ANNALS OF GASTROENTEROLOGY 2006, 19(2):203-208

Lecture

Current advances of genetics in Inflammatory Bowel Disease

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SUMMARY

Genetic factors play an important role in the pathogenesis of inflammatory bowel diseases (IBD), including both ulcerative colitis (UC) and Crohn's disease (CD). The research on genetic susceptibility of IBD has been tremendous and over 10 chromosomal regions have been identified by genome-wide scanning. The certain replicated linkage region in different studies, IBD1 (16q12), contains the CD susceptibility gene, NOD2/CARD15. Further fine mapping as well as candidate gene studies have already led to the identification of a number of other susceptibility genes including DLG5, OCT1 and 2, NOD1, HLA, and TLR4. Recent studies, particularly in CD, have highlighted a number of associations between genotype and phenotype. These, suggest that genetics also may influence the clinical manifestations of IBD including disease location, behavior, natural history and side effects of drug therapy. Genetic research in IBD has helped our understanding of the clinical heterogeneity of the disease and has started to explore the complex interactions between genetic risk factors and environmental risk factors in IBD. Although rapid advances in genomic medicine are yet to impact on routine clinical practice, it is anticipated that genetic markers in the future will be implemented in an integrated molecular diagnostic, therapeutic and prognostic approach of IBD patients.

INTRODUCTION

Crohn's disease and ulcerative colitis are chronic, relapsing inflammatory diseases of the gastrointestinal tract, widely known as inflammatory bowel diseases (IBD).[1] Both UC and CD have a worldwide distribution and are common causes of gastrointestinal morbidity in Western Europe and Northern America. Recent population based studies suggest that the combined prevalence of these diseases in Western countries approaches 400 per 100.000.[2]

Despite numerous studies performed over several decades, the cause of IBD remains poorly understood. Inflammatory bowel disease is thought to result from an inappropriate activation of the mucosal immune system driven by intestinal bacterial flora.[1] Several clinical observations suggest that genetic factors contribute to susceptibility to inflammatory bowel diseases. In particular, the role for genetic factors was suggested by studies showing familial aggregation of IBD and greater concordance in monozygotic twins compared with dizygotic twins.[3] Over the past 10 years, this evidence has been supplemented by molecular data from genome-wide linkage studies of multiply affected IBD families.

In 2001, three independent survey groups[4-6] reported the identification of the first CD susceptibility gene, named NOD2 (nucleotide-binding oligomerization domain), renamed recently CARD15 (caspase activating recruitment domain), on chromosome 16q12. NOD2/CARD15 is located in the IBD 1 locus and is highly associated with CD, but not UC.[4,5] NOD2/CARD15 is expressed in peripheral blood monocytes[7] and dendritic cells and can be upregulated in intestinal epithelial cells by TNF.[8] This major breakthrough firmly established a role for genetics in determining susceptibility to CD, underscored the importance of the bacterial flora and focused attention on the role of patern recognition receptors (PRRs) and other pathways of the innate immune system. Three years after this finding more genes (DLG5, OCTN1 and 2, NOD1, HLA,TLR4)[9] have been reported using positional cloning techniques and fine mapping of

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identified susceptibility regions from total genome scans.

Genetic epidemiology

Epidemiologic studies show that IBD incidence and prevalence vary significantly depending on geographic location and ethnic or racial background. In general, there is an increased risk for developing IBD in urban compared with rural areas, in cohorts with a higher socioeconomic class, as well as in developed rather than less developed countries. Many regions (Denmark, United Kingdom, Canada) show continued increase in CD incidence and prevalence, whereas rates for UC seem to be stable.[10-12] Incidence has been found to increase when populations emigrate from low-risk geographic areas to those with higher risk.[13,14]

Among Caucasians, the prevalence of CD and UC among Jews in the United States is significantly higher than in non-Jewish Caucasians.[15]

In population-based studies, approximately 5%-10% of all affected individuals with IBD report a positive family history, indicating higher risk factor for developing IBD when other family members have the disease.[16-18] Monozygotic twin concordance for CD is reported as 42%-58%, whereas the dizygotic twin concordance is not significantly different from that for all siblings. The rates for UC range between 6%-17% for monozygotic twins and between 0%-5% for dizygotic twins, respectively.[19,20] The greatest risk appers for children of whom both parents have IBD (>30% at the age of 28 years).[21]

The fact that disease concordance is significantly less than 100 % among monozygotic twins indicates a reduced penetrance for the IBD genotype, most likely owing to nongenetic factors, such as environmental triggers.

Genetic linkage studies in IBD

Two broad, complementary approaches are typically utilized in genetic studies of IBD, namely genetic linkage and association studies.[22] Genetic linkage typically implicates broad genomic regions, encompassing scores of potential associated genes. Once linkage is identified by genome-wide searches, the identification of specific disease gene(s) requires the use of genetic association studies. Genetic association studies test for differences in allelic frequencies in patients compared to control individuals. A total of 11 genome-wide scans have been performed in IBD resulting in a number of susceptibility regions on chromosomes [1,3,4,5,6,7,10,12,14,16,19] and X.[22,23] Table1.

The IBD1 locus, in the pericentromeric region of chromosome 16, represents the best replicated region, showing positive evidence for linkage only in CD and not in UC.[22] This locus on chromosome 12, represents a region where the linkage evidence may be relatively greater in UC compared with CD.[23] The IBD3 locus on chromosome 6p encompasses the major histocompatibility complex and has been implicated consistently for both CD and UC in a number of linkage studies. Additionally, this region contains the TNF (tumor necrosis factor) gene, for which functional promoter polymorphisms affecting TNF expression have been reported.[33] The IBD5 locus at chromosome 5q31-q33 region, contributed to CD susceptibility in families with early-onset disease. This region contains a number of immunoregulatory cytokines that might be important candidate genes in the pathophysiology of CD: interleukins 3,4,5 and 14, as well as other candidate genes, such as colony-stimulating factor isoform 2 and the transcription factor, interferon regulatory factor, isoform 1.[33] Significant linkage of IBD to chromosome 19p13 has been observed in Canadian sibling-pair families. Several candidate genes in this region are known, intercellular adhesion molecule 1, complement component 3, thromboxane A2 receptor and leukotriene hydroxylase. Furthermore, evidence for linkage to chromosome 1p was observed. A suggestion of linkage to chromosomes 7q and 3p were observed, which are the sites of the mucin 3 gene (chromosome 7) and several genes on chromosome 3p for the receptors for hepatocyte growth factor and epidermal growth factor and an inhibitory guanine nucleotide-binding protein, GNAI2 (33) Table1.

NOD2/CARD15 (molecular and clinical implications)

Fine mapping of the IBD1 locus led Hugot et al[4] to identify the underlying gene on chromosome 16 as the

Table 1. Chromosomal regions in IBD genetic linkage studies

Author	Year	Chromosomal regions of linkage
Hugot	1996	16cen
Satsangi	1996	12,7q22,3p21
Cho	1998	16cen,1p,3q,4q
Hampe	1999	16cen,10q,1q,6p,12,X.22,4q
Ma	1999	14p11,17q21,5q33
Duerr	2000	14q11
Rioux	2000	19p13,5q31,3p,6p
Williams	2002	16cen,11p,6p21
Paavola-Sakki	2003	11p12,2p11,12p13,12q23,19q13
Vermeire	2004	14q11,Xq,1q,6q,20p,4q,10q
Barmada	2004	12,6p,8q,15q,22,2p

CARD15 (previously NOD2) gene. Parallel to this finding, Ogura et al[5] and Hampe et al[6] also identified the CARD15 gene by means of the candidate gene approach.

NOD2/CARD15 a member of the NOD_1/Apaf-1 family of regulators of apoptosis, encodes an amino acid peptide chain containing several functional domains-two N-terminus CARDs, a central nucleotide binding domain (NBD), and a C-terminus leucine-rich repeat (LRR) domain. The CARDs are able to interact with other CARD containing proteins and explain the interaction with RICK (receptor-interacting CLARP-associated kinase) and putatively with proteins involved in apoptosis.[34] The NBD is involved in NOD2/CARD15 self-oligomerization. Finally, the C-terminus LRR domain is required for bacterial dependent induction of NFκB activity.[34]

Three major NOD2 polymorphisms have been implicated in CD, denoted as single nucleotide polymorphisms 8, 12, and 13 (SNP8, SNP12, SNP13). These correspond respectively to point mutations 2104C>T(R702W) and 2722G>C (G908A) and insertion 3020insC that results in premature stopping with a protein of 1007 instead 1040 amino acids.

NOD2/CARD15 is capable of activating nuclear factor κB (NFκB) through interactions with the serine threonine kinase, RICK (receptor-interacting CLARP-associated kinase). Thus, NOD2/CARD15 has proinflammatory properties, as expected for a susceptibility gene involved in a chronic inflammation. Lipopolysaccharides (LPSs) and peptidoglycans (PGNs) have been proposed as the relevant bacterial activators. Because NOD2/CARD15 is located within the cytoplasmic membrane, it is thus considered today as a cytosolic pattern recognition receptor of the innate immune system.The three main IBD associated mutations are located within the LRR region or in its immediate vicinity suggesting that the causative factor in IBD is an initial defect in the response to bacterial and to induce NκFB activation.[34-38] However, these functional models are not completely clarified and thus additional work is required in order to determine which contra-regulatory pathways are involved in IBD tissues.

The genetic effects varied across populations of different racial descent, being most prominent in non-Jewish Caucasians, substantially smaller in Jews, and absent in subjects of Asian descent.

The three common NOD2 variants confer different risks for CD as SNP8 increased the odds by two-fold, SNP12 by three-fold and SNP13 by four-fold in non-Jewish descent Caucasians. Carriage of at least two variants increased the odds about 20 times in non-Jewish descent Caucasians, and 5 times in Jewish descent populations. The same alleles were associated with specific disease phenotypes, most particular with ileal involvement. There is a strong association with stenotic disease and the strongest effect was seen with ileal location. These high-risk alleles may influence primarily the disease location and then ileal disease increases the risk of stenosis.[39] At the population level, the three variants may explain almost a quarter of the risk for CD in non-Jewish populations. The average risk for CD in the non-Jewish population is about 1 in 2,500. Carrying any of the three alleles makes the absolute risk 2-4 times greater at most. Thus, for a randomly selected individual, the additive absolute risk conferred by NOD2 is relatively small and there is no reason for screening the general population for NOD2 variants.[39]

Other genes associated with IBD

Recently, more genes have been reported an association with IBD using genetic techniques to identified susceptibility regions from total genome scans. Peltekova et al[40] showed that functional polymorphisms in the carnitine/organic cation transporter (OCTN) cluster on 5q31 are associated with CD. The 2 functional mutations create a 2-allele risk haplotype TC, which had a frequency of 54% in patients with CD compared with 42% in controls (*P* _.0003).Meanwhile replication studies have emerged but results are confliting.[41,42] Simultaneously with the OCTN report, Stoll et al[43] report that mutations in *DLG5* on the long arm of chromosome 10 (10q23) are associated with IBD. *DLG5* is a member of the membrane-associated guanylate kinase (MAGUK) family of scaffolding proteins involved in intracellular signal transduction. The investigators identified 2 haplotypes in *DLG5* with atransmission distortion in affected offspring. Whereas Daly et al[44] was able to show independent replication in two cohorts from Quebec/Italy and Quebec/UK, other studies were not able to show association.[41,42]

Last year, a strong association between a complex functional NOD1(CARD4) insertion/deletion polymorphism and IBD was found by investigators at the University of Oxford.[45] From a candidate approach, the MHC region is the region studied most extensively. In Japanese studies HLA DR2 has been implicated in UC, whereas HLA DR3 has been implicated in European studies[9] In CD, HLA associations are less convincing.[9]

Searching for specific ligands of NOD2, revealed that muramyl dipeptide derived from PGN appears to be the

essential structure recognised by NOD2.Thus defects in LPS and/or PGN signalling seem to impair the innate mucosal immune. Lipopolysaccharride signalling is mainly mediated through the cell surface toll-like receptors (TLRs). Interestingly, TLR4 Asp299Gly polymorphism has been shown to be associated with decreased bronchial responsiveness to LPS in humans. Patients bearing this polymorphism demonstrate increased susceptibility to Gram negative infections. Although a single polymorphism has a relative in vivo penetrance compared with the many other functional gene variants involved in LPS signaling, the TLR4 Asp299Gly polymorphism was associated with CD and ulcerative colitis (UC) in a Belgian study but not confirmed by others.[9]

These data are in line with the study of Ioannidis et al[46] that show that significant between-study heterogeneity (diversity) is frequent, and that the results of the first study correlate only modestly with subsequent research on the same association in genetics.

Implications of Pharmacogenetics for Clinical Practice

The efficacy and side effects of most drugs reflect the complex interplay of multiple, pharmacodynamic and pharmacokinetic factors, some of which may be encoded by polymorphic genes. Therefore, the prediction of drug response and adverse reactions for an individual is likely to require the profiling of a large number of genetic variants. However, the interpretation of such complex pharmacogenetic profiles will remain limited by the impact of nongenetic factors including age, diet, comorbidity, and concomitant drug usage. At present, the application and clinical usefulness of pharmacogenetics in the management of IBD remains limited. However, an increasing knowledge of the mechanisms of drug action, the identification of new drug targets, and a growing understanding of the genetic factors that determine drug response bring pharmacogenetics into clinical practice rapidly.[50]

CONCLUSIONS

Recent epidemiologic data strongly suggest that a major contributing factor to IBD is genetic susceptibility. In fact, the greatest risk factor for disease is a positive family history. Through genetic linkage analysis and association studies, several candidate regions of genes have been identified for both UC and CD. Tremendous progress has been made in unraveling the contribution of genetic, microbial, cellular and molecular factors in the pathogenesis of IBD. Important advances toward understanding this process have been the identification of a number of susceptibility genes (CARD15, DLG5, OCTN1 and 2, NOD1, HLA,TLR4) of which the CARD15 gene is undoubtedly replicated most widely and most understood at present. Genetic research in IBD has advanced our understanding of the clinical heterogeneity of the disease and has started to explore the complex interactions between genetic risk factors and environmental risk factors in IBD. The translation of this finding into clinical practice still remains a challenge.

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