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THE GENETIC PREDISPOSITION AND THE INTERPLAY OF HOST GENETICS AND GUT MICROBIOME IN CROHN'S DISEASE

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Abstract

Crohn's disease (CD) is a complex inflammatory bowel disease that results from a combination of genetic predispositions and environmental factors including microbiome in the digestive tract. Extensive genetic studies have identified more than 140 loci predisposing to CD. Many of those CD susceptibility loci encode genes that play essential roles in the regulatory networks of host immune responses. Specifically, several major CD susceptibility genes including *NOD2/CARD15* and *ATG16L1* have been shown to impair biological function with regard to immune response to recognizing and clearance of bacterial infection. Recent human microbiome studies suggest the gut microbiome composition is differentiated in carriers of many risk variants of major CD susceptibility genes, including *NOD2*, *FUT2*, *ATG16L1* and etc. This interplay between host genetics and its associated gut microbiome may play an essential role in the pathogenesis of Crohn's disease. The ongoing microbiome research is aimed to investigate the detailed host genetics-microbiome interacting mechanism.

Keywords

Gut microbiome; Host genetics; Crohn's Disease

HOST GENETICS AND CROHN'S DISEASE

Crohn's disease (CD) is an inflammatory bowel disease (IBD) resulting from defects in the regulatory constraints on mucosal immune response to enteric bacteria, which arises, in genetically predisposed individuals^{1,2}. Common manifestations of CD include inflammation, diarrhea, and weight loss. According to CDC report, CD may affect more than 700,000 individuals in United States along. Geographic statistics showed the incidence and prevalence of CD also increase across time and in other countries around the world,

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indicating its emergence as a global disease^{3–5}. CD has no gender preference and can occur at any age but more prevalent among adolescents and young adults between the ages of 15 and 35⁶. Extensive genetic studies involving linkage analyses, candidate gene studies, and, most recently, genome-wide association (GWA) studies with recently imputation and meta-analyses to combine the power of multiple individual GWAS have identified more than 140 loci predisposing to CD^{1,7,8}. Emerging evidences from network analysis and biological function studies showed many major CD susceptibility loci encode genes involved in cross-talked complex pathways of host immune responses. Jostins et.al⁸ further grouped these genes into several major immunological pathways including:

- Genes involved in T cell circulating, including many specific T cell subsets, such as T-helper cells (TH17 cells) (*STAT3*), memory T cells (*SP110*), and regulatory T cells (*STAT5B*).
- Genes in recognition of microbial-associated molecular patterns, including bacterial or fungi sensors *NOD1*⁹, *CARD9*, *NOD2/CARD15*^{10–17}, and Toll-like receptors (*TLRs*).
- Genes involved in autophagy process, including *IRGM*, encoding an autophagy protein that plays an important role in innate immunity against intracellular pathogens and Crohn's disease-associated AIEC bacteria^{18–20}; *ATG16L1*, a key component of the autophagy complex that processes and kills intracellular microbes^{11,13,17,21}, and *LRRK2*, encoding a complex protein with multiple functional domains, recently found to regulate autophagosome formation through a calcium-dependent pathway²²;
- Genes involved in maintenance of epithelial barrier integrity, including *DLG5*, encoding a member of the family of discs large (DLG) homologs with proposed function in the transmission of extracellular signals to the cytoskeleton and in the maintenance of epithelial cell structure²³; fucosyltransferase 2 (*FUT2*) encoding an enzyme to synthesize the H antigen in body fluids and on the intestinal mucosa. A recent study suggested its role in Crohn's disease pathogenesis by reprogramming the gut microbiome energy metabolism²⁴; and other genes including *BPI*, *DMBT1*, *IBD5*, *ITLN1*, *MUC1*, *MUC19*, *NKX2-3*, *SLC22A5*, *PTGER4*, *XBPI*, *ZNF365*, and etc.⁸.
- Genes in regulation of cytokine production, specifically interferon- γ , interleukin (IL)-12, tumor-necrosis factor- α , IL-10 signaling, *IL17*, *IL18RAP*, *CCR6*, and etc.
- Genes with proposed function in other immunological process.

MICROBIOME AND CROHN'S DISEASE

Although CD has strong genetic predisposition, overall, only ~14% total phenotypic variances of Crohn's disease can be explained by risk loci respectively⁸. Epidemiological studies suggest that environmental factors also are essential contributors to the CD pathogenesis. For instance, smoking has been shown to be a risk factor for Crohn's disease²⁵. Many other environmental factors for IBD, including diet, infectious agents,

medicine, stress and social factors have been investigated. Those environmental factors may act independently or synergistically with genetic factors on the CD pathogenesis.

Recently, more and more studies found that the identity and relative abundance of members of human-associated microbial communities are associated with different states of Crohn's disease^{26,27}. Microbes that live on and inside the human body (microbiota) consist of more than 100 trillion microbial cells and outnumber the quantity of the host cells by a factor of 10:1²⁸. Commensal bacteria provide a wide range of metabolic functions that the human body lacks. They facilitate diverse processes such as digestion, absorption and storage of nutrients, as well as protection against pathogen colonization through competition for nutrients, secretion of antimicrobial substances and microniche exclusion²⁹. Commensal bacteria also promote angiogenesis and development of the intestinal epithelium and have been shown to be essential for the normal development and function of the immune system²⁹. While we know that miniscule inoculations of particular pathogenic strains can cause disease, little is known about whether there are core microbiome profiles that we all share in health and disease^{30–35}. Although more studies on unrelated healthy adults have revealed substantial diversity in their gut communities, the sampling size are often moderate and yet how this diversity is affected by the host genetics or relates to function remains obscure.

Distinctive membership and composition of the gut microbiota have been shown to play a significant role in CD pathogenesis^{32,36,37}. One recent study with 231 IBD and healthy control subjects showed that microbiome profiles are different between CD patients and healthy controls. Particularly, in comparison with the healthy controls, the abundance of *Roseburia*, *Phascolarctobacterium*, *Ruminococcaceae*, and *Faecalibacterium* were reduced and *Clostridium* and *Escherichia/Shigella* were enriched in CD patients³⁸. Interestingly, some differences were only observed in tissue biopsies but not fecal samples. Another recent study on 447 pediatric CD patients and 221 controls showed enrichment in in *Enterobacteriaceae*, *Pasteurellaceae*, *Veillonellaceae*, and *Fusobacteriaceae*, and depletion in *Erysipelotrichales*, *Bacteroidales*, and *Clostridiales*, correlates strongly with disease status³⁹. This microbiome study also suggested that antibiotic exposure might amplify the microbial dysbiosis associated with CD.

EFFECT OF CD-ASSOCIATED HOST GENETICS ON GUT MICROBIOME

Because many CD-associated host genes are related to microbial recognition, response and clearance, it is expected that the variation on those genes may substantially affect the composition or structure of the gut microbiome. Indeed, many studies using host candidate gene deletions in animal models observed associated substantial changes in microbiota. Although few human studies have elucidated the role of host genotype in reshaping the microbiota composition, a recent study on pediatric CD patients demonstrated the co-variations between the host ileal gene expression and the ileal microbiome communities, suggesting a global link between the host genetics and microbiome⁴⁰. Up to date, several major CD susceptibility genes have been reported to modulate the gut microbiome. Those genes are involved in three host immune pathways:

1. Recognition of microbial-associated molecular patterns

NOD2/CARD15 gene is one of the major susceptibility genes for CD^{14,16}. Its gene product detects bacterial peptidoglycan found in both Gram-positive and Gram-negative bacteria and stimulates the host innate immune response. Several animal studies reported that the deficiency of *NOD2* in mice resulted in substantially altered gut microbiome composition^{41–43}. At phylum level, the abundance of both ileal- and fecal-associated *Bacteroidaceae* was significantly increased in *NOD2* deficient mice compared to wild type mice^{41,42,44}. In addition, the overall bacterial loads in the feces and terminal ileum of *NOD2*-deficient mice were significantly elevated⁴². This finding might be partly explained by the fact that *NOD2* regulate the expression of antimicrobial peptide Beta-defensin-2⁴⁵. In addition, the *NOD2* gene expression is inducible by the presence of commensal bacteria⁴¹, suggesting a possible feedback loop in regulating *NOD2* expression.

In consistent with the animal studies, human studies showed that the CD-associated frame-shift *NOD2* variant L1007fsinsC is associated with enhanced mucosal colonization by the *Bacteroidetes* and *Firmicutes*⁴² compared to the healthy controls. Other two human studies combined the three major CD risk alleles of *NOD2* (R702W, G908R, and L1007fsinsC) and confirmed that genotype and disease phenotype are associated with shifts in their intestinal microbial compositions^{46–48}.

However, two recent studies reported that only minimal differences were found in gut microbial composition between co-housed, littermate controlled *NOD2*-deficient and wild-type mice^{49,50}, suggesting that the shifts in bacterial communities were not dependent on genotype but correlated with housing conditions. Although those findings might be partly explained by the restoration of disturbed microbiota due to animal co-housing, more studies are required to fully understand the role of *NOD2* in host-microbe interactions.

Similar to *NOD2/CARD15*, *NOD1/CARD4* also recognizes peptidoglycan found predominantly in Gram-negative bacteria. In contrast to *NOD2*, CD susceptibility related to variants of the *NOD1* gene has been suggested but remains controversial^{51–53}. One animal study showed that recognition of peptidoglycan from the microbiota by *NOD1* not *NOD2* primes systemic innate immunity by enhancing the cytotoxicity of bone-marrow derived neutrophils in response to systemic infection with the bacterial pathogens *Streptococcus pneumoniae* and *Staphylococcus aureus*⁵⁴. However, the interplay between *NOD1* and gut microbiome have not been confirmed in human studies.

2. Autophagy

One of the major CD susceptibility genes, *ATG16L1* encodes a key component of the autophagy machinery to degrade damaged or obsolete organelles and proteins. Functional studies have shown that *ATG16L1* knockdown in IEC lines impairs the clearance of *S. typhimurium* infection⁵⁵. In *ATG16L1* expression suppressed mice, studies have shown that microbial compositions were substantially shifted compared to the wild type controls⁵⁶. In humans, two case-control studies on carriers with CD associated *ATG16L1* risk allele T300A confirmed the significant association between host *ATG16L1* gene and the shift of gut microbiome profile^{47,48}.

3. Maintenance of epithelial barrier integrity

Fucosyltransferase 2 (*FUT2*) is an enzyme that is responsible for the synthesis of the H antigen. The H antigen is an oligosaccharide moiety on the intestinal mucosa that acts as both an attachment site and carbon source for intestinal bacteria. The secretor status determines the expression of the ABH and Lewis histo-blood group antigens in the intestinal mucosa. Non-secretors, who are homozygous for the loss of function nonsense mutation of *FUT2* gene, have shown increased susceptibility to Crohn's disease (CD)⁵⁷. Several human studies found that the host secretor status, encoded by *FUT2*, altered the intestinal microbiota composition^{7,58,59}. *Bifidobacterial* diversity and abundance were significantly reduced in fecal samples from non-secretors compared with those from the secretor individuals⁵⁹. The distinct clustering of the overall intestinal microbiota and significant differences in relative abundances of several dominant taxa including *Clostridium* and *Blautia* were observed between the non-secretors and the secretors as well as between the *FUT2* genotypes⁵⁸. In addition, the non-secretors had lower species richness than the secretors.

Overall, the candidate gene approaches, in which the selected gene is deleted, suppressed or overexpressed in animal model or cell line, have certainly showed the host genetic effect on modulating the structure and diversity of the gut microbiota. In addition, even with moderate sample size, emerging evidences from human studies have confirmed the interaction between host genetics and the gut microbiome, supporting the results from animal studies.

FUTURE PERSPECTIVES

CD is a complex disease result from both genetic predispositions and environmental factors including the gut microbiota. While distinctive membership and composition of the gut microbiota have been shown to play a significant role in CD pathogenesis, due to the sample size, human studies were limited to study only the effect of one or two candidate genes on the gut microbiome of CD patients and unaffected individuals based on the carriage status. Therefore, a large cohort is required to compare the bacterial distribution and abundance in the intestine of the subjects with regard to disease status (CD versus no CD) and global genetic networks containing multiple CD risk loci. The gut microbiota profiles generated from this large cohort can be utilized to develop a predictive model combining both genetic and microbiome signatures to assess the overall risk of CD among individuals. With a better understanding of the microbiome--host gene interplay associated with CD pathogenesis, comprehensive diagnostic tools can be developed to identify individuals at risk of developing CD, as well as develop novel personalized treatments.

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KEY POINTS

1. Association between host genetics and Crohn's disease
2. Association between gut microbiome and Crohn's disease
3. Effect of Crohn's disease -associated host genetics on gut microbiome