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Minireview

The latest breakthrough on genetic characteristics of inflammatory bowel disease in Chinese and other East Asian ancestries

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Abstract

Inflammatory bowel diseases (IBDs) are complex chronic disorders of the gastrointestinal tract with the following two subtypes: Crohn's disease and ulcerative colitis. Disease presentation and progression within and across IBDs, especially Crohn's disease, are highly heterogeneous in the location, severity of inflammation, intestinal stenosis and obstruction, and extraintestinal manifestations. Clinical classifications fail to accurately predict the disease course and response to therapies. To date, most IBD genetic associations are derived from individuals of European ancestries, leading to a limitation of the discovery and application of IBD genetics in the rest of the world populations. In this mini-review, we summarize the latest progress of genome-wide association studies of IBD across global ancestries especially the Chinese population, the similarities and differences in genetic architecture between European and East Asian ancestries, as well as, the clinical significances relevant to IBD genetic study.

Keywords: Chinese population, Crohn's disease, East Asian, inflammatory bowel disease, susceptible gene, ulcerative colitis

Introduction

Inflammatory bowel diseases (IBDs) are a group of chronic non-specific inflammatory diseases in the gastrointestinal tract, mainly including ulcerative colitis (UC) and Crohn's disease (CD). The incidence and prevalence of IBD are increasing globally, particularly in China, while the specific pathogenesis of IBD has not been fully elucidated. A series of studies have demonstrated that IBDs are caused by an abnormal immune response to the intestinal microbiota in genetically susceptible individuals.[1,2] Genome-wide association studies (GWAS) have identified >240 genetic loci associated with human IBD. However, most IBD genetic associations have been derived using individuals from European populations, with only a few studies of much smaller sample sizes in non-European populations.[3,4] In this review, we highlight the latest progress of GWAS of IBD across global ancestries especially in the Chinese population. Moreover, this mini-review also focuses on the similarities and differences in the genetic architecture between European and East Asian ancestries, and the clinical significances relevant to IBD genetic study.

Pathogenesis of IBD

The contemporary view of the pathogenesis of IBD has advanced rapidly, due to recent breakthroughs and emerging applications in human genetics, intestinal mucosal immunology, and microbiome study. A role for genetic risk factors in the development of IBD has been highlighted by the identification of susceptibility loci in GWAS.[3,4] In addition to the genetic contributions to IBD pathophysiology, the mucosal immune system and the commensal microecosystem may also substantially contribute to both the development and progression of IBD. Gut microbes, together with the intestinal epithelial barrier and a variety of immune cells in gut mucosa, form the complex intestinal microecosystem, which does not merely induce immune cell activation and differentiation, but also impacts intestinal homeostasis.[5] Previous studies have shown that certain microbiota-derived antigens and metabolites play a vital role in inducing the differentiation of mucosal $CD4^+$ T cells. Polysaccharides produced by *Bacteroides fragilis* act as a ligand for Toll-like receptor 2 on the surface of $CD4^+$ T cells and participate in type 1 T helper cell (Th1) activation and differentiation.[6] However, some intestinal commensal microbes (e.g. *Clostridium nucleus*, *Peptostreptococcus*) could induce mucosal $CD4^+$ T cells to differentiate into regulatory T cells (Treg). Evidence also suggests that intestinal C-X3-C motif chemokine receptor 1 ($CX3CR1^+$) phagocytic cells enable the balance between Th1 and Treg cell immune responses by the induction of interleukin 10 (IL-10) production through recognizing symbiotic antigens.[7] Further, this process mainly depends on the cellular autophagy related proteins autophagy related 16 like 1 (ATG16L1) and nucleotide binding oligomerization domain containing 2 (NOD2). Consistently, dendritic cells in the intestinal mucosa of patients with ATG16L1 or NOD2 gene deficiency could restrain Treg cell differentiation and IL-10 secretion.[8] Moreover, various environmental factors such as smoking, air pollution, hygiene habits,

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and psychological stress have been identified to be the important factors involved in the development and progression of IBD.[2]

Susceptible variants are associated with human IBD

Pervious twin studies in IBD have provided evidence of a strong genetic contribution, with heritability of liability estimates of 0.75 for CD and 0.67 for UC.[9] More than 240 IBD-related susceptibility loci have been identified by genome-wide sequencing and GWAS, and most of them are co-susceptible to both CD and UC.[1] An analysis of 15 IBD GWAS cohorts from European populations has shown that 110 of the 163 IBD loci are common susceptibility genes of CD and UC, which are related to innate and adaptive immunity, including cytokine signal transduction (e.g. IL-23R, IL-10) and immune signal transduction (e.g. interferon gamma (IFNG), Janus kinase 2 (JAK2) , tumor necrosis factor super family 18 (TNFSF18)).[10] Specific susceptibility genes for CD are mainly concentrated on the IL-23 pathway (e.g. IL-23R, IL-12B, JAK2, and tyrosine kinase 2 (TYK2)). Several common mutations in IL-23R (e.g. Gly149Arg, Val362Ile, and Arg381Gln) have been found to be significantly associated with CD, but these susceptibility loci are ethnically different, especially the mutant Gly149Arg, which is the most common in the Han population.[11] Perianal CD-associated variant rs4151651 in complement factor B (CFB) is a loss-of-function mutation that impairs its cleavage, activation of alternative complement pathway, and pathogen phagocytosis, thus suggesting that targeting the alternative complement pathway may be a novel therapeutic approach in the treatment of perianal CD.[12] In addition, a missense variant in the autophagy gene ATG16L1 (rs2241880, Thr300Ala) is observed to be strongly associated with the incidence of CD. Besides, the T300A variant sensitizes ATG16L1 to caspase-3-mediated degradation, thereby suggesting a functional connection between CD, caspase activation, and autophagy.[13] Consistently, mice lacking the Atg16l1 gene in intestinal epithelial cells have an exacerbated intestinal injury, characterized by crypt epithelial cell death, heightened inflammation, and decreased survival. However, anti-IFN-γ treatment could abrogate epithelial cell death in Atg16l1$^{\Delta IEC}$ mice, suggesting that IFN-γ-targeted therapy may be appropriate for patients with CD with variants in ATG16L1.[14]

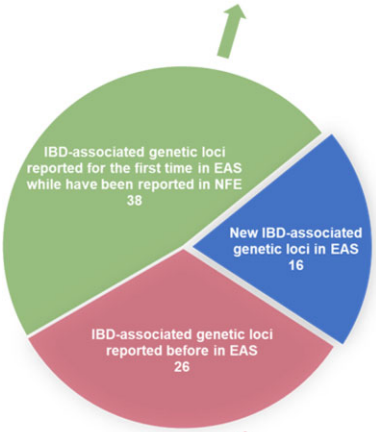
The susceptibility genes of UC are found to be mainly associated with epithelial barrier (e.g. hepatocyte nuclear factor 4 alpha (HNF4A), laminin subunit beta 1 (LAMB1), cadherin 1 (CDH1), and G protein subunit alpha 12 (GNA12)), T cell proliferation and activation (TNFSF14), type I interferon expression (raftlin family member 2 (RFTN2)), and the Toll-like receptor pathway (interferon regulatory factor 5 (IRF5)).[11] Further analysis of major histocompatibility complex (MHC) region variation has pointed out that human leukocyte antigen (HLA) shows the strongest correlation with UC.[15]

Latest progress of genetic study on IBD in Chinese and other East Asian populations

Since most IBD genetic associations have been derived using individuals from European populations, with only a few studies of much smaller sample sizes in non-European populations,[10] this strong bias toward European ancestry severely limits our insight into IBD biology and, further, decreases its application amongst most of the world's population. The first trans-ancestry association study of IBD has identified 38 risk loci, including the identified CD gene autophagy related 4B cysteine peptidase (ATG4B), which reinforces the importance of autophagy in CD pathogenesis. Likewise, the importance of epithelial barrier function in IBD pathogenesis is underscored by oncostatin M receptor (OSMR), which modulates a barrier-protective host response in intestinal inflammation. Moreover, many of the identified genes (e.g. lymphocyte antigen 75 (LY75), CD28, C-C motif chemokine ligand 20 (CCL20), NFKB inhibitor zeta (NFKBIZ), aryl hydrocarbon receptor (AHR), and nuclear factor of activated T cells 1 (NFATC1)) modulate the process of T cell activation and immune response. Five more new susceptibility loci (e.g. SHC adaptor protein 1 (SHC1), chromodomain Y like 2 (CDYL2)) for IBD have been identified in GWAS studies in Koreans.[3,16] Non-HLA region susceptibility genes specific to Asian UC patients have also been identified from samples from Japan and North India, including immunoglobulin receptors Fc gamma receptor IIa (FCGR2A), solute carrier family 26 member 3 (SLC26A3), and protein tyrosine phosphatase receptor type C (PTPRC).[17,18]

Recently, the largest reported IBD genetic study in China and other East Asian countries has been implemented and includes 5088 Chinese IBD patients and 6279 age- and sex-matched healthy donors, together with Korean and Japanese IBD genetic datasets, thus expanding the number of IBD patients from East Asian countries to 14 393, resulting in the largest IBD genetic study in the East Asian population.[19] Most interestingly, this study identified a total of 80 IBD loci in East Asians alone (Fig. 1). Moreover, the study also discovered 81 new genetic loci associated with IBD across both East Asian and European ancestries, thus increasing the number of IBD-associated genetic loci to 320 by comparing 30 713 IBD cases and 338 106 healthy donors from the International IBD Genetics Union and FinnGen.[19] Furthermore, Liu and co-authors compared the conditional effect sizes across East Asian and European ancestries for IBD putative causal variants at the locus level, and found that genetic effects for many IBD loci were consistent in both populations, with only a few loci as clear exceptions (e.g. TNFSF15, colony stimulating factor 2 receptor subunit beta (CSF2RB), and IL23R) (Table 1). Although both East Asian and European ancestries had largely consistent genetic effects in the MHC region, the MHC locus showed evidence of significant heterogeneity of the genetic effect across Chinese, Korean, and Japanese ancestries at the locus level. The observed heterogeneity does not necessarily suggest different biology within East Asian ancestries because the MHC locus is a highly complex locus with long-range linkage disequilibrium that spans several megabases. These data have shown that variances supported by IBD-associated loci differ across East Asian and European ancestries, which are, to a greater degree, driven by minor allele frequencies (MAFs) but less by the effect sizes (32% IBD associations have different MAFs, and 22% have different ORs). CD has a greater ancestral dependency than UC, with NOD2 and ATG16L1 as top CD drivers in European ancestries and TNFSF15 in East Asian ancestries, respectively.[19] Interestingly, ATG16L1 as a classical autophagy-regulating protein has been found to be down-regulated in different types of intestinal and accessory tissues in Chinese CD patients.[20] Another proteomics study provided a comprehensive characterization of the preclinical inflammatory profile by analyzing plasma samples from individuals who developed UC later in life and identified a prediagnostic protein signature consisting of matrix metallopeptidase 10 (MMP10), C-X-C motif chemokine ligand 9 (CXCL9), CCL11, signaling lymphocytic activation molecule family member 1 (SLAMF1), CXCL11, and monocyte chemotactic protein 1 (MCP-1).[21] The high-throughput profiling of multi-omics analysis has found that fibroblast growth factor 19 (FGF19) and zinc finger and

rsID	Subtypes	OR	P-value	Gene*
rs28468423	IBD	1.15	1.44×10^{-8}	CELA3B
rs10493860	UC	0.86	2.15×10^{-8}	TGFBR3
rs147935920	IBD	0.85	3.95×10^{-10}	SPRED2
rs34020101	IBD	0.85	1.76×10^{-17}	IL18RAP
rs142152795	CD	1.43	2.11×10^{-9}	NAB1
rs3769684	IBD	0.89	1.92×10^{-9}	CD28
rs4973341	CD	1.23	3.86×10^{-12}	CCL20
rs13411660	CD	1.17	1.45×10^{-9}	ATG16L1
rs796417	IBD	1.13	3.65×10^{-8}	NFKBIZ
rs6763931	CD	1.18	2.49×10^{-12}	ZBTB38



rsID	Subtypes	OR	P-value	Gene*
rs10903122	CD	0.86	2.84×10^{-11}	RUNX3
rs140466198	CD	1.30	1.05×10^{-8}	PTAFR
rs1317244	CD	1.17	2.65×10^{-8}	CD200
rs4712651	UC	0.83	2.53×10^{-11}	CASC15
rs77992257	IBD	0.83	1.04×10^{-13}	ADAP1
rs28581678	CD	1.22	3.02×10^{-10}	ELMO1
rs117026326	CD	1.37	8.91×10^{-11}	GTF2I
rs438041	CD	1.17	4.10×10^{-8}	DENND3
rs141340254	CD	0.62	4.66×10^{-8}	MPZL2
rs11108429	CD	1.19	7.93×10^{-10}	ELK3

rsID	Subtypes	OR	P-value	Gene*
rs10799591	UC	0.74	4.55×10^{-24}	OTUD3
rs76418789	IBD	0.57	2.03×10^{-34}	IL23R
rs3766920	IBD	1.39	1.15×10^{-13}	SHC1
rs6671847	UC	0.82	3.05×10^{-11}	FCGR2A
rs2953155	IBD	0.80	3.28×10^{-28}	GPR35
rs73243351	IBD	1.27	4.24×10^{-23}	LINC02513
rs56167332	IBD	1.24	2.77×10^{-29}	IL12B
rs9270984	IBD	0.83	1.21×10^{-12}	HLA-DRB1
rs10946198	CD	1.17	1.44×10^{-12}	CEP43
rs10817678	IBD	1.53	5.99×10^{-9}	TNFSF15

Figure 1. IBD-associated genetic loci in Chinese and other East Asian (EAS) populations. There are 80 genetic loci significantly associated with CD, UC, or both in the EAS population ($P < 5 \times 10^{-8}$). Among these 80 genetic loci, 16 genes are new IBD-associated loci, and 26 genes have been identified in the EAS population previously. A total of 54 genes were first reported in the EAS population, while 38 of these 54 loci have been reported in the non-Finnish European (NFE) population previously. The three tables show the most important IBD-associated loci based on the odd ratios (ORs) and *P* values. ORs and *P* values are from the inverse-variance-weighted fixed-effect meta-analysis (two-tailed) including all East Asian samples. ∗Nearest gene to the index variant.

BTB domain containing 16 (ZBTB16) are positively correlated with microbial richness, facilitate a priori determination of optimal therapeutics for patients, and serve as targets for novel therapies.[22] In conclusion, these multi-omics data serve as a blueprint to figure out more variants in different populations and facilitate a priori determination of optimal therapeutics for patients.

Clinical significance of IBD genetic study

Genetic studies allow us to better understand the clinical significance of IBD, including the pathogenesis, disease risk, and classification. Based on a broad array of studies, available evidence has demonstrated that host genetics is associated with IBD development, particularly with disease behaviors, locations, and medical response. A previous study has reported that CD patients could be classified into three phenotypes (ileal, colonic, and ileocolonic lesions) according to three variants (NOD2, MHC, and macrophage stimulating 1 (MST1)).[23] NOD2 has been found to act as a vital risk factor in the pathogenesis of CD, whose mutations are also associated with specific disease phenotypes (e.g. ileocoecal disease, ileocoecal resection, structuring, and perianal disease) in subsequent studies. Therapeutic drug monitoring in patients with a mutation in the NOD2 gene has also shown more frequent tumor necrosis factor (TNF) trough levels in the subtherapeutic range and lower anti-TNF trough levels compared to patients with no mutation in NOD2. In addition, these patients might require higher doses of anti-TNF agents in order to achieve sufficient anti-TNF trough levels.[24] Anti-TNF therapies are the most widely used biologic drugs for treating IBD, but repeated or long-term administration could induce the formation of anti-drug antibodies, thus increasing the risk of treatment failure. In a GWAS of a population of European descent, the variant HLA-DQA1∗05 has been observed to present a 2-fold increased risk of development of antibodies against infliximab and adalimumab in CD patients, regardless of concomitant immunomodulator use. Therefore, testing patients for HLA-DQA1∗05 might help physicians to de-

Table 1. Comparative genetic effect of putative causal variants across East Asian and European populations.

RS_ID	Gene	POP	Phenotype	EUR_AF	EAS_AF	PIP	Effect_cond_EUR	SE_cond_EUR	Effect_cond_EAS	SE_cond_EAS	P_het	Sig_het
rs7556897	CCL20	EAS	CD	0.3429	0.2024	0.409	0.0347	0.0172	1.93E-01	0.0315	1.08E-05	adj.P < 0.05
rs6856616	LINC02513	EAS	CD	0.0596	0.2321	0.874	0.1109	0.0315	2.84E-01	0.0254	1.83E-05	adj.P < 0.05
rs7043505	TNFSF15	EAS	CD	0.4503	0.6895	0.488	0.0310144	0.0271579	4.28E-01	0.0392266	9.28E-17	adj.P < 0.05
rs3812565	CARD9	EUR	CD	0.3549	0.1885	0.81471455	0.178248	0.0163733	4.00E-03	0.0284994	1.15E-07	adj.P < 0.05
rs7915475	AC067752.1	EUR	CD	0.3012	0.1468	0.52844728	-0.105578	0.0182737	0.0274657	0.0374278	0.00140178	adj.P < 0.05
rs11195128	DUSP5	EAS	CD	0.3201	0.1478	0.949	0.113	0.0172	2.82E-01	0.0348	1.39E-05	adj.P < 0.05
rs7307562	LRRK2	EUR	CD	0.393	0.494	0.9999	-0.0813516	0.0165517	0.00591389	0.0227686	0.0019344	adj.P < 0.05
rs9889296	CCL2	EUR	CD	0.3231	0.5496	0.51160938	-0.1523	0.0182	-3.33E-02	0.023	4.96E-05	adj.P < 0.05
rs2427537	ZBTB46	EAS	CD	0.4702	0.0437	0.967	0.0127391	0.0169923	-2.21E-01	0.0552614	5.38E-05	adj.P < 0.05
rs12628495	CSF2RB	EAS	CD	0.0895	0.3393	0.519	-0.0476638	0.0263475	2.51E-01	0.026149	9.03E-16	adj.P < 0.05
rs4655215	RNF186	EUR	UC	0.291	0.47	1	-0.133951	0.0186741	-0.0273661	0.0291071	0.00205579	adj.P < 0.05

The sample sizes used to derive ORs in East Asian and European populations were 22 828 and 40 266 for CD, and 22 318 and 45 975 for UC, respectively. Only non-Finnish European samples were used in the European analysis. Cochran's Q test (two-sided) was used for testing heterogeneity. We chose the number of putative causal variants tested for the correction such as an adjusted (adj.) $P < 0.05$ for CD or UC. EAS, East Asian population; EUR, European population.

cide whether patients should receive anti-TNF and combination immunomodulator therapy.[25] Recent studies identified four nudix hydrolase 15 (NUDT15) coding variants (p.Arg139Cys, p.Arg139His, p.Val18Ile, and p.Val18_Val19insGlyVal) that appear as a loss of nucleotide diphosphatase activity. NUDT15 inactivates thiopurine metabolites and decreases thiopurine cytotoxicity *in vitro*, and patients with defective NUDT15 alleles show excessive levels of thiopurine active metabolites and toxicity. These results indicate that NUDT15 variation plays a determinant part in thiopurine intolerance.[26] Further studies in the Chinese population also confirmed that NUDT15 variants (p.Arg139Cys, p.Val18Ile, and p.Val18_Val19insGlyVal) are risk factors for thiopurine-induced leukopenia. Combined detection of the three variants could increase the predictive sensitivity of thiopurine-induced leukopenia and help to distinguish early leukopenia in heterozygotes.[27] Therefore, NUDT15 variants are recommend to be detected before initiating thiopurine drugs in Chinese patients with IBD. Dose monitoring by NUDT15 variant detection is promising for future individualized therapy. A long duration of IBD may increase the risk in colorectal cancer. Whole-exome sequencing analyses of IBD and colorectal cancer have revealed that IBD-associated tumors have a different mutation spectrum. Several genes are mutated more frequently or uniquely in IBD-associated tumors, such as SRY-box transcription factor 9 (SOX9) and E1A binding protein p300 (EP300), which encode proteins in the wingless-type MMTV integration site (WNT) pathway, indicating an important role for WNT signaling in the development of colorectal tumors in IBD patients.[28] Primary sclerosing cholangitis (PSC) is a highly comorbid phenotype with IBD. Of note, 6 of the 14 loci associated with PSC and IBD display strong evidence of a shared causal variant with UC, CD, or both (MST1, IL21, histone deacetylase 7 (HDAC7), SH2B adaptor protein 3 (SH2B3), CD226, and proteasome assembly chaperone 1 (PSMG1)). Although comorbid gastrointestinal inflammation seen in the majority of PSC patients cannot be fully explained by shared genetic risk, the biliary and intestinal inflammation seen specifically in PSC should be studied to advance our understanding of the disease and improve clinical outcome for patients with this devastating disorder.[29]

Conclusions and perspectives

This mini-review provides a breakthrough in the genetic characteristics of IBD that clarifies genetic variants associated with IBD using the largest samples to date from the East Asian population including Chinese IBD patients. Many new IBD-associated loci discovered from this study are driven by variants with elevated MAF in the East Asian population, which highlights the potential of recruiting global populations in genetics studies to identify new disease associations. This will help us to better understand the pathogenesis and provide potential precision medicine in these emerging regions with high incidence of IBD. Although the data have shed some light on improving the statistical power for the East Asian population compared with European studies, fine-mapping resolution and the ability to compare genetic effects across different ancestries are fairly limited, especially at loci hosting multiple independent associations. Additionally, a comparison of genetic effects can only proceed in variants shared across East Asian and European populations. It is unreliable to evaluate extremely rare putative causal variants for their causal roles in East Asian or European populations. Rapidly expanding omics analytical platforms and techniques represent a paradigm shift in molecular epidemiological research. Advances in multi-omics analysis pave the path for advances in molecular

epidemiology of IBD, which may have important implications for the prediction of IBD onset and preventive strategies. Multi-omics analysis with genes is also needed to screen rare variants in non-European populations, particularly in Chinese IBD patients.

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Conflict of interest

The authors have no conflicts of interest to disclose. In addition, as an Editorial Board Member of *Precision Clinical Medicine*, the corresponding author Zhanju Liu was blinded from reviewing and making decision on this manuscript.

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