wide association study
- 1.25 M SNPs

Genetic risk score analysis
- MetS case-control
- TG, HDL, glucose

Copy number polymorphism tag-SNPs

MetS case-control

MetS component traits

MetS factor analysis

Selected SNPs for downstream analyses

- Gene expression
- Metabolites

Large and rare copy number variation
SNP GWA
MetS case control status

APOA1/C3/A4/A5 gene cluster region
rs964184

\[ P = 7.23 \times 10^{-9} \]

### Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio and 95% CI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2000</td>
<td>1.38 (1.16, 1.65)</td>
<td>1.38 (1.16, 1.65)</td>
</tr>
<tr>
<td>HBCS</td>
<td>1.41 (1.12, 1.77)</td>
<td>1.41 (1.12, 1.77)</td>
</tr>
<tr>
<td>Laseri</td>
<td>1.26 (1.02, 1.55)</td>
<td>1.26 (1.02, 1.55)</td>
</tr>
<tr>
<td>NFBC66</td>
<td>1.27 (1.08, 1.51)</td>
<td>1.27 (1.08, 1.51)</td>
</tr>
<tr>
<td>Summary</td>
<td>1.33 (1.20, 1.46)</td>
<td>1.33 (1.20, 1.46)</td>
</tr>
</tbody>
</table>
MetS case control SNP rs964184

- triglycerides  \( P=2.59 \times 10^{-31} \)
- HDL  \( P=5.83 \times 10^{-8} \)
- waist circumference  \( P=0.52 \)
- systolic BP  \( P=0.68 \)
- diastolic BP  \( P=0.98 \)
- glucose  \( P=0.73 \)

600 study samples from the National FINRISK Study 2007 Survey

Gene expression data

\( \rightarrow \) No genes whose expression was significantly affected by rs964184

Metabolite data, 135 metabolites

\( \rightarrow \) rs964184 associated with

- all VLDL metabolites  \( (N=30, P=0.024 - 1.88 \times 10^{-5}) \)
- several other TG related metabolites  \( (P=0.0025-3.31 \times 10^{-5}) \)
- HDL  \( (P=0.0097-0.00034) \) and apoB metabolites  \( (P=0.0059-0.0014) \)
SNP GWA
MetS component traits

Triglycerides

HDL cholesterol
SNP GWA
MetS component traits

Waist

Glucose

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### Risk score analysis

22 top SNPs from MetS component trait GWA results

MetS case control status vs number of risk alleles

<table>
<thead>
<tr>
<th>GRS quartile</th>
<th>All OR (95% CI)</th>
<th>H2000 OR (95% CI)</th>
<th>HBCS OR (95% CI)</th>
<th>Laseri OR (95% CI)</th>
<th>NFBC OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>2</td>
<td>1.15 (1.00-1.32)</td>
<td>1.32 (1.04-1.68)</td>
<td>0.78 (0.58-1.06)</td>
<td>1.46 (1.06-1.99)</td>
<td>1.13 (0.86-1.49)</td>
</tr>
<tr>
<td>3</td>
<td>1.27 (1.11-1.45)</td>
<td>1.22 (0.96-1.56)</td>
<td>1.11 (0.82-1.50)</td>
<td>1.24 (0.89-1.71)</td>
<td>1.49 (1.14-1.94)</td>
</tr>
<tr>
<td>4</td>
<td>1.55 (1.35-1.77)</td>
<td>1.30 (1.02-1.65)</td>
<td>1.49 (1.10-2.03)</td>
<td>1.69 (1.24-2.30)</td>
<td>1.82 (1.41-2.35)</td>
</tr>
</tbody>
</table>
## Risk score analysis

Variance explained, by genetic risk score (GRS) and conventional risk factors

<table>
<thead>
<tr>
<th></th>
<th>H2000 cases</th>
<th>H2000 controls</th>
<th>HBCS</th>
<th>Laseri</th>
<th>NFBC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRS + age + sex</td>
<td>11 %</td>
<td>9 %</td>
<td>6 %</td>
<td>9 %</td>
<td>8 %</td>
</tr>
<tr>
<td>GRS</td>
<td>5 %</td>
<td>4 %</td>
<td>5 %</td>
<td>3 %</td>
<td>3 %</td>
</tr>
<tr>
<td>age + sex</td>
<td>7 %</td>
<td>6 %</td>
<td>1 %</td>
<td>6 %</td>
<td>5 %</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRS + age + sex</td>
<td>19 %</td>
<td>20 %</td>
<td>16 %</td>
<td>16 %</td>
<td>21 %</td>
</tr>
<tr>
<td>GRS</td>
<td>8 %</td>
<td>4 %</td>
<td>4 %</td>
<td>3 %</td>
<td>6 %</td>
</tr>
<tr>
<td>age + sex</td>
<td>11 %</td>
<td>16 %</td>
<td>11 %</td>
<td>13 %</td>
<td>15 %</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRS + age + sex</td>
<td>9 %</td>
<td>9 %</td>
<td>9 %</td>
<td>16 %</td>
<td>12 %</td>
</tr>
<tr>
<td>GRS</td>
<td>3 %</td>
<td>2 %</td>
<td>2 %</td>
<td>3 %</td>
<td>2 %</td>
</tr>
<tr>
<td>age + sex</td>
<td>7 %</td>
<td>8 %</td>
<td>7 %</td>
<td>13 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>
Copy number polymorphism tag-SNPs

List of CNP tag-SNPs for 5,060 CNPs
• SNPs with $R^2 > 0.5$

→ 1,500 CNP tag-SNPs for our genetic analysis

No associations with MetS case control status
Copy number polymorphism tag-SNPs

HDL:

CNP tag-SNP  \( P=0.0009 \), 1.6 kb deletion, frequency 5 %  
**ABCA1**

CNP tag-SNP  \( P=0.01 \), 1 kb deletion, frequency 9 %  
**WWOX1**
Search for gene loci affecting the susceptibility for MetS and its component traits

- Genome-wide association study of genetic variation (SNPs + CNP tag-SNPs)
- 4 Finnish population cohorts

Association between MetS and the APOA1/C3/A4/A5 gene cluster region
- GWA result supported by metabolite analysis

Several gene loci associated with MetS component traits
- in the genetic risk score analysis individuals in highest GRS quartile had 1.5-fold risk of MetS compared to those in the lowest GRS quartile
- 2 – 8 % of the variance in TG, HDL, glucose levels explained by GRS

Copy number polymorphisms in gene regions that have been associated with MetS component traits in previous studies
- regions for further investigation, possible functional role of the CNP
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