Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients

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jejunum and ileum, respectively. As the FSR of MUC2 in the present study ranged from 12.1 to 89.7%/day, we conclude that the small intestinal epithelium has a high rate of MUC2 synthesis. Despite its wide range, the FSR of MUC2 might be valuable as a tool to study intestinal barrier function. Serial measurements of FSR of MUC2 may be used to monitor intestinal adaptation, and to assess treatment and feeding options in patients following bowel resection. We consider our data as a starting point to investigate the impact of different pathological situations and interventions, such as medication and nutrition, on the FSR of MUC2, and it could be implemented as a tool to improve medical management of patients with impaired gut function.

In conclusion, the development of a tracer method to determine MUC2 synthesis and the FSR of MUC2 in the small intestine in vivo provides the opportunity to study the determinants of intestinal barrier function in a detailed manner.

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The Dutch Digestive Diseases Foundation (Nieuwegein, the Netherlands) supported this study (MWO 02–69).

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Conflict of interest: None declared.

Table 1: Patient characteristics and kinetic parameters of small intestinal mucin 2 (MUC2)

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>GA (weeks)</th>
<th>BW (g)</th>
<th>AS (days)</th>
<th>Cause</th>
<th>Enterostomy</th>
<th>Residual small intestine</th>
<th>MUC2 secretion time (h)</th>
<th>FSR (%/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>34</td>
<td>1845</td>
<td>7</td>
<td>NEC (colon) End-ileostomy</td>
<td>Small intestine without 1.5 cm of the ileum and the ileocecal valve</td>
<td>&lt;6</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>34</td>
<td>2310</td>
<td>5</td>
<td>NEC (colon) End-ileostomy</td>
<td>Total small intestine</td>
<td>&lt;7</td>
<td>77.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>34</td>
<td>1905</td>
<td>6</td>
<td>NEC (colon) End-ileostomy</td>
<td>Small intestine without 10 cm of the ileum and the ileocecal valve</td>
<td>&lt;7</td>
<td>89.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>32</td>
<td>2190</td>
<td>7</td>
<td>NEC (colon) End-ileostomy</td>
<td>Small intestine without 10 cm of the ileum and the ileocecal valve</td>
<td>&lt;10</td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td>5†</td>
<td>F</td>
<td>33</td>
<td>1450</td>
<td>6</td>
<td>NEC (jejunum) Jejunostomy</td>
<td>24 cm jejunum and 25 cm ileum without the ileocecal valve</td>
<td>&lt;3</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34</td>
<td>1905</td>
<td>6</td>
<td>5–7</td>
<td></td>
<td></td>
<td></td>
<td>31.1</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>32–34</td>
<td>1450–2310</td>
<td>5–7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.1–89.7</td>
<td></td>
</tr>
</tbody>
</table>

GA, gestational age; BW, birth weight; AS, age at surgery; NEC, necrotising enterocolitis; FSR, fractional synthetic rate.

†Patient with a jejunostomy.

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References


Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients

Autoimmune pancreatitis is characterised by irregular narrowing of the main pancreatic duct, swelling of the pancreas, histological evidence of lymphoplasmacytic inflammation, and high serum immunoglobulin G4 (IgG4) concentration. Although the human leucocyte antigen DRB1*0401 haplotype has been associated with autoimmune pancreatitis, the role of genetic factors has not yet been fully defined. A new family of genes called Fc receptor-like genes (FCRLs), which have high structural homology with classical Fc receptor genes, has recently been identified. FCRL3 polymorphisms have been shown to be associated with various autoimmune diseases, such as rheumatoid arthritis, autoimmunity thyroid disease, and systemic lupus erythematosus, in Japanese populations. These polymorphisms alter the binding affinity of nuclear factor κB and regulate FCRL3 expression. FCRL3 expression on B cells has been observed in significant amounts and is known to augment autoantibody production in individuals with disease susceptible genotypes. We therefore investigated the association of disease susceptibility to autoimmune pancreatitis with FCRL3 polymorphisms in a Japanese population. Furthermore, we sought to determine whether serum IgG4 concentration was associated with FCRL3 polymorphisms in patients with autoimmune pancreatitis.

Patients and controls were recruited from Shinsyu University Hospital and affiliated hospitals in Japan. The test group consisted of 59 patients with autoimmune pancreatitis, 62 patients with chronic calcifying pancreatitis, and 97 unrelated Japanese controls. The diagnosis of autoimmune pancreatitis was based on clinical, imaging tests, and/or histopathological findings in accordance with the criteria of the Japan Pancreas Society, and all patients fulfilled these criteria. Serum IgG4 concentration was measured as reported previously. We found high serum IgG4 concentrations in 55 of 59 patients with autoimmune pancreatitis but not in patients with chronic calcifying pancreatitis or controls. We treated 32 of 59 patients with prednisolone, and all patients responded favourably to corticosteroid therapy.

DNA was extracted by standard techniques from EDTA blood. All subjects were genotyped for FCRL3 –369, –310, +358, and +1381 by TaqMan assay. The significance of allele distribution between patients with autoimmune pancreatitis and those with chronic calcifying pancreatitis or healthy subjects was tested using the χ² method with continuity correction. Serum IgG4 concentrations were regressed on the number of susceptible alleles.

The observed genotype frequencies of patients and controls were in Hardy-Weinberg equilibrium. Analysis of genotype distribution frequencies for FCRL3–110 polymorphisms revealed a significant difference between autoimmune pancreatitis patients...
and control subjects ($\chi^2 = 8.12$, $p = 0.017$). Positivity for the $\text{−}110G$ allele was significantly decreased in autoimmune pancreatitis patients ($p = 0.012$, odds ratio 0.13; table 1), indicating a significant association of the $−110G/A$ genotype with autoimmune pancreatitis. The frequency of $−110G/A$ alleles was significantly increased in patients with autoimmune pancreatitis compared with controls ($p = 0.012$, odds ratio $= 7.45$; table 1). There are two possible explanations for these findings: FCR3−110 may be functionally linked with susceptibility to autoimmune pancreatitis, or this allele may be a linkage marker for a neighbouring unidentified susceptibility gene on chromosome 1q21. No other alleles were found to be significantly associated with autoimmune pancreatitis.

Mean (SEM) serum IgG4 concentrations in patients with FCR3−110/GA, $−110G/A$, and $−110G/G$ were 1279.4 (404.8) mg/dl, 794.8 (194.9) mg/dl, and 669.2 (78.5) mg/dl, respectively. Serum IgG4 concentrations in patients with autoimmune pancreatitis were found to be significantly positively correlated with the number of susceptible alleles ($\chi^2 = 0.094$, $p = 0.014$). However, no association between the HLA DRB1*0405-DQB1*0401 haplotype and FCR3−110 alleles was found in this study (data not shown). These results suggest that both the HLA DRB1*0405-DQB1*0401 haplotype and FCR3−110 alleles are related to susceptibility for autoimmune pancreatitis but play different roles in the mechanisms inducing autoimmune pancreatitis.

<table>
<thead>
<tr>
<th>Allele genotype</th>
<th>Gly</th>
<th>A/G</th>
<th>G/G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>Autoimmune pancreatitis</td>
<td>Chronic calcifying pancreatitis</td>
<td>Healthy subjects</td>
</tr>
<tr>
<td></td>
<td>(n = 59)</td>
<td>(n = 62)</td>
<td>(n = 97)</td>
</tr>
<tr>
<td>A/A</td>
<td>13.6</td>
<td>6.5</td>
<td>2.1</td>
</tr>
<tr>
<td>A/G</td>
<td>30.5</td>
<td>32.3</td>
<td>36.1</td>
</tr>
<tr>
<td>G/G</td>
<td>55.9</td>
<td>61.9</td>
<td>69.9</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

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Conflict of interest: None declared.

References


Extensive intestinal ischaemic necrosis in Wegener’s granulomatosis

Wegener’s granulomatosis (WG) is a rare form of multisystemic vasculitis. WG most commonly presents as signs and symptoms of upper or lower respiratory tract disease, or both. Although clinical manifestations from the gastrointestinal disease have been described, presentation with extensive intestinal ischaemic perforation without renal or pulmonary disease has not been reported. We report a case of WG presenting with extensive small and large bowel ischaemic perforation without renal or pulmonary disease.

A previously healthy 44 year old female was referred for bronchoscopy with an eight week history of lethargy, polyarthalgia, vasculitic skin rash, and distal sensory and motor polyneuropathy. Laboratory analysis showed normal results on full blood count and urinalysis but an elevated erythrocyte sedimentation rate (79 mm/h; normal <15 mm/h) and positive cryoglobulin and antinuclear antibody (c-ANCA; titre 1: 89.10). Chest radiograph was normal. A diagnosis of systemic vasculitis secondary to WG was made and intravenous methyl prednisolone was started.

The following day the patient developed severe abdominal pain with signs of peritonitis. Plain film and computed tomography of the abdomen confirmed peritonitis. At laparotomy, multiple mid-ileal ischaemic bowel lesions and extensive colonic ischemia were noticed. One metre of small bowel was resected with ileocolic anastomosis and extended left hemicolectomy and a transverse end colostomy. Postoperatively, the patient was continued on intravenous methylprednisolone 1 g for five days followed by dexamethasone 16 mg intravenously daily and cyclophosphamide intravenously 150 mg daily. Histology of the small and large bowel showed extensive vasculitic involvement with fibrinoid necrosis (fig 1B).

On the 32nd day of admission, the patient again developed an acute abdomen and...