Diabetic retinopathy genetic variants identified in genome-wide association studies and the risk of microvascular complications in Chinese diabetic patients

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Introduction

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Methods & Materials

• Study design
  - Three cross-sectional case-control studies on (1) sight-threatening DR (STDR; 2) proliferative DR (PDR); and (3) DN, were performed based on subjects from the Hong Kong West Diabetes Registry.

• Subjects
  - STDR cases (n=576): Based on the United Kingdom National Screening Committee classification protocol for grading of retinopathy, patients having PDR (R3), or severe pre-PDR (R2), or having clinically significant macular oedema (CSMO), were considered as STDR cases.
  - PDR cases (n=309): Patients graded retinopathy level R3 were considered as PDR cases.
  - DN cases (n=984): DN cases included patients with the presence of either microalbuminuria or macroalbuminuria, as indicated by the patient’s urinary albumin-to-creatinine ratio (ACR) in two random urine samples, collected within 3 months, according to the American Diabetes Association criteria.
  - Non-DR & non-DN controls (n=1055): Subjects with normalalbuminuria (NA) and no retinopathy (R0) were considered as controls.

• Single nucleotide polymorphisms (SNPs) selection
  - 36 top associated SNPs (P<5x10⁻⁴, r²>0.9) previously identified in DR GWAS were selected for investigation.

• 4 monornorphic SNPs and 5 SNPs which failed to pass quality check (deviation from Hardy-Weinberg Equilibrium or genotype call rate <90%) were excluded from analyses.

• Statistical analysis
  - Binary logistic regression analyses, with adjustment for age, duration of diabetes, gender, systolic blood pressure, diastolic blood pressure, and HbA1c, were used to evaluate the independent associations of SNPs with DR and DN.

Objectives

• This study aimed (i) to validate the associations of these genetic variants with DR and (ii) to evaluate whether these DR-associated SNPs would also be associated with an increased risk of DN, in Chinese diabetic patients.

Results

Table 1. Association analyses of GWAS identified DR-associated SNPs with STDR, PDR and DN.

<table>
<thead>
<tr>
<th>C Chr</th>
<th>SNPs</th>
<th>Nearest Gene(s)</th>
<th>A1</th>
<th>A2</th>
<th>STDR (576 cases vs 1055 controls) Padj(DRR)</th>
<th>STDR (309 cases vs 1055 controls) Padj(DPR)</th>
<th>DN (984 cases vs 1055 controls) Padj(DNR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rs300779</td>
<td>GSF21-KLRC2</td>
<td>T</td>
<td>C</td>
<td>0.93(0.78-1.12) 0.463 0.94(0.75-1.18) 0.599 1.04(0.87-1.26) 0.847</td>
<td>0.95(0.80-1.12) 0.78 0.94(0.76-1.14) 0.847</td>
<td>0.90(0.75-1.08) 0.294 0.93(0.77-1.11) 0.642</td>
</tr>
<tr>
<td>2</td>
<td>rs2181939</td>
<td>MYSM1</td>
<td>C</td>
<td>T</td>
<td>1.05(0.86-1.28) 0.831 1.00(0.82-1.23) 0.983 1.00(0.85-1.16) 0.918</td>
<td>1.00(0.89-1.14) 0.953 1.00(0.85-1.16) 0.918</td>
<td>0.99(0.83-1.17) 0.811 1.00(0.85-1.16) 0.918</td>
</tr>
<tr>
<td>3</td>
<td>rs11499656</td>
<td>C6orf91</td>
<td>C</td>
<td>G</td>
<td>1.00(0.89-1.11) 0.949 1.00(0.89-1.11) 0.949 1.00(0.89-1.11) 0.949</td>
<td>1.00(0.89-1.11) 0.949 1.00(0.89-1.11) 0.949</td>
<td>0.99(0.83-1.17) 0.811 1.00(0.85-1.16) 0.918</td>
</tr>
<tr>
<td>4</td>
<td>rs1240308</td>
<td>TNFSF4-KLRK1</td>
<td>T</td>
<td>C</td>
<td>0.90(0.77-1.08) 0.309 0.80(0.71-0.90) 0.539 0.80(0.71-0.90) 0.539</td>
<td>0.80(0.71-0.90) 0.539 0.80(0.71-0.90) 0.539</td>
<td>0.90(0.80-1.02) 0.389 0.80(0.71-0.90) 0.539</td>
</tr>
<tr>
<td>5</td>
<td>rs1571942</td>
<td>C5orf36</td>
<td>A</td>
<td>T</td>
<td>1.00(0.84-1.21) 0.915 0.90(0.71-1.14) 0.406 0.90(0.71-1.14) 0.406</td>
<td>0.90(0.71-1.14) 0.406 0.90(0.71-1.14) 0.406</td>
<td>0.90(0.71-1.14) 0.406 0.90(0.71-1.14) 0.406</td>
</tr>
<tr>
<td>6</td>
<td>rs8662352</td>
<td>KIAA1804-KCNK1</td>
<td>T</td>
<td>C</td>
<td>1.09(0.91-1.31) 0.355 1.10(0.93-1.29) 0.301 1.10(0.93-1.29) 0.301</td>
<td>1.10(0.93-1.29) 0.301 1.10(0.93-1.29) 0.301</td>
<td>1.07(0.92-1.23) 0.589 1.00(0.86-1.14) 0.930</td>
</tr>
</tbody>
</table>

Conclusions

• We have successfully replicated the associated significances of several SNPs identified in previous GWAS with severe retinopathy (STDR and/or PDR) in Chinese diabetic patients.

• We have also demonstrated the significant association of a DR-associated SNP KRT18P34-VEP8H with DN, providing evidence for shared common pathogenic pathways between DR and DN.

• Whether these SNPs can be used for early identification of subjects at high risk of developing microangiopathic diabetic complications warrants further evaluation in prospective studies.

Key references


Acknowledgements

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