Genetic Variants Involved in Mitochondrial Oxidative Metabolism are associated with Type 2 Diabetes Mellitus in studies of 9,132 Danes

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Genetic Variants Involved in Mitochondrial Oxidative Metabolism are associated with Type 2 Diabetes Mellitus in studies of 9,132 Danes

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Objective
Type 2 Diabetes (T2D) is the most common form of diabetes and a dramatic increase in prevalence is being observed worldwide. Like T2D, obesity is an increasing problem in the Western World and has taken on epidemic proportions. T2D and obesity is in part inherited and therefore a lot of research focuses on finding genetic factors contributing to the diseases. T2D is characterized by insulin resistance (IR) and failure of the pancreatic beta cells to compensate for this defect. Several studies have demonstrated a link between IR and impaired mitochondrial oxidative phosphorylation (OXPhos) in skeletal muscle. OxPhos takes place in the mitochondria in the respiratory chain and ATP synthesis as shown in figure 1. Recently, mitochondrial defects have also been implicated in beta-cell dysfunction in T2D.

OxPhos consists of 5 complexes as shown in figure 2 below.

Figure 1: Oxidative phosphorylation consists of respiratory chain and ATP synthesis in mitochondria inside the cell.

Figure 2: The 5 Complexes in Oxidative Phosphorylation.

There are 119 known genes related to the 5 complexes. So far there is no knowledge of the genes and relation to T2D. That is what we which to are trying to investigate in this work.

Aim
We hypothesized that known common single nucleotide polymorphisms (SNPs) in OxPhos genes could contribute to the pathogenesis of T2D by investigating their association to T2D and related metabolic traits in a Danish Cohort.

Research Design and Methods
Exploring results from a meta-analysis of genome wide association studies (DIAGRAM Consortium), we found that among 2542 SNPs in 120 OxPhos genes, 46 SNPs showed potential association with T2D (uncorrected p<0.01). SNPs that were in linkage disequilibrium (r2>0.8) were excluded from further analysis. The resulting 10 SNPs in or near 6 OxPhos genes were genotyped in 4,089 T2D patients and 5,043 controls with normal glucose tolerance.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Chromosome</th>
<th>Position</th>
<th>Wildtype</th>
<th>Disease allele</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX5B</td>
<td>rs11904110</td>
<td>2</td>
<td>97,200</td>
<td>T/C</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>COX6B</td>
<td>rs13461010</td>
<td>2</td>
<td>97,000</td>
<td>A/T</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>UCRC1</td>
<td>rs2285561</td>
<td>3</td>
<td>480,001</td>
<td>G/A</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>COX10</td>
<td>rs22696796</td>
<td>16</td>
<td>84,305</td>
<td>G/A</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>COX10</td>
<td>rs10775377</td>
<td>17</td>
<td>130,905</td>
<td>A/G</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>COX10</td>
<td>rs10212535</td>
<td>17</td>
<td>130,918</td>
<td>A/G</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>COX10</td>
<td>rs10273202</td>
<td>17</td>
<td>130,927</td>
<td>G/T</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>COX10</td>
<td>rs1957203</td>
<td>17</td>
<td>130,926</td>
<td>C/T</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>NDUFP3</td>
<td>rs1345424</td>
<td>21</td>
<td>43,198</td>
<td>C/T</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: SNPs in OxPhos genes of Complex I, III and IV selected for genotyping and their chromosome location, position and wildtype/disease allele.

The resulting 10 SNPs in or near 6 OxPhos genes were genotyped in 4,089 T2D patients and 5,043 controls with normal glucose tolerance (see table 1).

Danish cohorts available for genotyping (n=17,781 Danes)

- Study group 1: Inter99 population-based cohort (n=6,514)
- Study group 2: T2D patients from Steno (n=1,820)
- Study group 3: Population-based sample from Steno (n=734)
- Study group 4: ADDITION screening cohort (n=8,664)

Genetic association studies were analysed in following study groups:

- Case-control study (study group 1-4)
- Metabolic traits (study group 1)

The genotyping was performed by Kbioscences (Heddesodden, UK) using KASPar allelic discrimination. Genotyping was performed by allelic discrimination by measuring Hardy Weinberg Equilibrium (HWE). HWE were obeyed by all 10 SNPs.

Results
Rs1466100 in COX5B (OR=1.67, p=0.004) and rs915302 in COX10 (OR=1.14, p=0.02) were significantly associated with T2D.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>n</th>
<th>T2D</th>
<th>OR</th>
<th>95% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX5B</td>
<td>rs11904110</td>
<td>3071,400</td>
<td>435,950</td>
<td>1.90</td>
<td>(1.60-2.26)</td>
</tr>
<tr>
<td>COX5B</td>
<td>rs13461010</td>
<td>3367,100</td>
<td>247,814</td>
<td>1.26</td>
<td>(1.21-1.32)</td>
</tr>
<tr>
<td>UCRC1</td>
<td>rs2285561</td>
<td>22,561,093</td>
<td>2,199,773</td>
<td>1.04</td>
<td>(1.01-1.07)</td>
</tr>
</tbody>
</table>

The results are promising but further validation/replication in other (larger) study populations are needed to validate the examined gene variants as susceptibility variants for T2D.

Analysis of quantitative traits, applying an additive model and adjusting for age and sex, revealed significant associations (p<0.05) between a surrogate marker (BIGTT-AIR) of insulin secretion and variants in COX5B (rs10775377 and COX10 (rs10521253) (shown as an example in table 3 below), between fasting plasma glucose and rs915302 in COX5B and 2-h post-GTT plasma glucose and rs1314542 in NDUFP3 (p<0.05).

Table 3: Meta-analysis of our data and data from the welcome trust study. The p-values are calculated assuming an additive model with adjustment for age, sex, and BMI.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>p-value (WTS)</th>
<th>p-value (our)</th>
<th>p-value (meta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX5B</td>
<td>rs10775377</td>
<td>8.6±1.1</td>
<td>3.7±1.1</td>
<td>8.6±1.1</td>
</tr>
<tr>
<td>COX5B</td>
<td>rs1092100</td>
<td>8.6±4.4</td>
<td>3.7±4.4</td>
<td>8.6±4.4</td>
</tr>
</tbody>
</table>

Table 4: Example of quantitative trait analysis. Study group 1 (Inter99 population based study sample) stratified according to COX10 rs10521253.

Conclusions
Genetic variants (COX5B, COX6B1, COX10) in or near subunits in complex IV could contribute to the pathogenesis of T2D.

Quantitative traits indicate beta cell defect as primary cause of T2D causes by variants in COX5B, COX10 and NDUFP3.

The results are promising but further validation/replication in other (larger) study populations are needed to validate the examined gene variants as susceptibility variants for T2D.

References

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