Inflammatory Bowel Diseases: the genetic revolution

Maladies inflammatoires intestinales : la révolution génétique

C. Jung\textsuperscript{a,b,c}, J.-P. Hugot\textsuperscript{a,b,c,*}

\textsuperscript{a} Hopital Robert Debré, Service de gastroentérologie et nutrition pédiatriques, 48, boulevard Séurier, 75019 Paris, France
\textsuperscript{b} INSERM U843, 
\textsuperscript{c} Université Paris Diderot UMR843.

Summary
The genetic component of Inflammatory Bowel Diseases is among the best known for complex genetic disorders. If the functional candidate gene approach was rarely fruitful in the past, genome-wide scans allowed finding several susceptibility genes for Crohn disease including NOD2, IL23R, ATG16L1, IRGM, TNFSF15, a region close to PTGER4, PTPN2, PTPN22, NKX2-3 and many others. Only one gene, ECM1, has been reported for ulcerative colitis alone. We now need to further explore these new genes before to understand their biological role. However they clearly demonstrate the importance of innate immunity and autophagy for Crohn’s disease and of the TH-17 differentiation for ulcerative colitis, Crohn’s disease and other inflammatory disorders.

© 2009 Elsevier Masson SAS. All rights reserved.

Résumé
Parmi les maladies génétiques complexes, les maladies inflammatoires chroniques intestinales font partie des mieux connues actuellement. Des études explorant l’ensemble du génome ont en effet permis d’identifier plusieurs gènes de susceptibilité, dont NOD2, IL23R, ATG16L1, IRGM, TNFSF15, une région proche du gène PTGER4, PTPN2, PTPN22, NKX2-3 et many others. Only one gene, ECM1, has been reported for ulcerative colitis alone. We now need to further explore these new genes before to understand their biological role. However they clearly demonstrate the importance of innate immunity and autophagy for Crohn’s disease and of the TH-17 differentiation for ulcerative colitis, Crohn’s disease and other inflammatory disorders.

© 2009 Elsevier Masson SAS. Tous droits réservés.

* Corresponding author:
E-mail address: jean-pierre.hugot@rdb.aphp.fr (J.-P. Hugot).

© 2009 Elsevier Masson SAS. Tous droits réservés.
The successes reported in the genetic dissection of Crohn’s disease (CD) and ulcerative colitis (UC) make these complex genetic disorders among the most popular for geneticists. Indeed, research on inflammatory bowel diseases (IBD) allowed demonstrating the feasibility of positional cloning in complex genetic diseases [1]. It contributed to the definition of the haplotype blocks and subsequently to the development of the large international Hapmap project [2]. Finally, genome-wide association studies (GWAS), when applied to IBD, were shown to be among the most efficient tools for gene discovery [3].

This review will mainly focus on the recent important advances on the genetics of IBD obtained by GWAS.

**Historical perspective**

A genetic component for IBD has been suspected since the initial description of familial CD by BB Crohn in 1934. Findings derived from the clinical observation of IBD families were reported from the 50’s to the 90’s. They are summarised in box 1. They indicate that IBD are complex genetic disorders where both environmental and genetic factors play an important role. The genetic component is supposed to be more important for CD than for UC and it is expected to be shared, at least in part, by both diseases. Finally, the genetic predisposition to IBD is certainly complex with no single susceptibility gene for one patient, one phenotype or one ethnic group.

When the genetic predisposition to IBD was firmly established and when sequencing and genotyping methods became more popular (since the 80’s), researchers explored their best candidate genes derived from their understanding of disease mechanisms. Many genes have been studied which are summarised in Table 1. Among them, the most studied genes are the HLA genes and the genes located in the major histocompatibility complex (MHC), multidrug resistance 1 (MDR1), Toll Like Receptor 4 (TLR4), Nucleotide Oligomerisation Domain 1 (NOD1) and more recently the myosin IXb (MYO9B) (4) and interferon regulatory factor 5 (IRF5) [5]. Unfortunately and despite a large amount of work, very few of these genes have obtained the label of true susceptibility genes with time. Indeed, except for genes in the major histocompatibility complex including TNFα and HLA genes (most consistent reported associations: HLA-DRB1*0103 with UC and colonic CD) [6, 7], few associations were substanciated by several replication studies.

In the 90’s, genome-wide scan approaches were applied to IBD, taking advantage of the newly developed genome maps. About 10 areas in the genome were suspected to contain IBD susceptibility genes (Figure 1A). Further studies allowed identifying the first CD susceptibility genes: Nucleotide Oligomerisation Domain 2 (NOD2) [8] and likely SLC22A4/5 (coding for Organic Cathionic Transporters OCTN1/2) [9, 10]. These discoveries were important because they confirmed that IBD are genetic disorders and because they dealt for the first time with the initial causality in IBD. They also indicated that there is no gene able to explain a large proportion of the heritability but that IBD have to be seen as the result of the interaction of numerous genes at both the individual and populational levels. As an example, NOD2 (the strongest associated gene) does not represent more than 20% of the overall population attributable fraction.

If the first genome-scans were fruitful, it is however to note that only a limited number of genes localized through the classic positional cloning approach were finally identified. Failures are related to the well known lack of power of linkage analyses performed on IBD families. As a result, linkage analyses have identified only the genes with the largest effects, failing to detect the many susceptibility genes with a minor effect (see below). This is especially true for detecting alleles common in the general population (while at the opposite GWAS may miss rare risk alleles). This may explain retrospectively why the IBD1 (NOD2) (and perhaps IBD2) loci were localized first: they correspond to the genes with the lowest risk allele frequencies reported in the GWAS. At the opposite, IL23R which has one of the strongest effects but a very high risk allele frequency was undetectable by linkage studies.

Very recently, our increasing knowledge on the Human genome sequences, the definition and the organisation of the Human genetic polymorphisms in haplotype blocks and the development of micro-array technologies provided new tools able to perform case-control association studies at the scale of the genome [11]. The number of tested single nucleotide polymorphisms (SNPs) for exploring the full genome in populations of European ancestry has been estimated between 500,000 and 1,000,000. Genotyping platforms are
Table 1 Functional candidate IBD susceptibility genes proposed in the literature. 

<table>
<thead>
<tr>
<th>Genes with reported positive associations</th>
<th>Genes without reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA Class II</td>
<td>IL2</td>
</tr>
<tr>
<td>TNFα</td>
<td>IL4</td>
</tr>
<tr>
<td>IL1/IL1ra</td>
<td>IL10</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Interferon γ</td>
</tr>
<tr>
<td>Vitamine D Receptor</td>
<td>Mucins</td>
</tr>
<tr>
<td>CCR5</td>
<td>hMLH1</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>TCR</td>
</tr>
<tr>
<td>MDR1</td>
<td>Motilin</td>
</tr>
<tr>
<td>TNFR1/TNFR2</td>
<td>TAP1/TAP2</td>
</tr>
<tr>
<td>NOD1</td>
<td>Complement</td>
</tr>
<tr>
<td>TLR4</td>
<td>TLR2</td>
</tr>
<tr>
<td>NF-κB1</td>
<td>PTPN22</td>
</tr>
<tr>
<td>PPARγ</td>
<td>FOXP</td>
</tr>
<tr>
<td>Stromelysin 1</td>
<td></td>
</tr>
<tr>
<td>CD14</td>
<td></td>
</tr>
<tr>
<td>IL18</td>
<td></td>
</tr>
<tr>
<td>MYO9B</td>
<td></td>
</tr>
<tr>
<td>IRF5</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 Schematic representation of the IBD genes (in black) or loci (in red) localized by a classic positional cloning approach (A) or genome-wide association studies (B). Each blue bar represents one Human chromosome (from 1 to X).

Table 1 Functional candidate IBD susceptibility genes proposed in the literature. Gènes proposés dans la littérature comme gènes de susceptibilité potentiels dans les MICI, du fait de leurs fonctions biologiques.

Considering the average informativity of each SNP and the multistest correction required for a genome-wide approach, several thousands of patients and healthy controls are ideally required. As a result, genetic studies are now under the responsibility of very large international consortia able to include thousands of patients and to analyse several billions of genotypes on high-tech plateforms. Despite of this enormous amount of work, GWAS were proved to be feasible and powerful for identifying new susceptibility genes [11]. As a result, more than 100 susceptibility genes have been recognised for many traits including autoimmune diseases, diabetes type 2, cancer, height, hair color, body mass index, celiac disease, etc. (for more information see: http://www.genome.gov/26525384).

For IBD, since 2005, seven GWAS performed for CD allowed discovering more than 10 susceptibility genes in Caucasian populations [12-18]. Only one GWAS was performed for UC providing the first specific UC susceptibility gene [6]. The mostly replicated genes or regions playing a role in CD and UC predisposition are indicated in table 2. Recently a meta-analysis has combined the results of several different GWAS, including more than 8,000 cases and controls [3]. Twenty supplementary genes have been identified (Figure 1B, Table 2) and several more are expected to be discovered in the next months or years.

IBD associated variants

NOD2/CARD15/NLRC2 was the first described CD gene. The association between NOD2 mutations and CD has been replicated many times in populations from European ancestry while NOD2 mutations appear to be rare in Asian or African people [19]. In addition to more than 30 private mutations observed in only few patients, three mutations are frequently found associated with CD: R702W, G9068R...
and 1007fs. The odds ratio (OR) of CD are respectively 2, 3 and 4.5 for the heterozygotes and 3, 12 and 35 for the homozygotes [20]. There is thus a dosage effect for NOD2 mutations associated with CD. NOD2 mutations are mainly associated with CD in case of ileal lesions. They are also associated with fistulising/stenosing phenotypes. They have no role in UC.

The major allele of the Arg381Trp variant of the interleukin 23 receptor (IL23R) has a frequency of 0.93 in the general population [13]. Its frequency in CD patients is even higher.

<table>
<thead>
<tr>
<th>Chr</th>
<th>Gene of interest</th>
<th>Causal genetic variant</th>
<th>RAF</th>
<th>OR*</th>
<th>UC</th>
<th>Gene function</th>
</tr>
</thead>
<tbody>
<tr>
<td>16q12</td>
<td>NOD2</td>
<td>R702W, G908R, 1007fs</td>
<td>0.01/0.04</td>
<td>4</td>
<td>No</td>
<td>Innate immunity</td>
</tr>
<tr>
<td>1p31</td>
<td>IL23R</td>
<td>known: A381T</td>
<td>0.933</td>
<td>2.5</td>
<td>Yes</td>
<td>TH-17 differentiation</td>
</tr>
<tr>
<td>2q37</td>
<td>ATG16L1</td>
<td>known: A197T</td>
<td>0.533</td>
<td>1.28</td>
<td>No</td>
<td>Autophagy</td>
</tr>
<tr>
<td>9q32</td>
<td>TNFSF15</td>
<td>uk</td>
<td>0.677</td>
<td>1.22</td>
<td>?</td>
<td>Inflammation</td>
</tr>
<tr>
<td>5q33</td>
<td>IRGM?</td>
<td>uk: Flanking region</td>
<td>0.09</td>
<td>1.33</td>
<td>No</td>
<td>Autophagy</td>
</tr>
<tr>
<td>5p13</td>
<td>PTGER4?</td>
<td>uk: Gene desert region</td>
<td>0.125</td>
<td>1.32</td>
<td>No</td>
<td>Inflammation</td>
</tr>
<tr>
<td>18p11</td>
<td>PTPN2</td>
<td>uk: Flanking region</td>
<td>0.152</td>
<td>1.35</td>
<td>No</td>
<td>Autoimmunity</td>
</tr>
<tr>
<td>10q21</td>
<td>ZNF365?</td>
<td>uk</td>
<td>0.387</td>
<td>1.25</td>
<td>Yes</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>5q31</td>
<td>SLC22A4/5?</td>
<td>uk: several SNPs are putative candidates</td>
<td>0.425</td>
<td>1.25</td>
<td>No</td>
<td>Carnitin/Xenobiotic transporter</td>
</tr>
<tr>
<td>6p21</td>
<td>MHC?</td>
<td>uk: large region DRB1*0103</td>
<td>0.188</td>
<td>1.19</td>
<td>Yes</td>
<td>Immunity</td>
</tr>
<tr>
<td>10q24</td>
<td>NKX2-3</td>
<td>uk: Upstream the gene</td>
<td>0.478</td>
<td>1.20</td>
<td>Yes</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>3p21</td>
<td>MST1?</td>
<td>R689C?</td>
<td>0.271</td>
<td>1.20</td>
<td>Yes</td>
<td>TH-17 differentiation</td>
</tr>
</tbody>
</table>

**Table 2** Inflammatory Bowel Disease susceptibility genes revealed by genome-wide scans. Gènes de susceptibilité aux maladies inflammatoires chroniques intestinales identifiés par les criblages systématiques du génome.

Chr: chromosome. RAF: Risk Allele Frequency in the general population. UK: Ulcerative Colitis.
and 1.4 (Table 2). Most of these variants are considered to be associated with IBD. However, the contribution of IL23R and UC has also been reported. The region around IL23R may also play a role but they need to be further characterized before concluding. An association between IL23R and UC has also been reported.

Many additional genes or genetic regions have been reported to be associated with IBD. However, the contribution of these variants is modest with odds ratio varying between 1.1 and 1.4 (Table 2). Most of these variants are confirmed by replication studies but their recent discovery did not always allow multiple replications for both phenotypes (UC and CD). Finally, several associated SNPs are likely tags of the true causal variant which remains to be identified.

British, German and US consortiums reported near simultaneously an association between CD and the Autophagy-Related 16-like 1 (ATG16L1) gene [16-18]. The best signal was found for the non conservative variant (Thr300Ala). The mutation occurs in a functional domain of the protein but its functional impact is not still understood. Indeed, the CD risk allele is the most frequent one (frequency of 0.53 in the general population and 0.60 in CD patients). There is no reported dosage effect for this allele. No association was found between ATG16L1 and UC.

The Tumour Necrosis Factor (ligand) SuperFamily member 15 (TNFSF15) was the first discovered gene through a GWAS. It was found in 2005 by Yamazaki et al. in a Japanese population [12]. Several haplotypes are associated with CD but the causal variant is still unknown. Despite of large ethnic differences in SNP allele frequencies, the initial result was further replicated in populations of European ancestry [21, 22 and personal data]. The association with UC remains to be clarified.

An association between CD and the Immunity related GTPase Family M (IRGM) has been reported by the Welcome trust consortium [15]. The rare allele of a polymorphism flanking the gene was found associated with CD but not UC. Its functional impact is not yet known.

The region on chromosome 5q31 has been found through a positional cloning approach [9]. The association has been well replicated by many groups. The main candidate genes are SLC22A4/5 coding for OCTN1/2 which are involved in the transport of xenobiotics and carnitine [10]. However, the associated region encompasses several genes and it is today difficult to formally retain these two genes. It is unclear if the gene is also a UC susceptibility gene.

HLA class II locus has been previously implicated in CD and in UC. The hotspot association is also clear on the positional cloning approaches and in the recent meta-analysis of the GWAS. Nevertheless, the associated region remains large and contains many polymorphisms in strong linkage disequilibrium with each others making difficult to identify the causal variants.

A Belgian-French consortium identified a genetic region on chromosome 5p13.1 in a gene desert [14]. The region is flanked by numerous genes including prostaglandin receptor EP4 (PTGER4), CARD6 and complemental factors C6, C7 and C9. Libioulle et al. have shown variations in PTGER4 mRNA level expression for several alleles suggesting PTGER4 as the best candidate gene [14]. The initial association was further replicated but the causal variation is still undefined. Nine other gene deserts regions have been identified through GWAS or the meta-analysis on 1q24, 1q32, 5q31, 6q21, 7p12, 8q24, 10p11, 13q14, 21q21 [3].

The only GWAS performed for UC pointed out the extra-cellular matrix protein 1 (ECM1) gene [6]. ECM1 is expressed in small and large intestine and it is able to inhibit the matrix metalloproteinase 9 and to activate NF-kB signaling. Other GWAS including a higher number of UC patients and more SNPs are now expected to confirm these results and to provide additional UC susceptibility genes.

**Biological implications**

NOD2 is a gene coding for an intracellular protein which can be activated by muropeptides, which are components derived from the peptidoglycan of the bacterial cell wall [23-25]. Under activation, NOD2 induces activation of the transcription nuclear factor, NF-kB and production of pro-inflammatory cytokines. The effect of NOD2 seems to depend on the network of other signaling molecules. For example, NOD2 is able to activate or inhibit the NF-kB pathway depending on the presence of co-activators like TLRs [26].

NOD2 knock out mice have no spontaneous clinical symptoms. However, NOD2 deficiency is associated with an increased number of Peyer’s patches which are characterized by an increased number of CD4+ T-cells producing IFNγ and TNFα, increased macromolecules and bacterial passages and finally an increased response to TNBS [27]. NOD2 invalidated mice are more susceptible to oral *Listeria monocytogenes* and *Salmonella typhimurium* infection but more resistant to oral *Yersinia pseudotuberculosis* infection [28].

The identification of NOD2 as a CD predisposing gene has thus confirmed that the disease is related with an abnormal response to bacterial components of the digestive tract. However, the exact molecular mechanisms and the bacterial agents causing CD are still unknown.

The implication of several autophagy genes (ATG16L1, IRGM and putatively LRRK2) in CD has recently focused on this biological function. Autophagy is a catabolic process by which the cell is able to recycle its damaged organelles via the lysosomal machinery. However, autophagy also plays a role in bacterial defense against intracellular bacteria and antigen presentation by phagocytic cells. A defect of ATG16L1 function has been associated with a defect of autophagy of *Salmonella typhimurium* [17] while IRGM deficient cells have an impaired response toward intracellular *Toxoplasma gondii*, *Listeria monocytogenes* and *Mycobacterium tuberculosis* [29].

It is tenting to postulate that a defect of autophagy function is a causal mechanism for CD. However, we do not know today the effects of the CD associated mutations. As an example, the allele of ATG16L1 associated with the risk of disease is the most common one and its functional effect has not yet been explored. The exact consequences of the single nucleotide polymorphisms (SNPs) associated with CD in the IRGM gene are also unknown. LRRK2 mutations associated with Parkinson disease are associated with an increased rate of autophagy [30]. As a result, it is too early to conclude that CD is associated with a defect of autophagy functions.

Whatever the role of the SNPs associated with CD in autophagy, by pointing out this pathway, genetic studies indicate that the clearance of intracellular bacteria may
be important for CD. The relationship between CD and invasive bacteria is a long story and several bacteria have been proposed as candidates for driving the gut inflammation without definitive conclusion. However, it is possible that the newly described polymorphisms associated with CD will provide the opportunity to test their role against these candidate bacteria. Interestingly, if the genes involved in intracellular bacterial recognition and clearance have a crucial role in CD, they do not seem to play any role in UC while the genes involved in TH-17 differentiation predispose to both disorders.

Nearby the first line host defense, implication of Arg381Glu IL23R variant and other genes of the IL23R pathway - IL-12B, CCR6, JAK2, STAT3 - in IBD confirm the role of the adaptative immune system [3]. IL23R gene codes for a protein specifically expressed on the surface of TH-17 lineage of CD4+ T cells. IL-23 cytokine is mainly produced by activated macrophages and dendritic cells and is able to activate TH-17 cells promoting the pro-inflammatory cascade via IL-17 production. Indeed, affected gut areas of CD patients present an increased number of CD4+ T-cells producing IL-17 compared to healthy gut areas [31]. Antibodies blocking the p19 subunit of IL-23 ameliorate the spontaneous colitis in IL-10 deficient mice [32] and an experimental study has identified a cross-talk between IL-12 and IL-23 cytokines during T cell dependant colitis [33]. Moreover, several authors suggested interactions between IL-23 and pattern recognition receptors such as TLRs or NODs [34-36].

Several other CD-associated variants are implicated in inflammation in general: TNFSF15 codes for a cytokine induced by TNFα and able to activate NF-κB; PTPN2, negatively regulates the inflammatory response; NKK2-3 has a role in the localization of adaptive immune cells; PHOX2B is involved in regulating the formation and maintenance of autonomic ganglia; IRF5 upregulates interferon production during viral infection; MST1 (Macrophage stimulating 1) encodes for mst1 protein reported to play an important role as a caspase effector that contributes to apoptosis [37]; ICOSLG is involved in T-cell differentiation after dendritic cell contact; etc. All these genes contribute to give new molecular targets for functional studies.

**Further researches**

The GWAS have pointed out a set of genes that now need further work to translate a statistical association in terms of biological findings in the next months or years. This task will include defining the causal genetic variants and their biological impact on *in vitro* and *in vivo* models. The knowledge of the true causal variant will also allow better calculating its genetic impact in terms of associated relative risk, population attributable fraction, penetrances and finally gene-gene interactions.

Because there is no way to prevent the disease, the impact of genetic markers on pre-symptomatic screening is limited. In addition, the impact of each susceptibility gene (including NOD2) is too small to provide efficient information in clinical practice. Even taking into account all the 32 reported genetic markers, no more than 10% of the total variance is explained [3]. This estimate is likely underscored in the absence of definition of the true causal genetic variants but it raises some doubts that genetic studies will define an individual disease risk with enough confidence to be clinically relevant.

An important aim of genetic studies is to establish genotype-phenotype correlations and thus to help clinicians to predict disease outcomes including risk for complications and response/intolerance to therapies. NOD2 variants are associated with a younger age of onset, the presence of ileal lesions, and a trend toward developing intestinal complications [38]. No disease sub-phenotype has been associated with IL23R [39]. Little is known for most of the other genes even if initial reports do not argue for a strong relationship between genes and sub-phenotypes. Thus additional studies are required before to conclude on the impact of genotyping in clinical practice.

Because the contribution of each disease susceptibility marker is modest it is not expected that a predisposing marker would be sufficient to define alone a sub-phenotype and studies combining several susceptibility variants will be required to provide predictive factors of disease course and therapies. Considering the quantity of reported genetic markers, a huge number of patients will be required to explore this question.

Overlaps between IBD and others immune complex disorders are suggested by frequent coexistence of associated auto-immune diseases like spondyloarthopathies. A common background between these disorders begins to be confirmed by genetics data. The TH-17 pathway is implicated not only in UC and CD but also in psoriasis [40] and ankylosing spondylarththritis (AS) [41]. IRF5 is associated with systemic lupus erythematosus (SLE) [42] and rheumatoid arthritis (RA) [43]; PTPN2 is associated with diabetes type I (T1D) [44]. PTPN22 is associated with CD, T1D, SLE and thyroiditis [45]. However, the allele predisposing to CD is the opposite of the allele predisposing to T1D and RA. CD and Type 2 Diabetes (T2D) are both associated with CDKAL1 but not with the same allele [46]. The CD associated allele of ORMDL3 is also associated with asthma [47]. A specific mutation of LRRK2 is associated with Parkinson’s disease. MYO9B, IL12 and IL18 seem to play a role in both CD and celiac disease [48]. Finally NOD2 is also involved in Graft Versus Host Disease (GVHD) [49] and Blau syndrome (a auto-inflammatory disorder) [50]. GWAS for immune or inflammatory disorders thus provide related findings which highlight the classic clinical observations or provide new links to explore.

**Conclusion**

The dissection of complex genetic disorders is a challenge of this decade. The recent advances in genome annotation and micro-array technologies have provided the tools to answer the question and IBD appears as a successful example of such an approach.

Interestingly, the genetics of IBD has really emerged with the genome-wide, hypothesis-free methods. In other words, the mechanisms of the disease seem to be too complex to easily provide relevant candidate genes. This observation may be explained by the fact that the impaired function responsible of the disease is under the dependency of many genetic and environmental factors. Complex genetic traits are thus traits affecting functions with complex regulations
and, somewhere, their dissection consists in the description of a complex network of functionally linked genes. The recent discovery of more than 32 IBD genes illustrates this opinion.

The newly identified IBD genes represent only the emerged part of the iceberg. As indicated above, the 32 susceptibility genes do not explain all the expected genetic variance and additional signals in the genome are under exploration. In addition, it is to note that the reported GWAS may have failed to detect genes with rare risk alleles. As a result, more than 50 IBD genes are expected and may be much more.

By consequence, the definition of a susceptibility gene for a complex genetic trait may be questionable. From the functional point of view, many disease associated alleles are not well characterized. Sometimes, they are even located in desert gene regions. It is thus difficult to understand how they may contribute to the trait and sometimes their role could be very subtle. The lack of gene-gene interaction usually reported does not allow classifying genes in subgroups defining more specific functions. Considering that the susceptibility genes are involved in a network modulating the impaired function, the design of experiments able to describe the subtle functional effect of a specific gene may be very complex due to the large number of inter-related parameters to control. Finally and as mentioned above, the clinical definition of a susceptibility gene may be difficult considering the low individual risk associated to the disease allele (most often ORs are below 1.3).

Despite of the genetic complexity of the traits and the limits of the genome-wide approach, the impact of the recent genetic studies on the understanding of the complex disease mechanisms is very high. Genetic analyses clearly demonstrate the importance of the TH-17 pathway in IBD (and other inflammatory disorders) and the role of recognition/clearance of intracellular bacteria in CD. These discoveries give the opportunity to develop new drugs (by modulating the IL23 pathway for example). They also provide the opportunity to explore which bacteria in our environment have a role in CD. This may help to develop preventive actions in the future.

Conflict of interest:

Jean-Pierre Hugot and Camille Jung have no conflict of interest.

References


[23] Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R,


