COMT genetic polymorphisms and Irritable Bowel Syndrome

Research Presentation
Chief of Medicine Conference
May 12th 2009
Research Goals

Investigate how genetic polymorphisms of the catechol-o-methyltransferase (COMT) gene affect pain thresholds in irritable bowel syndrome (IBS)
Irritable Bowel Syndrome

• Historically described as a “functional gastrointestinal disorder” largely due to its lack of pathologic findings on endoscopy and/or pathology

• Functional GI disorders are extremely common in the United States
  – Afflict approx 22% of Americans
  – Involve up to 50% of referrals to gastroenterologists

• Psychiatric factors have long been thought to play a predominant role over biological factors in IBS because of the interplay between psychosocial stressors and abdominal symptoms
IBS, cont...

• However, recent advances now point to an underlying organic etiology in IBS:
  – Patients with IBS respond well to antidepressants with improvement in their GI symptoms
  – In repeated studies, patients with IBS have demonstrated altered rectal perception to balloon inflation, with lower discomfort thresholds and higher perceived intensities when compared to matched control subjects
  – Patients with IBS activate the anterior cingulated cortex (a critical CNS pain center) to a greater extent than controls in response to painful rectal stimulus

• Suggests that patients with IBS have a heightened pain sensitivity of the brain-gut axis
COMT

- Enzyme responsible for the degradation of dopamine, epinephrine, and norepinephrine in the nervous syndrome
- COMT initially became of interest after the genetic mutation for velocardiofacial syndrome was found to involve a microdeletion on chromosome 22q11 that included the COMT gene
- Velocardiofacial syndrome was associated with a high rate of psychosis, particularly schizophrenia
  - COMT gene encoding for the COMT enzyme is a clear functional candidate gene for schizophrenia because COMT is involved in the catabolic clearance of dopamine, whose levels have been implicated in this disease
COMT, cont...

- A single nucleotide polymorphism (SNP) of the COMT gene results in the substitution of valine (val) with methionine (met) in the protein sequence.
- The met mutation produces an enzyme that is unstable at body temperature.
  - Leads to a 3-4 fold reduction in the activity of the enzyme.
- The gene is inherited in Mendelian fashion, producing 3 genotypes: Val/Val, Val/Met, Met/Met.
Early work

- Subjects with low COMT enzyme activity have chronically over-activated dopamine neurotransmission, decreasing the neuron’s ability to counteract painful stimuli.
- Based on this information, Zubieta et al (2003) demonstrated that subjects with the mutant Met/Met polymorphism tolerated significantly lower infusion rates of painful hypertonic saline into their masseter muscles.
  - Also confirmed significant differences in brain PET scan between genotypes during the infusion and higher levels of perceived pain on a standardized questionnaire.
Hypothesis

Based on Zubieta’s findings that pain thresholds are lower in patients with the COMT Met/Met genotype, we hypothesize that IBS patients, who have been shown to have lower pain thresholds, will have a higher incidence of the Met/Met polymorphism.
Methods

• Descriptive study of IBS patients with chronic pain symptoms
  – pain and disease severity tracked with the Bowel Disease Questionnaire
• Patients meet Rome II criteria for irritable bowel syndrome
  – Sample size of 50 IBS patients and 50 controls patients
• Blood samples for all patients have been drawn and tested for the Val or Met alleles with PCR
Data Analysis

• Statistical analysis of differences in the distribution of COMT genotypes between IBS patients and controls
  – Met/Met genotype frequency will be compared with the frequency of the other genotypes
  – Subanalyses to compared groups with respect to symptoms
Results: Allele frequencies

The Met and Val alleles were distributed evenly among IBS and control patients.

<table>
<thead>
<tr>
<th>Allele</th>
<th>IBS 2N=104</th>
<th>Controls 2N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val</td>
<td>53 (51%)</td>
<td>55 (53%)</td>
</tr>
<tr>
<td>Met</td>
<td>51 (49%)</td>
<td>49 (47%)</td>
</tr>
</tbody>
</table>
## Results:
### Genotype crosstabulation

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Count</th>
<th>Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>IBS</td>
</tr>
<tr>
<td>Val/val</td>
<td>12</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>% within group</td>
<td>23.1%</td>
<td>30.8%</td>
<td>26.09%</td>
</tr>
<tr>
<td>Val/Met</td>
<td>31</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>% within group</td>
<td>59.6%</td>
<td>40.4%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Met/met</td>
<td>9</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>% within group</td>
<td>17.3%</td>
<td>28.8%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>52</td>
<td>104</td>
</tr>
<tr>
<td>% within group</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Results: Genotype analysis

- There is no statistical significance between groups, although the met/met genotype is higher in IBS than controls.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>3.995</td>
<td>0.136</td>
</tr>
<tr>
<td>Likelihood Ratio</td>
<td>4.025</td>
<td>0.134</td>
</tr>
</tbody>
</table>
Future Directions

- Sub-analyses of genotype related to disease frequency, severity, age, specific complaints
- Potential to increase the sample size
  - Results trend toward significance and could be more powerful with larger number
Thank you

- Dr. Chris Carlson
- Dr. Christina Surawicz
- Dr. Scott Weigle
- Margaret Heitkemper
- Internal Medicine Residency Program
- Shane O’Mahony