The Contribution of the Belgian IBD genetics consortium (within the BIRD) to the genetics of Inflammatory bowel disease (IBD).

IBD are complex and heterogeneous inflammatory diseases of the gastrointestinal (GI) tract that result from a dysregulated mucosal immune response towards the intestinal microbial flora in a genetically susceptible host (1-2). High concordance rate in twins and familial aggregation were the first indicators of the genetic component of IBD. Between 1996 and 2004, more than 10 linkage studies and 2 meta-analysis were done in IBD (3).

From these studies, the first and most replicated susceptibility gene identified by positional and candidate approaches was NOD2 (also designed CARD15 or IBD1) (4-5). This gene shed light on the importance of bacterial recognition in the triggering of the disease. NOD2 is expressed in macrophages, dendritic cells, intestinal epithelial cells and Paneth cells. Muramyl dipeptide (MDP) in the bacterial peptidoglycan is recognized by the leucine repeat repeat (LRR) domain of NOD2 and leads to the activation of NFκB trough a receptor -interacting serine-threonine kinase-2 (RIPK2)-dependent signaling pathways. Homozygotes individuals carriers of one of the three common identified variants of NOD2 can have until a 40-fold increased likelihood of developing ileal Crohn's disease (CD) (6). Beside the discovery of NOD2 gene, the data generated from linkage studies were very disappointing. The IBD community had to wait until 2006 with the venue and development of the Genome Wide Array Screening (GWAS) thanks to the SNP Consortium, Human Genome Project and the HAPMAP project allowed to obtain more insight in the understanding of the genetic architecture of IBD. In total, 15 GWAS were done by different groups implicated in IBD.

The Belgian GWAS led by Michel Georges (GIGA, ULG, Liège, Belgium) funded by the Region Wallonnie was one of the first three GWAS published in the world with the GWAS from the Welcome Trust (Cambridge, UK) and the NIDDK (Washington DC, USA and CANADA). The Belgian GWAS was possible thanks to the great enthusiasm of 4 groups within the Belgian IBD genetic consortium: The University of Liège (CHU Sart Tilman, ULG, with Edouard Louis, Michel George and Emilie theatre), the Catholic University of Leuven (Gastuisberg Ziekenhuis, KUL, with Séverine Vermeire, Isabelle Cleynen and Paul Rutgeerts), the University of Gent (UZ Gent, with Martine De Vos and Debby Laukens), and the Free University of Brussels (Erasme Hospital, ULB, with Denis Franchimont, Andre Van Gossum and Leila Amininejad). This group discovered PTGER4 as a susceptibility gene for IBD (7) and actively contributed to the collaborative effort of the international IBD Genetic consortium (IIBDGC) to realize 2 meta-analyses in 2008 and 2010 allowing the discovery of an additional set of 99 IBD susceptibility loci with 71 CD and 47 Ulcerative colitis (UC) loci, accounting for 23% and 16% of disease heritability respectively (8-9). These genetic loci herald several pathways that are critical to intestinal homeostasis which may be altered and lead to the development of IBD; these include intestinal barrier function, epithelial restitution, microbial defense, innate immune regulation, reactive oxygen species (ROS) generation, autophagy, adaptive immune regulation, endoplasmic reticulum (ER) stress and metabolic pathways associated with cellular homeostasis (10).
Based on these findings, the IIBDGC, with collaboration of dozen research groups including the Belgian IBD genetic consortium, started in 2010 the Immunochip project with a custom-designed genotyping array containing high-density genomic coverage of SNP implicated by GWAS in IBD to fine map disease loci and implicate new genes. In combination with imputed GWAS data, Immunochip validation studies on over 25,000 IBD cases identified 71 new loci for a total of 163 loci associated with IBD, increasing the estimated disease heritability for both CD and UC.

These results also highlighted 110 shared loci for both disease subtypes, while 30 are classified as specific for CD and 23 for UC. IBD shares the largest number of loci with type I diabetes, ankylosing spondylitis, psoriasis and susceptibility to mycobacterial infection. Such overlap in the genetic susceptibility of autoimmune and autoinflammatory diseases point to several common immune processes, such as regulation of mucosal immunity, in the mediation of inflammatory pathology (11-12). Further studies will now focus not just on searching and identifying all the (new) susceptibility genes within the reported associated IBD loci, and turning these genetic findings into the biological and clinical understanding of the disease. This will ultimately allow the discovery of new pharmaceutical targets for our IBD patients.

References:


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