Association of genetic variants with myocardial infarction in Japanese individuals with different lipid profiles

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Purpose

Dyslipidemia is an important risk factor for myocardial infarction (MI). We previously showed that gene polymorphisms associated with MI differed among individuals with different lipid profiles (1).

To further examine whether the association of polymorphisms with MI is influenced by the baseline lipid profiles, we have performed an association study for 150 polymorphisms of 144 candidate genes in MI in 5279 Japanese individuals with low or high serum concentrations of triglycerides, HDL-cholesterol, or LDL-cholesterol.

The purpose of the present study was to identify genetic variants that confer susceptibility to MI in Japanese individuals with different lipid profiles independently and thereby to assess the genetic risk of MI in such individuals separately.

Methods

Study population

A total of 150 polymorphisms examined in the present study (data not shown) were chosen by genome-wide association studies of MI and ischemic stroke (P value for allele frequency < 1.0 x 10⁻⁶) with the use of the Affymetrix GeneChip Human Mapping 50K Array Set (2,3).

Genotyping of polymorphisms

Genotypes of the 150 polymorphisms were determined at G&G Science (Fukuushima, Japan) by the multiplex bead-based Luminex assay, a method that combines PCR and sequence-specific oligonucleotide probes with suspension array technology (Luminex, Austin, TX). Genotyping involved PCR amplification, hybridization, streptavidin-phycoerythrin reaction, and measurement of fluorescence (4).

Statistical analysis

Allele frequencies

<table>
<thead>
<tr>
<th>Allele</th>
<th>Chi-square test</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7.7 x 10⁻²</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Multivariable logistic regression analysis with adjustment for covariates

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>OR (95% CI)</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEMA3F</td>
<td>A→G</td>
<td>1.51 (1.00, 2.28)</td>
<td>0.0484</td>
</tr>
</tbody>
</table>

Table 1. Relation of SNPs to MI among individuals with low or high serum concentrations of triglycerides as determined by the chi-square test.

Results

Table 2. Relation of SNPs to MI among individuals with low or high serum concentrations of HDL-cholesterol as determined by the chi-square test.

<table>
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<tr>
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<td>0.0484</td>
</tr>
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Table 3. Relation of SNPs to MI among individuals with low or high serum concentrations of LDL-cholesterol as determined by the chi-square test.

Figure 1. Stepwise forward selection procedure of MI among individuals with high serum LDL-cholesterol or low serum LDL-cholesterol concentrations.

Table 4. Multivariable logistic regression analysis of SNPs related (FDR < 0.05) to MI by the chi-square test among individuals with high serum HDL-cholesterol or low serum LDL-cholesterol concentrations.

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<tr>
<td>SEMA3F</td>
<td>A→G</td>
<td>0.50 (0.31, 0.81)</td>
<td>0.0045</td>
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</tbody>
</table>

References


Discussion

Our results suggested that the A→G polymorphism (rs12632110) of SEMA3F was significantly associated with MI in individuals with high serum HDL-cholesterol and in those with low serum LDL-cholesterol.

The SEMA3F-NRP2 signaling pathway guides axonal extension by means of a chemotactic repelling effect on the axons (7).

The SEMA3F was isolated from a region of 3p23L involved in homozygous deletions in small cell lung cancer cell lines and was recognized as a candidate tumor suppressor gene, given that p3 inhibits tumor vessel formation and cell growth through the SEMA3F-NRP2 pathway (8).

Study limitations

It is possible that the polymorphism associated with MI in the present study is in linkage disequilibrium with other polymorphisms in the same gene or in other nearby genes that are actually responsible for the development of this condition.

The functional relevance of the identified polymorphism to gene transcription or to protein function was not determined in the present study.

Although we adopted the criterion of FDR < 0.05 for association to compensate for the multiple comparisons of genotypes with MI, it is not possible to exclude completely potential statistical errors such as false positives.

Given that the results of the present study were not replicated, validation of our findings will require their replication with independent subject panels.

Conclusions

The A→G polymorphism (rs12632110) of SEMA3F was significantly associated with the prevalence of MI in individuals with high serum HDL-cholesterol and in those with low serum LDL-cholesterol, and with the A allele protecting against MI, although the underlying mechanism remains unclear.

Genetic variants that confer susceptibility to MI differ among individuals with different lipid profiles, and that genetic component for the development of MI is more apparent in individuals at low-risk (high HDL- and low LDL-cholesterol levels) compared to those at high-risk.

Stratification of subjects according to lipid profiles may thus be important for personalized prevention of MI based on genetic information.