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Current view

Inflammatory bowel disease genetics and pharmacogenetics: An overview

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SUMMARY

In the last decade significant advances in the field of IBD genetics have taken place and various putative loci of genetic susceptibility to IBD have been identified. Since the discovery in 2001 of the only confirmed Crohn's disease susceptibility gene (CARD15/NOD2), various other genes have been extensively investigated with conflicting results. Apart from a risk haplotype in chromosome 5 no other widely confirmed associations with IBD have been discovered. Pharmacogenetics is the study of the relation between genetic variability and variability in drug response or toxicity. Pharmacogenetic studies examined the role of gene variations in the treatment of IBD patients with sulphasalazine, mesalazine, methotrexate, thiopourines, corticosteroids and infliximab but the only discovery partially translated into clinical use is the relation between TPMT gene polymorphisms and hematological toxicity of thiopourines. At present the application of genetic testing in routine clinical practice for the diagnosis and treatment of IBD seems premature and cannot be recommended. Perhaps in the future a panel of genetic markers will be put into clinical use in order to predict the diseases's course, complications and response to therapy.

Key Words: ulcerative colitis, Crohn's disease, inflammatory bowel disease, genetics, pharmacogenetics, susceptibility genes.

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBDs), are chronic relapsing inflammatory disorders of the gastrointestinal track. They are currently thought to result from an inappropriate activation of the innate immune system driven by intestinal microflora, in genetically susceptible individuals.[1]

Data supporting a genetic predisposition to IBD were initially obtained from epidemiological studies that showed a higher frequency in certain ethnic groups, familial aggregation with low prevalence in spouses of patients and increased concordance in monozygotic than dizygotic twins.[2]

In the last decade genome wide scans have identified putative loci of genetic susceptibility to IBD in many human chromosomes but only 7 of these meet strict criteria for significant linkage. These are located in chromosomes 16, 12, 6, 14, 5, 19, 1 and were designated IBD1 to IBD7 respectively.[3]

The only confirmed IBD susceptibility gene to date is CARD15 (previously named NOD2) located in the IBD1 locus. In 2001 three independent groups reported an association between CARD15/NOD2 gene mutations and susceptibility to Crohn's disease,[4-6] results that were subsequently replicated by other investigators. The CARD15/NOD2 gene (located at chromosome 16q12) encodes an intracellular protein present in monocytes, macrophages, dendritic, epithelial and Paneth cells that recognizes bacterial components and results in the activation of NF-κB and induction of apoptosis.[7] Two common missence mutations (R702W, G908R resulting in amino acid substitutions) and a frameshift mutation (L1007fs resulting in a premature stop codon that truncates the last 3% of the protein) have been strongly associated with Crohn's disease, but not ulcerative colitis. Up regulation of NF-kB has been demonstrated in IBD patients' tissues suggesting that this transcriptional factor plays a crucial role in the pathogenesis of the disease but interestingly, data show that these three CARD15 variants represent loss of function mutations associated with decreased activation of NF-KB.[3] This paradox has not been adequately clarified so far.

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CARD15 mutations have been associated with specific CD phenotypes like ileal disease, earlier age of onset, stricturing behavior and increased frequency of surgical resection.[8] World wide and racial differences exist in the prevalence of CARD15 mutations. They seem to be rare or absent in Asian, Arab, African populations, and relatively frequent in Caucasians.[8]

Role of CARD15 in developing Crohn's disease

Healthy homozygous carriers of the L1007fs mutation in IBD affected families have been identified[9] emphasizing the importance of both environmental factors in the pathogenesis of CD and the complexity of genetic susceptibility in this disease.

According to a recent meta-analysis the relative risk for developing Crohn's disease is 2.4 in carriers of a single mutation and it increases to 17.1 for compound heterozygotes or homozygotes. The overall proportion of CD cases in Caucasians attributed to CARD15 mutations was approximately 22%.[10]

Limited and conflicting data exist concerning the presence and role of these mutations in Greek IBD patients. Gazouli et al, reported a significant association between CARD15 variants with CD and curiously ulcerative colitis, in Greek IBD patients,[11] but a smaller study from Crete failed to show an association between the frameshift mutation and CD in Cretan IBD patients.[12]

The IBD5 locus is the only other locus that has been clearly associated with increased risk for IBD. A 250 kilobase haplotype in the IBD5 locus has been consistently shown to confer susceptibility to CD.[13-17] Unlike IBD1 the causal gene(s) in the IBD5 locus has not been recognized so far. The organic cation transporter genes 1 and 2 (OCTN1 and OCTN2) have been extensively studied as causal genes located in this locus. Although studies (including one from Greece)[18] showed an association between a two-allele risk haplotype of these genes and CD[19-22] there is growing skepticism that they may not represent causal factors but rather be in tight linkage with other yet unidentified causal gene(s).[23] Association of the IBD5 locus with perianal CD,[14] severe penetrating and stricturing CD disease[20] as well as a possible association with UC[17,24] has been reported but data are conflicting and no firm conclusions can be made.

The role of HLA

Several linkage and association studies have implicated the HLA region in chromosome 6 in IBD susceptibility and determination of IBD phenotype. The HLA region is located within the IBD3 locus. A variety of HLA class II DRB1 alleles have been associated with CD and UC.[25] The DRB1*1502 is positively associated with UC,[26,27-30] while the DRB1*07 with ileal CD specifically in the absence of CARD15 mutations.[25,31-33] The DRB1*1030 is a rare allele that has been strongly linked to severe or extensive UC[26,27,34-37] and isolated colonic CD.[31-33] In addition this allele has been associated with extraintestinal manifestations of IBD like uveitis[38] and type I arthritis (along with HLA B*27).[39] In contrast type II arthritis has been associated with HLA B*44.[39] It is speculated that HLA plays a more important role in determining the IBD phenotype and extraintestinal manifestations than contributing in overall disease susceptibility.

Other genes

Numerous others genes are being investigated for their role in the pathogenesis of IBD but no conclusive evidence exists so far.

The toll-like receptor 4 (TLR4) is a transmebrane glycoprotein that recognizes gram-negative bacterial lipopolysaccharides and plays a crucial part in the innate immune response. Polymorphisms in the TLR4 gene have been associated with CD and UC in some cohorts,[40-42] including a cohort of Greek CD patients[43] but not in others.[44,45]

The MDR1 gene located on chromosome 7 encodes P-glycoprotein 170 (P-gp) an efflux pump protein for many substrates, found mainly in lymphocytes and epithelial cells.[46] This gene is of particular interest because MDR1 deficient mice have been shown to develop a spontaneous colitis that resembles histologicaly human ulcerative colitis if not treated with antibiotics.[47] Two single nucleotide polymorphisms (SNPs) of MDR1 have been extensively investigated; the silent C3435T that is associated with decreased P-gp expression due possibly to alterations in mRNA stability and the rarer G2677T/A polymorphism. Some studies have demonstrated an association of C3435T SNP with UC[48,49] but others failed to verify this association.[50,51] It is thought that probably this SNP is in tight linkage disequilibrium with another causal mutation or that the susceptibility observed between MDR1 gene and UC is rather haplotypic than depending on a single SNP. A study from Greece failed to show a relation of the C3435T SNP and UC but was strongly criticized because the investigated populations were not in Hardy-Weinberg equilibrium.[52]

The NOD1/CARD4 gene shares many functional and structural similarities with the CARD15 gene[53] and therefore is an attractive candidate susceptibility gene for IBD. A complex insertion/deletion polymorphism has been linked to increased risk for IBD and ulcerative colitis spe-

cifically[54] but a more recent study failed to confirm this result.[55] Further data are required for the role of this gene in racially diverse populations.

The drosophila discs large homologue 5 (DLG5) is also an attractive candidate gene because of its potential role in epithelial barrier integrity. Data suggested an overall association with IBD rather than CD alone.[56] These findings were replicated in some studies[57,58] but not in others.[59,60] In the only Greek study so far the DLG5 SNP G113A was completely absent in IBD patients or healthy controls[18] raising doubts for a possible relation of this gene with IBD susceptibility in the Greek population.

Pharmacogenetics

Pharmacogenetics refers to the study of the relation between genetic variability and variability in drug response and (or) drug toxicity. It is estimated that polymorphisms in genes can account for a 20-90% of variability in drug effects.

The most common drugs currently used in the treatment of IBD patients include sulphasalazine, mesalazine, azathioprine or 6-mercaptopourine, infliximab, methotrexate and corticosteroids.

Mesalazine (5-ASA) in its various formulations is released in the distal ileum and the colon where it exerts its action, while a small proportion is acetylated by the N-acetyltransferase 1 (NAT1) enzyme in the colonic mucosa and the liver and excreted in the urine. Sulphasalazine is cleaved in the colon by bacterial azoreductases into sulphapiridine and 5-ASA. Sulphapiridine is absorbed and metabolized in the liver by the NAT2 enzyme. Polymorphisms in these genes result in slow or rapid acetylator phenotypes.[61] A retrospective study of 77 UC patients failed to show an association between NAT1 gene polymorphisms and efficacy or side effects of 5ASA, as well as a relation between NAT2 polymorphisms and sulfasalazine toxicity.[62]

Despite these data, case reports[63,64] and a recent study from China[65] suggested an association between NAT2 variants and systemic side effects of sulphasalazine.

Methotrexate is used in low doses for weaning patients from steroids and maintenance of remission in Crohn's disease. Most pharmacogenetic studies on methotrexate are derived from the oncologic literature where patients are treated with high doses of this drug. Only one pilot study so far exists examining the role of genetic polymorphisms in the treatment of IBD patients with methotrexate. This retrospective study showed an association between a SNP in the MTHFR gene that is crucial for folate homeostasis and increased overall toxicity from the drug.[66]

6-merkaptopourine (6-MP) and its prodrug azathioprine (AZA) are used in the treatment of IBD patients, especially those with Crohn's disease, for steroid sparing and maintenance of remission. AZA is nonenzymaticaly converted in the liver into 6-MP. Three enzymes compete for the metabolism of 6-MP. Xanthine oxidase converts 6-MP into inactive 6-thiouric acid, thiopourine-s-methyltransferase (TPMT) converts it into 6-methyl-MP (6MMP). Hypoxanthine guanine phosphoribosyltransferase is the main enzyme in the conversion of 6-MP into thioguanine nucleotides (TNGs) which are responsible for the drugs actions as well as for its side effects, especially hematotoxicity. TPMT displays genetic variability and various alleles have been recognized that result in genotypes with high/normal, moderate or low/absent enzyme activity. Patients that are homozygous of compound heterozygotes for the low activity alleles of TPMT are almost certain to develop severe myelosuppresion which may be irreversible and should not receive the drug.[67] A socioeconomic study showed the cost-effectiveness of TPMT genotyping or phenotyping before the initiation of therapy with AZA/6MP in order to avoid treating patients with minimal or absent enzyme activity and therefore prevent severe hematological complications.[68] However no consensus currently exists about this issue as severe myelotoxicity can occur even in the presence of normal TPMT activity making periodic measurements of blood count mandatory. The hepatotoxicity of AZA/6MP has been linked to increased TPMT activity resulting in high levels of 6MMP and TPMT variant alleles have been shown to be very rare in such patients in one study.[69]

The P glycoprotein 170 encoded by the MRD1 gene actively transports glucocorticosteroids (GS) and other drugs out of intestinal epithelial cell and has been implicated in determining therapeutic response to GS.[46] Pgp levels and MDR1 expression were found to be higher in patients with IBD requiring surgery due to failure of medical therapy.[70] An association between steroid refractory CD and MDR1 polymorphisms has been described,[71] but prospective studies in large IBD patients cohorts treated with standardized GS regimens and followed with well defined activity scores are needed in order to clarify the role of the MDR1 gene variants in the response to GS.[67]

Pharmacogenetic studies revealed no significant association between the three common CARD15 variants as well as various polymorphisms in the TNF-a, TNF-b and their receptors' genes and response to therapy with the anti-TNFa chimeric monoclonal antibody infliximab.[72-76] In contrast, an association was found between response to

infliximab and polymorphisms in FcG receptor 3a gene which is expressed in macrophages and NK cells and is involved in antibody dependent cell mediated cytotoxicity.[77] Another significant association was found in one study between the Fas ligand polymorphisms, caspase 9 polymorphisms and response to therapy with infliximab.[78] Interestingly in this study the low response rates observed with certain genotypes were improved with the concomitant use of AZA/6MP.

Use of genetic testing

At present the use of genetic testing in order to determine accurately an individual's probability to develop IBD is still not possible, due to the relatively low specificity and sensitivity of the only confirmed IBD susceptibility gene CARD15 and the unidentified complex interactions between environmental and genetic factors in the penetrenance of the disease's genotype. Even if we identify individuals genetically at risk for developing IBDs there are currently no preventive measures that can be applied (except perhaps stopping smoking) making genetic testing for asymptomatic persons unnecessary. The same is true for the classification of IBD in newly diagnosed patients and for the cases of indeterminate colitis as the presence or absence of CARD15 variants does not definitely determine the disease's phenotype. Genetic testing may play a more significant role in predicting the disease's course and complications allowing more specific or more aggressive therapy to be applied at an earlier point.

Despite extensive investigation the only discovery of pharmacogenetics translated until now into clinical practice is the relation between TPMT gene polymorphisms and hematological toxicity of thiopourine treatment in IBD patients. Genetic testing in clinical drug trials should however continue to be encouraged as the discovery of different responses to specific therapies according to an individual's genetic composition may allow tailoring drug therapy to specific patients' genotype in the future.

In conclusion, despite rapid advances in the past decade the field of IBD genetics is still in its infancy. It has undoubtedly offered us a better understanding of the pathogenesis of the disease and may provide means for developing more effective and targeted therapies for IBD patients. At present however, the application of genetic testing in routine clinical practice for the diagnosis and treatment of IBD is premature and cannot be recommended. One possible exception is the determination of the TPMT genotype in patients about to receive therapy with thiopourines (AZA/6MP). It is likely that in the near future the use of a panel of genetic markers is put into clinical use in order to predict the disease's course, complications and response to therapy in IBD affected individuals allowing physicians to optimally treat these patients. Until then, physicians will continue to rely on standard laboratory and endoscopic findings as well as their clinical judgment to treat patients with IBD.

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