The Relationship between the Val158Met Catechol-o-Methyltransferase (COMT) Polymorphism and Irritable Bowel Syndrome

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Abstract

Background: The catechol-O-methyltransferase (COMT) enzyme has a key function in the degradation of catecholamines and a functional polymorphism is val158met. The val/val genotype results in a three to fourfold higher enzymatic activity compared with the met/met genotype, with the val/met genotype exhibiting intermediate activity. Since pain syndromes as well as anxiety and depression are associated to low and high COMT activity respectively and these conditions are all associated with irritable bowel syndrome (IBS) we wanted for the first time to explore the relationship between the polymorphism and IBS.

Methodology/Principal Findings: 867 subjects (445 women) representative of the general population and 70 consecutively sampled patients with IBS (61 women) were genotyped for the val158met polymorphism and the IBS patients filled out the Hospital-Anxiety-and-Depression-Scale (HADS) questionnaire, and an IBS symptom diary.

Results: There was a significantly higher occurrence of the val/val genotype in patients compared with controls (30% vs 20%; \( \chi^2 = 3.98; p = 0.046 \)) and a trend toward a lower occurrence of the val/met genotype in IBS patients compared with controls (39% vs 49%; \( \chi^2 = 2.89; p = 0.089 \)). Within the IBS patients the val/val carriers exhibited significantly increased bowel frequency (2.6 vs 1.8 stools per day; \( \chi^2 = 5.3; p = 0.03 \)) and a smaller proportion of stools with incomplete defecation (41% vs 68%; \( \chi^2 = 4.3; p = 0.04 \)) compared with the rest (val/met+met/met carriers). The val/val carriers also showed a trend for a smaller proportion of hard stools (0% vs 15%; \( \chi^2 = 3.2; p = 0.08 \)) and a higher frequency of postprandial defecation (26% vs 21%; \( \chi^2 = 3.0; p = 0.08 \)).

Conclusions/Significance: In this study we found an association between the val/val genotype of the val158met COMT gene and IBS as well as to specific IBS related bowel pattern in IBS patients.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal discomfort in combination with altered bowel habits in the absence of organic disease. The prevalence of IBS in the western population is estimated to 5–11% [1]. The causes of IBS are not known. Abnormalities in gut immunology, inflammation [2] and brain-gut communications have been proposed [3]. Visceral hypersensitivity is demonstrated in 50–80% of patients with IBS and the origin of this phenomenon is probably based on both peripheral and central nervous system (CNS) mechanisms [1,4]. Abnormalities in CNS interpretation of visceral afferent signals and dysfunction in the endogenous pain modulation system may contribute to visceral hypersensitivity [3,5]. Patients with IBS also have high rates of anxiety and depression and patients suffering from anxiety and depression have more IBS-like symptoms [6–8]. The pathophysiological links between anxiety and depression and the gut is not fully understood but it has been proposed that changes in the endogenous pain modulation system, the autonomic nervous system (ANS) and the hypothalamus-pituitary-adrenal (HPA) axis may each play a role [3].

Catechol-o-methyltransferase (COMT) has a key function in the degradation of catecholamines (dopamine, noradrenaline and adrenaline). A common polymorphism in the COMT gene (located at chromosome 22q11.2) is val158met (rs4680), which causes a valine (val) substitution to methionine (met) and is responsible for a variation in function of the enzyme. The val/val
IBS patient and control samples

Methods

Val158Met COMT

Results

Statistics

The control subjects were older (mean age 43.5 years vs 31.1 years; p<0.001) and had more male subjects (49% vs 13%, Chi² (1) 33.1; p<0.001) compared to the patients with IBS. There was a higher occurrence of the val/val genotype in patients compared with controls (30% vs 20%; Chi² (1) 3.98; p = 0.046) and a trend...
Gastrointestinal symptoms in patients with IBS in relation to val158met COMT polymorphism

Within the IBS patient sample, the val/val genotype, based on a two week validated symptom diary, was significantly associated with increased bowel frequency (2.6 vs 1.3 stools per day; Chi² (1) 5.3; p = 0.05) and with a smaller proportion of stools with incomplete defecation (41% vs 60%; Chi² (1) 4.3; p = 0.04) compared with the rest (val/met+met/met carriers). There was also a trend towards a smaller proportion of hard stools (0% vs 15%; Chi² (1) 3.2; p = 0.08) and a higher frequency of postprandial defecation (26% vs 21%; Chi² (1) 3.0; p = 0.08) among the val/met carriers compared with the rest (Table 2).

Table 1. The distribution of the val158met COMT polymorphism in patients with IBS compared to a sample representative of the general population.

<table>
<thead>
<tr>
<th></th>
<th>met/met</th>
<th>val/met</th>
<th>val/val</th>
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<tbody>
<tr>
<td>IBS women+men (n = 70)</td>
<td>31%</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>Controls women+men (n = 867)</td>
<td>31%</td>
<td>49%</td>
<td>20%</td>
</tr>
<tr>
<td>IBS women (n = 61)</td>
<td>36%</td>
<td>38%</td>
<td>26%</td>
</tr>
<tr>
<td>Controls women (n = 445)</td>
<td>42%</td>
<td>48%</td>
<td>20%</td>
</tr>
<tr>
<td>IBS men (n = 9)</td>
<td>0%</td>
<td>44%</td>
<td>56%</td>
</tr>
<tr>
<td>Controls men (n = 422)</td>
<td>30%</td>
<td>51%</td>
<td>19%</td>
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</table>

There was a higher occurrence of the val/val genotype in patients compared with controls (30% vs 20%; Chi² (1) 3.98; p = 0.046) and a trend toward a lower occurrence of the val/met genotype in IBS patients compared with controls (39% vs 49%; Chi² (1) 2.89; p = 0.089).

Statistical Power analyses

Power calculations were performed for key analyses within the study. The statistical power using a one-tail test and an alpha error of 5% concerning the frequency difference of the val/met genotype between IBS patients and controls was 62%. We calculated that the preferable number of IBS patients should have been 127 patients to reach 80% statistical power. The statistical power employing a one-tail test and an alpha error of 5% concerning the frequency difference in the number of stools between IBS patients carrying the val/met genotype compared to the IBS patients carrying the val/met and the met/met genotypes was 72%, with an additional 10 more subjects needed to reach 80% statistical power.

Discussion

COMT is a key regulator in the degradation of catecholamines and individual differences in the activity of the enzyme have been shown to influence the interpretation of pain and negative environmental stimuli [9,25]. This study is to our knowledge the first study to explore the relationship between COMT polymorphism and IBS. We found a significantly higher occurrence of the val/met genotype and a trend towards a lower occurrence of the val/met genotype among the patients with IBS compared to the control population from the same geographical region (Umeå, Sweden). These differences were based on comparisons between the total patient and control samples but did not remain significant if only female IBS patients and female controls were included in the analysis. The study was slightly underpowered and since the control sample was representative of the general population the sample is expected to contain subjects suffering from IBS but the diagnostic status with respect to IBS within the control sample was not available. These facts might explain the loss of significance when the women were analyzed separately.

However, using logistic regression, adjusting for age and gender there was a borderline significant association between the val/met genotype and IBS and a trend towards a protective effect of the heterozygous val/met genotype. Patients seeking help for IBS are predominately women and there are also some differences in symptom presentation between men and women, where abdominal pain and constipation-related symptoms are more common in women whereas men more likely report diarrhea-related symptoms [26]. The patients with the val/met genotype in our study (both men and women) reported prospectively more bowel movements, fewer harder stools and more stools after meals than the patients with the other genotypes indicating an association between the val/met genotype and the diarrhea-dominant IBS subtype.

Both population studies and studies on patient with IBS show a significant correlation between symptom of anxiety and diarrhea [8,19]. The val/met genotype has been associated with anxiety (Caucasian women) [16], to faster and better recognition of negative facial expression [25], and a reduction in the ability to experience rewards [27]. Anxiety and confrontation with fearful faces have also been shown to enhance perception of signals from the gut [28–30] which raises the question whether the val/met genotype predisposes towards increased perception of abnormal gut physiological events. In the present study the patients with IBS showed no differences in HADS-anxiety score between the three different COMT genotypes. There was a trend towards more consulting for pain in the met/met genotype compared to the other genotypes almost reaching statistical significance for neck pain (36% vs 19%; Chi² (1) 2.3; p = 0.12 (Table 3)).
different genotypes but this does not exclude that the gastrointestinal tract of the "val/val" individuals are more sensitive to activation of the stress system resulting in increased bowel movements and/or lower threshold for defection signals. In addition, other mechanisms than stress related pathways could be involved, and the influence of an increased degradation of catecholamines (high COMT activity) on the gastrointestinal tract is probably complex and may involve both central and peripheral actions.

A recent Japanese study on patients with functional dyspepsia also showed in consistency with our data a lower frequency of the met allele among dyspeptic patients but the difference was not significant [31].

The met/met genotype with a decreased COMT activity has been associated with a decreased activity level of the endogenous pain inhibitory system and increased chronic somatic pain. For example a low COMT activity has been associated with chronic facial pain [12,13], fibromyalgia [14] and women with non-migrainous headache [15].

In the present study we found no significant differences in consulting behaviour for chronic pain, but a trend for more chronic pain, especially neck pain in the IBS patient carrying the met/met allele. However within the present study the met/met genotype carriers did not differ in prospectively reporting abdominal pain, in comparison with the other genotype carriers. In a large Norwegian study, investigating musculoskeletal symptoms in a sample representative of the general population they found no association between different musculoskeletal symptoms including chronic chest/abdominal pain and the different val158met COMT genotypes [32]. Neither did they find

<table>
<thead>
<tr>
<th>Table 2. Characteristics of the patients with IBS in relation to val158met COMT polymorphism based on the symptom diary.</th>
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<tbody>
<tr>
<td>met/met carriers (n = 19)</td>
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<tr>
<td>Mean pain hours per day</td>
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<tr>
<td>Mean bloating hours per day</td>
</tr>
<tr>
<td>Mean stools per day</td>
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<tr>
<td>Percentage of days with no stools</td>
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<tr>
<td>Percentage of loose stools</td>
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<td>Percentage of hard stools</td>
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<td>Percentage of stools with urgency</td>
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<td>Percentage of stools with straining</td>
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<td>Percentage of stools with incomplete emptying</td>
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<td>Percentage of meals followed by defection (Gastro-colon reflex)</td>
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Table 3. Anxiety, depression, health seeking behaviour and consulting for chronic pain in relation to the val158met COMT polymorphism among patients with IBS.

<table>
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<tbody>
<tr>
<td>met/met carriers (n = 22)</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Mean BMI</td>
</tr>
<tr>
<td>HADS-Anxiety</td>
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<tr>
<td>HADS-Depression</td>
</tr>
<tr>
<td>Visits per year in primary care</td>
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<tr>
<td>Two or more parts of the body with chronic somatic pain</td>
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<tr>
<td>Chronic headache</td>
</tr>
<tr>
<td>Chronic neck pain</td>
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<tr>
<td>Chronic lumbago</td>
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</table>

There was no significant difference in age, BMI, HADS scores, health seeking behavior and consulting for chronic pain between different genotypes among 70 patients (61 women) with IBS. However, the val/met carriers tended to have less HADS-depression score compared to the other genotypes and the met/met genotype tended to have more visits per year in primary care and more chronic neck pain. BMI = Body mass index. HADS = Hospital anxiety depression scale. ns = Non-significant.

*Statistically significant: p < 0.05. Borderline statistically significant: p values between 0.05–0.15. ns = non-significant.

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an association between neuropathic pain and the val158met COMT polymorphism [33]. However, these conflicting data does not exclude that the met/met genotype predisposes to pain in subgroups of patients, for example in individuals with severe multifocal pain. Lastly, there is diversity in the pathophysiological mechanisms of visceral and somatic nociceptive pain [4], so COMT activity may influence the perception of musculoskeletal and abdominal pain differently.

To conclude, in this study we aimed to study the relationship between COMT function and IBS, both of which have been demonstrated to be associated with pain and anxiety/depression. We found a significant association between the val/val genotype and IBS and a trend towards a protective role of the heterozygous val/met genotype for IBS. The val/val genotype was associated with diarrhea-like symptomatology in patients with IBS. We believe that this study justify further research of the val158met COMT polymorphism in a larger samples of IBS patients. It would be warranted and interesting to investigate these genotypes in different subgroups of IBS patients, for example in IBS patients with and without other unexplained pain syndromes, and in IBS patients with different bowel patterns.

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Author Contributions

Conceived and designed the experiments: PK AD RA KFN. Performed the experiments: PK IS JDF KFN. Analyzed the data: PK MW KFN. Contributed reagents/materials/analysis tools: IS JDF RA KFN. Wrote the paper: PK AD MW KFN.

References