Polymorphisms in the RelB gene identify a haplotype associated with reduced risk of pangastric atrophy

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1. Introduction

• Members of the NF-κB protein family are important regulators of gastric carcinogenesis.
• We have recently demonstrated that NF-κB2 null mice infected with H. felis show resistance to developing gastric pre-neoplasia following infection¹.
• Single Nucleotide Polymorphisms (SNPs) in the NF-κB2 gene have previously been correlated with susceptibility to multiple myeloma in China².
• Associations between SNPs affecting alternative pathway NF-κB signaling and gastric cancer have not previously been investigated.
• We assessed whether there is an association between genetic variants in alternative pathway NFκB signaling and gastric pre-neoplasia in a cohort of 1400 patients.

2. Methods

• Cohort contains patients who attended for symptom directed diagnostic upper gastrointestinal endoscopy. All patients had antral and corpus histology and H. pylori status determined.
• Patients with pre-neoplastic pathology were identified as having atrophic gastritis and/or intestinal metaplasia and/or dysplasia. Patients were genotyped using MALDI-TOF mass spectrometry (Sequenom® MassARRAY®). SNPs and patients with <90% call rates were excluded from further analysis.
• Patient genomic DNA from was extracted from whole blood.
• SNPs were identified from dbSNP using HapMap minor allele frequency data, and Haploview was used to identify tag SNPs.
• 50 SNPs were selected for analysis, each with a MAF of >5%.
• Patients were genotyped using MALDI-TOF mass spectrometry (Sequenom® MassARRAY®). SNPs and patients with <90% call rates were excluded from further analysis.
• Association analyses for individual markers and haplotypes were carried out using Haploview with correction for multiple comparisons by permutation analysis and Benjamini-Hochberg false discovery rate (FDR).

3. Identification of SNPs associated with pre-neoplastic pathology

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Assoc. Allele</th>
<th>Case, control ratios</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIK</td>
<td>rs4793811</td>
<td>A</td>
<td>101-313, 104-444</td>
<td>0.0422</td>
</tr>
</tbody>
</table>

Table 1: SNP identified in the NIK gene of patients with gastric pre-neoplastic pathology (atrophic gastritis and/or intestinal metaplasia and/or dysplasia). Did not remain significant after FDR analysis.

4. Identification of a RelB Haplotype in pangastric atrophy

Figure 1: Haplotype analysis carried out in Haploview. A linkage disequilibrium (LD) plot of all 42 SNPs analysed in the study. Three haplotype blocks were identified with high LD, Block 1 identified as containing two SNPs in the NIK gene considered to be statistically significant.

<table>
<thead>
<tr>
<th>Block 1</th>
<th>SNPs</th>
<th>P Value</th>
<th>Corrected P Value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>0.03</td>
<td>0.26</td>
<td>0.107-0.627</td>
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<tr>
<td></td>
<td>rs4803789</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2: SNPs observed as conferring an altered risk of having pangastric atrophy, considered statistically significant upon individual testing in Haploview, but did not remain significant following FDR analysis.

5. Conclusions

• We identified a RelB haplotype that may be associated with a reduced risk of developing pangastric atrophy. This provides further evidence of a role for the alternative NF-κB activation pathway in gastric carcinogenesis.
• These findings require validation in other cohorts of patients with pre-neoplastic gastric pathology, and support that we should investigate how the identified RelB haplotype influences NF-κB signaling.

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References: