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The Functional $-765G\rightarrow C$ Polymorphism of the COX-2 Gene May Reduce the Risk of Developing Crohn’s Disease

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Abstract

Background: Cyclooxygenase-2 (COX-2) is a key enzyme involved in the conversion of arachidonic acid into prostaglandins. COX-2 is mainly induced at sites of inflammation in response to proinflammatory cytokines such as interleukin-1α/β, interferon-γ and tumor necrosis factor-α produced by inflammatory cells.

Aim: The aim of this study was to investigate the possible modulating effect of the functional COX-2 polymorphisms $-1195 A\rightarrow G$ and $-765G\rightarrow C$ on the risk for development of inflammatory bowel disease (IBD) in a Dutch population.

Methods: Genomic DNA of 525 patients with Crohn’s disease (CD), 211 patients with ulcerative colitis (UC) and 973 healthy controls was genotyped for the $-1195 A\rightarrow G$ (rs689466) and $-765G\rightarrow C$ (rs20417) polymorphisms. Distribution of genotypes in patients and controls were compared and genotype-phenotype interactions were investigated.

Results: The genotype distribution of the $-1195A\rightarrow G$ polymorphism was not different between the patients with CD or UC and the control group. The $-765GG$ genotype was more prevalent in CD patients compared to controls with an OR of 1.33 (95%CI 1.04-1.69, p=0.05). The $-765GC$ and $-765CC$ genotype carriers showed a tendency to be less frequent in patients with CD compared to controls, with ORs of 0.78 (95%CI: 0.61-1.00) and 0.49 (95%CI: 0.22-1.08), respectively. Combining homozygous and heterozygous patients with the $-765C$ allele showed a reduced risk for developing CD, with an OR of 0.75 (95%CI: 0.59-0.96). In the context of this, the $G^\rightarrow C$-combined $-765GG+GC$ diplotype was significantly less common in patients with CD compared to controls, with an OR of 0.62 (95%CI: 0.39-0.98). For UC however, such an effect was not observed. No correlation was found between COX-2 diplotypes and clinical characteristics of IBD.

Conclusions: The $-765G\rightarrow C$ polymorphism was associated with a reduced risk for developing Crohn’s disease in a Dutch population.

Introduction

Inflammatory bowel disease (IBD) is an idiopathic, chronic, relapsing auto inflammatory disorder of the gastrointestinal tract. The two major types of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). Genetic, immunological and environmental factors are thought to play a role in the pathogenesis of IBD [1]. A dysregulated immune response against the intestinal microbiota in genetic susceptible individuals has been heavily implicated in the pathogenesis of inflammatory bowel disease [2]. Therefore, genes involved in inflammatory responses are under investigation to look for variants predisposing to IBD.

Cyclooxygenase (COX) is a modifier gene and key enzyme in the conversion of free arachidonic acid into prostaglandins and is involved in the regulation of inflammatory processes through its products, mainly prostaglandin E2 (PGE2) [3]. The COX family consists of two main isozymes: COX-1 and COX-2. COX-1 is constitutively expressed in most cell types, including the mucosal compartment of the gastrointestinal tract, and is important for maintaining mucosal integrity, mucosal defence and regulation of the mucosal blood flow [4,5]. Being very low expressed in the normal gut mucosa, COX-2 expression can be induced by mitogenic and proinflammatory stimuli [5,6].

The relevance of COX-2 in the pathogenesis of IBD has been demonstrated; increased expression of COX-2 has been observed in colonic epithelial cells, the myenteric plexus and in the medial layer of arteries from patients with active IBD [7-9]. In addition, a relationship between endoscopic activity of IBD and mucosal COX-2 mRNA levels was noticed [10]. Although COX-2 is involved in the regulation of inflammatory processes, it also seems
to play a physiological role in the defence of the gastric mucosa, as well as in the maintenance of gastric mucosal integrity when other defence mechanisms are impaired or COX-1 activity is latent [3,5]. Moreover, COX-2 seems to be a major contributor to the processes that lead to resolution of inflammation [11]. In line with this, the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with IBD, may be associated with exacerbation of the underlying IBD and gastrointestinal-related complications [12–14]. Overall, these findings suggest that COX-2 has a dual role by both initiation as well as resolution of inflammation.

Functional polymorphisms in the COX-2 promoter, being \(-765G\) to \(765G\) (rs20417) and \(-1195A\rightarrow G\) (rs689466), may alter the enzyme function of COX-2 by differential regulation of COX-2 expression [15]. Recently, a study by Østergaard et al. reported an association of the \(-765G\rightarrow C\) polymorphism with IBD in a Danish population [16]. Another study from a previous relatively small sample size study performed in the Netherlands however, showed no association between these two polymorphisms and IBD [17]. We therefore investigated the COX-2 \(-1195 A\rightarrow G\) and \(-765G\rightarrow C\) polymorphisms in relation to the development and clinical severity of IBD in a phenotypically well characterized and relatively large IBD cohort of Dutch origin and hypothesized that carriers of the \(-1195 A\rightarrow G\) and/or \(-765G\rightarrow C\) polymorphisms might be at risk for developing IBD.

Materials and Methods

Patients and controls

This case-control study included 736 patients with inflammatory bowel disease (39% men, mean age 45.0±13.9 years), being 525 patients with Crohn’s disease (35% men, mean age 44.5±13.9) and 211 patients with ulcerative colitis (48% men, mean age 46.1±14.0) and 973 disease-free controls (43% men, mean age 47.2±16.6 years). All patients were of Dutch origin and were recruited from the outpatient clinic of the Radboud University Nijmegen Medical Center, the Netherlands. Controls were recruited from the Nijmegen area by advertisement in local papers. The clinical characteristics of the patients are summarized in Tables 1 and 2. Diagnosis of inflammatory bowel disease was based on accepted clinical, endoscopic, radiological and histological findings [18]. Clinical data of the patients were retrieved by retrospective collection from patients’ clinical charts. Phenotypes of the patients were described according to age of onset, necessity of surgery, family history of IBD, the occurrence of extra-intestinal manifestations and maximum extent of disease according to the Vienna [19] and Montreal [20] classifications for Crohn’s disease and ulcerative colitis respectively.

Information on development of dysplasia and colorectal cancer (CRC) in our patient cohort was retrieved using PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands [21]. The ethical committee of region Nijmegen and Arnhem reviewed and approved the protocol under number CWOM nr 9804-0100. Verbal informed consent was obtained from each patient before study participation in agreement with the approval and all samples were anonymized. Since research data were collected anonymously, at least verbal informed consent was needed according to national regulations. Therefore, no written informed consent procedure was introduced at time of data collection.

Genotyping

Whole blood from patients and healthy controls was obtained by venapuncture in sterile vacutainer tubes, anti-coagulated with EDTA and stored at \(-20^\circ\)C until use. DNA from patients and controls was isolated from whole blood using the Pure Gene DNA isolation kit, according to the instructions of the manufacturer (Gentra Systems, Minneapolis, MN) and stored at 4°C. Genotypes of the COX-2 \(-1195A\rightarrow G\) polymorphism was determined by polymerase chain reaction (PCR)-based restriction fragment length polymorphism assays, as described by Zhang et al [15]. The COX-2 \(-765G\rightarrow C\) polymorphism was determined by a dual-color discrimination assay using the iCycler iQ Multicolour Real-Time Detection System (Bio-Rad Laboratories, Hercules, CA), as described by Peters et al [22].

Statistical analysis

Baseline and clinical characteristics were analysed with standard descriptive statistics. The observed genotype frequencies were tested for deviation from the Hardy-Weinberg equilibrium. Estimates of linkage disequilibrium (LD) between SNPs were determined by calculating pair-wise D’ and r² statistics in unrelated individuals, using Haploview. Differences in \(-1195A\rightarrow G\) and \(-765G\rightarrow C\) genotype distributions between the patient and control groups were determined by Chi-square analysis. Odds ratios (ORs) with 95%
confidence interval (95% CI) were calculated for genotypes associated with predicted normal versus predicted altered enzyme activities (variant genotypes) between IBD patients and controls. These analyses were also applied for testing of either UC or CD with the control group. Based on the two polymorphisms investigated, a diplotype analysis was performed. Diplotypes were compared with regard to phenotypical characteristics and comparisons were given as ORs with 95% CI. Additionally, we investigated in patients with IBD whether the $-1195A\rightarrow G$ and $-765G\rightarrow C$ polymorphisms were associated with development of mucosal dysplasia or colon cancer. Data analysis was performed using SPSS software (Version 16.0, SPSS, Chicago, IL, USA). A p-value of <0.05 was used as a criterion for statistical significance.

Results

In this study 736 patients with inflammatory bowel disease, 525 patients with Crohn’s disease and 211 patients with ulcerative colitis as well as 973 healthy controls were included. No statistical significant differences were observed between patients with IBD and controls regarding age and gender. However when the CD or UC patient groups were compared to controls separately, significant more females were present in the group with Crohn’s disease (p<0.01).

Distribution of the $-1195$ and $-765 COX-2$ genotypes in both patient and control groups fitted the Hardy Weinberg equilibrium; for the $-1195$ genotypes, p-values of $p=0.14$, $p=0.17$ and $p=0.99$, for the patients with Crohn’s disease, ulcerative colitis and controls were found; whereas corresponding p-values for the $-765$ genotypes were $p=0.64$, $p=0.26$ and $p=0.87$, respectively. As been reported before by others [15,17,23], both SNPs were found to be in strong linkage disequilibrium ($D'=1$, $r^2=0.05$).

Genotype distribution and association with inflammatory bowel disease

The distribution of the $-1195$ and $-765 COX-2$ genotypes as found in patients with IBD and controls is given in Table 3. The $-1195$ genotype distribution was not different between the patients with Crohn’s disease, ulcerative colitis, or all IBD patients taken together in comparison with the control group. However, the $-765$ genotype distribution showed a tendency towards a significant difference between patients with Crohn’s disease and controls, with the $-765GC$ and $-765CC$ genotypes being less prevalent in patients, with ORs of 0.78 (95%CI 0.61–1.00, p<0.05) and 0.49 (95%CI 0.22–1.08) respectively and the $-765GG$ genotype being more prevalent in patients (OR 1.33, 95%CI 1.04–1.69, p<0.05). No differences were found between patients with ulcerative colitis and controls. Combining homozygous ($-765CC$) and heterozygous ($-765GC$) patients bearing the $-765C$ allele, showed a reduced risk for developing Crohn’s disease in this group (OR = 0.75, 95%CI 0.59–0.96, p<0.05).

The effects of the two $COX-2$ polymorphisms were then studied in the context of diplotypes. Six diplotypes were identified, with the A$_{-1195}$G$_{-765}$/A$_{-1195}$G$_{-765}$ diplotype being the most prevalent in both patients and controls (Table 4). The G$_{-1195}$G$_{-765}$/A$_{-1195}$C$_{-765}$ diplotype was significantly less frequent in patients with Crohn’s disease compared to controls with an OR of 0.62 (95%CI: 0.39–0.96, p<0.05).

Correlation of the $COX-2$ diplotypes with clinical characteristics of IBD patients

Additionally, clinical characteristics of patients with Crohn’s disease and ulcerative colitis were studied in the context of diplotypes in which the most common A$_{-1195}$G$_{-765}$/A$_{-1195}$G$_{-765}$ diplotype served as reference. No significant association between the $COX-2$ diplotypes and clinical characteristics of either Crohn’s disease or ulcerative colitis was found (Tables 5 and 6). When data were corrected for age and gender, no significant changes in data were observed.

$COX-2$ polymorphisms and the risk for developing dysplasia and colon cancer in patients with inflammatory bowel disease

The PALGA search regarding dysplasia and colon cancer in our IBD cohort demonstrated that 29 patients (15 patients with CD and 14 patients with UC) developed mucosal dysplasia, which is significant different from patients and controls. Combining homozygous ($-765CC$) and heterozygous ($-765GC$) patients bearing the $-765C$ allele, showed a reduced risk for developing Crohn’s disease in this group (OR = 0.75, 95%CI 0.59–0.96, p<0.05).

Discussion

This study was performed to determine the possible modulating effect of the $COX-2$ $-1195 A\rightarrow G$ and $-765G\rightarrow C$ polymorphisms...
on the risk of developing inflammatory bowel disease. Carriers of the −765C allele showed a reduced risk for developing CD. This result suggests that the −765G→C change induces an altered enzyme expression and enzyme activity with potential anti-inflammatory consequences.

Studies regarding the functional consequences of the −765G→C polymorphism in the COX-2 promoter are conflicting. Therefore, the physiological consequences of our findings are difficult to interpret. First of all, the −765G-containing COX-2 promoter was reported to drive lower reporter gene expression in vitro compared to the −765C-containing counterpart [15,24]. Furthermore, serum prostaglandin E2 (PGE2) concentrations of renal transplant recipients patients with the GG genotype were significantly higher than PGE2 concentrations from patients with the GG-containing counterpart [26]. Besides this, Szczeklik and co-workers reported an increased production of prostaglandin E2 (PGE2) by monocytes obtained from female renal transplant recipients patients with the GG genotype were not able to retrieve the smoking status of our patients and controls, as Zhao et al. [26] demonstrated an effect of smoking on the expression of the −765G→C polymorphism. Secondly, the effect of the COX-2 −1195A→G and −765G→C polymorphisms on colonic mucosal COX-2 expression and/or PGE2 production in patients with IBD is unknown. However, regardless of these data, the functional consequences of PGE2 in IBD still remains conflicting as pointed out above.

The results of our study are in conflict with a Danish case control study by Østergaard et al. who identified that carriers of the homozygous −765CC variant had a relatively high risk for developing CD as well as UC, with an OR of 2.78 (95% CI = 1.33–5.88, p = 0.006) and 2.63 (95% CI = 1.35–5.26, p = 0.005) respectively [16]. The −765CC variant however is very rare in our population of IBD patients (n = 28, 2.9%) as is the case in another Dutch study by Cox et al., in which (2.4%) of the patients and (2.4%) of the controls had this variant [17]. In the study of Cox et al., no significant association between the −1195 A→G and −765G→C polymorphisms and IBD was found, although the number of patients with IBD involved (n = 291) was rather small. However, a recent subsequent study from the Danish group of Østergaard and co-workers extended the original data with data from Scottish IBD patients and showed no association any more with the −765G→C polymorphism and development of IBD [34]. The differences between our results and the Danish and Scottish findings could be attributed to the fact that the genetic contribution to the etiology of IBD in the northern part of Europe differs from central Europe. Mutations in the three common CD-associated variants of CARD15, R702W, G908R and 1007fsinsC, are relatively rare in Northern countries including Denmark and Scotland, while the mutation frequencies are relatively high in Central Europe [35].

As stated before, patients with IBD show increased expression of COX-2 in the gastrointestinal tract [7,8,10,27]. This increased expression of COX-2 has also been observed in gastrointestinal adenocarcinomas and in UC-associated neoplasia [36,37].

<table>
<thead>
<tr>
<th>Diplotype</th>
<th>All patients</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2</td>
<td>n = 231</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>n = 252</td>
</tr>
<tr>
<td>A−765G−765/</td>
<td>322 (43.8)</td>
<td>Reference</td>
<td>-</td>
<td>237 (45.1)</td>
</tr>
<tr>
<td>A−765G−765/</td>
<td>133 (18.1)</td>
<td>0.84 (0.65–1.10)</td>
<td>0.20</td>
<td>94 (17.9)</td>
</tr>
<tr>
<td>A−765G−765/</td>
<td>46 (6.5)</td>
<td>0.72 (0.49–1.07)</td>
<td>0.11</td>
<td>29 (5.5)</td>
</tr>
<tr>
<td>A−765G−765/</td>
<td>39 (5.3)</td>
<td>1.20 (0.75–1.90)</td>
<td>0.45</td>
<td>27 (5.1)</td>
</tr>
<tr>
<td>A−765C−765/</td>
<td>17 (2.3)</td>
<td>0.75 (0.40–1.39)</td>
<td>0.35</td>
<td>8 (1.5)</td>
</tr>
</tbody>
</table>

OR = Odds ratio; CI = confidence interval.
DOI:10.1371/journal.pone.0015011.s004
Table 5. Diplotype-phenotype correlations in patients with Crohn's disease.

<table>
<thead>
<tr>
<th>Disease localization</th>
<th>n = 525</th>
<th>AG/AG</th>
<th>GG/AG Odds ratio (95%CI)</th>
<th>p-value</th>
<th>AG/AC</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
<th>GG/GG</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal</td>
<td>83</td>
<td>51</td>
<td>Reference</td>
<td>-</td>
<td>34</td>
<td>Reference</td>
<td>-</td>
<td>8</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Colonic</td>
<td>63</td>
<td>26</td>
<td>0.67 (0.38-1.19)</td>
<td>0.17</td>
<td>23</td>
<td>0.89 (0.48-1.66)</td>
<td>0.72</td>
<td>8</td>
<td>1.32 (0.47-3.70)</td>
<td>0.60</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>91</td>
<td>53</td>
<td>0.95 (0.58-1.54)</td>
<td>0.83</td>
<td>37</td>
<td>0.99 (0.57-1.73)</td>
<td>0.98</td>
<td>13</td>
<td>1.48 (0.59-3.76)</td>
<td>0.41</td>
</tr>
<tr>
<td>Isolated upper disease*</td>
<td>18</td>
<td>7</td>
<td>0.63 (0.25-1.62)</td>
<td>0.34</td>
<td>8</td>
<td>1.09 (0.43-2.73)</td>
<td>0.86</td>
<td>2</td>
<td>1.15 (0.23-5.89)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease behavior</th>
<th>n = 525</th>
<th>AG/AG</th>
<th>GG/AG Odds ratio (95%CI)</th>
<th>p-value</th>
<th>AG/AC</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
<th>GG/GG</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non stricturing/</td>
<td>75</td>
<td>44</td>
<td>Reference</td>
<td>-</td>
<td>37</td>
<td>Reference</td>
<td>-</td>
<td>10</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Penetrating</td>
<td>119</td>
<td>68</td>
<td>0.97 (0.61-1.57)</td>
<td>0.91</td>
<td>43</td>
<td>0.73 (0.43-1.24)</td>
<td>0.25</td>
<td>11</td>
<td>0.69 (0.28-1.71)</td>
<td>0.43</td>
</tr>
<tr>
<td>Surgery</td>
<td>146</td>
<td>87</td>
<td>1.26 (0.81-1.98)</td>
<td>0.31</td>
<td>50</td>
<td>0.71 (0.44-1.15)</td>
<td>0.16</td>
<td>16</td>
<td>0.77 (0.35-1.67)</td>
<td>0.50</td>
</tr>
<tr>
<td>Extra-intestinal</td>
<td>77</td>
<td>32</td>
<td>0.69 (0.43-1.13)</td>
<td>0.14</td>
<td>37</td>
<td>1.39 (0.84-2.30)</td>
<td>0.21</td>
<td>8</td>
<td>0.80 (0.34-1.92)</td>
<td>0.62</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td>36</td>
<td>18</td>
<td>0.82 (0.43-1.59)</td>
<td>0.57</td>
<td>14</td>
<td>1.08 (0.52-2.26)</td>
<td>0.84</td>
<td>2</td>
<td>0.62 (0.13-3.05)</td>
<td>0.55</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>7</td>
<td>4</td>
<td>1.04 (0.30-3.63)</td>
<td>0.95</td>
<td>1</td>
<td>0.35 (0.04-2.91)</td>
<td>0.31</td>
<td>1</td>
<td>1.17 (0.14-9.89)</td>
<td>0.88</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>4</td>
<td>3</td>
<td>0.73 (0.16-3.30)</td>
<td>0.68</td>
<td>0</td>
<td>-</td>
<td>0.21</td>
<td>0</td>
<td>-</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Diplotype-phenotype correlations in patients with Crohn's disease in which the AG/AG diplotype served as reference.

*Patients could be classified as having disease localisation in the upper gastrointestinal tract next to ileal, colonic or ileocolonic localisation.

For full notation see Table 4.

doi:10.1371/journal.pone.0015011.t005

Table 6. Diplotype-phenotype correlations in patients with ulcerative colitis.

<table>
<thead>
<tr>
<th>Disease localization</th>
<th>n = 198</th>
<th>AG/AG</th>
<th>GG/AG Odds ratio (95%CI)</th>
<th>p-value</th>
<th>AG/AC</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
<th>GG/GG</th>
<th>Odds ratio (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctitis</td>
<td>6</td>
<td>2</td>
<td>Reference</td>
<td>-</td>
<td>2</td>
<td>Reference</td>
<td>-</td>
<td>2</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Left sided</td>
<td>27</td>
<td>13</td>
<td>1.44 (0.26-8.16)</td>
<td>0.676</td>
<td>15</td>
<td>1.67 (0.30-9.31)</td>
<td>0.558</td>
<td>7</td>
<td>0.28 (0.13-4.72)</td>
<td>0.784</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>46</td>
<td>28</td>
<td>1.83 (0.35-9.68)</td>
<td>0.474</td>
<td>21</td>
<td>1.37 (0.26-7.36)</td>
<td>0.713</td>
<td>8</td>
<td>0.52 (0.09-3.06)</td>
<td>0.465</td>
</tr>
<tr>
<td>Surgery (n = 206)</td>
<td>24</td>
<td>11</td>
<td>0.85 (0.37-1.94)</td>
<td>0.695</td>
<td>11</td>
<td>1.00 (0.43-2.32)</td>
<td>0.997</td>
<td>8</td>
<td>2.26 (0.78-6.54)</td>
<td>0.127</td>
</tr>
<tr>
<td>Dysplasia (n = 211)</td>
<td>5</td>
<td>3</td>
<td>1.17 (0.27-5.14)</td>
<td>0.835</td>
<td>2</td>
<td>0.87 (0.16-4.67)</td>
<td>0.866</td>
<td>0</td>
<td>-</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Diplotype-phenotype correlations in patients with ulcerative colitis in which AG/AG served as reference.

*For full notation see Table 4.

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tionally, the COX-2 −1195 A→G and −765G→C polymorphisms were demonstrated to influence the expression of COX-2 and confer a risk for developing (adeno)carcinomas in the gastrointestinal tract [15,38,39]. Chronic intestinal inflammation-associated colorectal carcinogenesis is thought to occur via a stepwise progression beginning with epithelial hyperplasia, leading to various grades of dysplasia, adenoma, and then to adenocarcinoma [40]. We investigated whether or not an association could be found between the COX-2 polymorphisms and dysplasia or CRC in patients with IBD. Due to the restricted number of patients who developed dysplasia or CRC, no differences could be observed.

In conclusion, subjects with the −765C allele showed a reduced risk for developing CD. No correlation could be found between the COX-2 diplootypes and clinical characteristics of IBD patients and the development of colorectal dysplasia or cancer. Further studies are required to confirm the association we found and efforts should be made to unravel the role of COX-2 and its derived prostaglandins in the pathogenesis of IBD.

Author Contributions
Conceived and designed the experiments: HvD DJJ WHMP. Performed the experiments: RHMM. Analyzed the data: HvD MGHO. Contributed reagents/materials/analysis tools: IDN. Wrote the paper: HvD.

References