Multi Drug Resistance Gene Single Nucleotide Polymorphisms in Inflammatory Bowel Disease

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The multidrug resistance gene (MDR) is a typical stress-response gene and is highly polymorphic. Most of the detected polymorphisms are intronic or silent.1 In humans, 2 members of the MDR gene family (MDR1 and MDR3) exist, whereas 3 genes are present in rodents-mdr1a, mdr1b and mdr2.2

The MDR1 gene product, P-glycoprotein (PGP), was initially observed as a transport protein which was over-expressed in tumors developing resistance to chemotherapeutic agents, resulting from PGP-mediated efflux of drug from tumor cells. The physiological role of PGP although not fully understood, involves hormone and metabolite secretion, bacterial product detoxification, and transport of several drugs to the extracellular space, thus inhibiting their toxic or therapeutic effects.3

The human MDR gene is composed of 28 exons. To date 29 SNPs have been reported in the MDR1 gene. Among polymorphisms within MDR1, there has been some controversy regarding the functional significance of a missense polymorphism within exon 21 (G2677T/C-Ala893Ser/Thr) and of a wobble polymorphism within exon 26 (C3435T-Il1145Ile). Various reports have suggested that one or the other are associated with altered transporter or gene expression activity.1

It is significant that, although developmentally normal, mdr1-deficient mice spontaneously develop colitis.4 This suggests that functional polymorphisms within MDR1, which result in a loss of or decrease in PGP activity, might increase susceptibility to IBD. Epidemiologic studies have observed a lower incidence of IBD in Africans as compared to Caucasians, consistent with the ethnic differences in the allelic frequency of polymorphism in exon 26.1 In a case-control study by Schwab et al.5 the C3435T variant was found to be significantly associated with UC but not with CD. However, these results were not confirmed in the Greek UC population.6

Brant et al.2 observed a significant association of CD with the Ala893 variant, which has been associated with decreased activity relative to the 893Ser variant as shown by Kim et al.7 Furthermore, no evidence for UC or CD association for the 3435T was observed. Ho et al8 showed that the MDR1 3435TT genotype and T-allelic frequencies were significantly higher in patients with UC-especially in those with extensive disease- compared with controls. No association was seen with CD. The G2677T SNP was not associated with UC or CD.

Key words: multidrug resistant gene, P-glycoprotein, polymorphism, inflammatory bowel disease, ulcerative colitis, Crohn’s disease

Abbreviations
CD= Crohn’s disease
IBD = Inflammatory bowel disease
MDR1 = multidrug resistance gene 1 (human)
mdr1 = multidrug resistance gene 1 (murine)
PGP = P-glycoprotein (the MDR1 gene product)
SNP(s) = single nucleotide polymorphism(s)
UC = ulcerative colitis
Fig. Multidrug resistance (MDR1) gene single nucleotide polymorphisms of possible importance in inflammatory bowel disease: G2677A, G2677T and C3435T. (Agarose gel electrophoresis of digested PCR product, W/W=Homozygous wild type, M/M=Homozygous mutated, W/M=heterozygous).
Table. Overview of the reported prevalence of MDR1 single nucleotide polymorphisms G2677T/A and C3435T and their relation to disease phenotype in patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Author</th>
<th>MDR1 SNP of importance</th>
<th>No controls</th>
<th>No UC</th>
<th>No CD</th>
<th>Significantly increased in</th>
<th>IBD phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsanos et al (submitted)</td>
<td>C3435T</td>
<td>383</td>
<td>121</td>
<td>716</td>
<td>CD (T allele)</td>
<td>-Stronger association with fistulizing CD -No association with UC</td>
</tr>
<tr>
<td>Ho et al⁷</td>
<td>C3435 T</td>
<td>370</td>
<td>335</td>
<td>268</td>
<td>UC (T allele &amp; TT genotype)</td>
<td>-Strongest association in extensive UC -No association with CD</td>
</tr>
<tr>
<td>McGovern et al¹⁴</td>
<td>C3435T</td>
<td>247</td>
<td>272</td>
<td>-</td>
<td>UC (T allele)</td>
<td>Included in a serology panel predicting colectomy in UC No association with CD</td>
</tr>
<tr>
<td>Schwab et al⁵</td>
<td>C3435T</td>
<td>275 (Age-sex matched) 998 (non sex-matched)</td>
<td>149</td>
<td>126</td>
<td>UC (TT genotype)</td>
<td></td>
</tr>
<tr>
<td>Brant et al²</td>
<td>G2677T</td>
<td>650</td>
<td>119</td>
<td>409</td>
<td>CD</td>
<td>Similar but non-significant trends in UC</td>
</tr>
<tr>
<td>Farrell et al¹¹</td>
<td>MDR in peripheral blood lymphocytes (low cytometry)</td>
<td>50</td>
<td>153</td>
<td>IBD</td>
<td>CD</td>
<td>CD patients requiring bowel resection after medical therapy failure</td>
</tr>
<tr>
<td>Croucher et al¹⁰ (German cohort)</td>
<td>C3435T</td>
<td>531</td>
<td>134</td>
<td>262</td>
<td>NONE (UC or CD)</td>
<td></td>
</tr>
<tr>
<td>Croucher et al¹⁰ (UK cohort)</td>
<td>C3435T</td>
<td>164</td>
<td>87</td>
<td>164</td>
<td>NONE (UC or CD)</td>
<td></td>
</tr>
<tr>
<td>Glas et al¹²</td>
<td>C3435T</td>
<td>265 (2 groups)</td>
<td>123</td>
<td>135</td>
<td>NONE</td>
<td>Trend for T allele/TT</td>
</tr>
<tr>
<td>Gazouli et al⁶</td>
<td>C3435T</td>
<td>100</td>
<td>85</td>
<td>120</td>
<td>NONE</td>
<td>Absence of CC genotype</td>
</tr>
<tr>
<td>Potocnik et al¹³</td>
<td>C3435T G2677T C1236T</td>
<td>355</td>
<td>144</td>
<td>163</td>
<td>CD and UC</td>
<td>Refractory and fistulizing CD and refractory UC</td>
</tr>
</tbody>
</table>

A unifying model for genes that increase susceptibility to IBD is that they fundamentally affect host-environment interactions. Just as NOD2/CARD15 risk alleles result in decreased responsiveness to bacterial cell wall products, the Ala893 variant in MDR1 has been associated with relatively decreased transporter function.

A remarkably large number of MDR1 genotype-phenotype studies have been carried out by many laboratories⁶-¹⁴ and as noted previously, a number of such studies have yielded conflicting results which are summarized in Table.

PGP is widely expressed in many normal tissues including enterocytes, hepatocytes, brain choroids plexus, placenta, ovaries and testes. Gender differences have also been noted in the MDR1hepatic expression with women displaying only one third to one half of the hepatic PGP level of men.¹⁵

To minimize the chance of a spurious association between MDR1 genotypes and in vivo phenotypes, careful attention must be paid to haplotypes, gender, environmental factors and sample size. Indeed, such studies should try to ensure that demographic data of subjects selected for the various MDR1 SNPs do not differ.
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REFERENCES