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TOPIC HIGHLIGHT

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Genetic factors associated with the development of inflammatory bowel disease

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Abstract

Crohn's disease (CD) and ulcerative colitis (UC) are complex polygenic disorders, characterized by several genes together with environmental factors contributing to the development of inflammatory bowel disease (IBD). Recent advances in research on genetic susceptibility have allowed the identification of diverse genes at different levels: (1) Innate immunity; (2) Antigen presentation molecules; (3) Epithelial integrity; (4) Drug transporter; (5) Cell adhesion. The application of genetic testing into clinical practice is close and all genetic markers may have several clinical implications: prediction of disease phenotype, molecular classification, prevention of complications, and prognosis.

Key words: Genetic; Susceptibility; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory bowel diseases (IBD) of unknown etiology. CD and UC are complex polygenic disorders, characterized by several genes together with environmental factors contributing to the development of IBD.

A variety of epidemiological and clinical data suggest that genetic factors are intimately involved in the pathogenesis of IBD including familial aggregation pattern of disease with a much higher disease frequency in first degree relatives of affected individuals compared with the general population. Twin studies provide the argument for a genetic basis for IBD, with a much higher rate of disease concordance observed in monozygotic than in dizygotic twins and wide variations in the incidence and prevalence of IBD among different populations[1].

IBD is now considered a non-Mendelian polygenic disorder with important environmental interactions (e.g., microbial factors, smoking).

There are two main approaches to identifying genes in complex multifactorial diseases: the positional cloning approach based on linkage studies, and the candidate gene approach based on association studies. Linkage analysis studies the cosegregation of the disease with a marker within the families. Linkage analysis allows scanning of the whole genome. Eleven of these total genome scans have been undertaken in IBD, resulting in a number of susceptibility regions on chromosomes 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19 and X[2]. According to their initial date of reporting and independent confirmations, the regions on chromosomes 16q, 12, 6, 14, 5, 19, 1, 16p and 10 have been renamed IBD 1 to IBD 9, respectively. However, new genes have been reported recently. All susceptibility genes discovered can be categorized into different levels of susceptibility: (1) Innate immunity; (2) Human leucocyte antigen (HLA) molecules; (3) Epithelial integrity (4); Drug transporter; and (5) Cell adhesion.

INNATE IMMUNITY

Understanding of innate immunity has progressed enormously with the discovery of many microbial sensors called pattern recognition receptors (PRRs). The toll-like receptor (TLR) and nucleotide oligomerization domain (NOD) receptor families of PRRs appear to play essential roles in mucosal homeostasis and their alterations contribute to the pathogenesis of IBD.

NOD2 is expressed constitutively in macrophages, neutrophils and dendritic cells[3], as well as in Paneth cells and is induced in epithelial cells[4]. NOD2 is a cytoplasmic protein that serves as a microbial sensor, and its leucine-rich repeat (LRR) domain is required for recognition of muramyl dipeptide (MDP), a fragment of peptidoglycan

present in bacterial cell walls. The ligand MDP ultimately leads to activation of the transcription factor nuclear factor kappa B (NF-κB), and induction of proinflammatory cytokines[5,6]. Specific mutations of the NOD2 gene have been definitively associated with increased susceptibility to ileal Crohn's disease in Western (but not Asian) populations: Arg702Trp, Gly908Arg, and leu1007fsinsC (a frame shift mutation that truncates the carboxy terminal 33 aminoacids)[7,8]. Heterozygous carriage of the risk alleles confers a 2-4 fold increased risk, and homozygotes or compound heterozygotes have a 20-40 fold increased risk[9]. More than 90% of all CD- associated mutations are located in the LRR domain, suggesting that these may affect the function of NOD2 with respect to bacterial recognition and signaling.

NOD1/ CARD4 (Caspase Recruitment Domain 4) plays a role in colonic epithelial defense against *E. coli* and *S. flexeneri* and mediates NF-κB activation[3,10]. Recently, genetic variants of NOD1 have been shown to be associated with disease susceptibility. In a recent study of 556 patients with IBD (294 CD and 252 UC), an association between the variant (rs695857) in nucleotides 30, 258 and 950 of NOD1 and the development of IBD was found. Another variant known as rs2907748 in nucleotides 30, 246 and 263 was also associated with the presence of UC and CD and even with the early onset of the disease (< 25 years of age)[11].

TLRs are abundantly expressed on the surface of monocytes, macrophages, dendritic and epithelial cells. Alterations of TLR3 and TLR4 expression by intestinal epithelial cells have been described in IBD[12], suggesting that there is differential expression of TLR family members. Two common polymorphisms of TLR4 (Asp299Gly and Thr399Ile) have been described in humans. Asp299Gly has been associated with reduced responsiveness following lipopolysaccharide stimulation[13]. These polymorphisms have been associated with the development of CD and UC in Caucasian populations[14-16]. Pierik *et al*[17] showed that TLR1 R80T and TLR2 R753G polymorphisms were associated with pancolitis in UC patients, while a negative association was observed between TLR6 S249P and proctitis in patients with UC. These results suggest that TLR2 and its co-receptors TLR1 and TLR6 are involved in the initial immune response to bacteria in the pathogenesis of IBD.

ANTIGEN PRESENTATION MOLECULES

The major histocompatibility complex (MHC) region is the region studied most extensively. Human leucocyte antigen (HLA) class Ⅱ molecules present partially digested antigen to the T-cell receptor and play a central role in the immune response. The mechanism by which classical HLA class Ⅱ genes exert their influence in IBD is unknown. Different HLA molecules may bind preferentially to different peptides, or bind the same peptide with varying affinity. In IBD, cross reactivity (known as molecular mimicry) may exist between the peptides derived from bacterial luminal flora and from self antigens present in the gut. This may lead to the generation of auto reactive T cells which contribute to disease pathogenesis. HLA-DRB1 is the most extensively studied gene in IBD. In a meta-analysis made by Stokkers *et al*[18], positive associations between UC and HLA-DR2, HLA-DRB1*1502 (OR = 3.74, CI: 2.2-6.38), HLA-DR9 (OR = 1.54, CI: 1.06-2.24) and HLA-DRB1*0103 (OR = 3.42, CI: 1.52-3.69) were found; a negative association was found with HLA-DR4 (OR = 0.54, CI: 0.43-0.68). Another study found that HLA-DRB1*0103 allele was associated with UC and its severe manifestations such as colectomy and pancolitis (P = 0.003, OR = 3.6, CI 95%: 1.46-8.9), while HLA-DRB1*15 allele was only associated with pancolitis in patients with UC (P = 0.001, OR = 8.5)[19].

On the other hand, HLA class Ⅲ genes have been associated with IBD. Several studies have shown the role of tumor necrosis factor α (TNF α) polymorphisms in IBD. There are specific genetic polymorphisms involving TNFα that influence the amount of cytokine produced. Bouma *et al*[20] reported an association between the polymorphism of *TNF*α gene promoter region at -308 position and UC, and this finding was confirmed by other studies[21, 22].

EPITHELIAL INTEGRITY

The organic cation transporter (OCTN) is a family of transporter proteins for organic cations, and may also transport carnitine, an essential cofactor of the metabolism of lipids. Carnitine is involved in the transport of long-chain fatty acids into the mitochondria. There is evidence that inhibition of fatty acid oxidation in the epithelium of the colonic mucosa is associated with the development of UC. There are two subtypes of this gene, OCTN1 and OCTN2, and some mutations have been reported in them: SLC22A4 1672C/T for OCTN1 and SLC22A5-207G/C for OCTN2, which are associated with the development of CD. The presence or combination of these mutations constitutes TC haplotype, which is associated with ileal, colonic and perianal affection and onset and the need of surgical treatment in CD[23, 24].

DLG5 (Drosophila long disc homologue 5) gene is a member of the membrane associated guanylate kinase gene family which encodes cell scaffolding proteins and seems to play a role in the maintenance of intestinal epithelial cells, and its mutations have been involved in a rise in intestinal permeability[25]. DLG5 is a widely expressed protein found in many tissues such as the placenta, small bowel, colon, heart, skeletal muscle, liver and pancreas. It is important in signal transduction and epithelial cell integrity. Four haplotypes have been identified, but only D haplotypes were associated with UC and CD in a European cohort[26]. Another variant of this gene (rs37462) was found in Japanese people with CD[27]. The haplotype characterized by the haplotype-tagging single nucleotide polymorphisms (SNP) G113A called haplotype D, was found substantially over-transmitted in patients with IBD.

DRUG TRANSPORTER

The multidrug-resistance (MDR-1) gene encodes the drug efflux pump P-glycoprotein 170 (Pgp-170). Various polymorphisms have been identified within MDR-1: a

mutation C3435T in exon 26 and a mutation G2677T in exon 21 have been correlated with altered Pgp expression and function in humans. Overexpression of MDR-1 leads to an increased efflux of drugs and decreased cytoplasmic drug concentrations. Several drugs, including glucocorticoids, are known Pgp-170 substrates. Farrell *et al*[28] showed that MDR was significantly elevated in CD and UC patients who required bowel resection and proctocolectomy after failed medical therapy. Variant C3435T was related to the presence of pancolitis in patients with UC in Scotland[29]. However, the frequency of SNPs is low and is different among populations, with the exception of three SNPs in exon 12 (C1236T), exon 20 (G2677T/A) and exon 26 (C3435T), and some of them are correlated with different diseases and clinical characteristics[30].

CELL ADHESION

Cell surface adhesion molecules conveying leukocyte-endothelial interactions, govern homing of activated inflammatory cells into gut. Extravasation and migration into the site of inflammation are mediated by integrins and selectins, and these molecules are increased in IBD patients. There are targeting therapies against adhesion molecules in clinical trials to date including natalizumab (integrin α4 subunit) and MLN-02 (selective adhesion molecule blocker for integrin $\alpha 4\beta 7$). In Japanese patients with IBD, the intercellular adhesion molecule-1 (ICAM-1) K469 allele is associated with CD and UC[31].

CONCLUSION

There are increasing numbers of genetic markers associated with the development of IBD at different levels: innate immunity, antigen presentation, epithelial integrity, drug transporter and cell adhesion that contribute, in genetic susceptibility, to the development of IBD in conjunction with environmental and immunological factors.

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