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*Lecture*

# Implications of IBD genetics on disease phenotype

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Inflammatory bowel disease (IBD) is a complex disease which is controlled by multiple risk factors that are evolving and interacting together. It has been suggested that in the series of events from environmental exposure to the clinical and biological expression of any IBD-related phenotypes, there are multiple processing steps controlled by the host and the environment.[1] The term IBD phenotype includes location, disease behavior, and other associated features of IBD which have important implications for the disease management. The currently proposed genetic model for IBD phenotypes suggests complex interactions between environmental factors, promoting and modifying genetic determinants, resulting in the clinical expression of the disease at the gastrointestinal tract of genetically predisposed individuals. [2,3] It has been demonstrated that specific mutations in the disease-promoting genes influence the development of distinct clinical phenotypes, whereas mutations in the modifying genes influence specific features of the disease phenotype such as disease penetrance, progression, complications, or response to treatment.

## *CARD15/NOD2* and disease phenotype

As is consistent with a polygenic etiology for IBD, linkage data from over 10 independent genome-wide screens and many locus-specific replication studies[2] have delineated at least nine IBD susceptibility loci (*IBD1-IBD9*) and enabled identification of *CARD15/NOD2* as the Crohn's disease (CD) susceptibility gene at the *IBD1* locus.[4,5] *CARD15/NOD2* mutations have been studied extensively in genotype–phenotype correlation studies and a consistent pattern is that *CARD15/NOD2* variants are associated with younger age at onset, presence of ileal involvement, and a tendency to develop strictures and/or fistulas.[6-10] Furthermore, a significant gene dosage effect has been observed for CD site and complications. For instance, at least 95% of the patients homozygous for *CARD15/NOD2* mutations present with ileal lesions. On the other hand the existing data are conflicting as to whether *CARD15/NOD2* carriage is associated with a more severe disease course, suggesting that this feature depends on modifying genes and/or environmental risk factors. However, important data come from pediatric studies showing that stricturing complications leading to early surgery were found more frequently in patients with the 1007fs mutation compared with those children without mutations. [11,12] Children with this mutation were found to have a 6.6-fold increased risk for developing a stricturing phenotype requiring surgery.[12] As result of these findings it has been suggested that genotyping at presentation might identify a subgroup of CD children who are at risk for more rapid development of complications and that these patients may benefit from the early use of more aggressive therapies.[12]

## *Other IBD genes and disease phenotype*

The results from genotype–phenotype analysis using other IBD susceptibility genes are still preliminary. In a Canadian study, the *SLC22A4-TC* haplotype did not influence the age of disease diagnosis. The effect of this haplotype on risk for CD was the same in familial and sporadic cases and stronger in the non-Jewish than in the Ashkenazi Jewish white populations.[13] Given the epistasis effect (ie, the interaction of 2 or more genes controlling the expression of a phenotype) between *CARD15/NOD2* and *SLC22A4-TC* with ileal involvement in CD, genetic effects of this *SLC22A4-A5* and *CARD15/NOD2* mutation may result from a common physiopathologic mechanism in the ileum. An association between the IBD5 risk haplotype and ileal disease was shown initially in British patients to occur only in the context of coexisting perianal

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disease.[14,15] In addition, a Canadian study showed an association between homozygosity for the *SLC22A-TC* haplotype and ileal disease without any perianal lesions.[13] Finally, the presence of the *SLC22A-TC* haplotype was not associated with UC in the presence or absence of *CARD15/NOD2* risk alleles. It has been suggested that the *SLC22A-TC* haplotype constitutes a CD-specific variant that acts together with *CARD15/NOD2* risk alleles to predispose to CD and to ileal involvement in patients with CD.[13] The studies conducted to date have indicated no correlation between *DLG5* and any particular phenotypes. Recently an association between nonsynonymous variants in the TLR1, -2, and -6 genes and extensive colonic disease in UC and CD has been reported.[16]

Finally, there is increasing evidence that the genes in the IBD3 locus located on chromosome 6p known and as HLA genes have been found associated with extraintestinal manifestations of IBD, perhaps suggesting a role as modifier genes rather than susceptibility genes. Type I peripheral arthropathy (i.e., migratory pauciarticular large joint arthritis) has been associated with HLA-B*27, HLA-B*35, and HLA DRB*103. Type II peripheral arthropathy (i.e., chronic, symmetrical, small joint arthritis) was associated with HLA-B*44.[17] Uveitis has been associated with HLA-B27 and DRB*0103, and erythema nodosum has been associated with the tumor necrosis factor promoter polymorphism TNF-1031C.[18] Given the tight linkage disequilibrium across the gene-dense region in chromosome 6p, it is not possible to identify the precise allele that is specifically associated with each phenotype. Furthermore, given the relative infrequency of extraintestinal manifestations, replication studies are urgently needed.[2]

## *Pharmacogenetics in IBD*

The recent advances in genetics have generated expectations that medicines can be customized to match the genetic makeup of patients, thereby dramatically improving efficacy and safety. Although the prospects for basic research in pharmacogenetics in IBD look very promising, its incorporation into clinical practice presents considerable challenges. Future management of IBD based on pharmacogenetics is believed to be tailoring treatment towards homogenous subgroups of patients or even individual patients.[19] Genotype-based therapies may be applied both to improve the effectiveness and to diminish the side-effects of drug treatment as well as to select patients for a particular treatment based on a genetic abnormality.

Recent data clearly demonstrate that genes influence both therapeutic responses and toxicity to commonly used IBD drugs. The best example of them, regarding the pharmacogenetic parameters, is that of azathioprine or 6-mercaptopurine (6MP), a drug that is subsequently metabolized by thiopurine methyltransferase (TPMT) to xanthine oxidase, hypoxanthine phosphoribosyl transferase, and finally to the active 6-tioguanine nucleotides. TPMT enzymatic activity, which can be measured by radioimmunoassay, depends on the activity of the *TPMT* gene; thus far, nine genetic polymorphisms leading to decreased activity have been described. An absence of TPMT activity may lead to bone marrow failure and low TMTP activity may require larger doses of the drug to achieve greater effectiveness. We can apply this knowledge to improve the effectiveness of therapy and diminish its side-effects by a pre-treatment determination of TPMT activity, determining the genotype of the *TPMT* gene, and finally by monitoring of 6-thioguanine metabolites.[20,21]

Pharmacogenetic studies of infliximab, MDR and the efficacy of CSs have contributed to understanding the mechanism of action of these drugs.[22,23] There are however many problems with pharmacogenetic studies besides the normal shortcomings of association studies (i.e. low power, population stratification and multiple testing). Mutations in the TNF-α gene have been extensively studied as predictors of response to infliximab with various results.[23]

We can therefore conclude that pharmacogenetics remains a promising field that has already contributed to the better understanding of the molecular mechanisms of some of the drugs used in IBD.[24] Until now however, the only clinical useful discovery is the relation between TPMT polymorphisms and hematological toxicity associated with thiopurine treatment.

## *Conclusions*

The reviewed data from recent genotype-phenotype studies could lead to stratification in genetic studies and may explain some of the apparent discrepancies in earlier genetic studies. Although we have these important recent advances, the current knowledge of the genetic basis of IBD phenotype is of little clinical value in the diagnosis, classification, or prediction of disease course. However, the greater understanding will guide future research, which should accelerate the translation of useful information into clinical practice.

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