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# IBD Associated Genetic Polymorphisms: Novel Insights into the Pathogenic Mechanisms

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There is a dramatic increase in the prevalence of inflammatory bowel disease (IBD), particularly in the western world [1]. The etiology of IBD, which comprises two distinct entities Crohn's disease (CD) and ulcerative colitis (UC), remains unknown. CD is a chronic, discontinuous, transmural inflammation of the bowel, but that can affect any part of gastrointestinal tract whereas, UC represents an intestinal inflammation limited to the colonic mucosa [2].

IBD pathogenesis it is thought to rely on genetic risk factors, environmental triggers (e.g., diet, gut microbiota) and immune response. Population based studies have shown familial aggregation of IBD with greater risk among first-degree relatives. Also, higher monozygotic concordance observed in CD relative to UC is indicative of a larger contribution of the genetic component in CD pathogenesis [3].

As a result of the genome wide association studies (GWAS) and meta–analyses performed, the number of identified common genetic polymorphism that are associated with IBD has continuously increased. These IBD associated genetic risk loci have implicated previously unknown pathogenic pathways. The most recent study on IBD genetics by Jostins et al. reported 163 IBD risk loci, many of which were found to be shared with host response pathways to mycobacterial infection and other immune mediated disorders such as ankylosing spondilitis, psoriasis and type 1 diabetes [4].

Specific mutations of the *NOD2/CARD15* gene, which was the first CD susceptibility gene identified, have been associated with ileal disease and a decrease in alpha-defensins' production [5,6]. *NOD2/CARD15* is a cytoplasmic protein with a role in detection of intracellular bacterial peptidoglycan. *NOD2/CARD15* gene mutations that predispose to ileal involvement in CD can lead to a dysfunction in antimicrobial activity of Paneth cells which are critical to the innate mucosal defense.

Whereas, SNPs of autophagy genes such as *ATG16L1* and *IRGM* have been identified by GWAS to be associated with CD [7,8]. Autophagy is the process of degradation of intracellular components by lysosomes, and plays an important role in nutrient deprivation and infection (i.e., degradation of intracellular pathogens). As CD pathogenesis appears to rely heavily on the immune response to microbiota, a disruption in autophagic killing of intracellular bacteria (important for gut homeostasis), caused by mutations of *ATG16L1* and *IRGM* genes, and consequent changes in gut microbiota can lead to the development of CD.

Furthermore, the association of IBD with SNPs of genes such as *IL-10*, *IL-10R*, *IL-23R* or *IL-18 RAP* has highlighted the role of the immune response and cytokines in IBD pathogenesis [9-12].

On the other hand, UC is specifically associated with the polymorphisms of genes such as *ECM1, CDH1, HNF4a* and *LAMB1*, which are involved in the regulation of gut epithelial barrier, indicating that mechanisms that enhance the permeability of the gut mucosa causing a "leaky gut" are important in UC pathogenesis [13].

Similarly, GWAS results of IBD patient cohorts reported by Kaser et al., showed that common SNPs located in the region of XBP1 gene, are associated with both forms of IBD (CD and UC) [14]. XBP1 encodes for an important transcription factor (TF) in the endoplasmic reticulum (ER) stress response, otherwise known as unfolded protein response (UPR). The *XBP1* protein, encoded by the unconventionally spliced *XBP1* mRNA, is a potent transcription factor that mediates transcription of ER stress target genes such as those involved in protein folding and ER associated degradation (ERAD). In addition, Kaser et al. after performing deep resequencing of the *XBP1* gene region, identified rare or private SNPs present only in IBD patients (and not in controls), and showed that two of these rare variants were hypomorphic.

Concomitant with the increased availability of new sequencing technologies (e.g., next generation sequencing, NGS) the deep resequencing of regions found by GWAS to be associated with the disease can be performed to identify low-frequency SNPs that are more likely to represent functional variants [15]. The modern sequencing technologies combined with the decrease in sequencing costs is now making possible sequencing of whole genomes, exomes or transcriptomes. In addition, reference databases for human DNA variants, such as those provided by the 1000 Genomes Project, are now shaping a new era for human genetics to better understand how genotype influences phenotype [16]. This progress in sequencing technologies will translate in discoveries that will open new avenues for the investigation of the pathogenesis of complex diseases such as IBD.

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### References

1. Van Limbergen J, Wilson DC, Satsangi J (2009) The genetics of Crohn's disease. Annu Rev Genomics Hum Genet 10: 89-116.

2. Bamias G, Nyce MR, De La Rue SA, Cominelli F; American College of Physicians; American Physiological Society (2005) New concepts in the pathophysiology of inflammatory bowel disease. Ann Intern Med 143: 895-904.

3. Brant SR (2013) Promises, delivery, and challenges of inflammatory bowel disease risk gene discovery. Clinical gastroenterology and hepatology. American Gastroenterological Association 11: 22-26.

4. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, et al. (2012) Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491: 119-124.

5. Wehkamp J, Harder J, Weichenthal M, Schwab M, Schäffeler E, et al. (2004)

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NOD2 (CARD15) mutations in Crohn's disease are associated with diminished mucosal alpha-defensin expression. Gut 53: 1658-1664.

6. Hugot JP (2006) CARD15/NOD2 mutations in Crohn's disease. Ann N Y Acad Sci 1072: 9-18.
7. Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, et al. (2007) A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet 39: 207-211.
8. Parkes M, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, et al. (2007) Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. Nat Genet 39: 830-832.
9. Hisamatsu T, Kanai T, Mikami Y, Yoneno K, Matsuoka K, et al. (2013) Immune aspects of the pathogenesis of inflammatory bowel disease. Pharmacol Ther 137: 283-297.
10. Zhernakova A, Festen EM, Franke L, Trynka G, van Diemen CC, et al. (2008) Genetic analysis of innate immunity in Crohn's disease and ulcerative colitis identifies two susceptibility loci harboring CARD9 and IL18RAP. Am J Hum Genet 82: 1202-1210.
11. Glocker EO, Kotlarz D, Klein C, Shah N, Grimbacher B (2011) IL-10 and IL-10 receptor defects in humans. Ann N Y Acad Sci 1246: 102-107.
12. Cho JH, Brant SR (2011) Recent insights into the genetics of inflammatory bowel disease. Gastroenterology 140: 1704-1712.
13. Thompson AI, Lees CW (2011) Genetics of ulcerative colitis. Inflamm Bowel Dis 17: 831-848.
14. Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, et al. (2008) XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. Cell 134: 743-756.
15. Morey M, Fernández-Marmiesse A, Castiñeiras D, Fraga JM, Couce ML, et al. (2013) A glimpse into past, present, and future DNA sequencing. Mol Genet Metab 110: 3-24.
16. 1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD, DePristo MA, et al. (2012) An integrated map of genetic variation from 1,092 human genomes. Nature 491: 56-65.