Dissecting the genetics of Inflammatory Bowel Disease

Heather Elding

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I, Heather Elding confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
Abstract

Inflammatory Bowel Disease (IBD) can be classified into two main subtypes: Crohn’s Disease (CD) and Ulcerative Colitis (UC). The aim of this study is to identify the genetic contribution to the susceptibility to IBD. In the first part of the study, I focused on Crohn’s Disease, the subtype that shows the greatest heritability. Using both pooled and sub-phenotype data, followed by replication, the results reveal substantial genetic heterogeneity and the total number of confirmed CD susceptibility loci was increased from 71 published by others to 200. This was achieved by analyzing the data using a multi-marker approach and high-resolution genetic maps in Linkage Disequilibrium Units. In the second part of the study, I focused on Ulcerative Colitis. The results show that although UC has a lower reported heritability, many loci were also found for Ulcerative Colitis. Some of these overlap with those found for Crohn’s Disease.
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I would firstly like to thank my primary Ph.D supervisor Dr. Nikolas Maniatis for providing me with this opportunity and for his expert guidance and significant support throughout my time at UCL. Dr. Nikolas Maniatis’s challenging ideas, creativity, and moral support have greatly helped me in shaping my thoughts as a researcher and for successfully carrying out my PhD research. I would also deeply like to thank my secondary Ph.D supervisor Professor Dallas M. Swallow for her invaluable and exemplary scientific expertise and constant support throughout my Ph.D. Professor Dallas M. Swallow has been, and will be, a great inspiration on both a professional and personal level and I have learnt a lot and made significant progress under her supervision, both as a scientist and as an individual. I would also like to thank Dr. Winston Lau for his patience at always taking time to teach me the novel skills and tools that were crucial for carrying out my Ph.D and for always being there to answer my questions.

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CHAPTER I. GENERAL INTRODUCTION

I. INFLAMMATORY BOWEL DISEASE: THE STORY OF TWO DISEASES.

Inflammatory Bowel Disease (IBD) is an immunologically mediated relapsing inflammatory condition of unknown causes. IBD can be subdivided into two sub-types: Crohn’s Disease (CD) and Ulcerative Colitis (UC), as illustrated in Table 1. In the second half of the twentieth century, the incidence of IBD has been on the increase in the developed western world (Sartor, 2006). This suggests the presence of a strong environmental contribution to the aetiology of IBD. Therefore, why study the genetics of IBD? Evidence for a genetic contribution comes from increased concordance in Monozygotic twins (MZ) (~50% for CD and ~10% for UC) in comparison with Dizygotic twins (DZ). Although the MZ concordance is not 100% as would be expected for a Mendelian disease, there is a five-fold or greater increased risk of IBD in first-degree relatives with either disease than in the general public (Xavier and Podolsky, 2007), which substantiates the fact that there is a significant genetic contribution towards the development of IBD. Thus, the findings on families (Ohmen et al., 1996) also point to the idea that some genes will be
phenotype-specific, while some overlap in susceptibility loci is to be expected between the two sub-types (Giallourakis et al., 2003; Parkes et al., 2000).

Although both types of IBD involve chronic intestinal inflammation, they differ from each other in several genetic and phenotypic respects, including cytokine profiles and intestinal location of disease manifestation. CD primarily affects the ileal region of the intestine in a transmural (penetrating all layers) fashion. However, CD is also characterized by segmental inflammation (segments of the intestine affected) as well as extra-intestinal manifestation. Unlike CD, the inflammation in UC is uninterrupted and mostly confined to the mucosal layer of either the proximal or distal colon (large intestine, see Figure 1). Table 1 summarizes the overlapping and distinct features between these two sub-types of IBD.
Table 1. Differences and similarities between CD and UC

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>26-199 per 100 000 (Loftus, 2004)</td>
<td>37-246 per 100 000 (Loftus, 2004)</td>
</tr>
<tr>
<td><strong>Disease manifestation</strong></td>
<td>Can affect the entire gastrointestinal tract, from mouth to anus</td>
<td>Inflammation is confined to the colon.</td>
</tr>
<tr>
<td></td>
<td>Inflammation is chiefly located in the ileocaecal region.</td>
<td>Inflammation affects the proximal/distal end of the colon.</td>
</tr>
<tr>
<td></td>
<td>Intestinal inflammation has a discontinuous (segmental) pattern, where affected parts of the gut can be separated by healthy tissue.</td>
<td>Intestinal inflammation is continuous, first occurring in the rectum and then extends proximally.</td>
</tr>
<tr>
<td></td>
<td>Can affect all layers of the gut (transmural inflammation)</td>
<td>Mucosal inflammation only.</td>
</tr>
<tr>
<td><strong>Genetic Contribution</strong>*</td>
<td>~50%</td>
<td>~10%</td>
</tr>
<tr>
<td><strong>Environmental Factors</strong></td>
<td>Smoking, diet</td>
<td>Diet, smoking and appendectomy are protective for UC (Budarf et al., 2009)</td>
</tr>
</tbody>
</table>

* Estimated from Monozygotic/Dizygotic twin concordance rates.
It is understood and widely accepted that the pathogenesis of IBD arises from the complex interplay between the innate and adaptive immunity of a susceptible individual, environmental triggers and the host microbiota (Xavier and Podolsky, 2007). This interplay increases the level of complexity in unraveling the pathogenesis of IBD since the contribution of environmental factors and that of the genetic inheritance of several susceptibility loci and the interaction of these is still unknown (See Figure 2).
Figure 1. The Human gut and structure of the small-intestinal epithelial

[A] Structure of the human intestine depicting the ileal region where the most common form of CD occurs. [B](a) The five layers of the gut: i: mucosa (the inner-most layer), ii: the submucosa, iii-iv: underlying muscular layers, v: serosa, lining the outer muscular layer. (b) Structure of the small intestinal epithelium containing cells important in the gut’s biochemical barrier, for example the Goblet cells (c) and the Paneth cells (d). [A] Adapted from http://www.nlm.nih.gov/medlineplus/ency/imagepages/19221.htm[B] Adapted from Budarf et al, 2009.
Figure 2. Interaction of the major IBD-contributory factors. Illustration of the major factors that influence and interact to contribute towards the development of IBD. The individual contribution of each of these components is still unclear, although the environmental component in the development of UC is much stronger than that of CD development.
II. AN OVERVIEW OF THE IMMUNE RESPONSE AND INFLAMMATORY BOWEL DISEASE

The anatomical and physiological properties of the intestinal tract play an important role in the mechanism of IBD. The gut is made up of five different layers, namely the mucosa, consisting of the inner-most layer, which lines the gut lumen, the submucosa, an inner and outer muscular layer and the serosa, which lines the outer muscular layer. (See Figure 1B(a). The epithelial cells of the mucosa are in close contact with the venous system (at their base), as well as being in direct contact with the gut contents at their apical surfaces. The mucosal epithelial layer contains several different cell types (See Figure 1B(b,c,d). The mucus-secreting Goblet cells (See Figure 1B(c) are responsible for forming a protective layer on the luminal surface of the gut while the Paneth cells (See Figure 1B(d), located in the ileal crypts, drive the production of anti-microbial peptides (Wehkamp et al., 2007) and form the biochemical barrier of the gut. The correct function of this dual barrier represents a crucial first defence mechanism in the innate immune system (Budarf et al., 2009), which is the first response upon epithelial penetration of microbes.
If the gut epithelial barrier is penetrated, **White Blood Cells** (WBCs) are immediately recruited to the epithelial surface where their phagocytic properties come into play. The specialized receptors on WBCs, called **Pattern Recognition Receptors** (PRRs), are able to recognize the patterns of macromolecules present on the bacterial cell wall and hence initiate phagocytosis (cell-eating), which engulfs and destroys microbes. The recruitment of these cells initiates a cascade involving the production of the necessary cytokines and chemokines as well as triggering the killing of microbes, which will lead to the appropriate signals required to initiate the adaptive immune system (Budarf et al., 2009).

In the situation where the response from the innate immune system fails to contain the microbial invasion, the adaptive immune system is activated, mediated by the specialised B and T Lymphocytes.
III. THE GUT MICROBIOTA AND INFLAMMATORY BOWEL DISEASE

The involvement of bacteria in the pathogenesis of IBD is well established, both through lab based studies of the gut bacteria, which show abnormal bacterial flora (microbiota) in IBD and through association studies on IBD that identified susceptibility genes involved in bacterial recognition. However, the exact role of the microbiota in the pathogenesis of IBD is still unclear. In healthy conditions, the gut microbiota plays a commensal as well as beneficial role in the human gut. The microbiota assists the nutrition of the human host, via the production of short chain fatty acids and vitamins, such as vitamin K, vitamin B12 and folic acid, but also prevents the colonisation of the gut by harmful bacteria (Mai and Draganov, 2009). In contrast to this commensal role, the gut bacteria carry antigens such as lipopolysaccharide and peptidoglycans which can stimulate an immune response. There is a crucial fine balance between host immune tolerance and response and the gut microbiota. Dysbiosis, which is the imbalance of microbial communities inside the digestive tract, of the mucosal and faecal microbiota has been reported for both CD and UC (Cobrin and Abreu, 2005; Targan and Karp, 2005). A loss in microbial diversity is also commonly observed in IBD patients (Ott et al., 2004).
In the case of CD, dysbiosis of the faecal microbiota has also been reported in the unaffected family members of CD patients, when compared to healthy controls in the general population. Joossens et al. (Joossens et al., 2011) reported that this dysbiosis in the CD patients was mainly characterised by five predominant bacterial species. A decrease in the population levels of *Bifidobacterium adolescentis*, *Dialister invisus*, *Clostidium* cluster XIVa (uncharacterised species), and *Faecalibacterium prausnitzii* and an increase in levels of *Ruminococcus gnavus* have been identified in CD patients (Joossens et al., 2011). *F. prausnitzii* are bacteria that produce butyrate, which have anti-inflammatory properties, and even lower numbers of *F. prausnitzii* are seen in patients who have had an ileocaecal resection (Joossens et al., 2011). *R. gnavus* do not produce butyrate but are known to degrade gastrointestinal mucin and exhibit high levels of β-glucuronidase (Beaud et al., 2005). This elevated enzymatic activity can lead to the production of compounds in the colon which are toxic and possibly lead to local inflammation (Joossens et al., 2011). This could suggest that increase in the levels of *R. gnavus* in certain regions of the colon and not others could at least in part explain the segmental nature of the inflammation, which is characteristic of CD. In the same study, the unaffected members of the CD families exhibited a decrease in the population levels of *Collinsella aerofaciens*, a member of the *Escherichia coli-Shigella* group and an increase in that of *Ruminococcus torques*. As *R.gnavus*, *R. torques* do not produce butyrate but have gastrointestinal mucin-degradation capacities. These findings suggest that there is a lack of butyrate-producing activity in CD patients, coupled with enhanced mucin-degradation capacity.
As previously shown in Table 1, CD has a disease prevalence of somewhere between 26 to 199 per 100,000 in populations of European ancestry (Loftus, 2004). Although it is a complex disease there is strong evidence for genetic susceptibility. The estimated sibling recurrence risk ratio ($\lambda_s$) ranges from 15-35 (Schreiber et al., 2005), where $\lambda_s$ is defined as the ratio of disease manifestation, given that one sibling is affected, compared with the disease prevalence in the population. However, it was reported earlier (Satsangi, 1994) that the highest $\lambda_s$ of 35 was found in a study that only included patients with early onset CD (disease onset prior to the age of 21) and the high values could also be attributable to inclusion of different ethnicities in the studies, in comparison with the general population, in particular Ashkenazi Jewish patients, (Ashkenazi Jewish communities are known to have a high CD prevalence and a tendency towards familial CD). A UK-based study of homogeneous ethnicity and adult-onset disease put the $\lambda_s$ estimate closer to 24.7 (Satsangi, 1994). Other studies have shown a high heritability of around 0.50, with the heritability being measured from the difference in correlation between monozygotic and dizygotic twins (Tysk et al., 1988). Because of this high $\lambda_s$ and high heritability for a polygenic disease, CD is one of the most widely studied multifactorial diseases.
Early linkage studies, followed by Genome Wide Association Studies (GWAS), were crucial in identifying the first gene involved in IBD. Linkage analysis revealed several different linkage peaks across the genome (Cavanaugh, 2001; Parkes et al., 2000). In particular there was an extensive linkage peak in Non Jewish CD families on Chromosome 16q, at the IBD1 locus, where the gene NOD2 is located (Cavanaugh, 2001). Subsequent analyses of this linkage region lead to the first breakthrough, with the discovery that three common NOD2 (previously known as CARD15) variants were associated with CD (Figure 3) (Hugot et al., 2001). The encoded protein, NOD2 is a Nucleotide-binding Oligomerisation Domain protein that has the ability to recognize, intracellularly, microbial cell-wall components, namely Muramyldipeptide (MDP), through its Leucine Rich Repeats (LRRs) (Figure 3). The three NOD2 mutations identified are located within or close to the LRRs, with the framshift mutation resulting in truncated version of the protein. No mutations within NOD2 that ablate the production of the entire protein have yet been identified (Eckmann and Karin, 2005). Functional evidence of the three identified NOD2 mutations, which are illustrated in Figure 3 and in Table 2, will be further discussed in Chapter II.
Table 2. The CD-associated NOD2 mutations.

<table>
<thead>
<tr>
<th>rsID</th>
<th>Change</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2066844</td>
<td>R702W</td>
<td>Missense</td>
</tr>
<tr>
<td>rs2066845</td>
<td>G908R</td>
<td>Missense</td>
</tr>
<tr>
<td>rs5743293</td>
<td>3020insC</td>
<td>Frameshift</td>
</tr>
</tbody>
</table>

Figure 3. Representation of the NOD2 gene and the relative positions of the three common CD-associated NOD2 mutations (rs2066844- R702W, rs2066845- G9608R and rs5743293- 3020insC).
*NOD2* is constitutively expressed in cells of the myeloid lineage including neutrophils and macrophages and its discovery thus provided the first genetic link between CD and an aberrant immune system (Budarf et al., 2009; Eckmann and Karin, 2005; Hugot et al., 2001). However, the strong evidence of linkage on Chromosome 16q could not be fully accounted for by *NOD2* alone since linkage on 16q is still observed in families that do not carry the common *NOD2* mutations. This suggested that there were other, yet unreported, susceptibility genes in the 16q region.

UC is the more prevalent form of IBD, with a disease prevalence of around 37-246 per 100,000 in populations of European ancestry (Loftus, 2004). The estimated siblings recurrence risk ratio $\lambda_s$ is approximately 8.5 (Orholm et al., 1991). UC has a lower genetic component than CD, with heritability estimated at about 10% (Thompson and Lees, 2011). Despite the complex nature of UC and the lower genetic contribution, early linkage studies still successfully identified linkage peaks for UC, notably on chromosomes 1, 4, 6, 12, 22 and X, some of which were shared with CD (Hampe et al., 1999; Parkes et al., 2000). Unlike for the case of CD, no genes were pin-pointed and linkage was not observed for UC at the *IBD1* locus (*NOD2* region) on chromosome 16q (Ohmen et al., 1996). This was one of the first indications for the existence of genetic differences between CD and UC, with *NOD2* being a CD-specific factor with a large effect.
Subsequent advances in genomics, including the creation of the International HapMap Project, followed by the advent of high-throughput Single Nucleotide Polymorphism (SNP) genotyping made possible large-scale GWASs, and it is data from these that will be used in my project. HapMap is a multi-national effort that aims to catalogue human genetic variation in order to help scientists identify susceptibility genes predisposing to disease as well as genes involved in individual responses to pharmacological drug metabolism and gene-environment interactions (Risch and Merikangas, 1996).

The term polymorphism is usually applied to variation which is present at a frequency of 1% or more in the general population. Although the data that will be discussed in this thesis will consist of genome-wide SNP data, there are other types of genetic variation present in the human genome. Genetic variation can be subdivided into small-scale sequence variation and large-scale structural variation. The latter include Copy Number Variation (CNV), which involves the loss or gain of a copy of a sequence segment, which may include part or all of a gene, as well as Chromosomal Rearrangements such as translocations and inversions. Small-scale sequence variation includes Variable Number Tandem Repeats (VNTRs), such as Microsatellites, which consist of simple-sequence repeats in the genome. Microsatellites have been extensively used in Linkage studies as they exhibit substantial heterozygosity due to the fact that they are multi-allelic. Base insertions or deletions, also known as Indels, are also a common source of genetic small scale sequence
variation in addition to SNPs. While SNPs (due to allelic imbalance) can be used to detect CNVs genome-wide, CNVs are hard to analyze in genome-wide studies. The same applies to VNTRs, and microsatellites. Small indels are also not included in SNP arrays and all these types of variations may be important particularly in regulatory regions of the human genome.

i. Association Studies

Before the advent of GWAS, SNPs in candidate gene/regions, often but by no means always selected as the result of linkage studies, and most often with a strong hypothesis of putative function, were genotyped and tested for association with the underlying phenotype. Candidate gene association studies that were selected as a result of linkage studies would attempt to narrow down the very large linkage regions, generally spanning more than one megabase in length, in order to ultimately pin-point the causal variant. Indeed, this was the case for the breakthrough with NOD2 in relation to CD, where the linkage was followed up through fine-mapping by positional cloning and subsequent candidate gene analysis (Hugot et al., 2001). Linkage analysis comes with several advantages, particularly the ability to detect genetic variants of large effect with just a thousand genome-wide genetic markers from a few transmissions within the families studied. Linkage studies are also robust to confounding effects and information can be combined across families even in cases where there are different mutations presenting at the same locus. For these reasons, linkage analysis performs well for
highly penetrant, single–gene disorders but success has been more difficult when linkage analysis was employed for complex traits, which are polygenic conditions thought to be caused by a multitude of variants of low effect-size. Thus, association studies have become the preferred approach in identifying susceptibility loci for complex conditions (Risch and Merikangas, 1996). Although association studies are not robust to effects resulting from population structure, association studies are not limited to families and it is thus easier to recruit a large number of patients and they provide better power for detecting common variants of low effect sizes. However the false-positive rate is higher in association studies than it is for linkage studies.

A GWAS consists of the hypothesis-free analysis of SNPs across the genome to investigate whether the genotype (genotypic test) or allele (allelic test) frequencies for each SNP is significantly different between cases (group affected by the trait) and ethnically matched controls (healthy group). A statistically significant difference provides evidence for association between a particular marker and the trait under study, which requires replication in an independent cohort. SNP genotyping platforms currently used in GWAS can accommodate around one million SNPs, beneficially increasing the SNP resolution across the genome but also giving rise to multiple testing issues due to the individual testing of each SNP. The consequent lack of power means that meta-analyses are now used to improve the number of genetic hits. A meta-analysis combines genotypic or allelic test statistics for the individual SNPs across all the independent GWASs in order to increase
power to detect association by having a much higher sample size. The significant results from a meta-analysis require validation and are followed up in an independent replication sample.

Despite their lack of power, the hypothesis-free nature of GWASs, coupled with the exponential improvement in high-throughput SNP analysis, has nowadays made GWAS the most favourable type of population-based disease-association mapping for complex diseases.

ii. Linkage Disequilibrium

Linkage analysis relies on current recombination, and is thus low resolution due to the limited number of markers that can be informative to obtain linkage phase since there are only a few meioses within the families studied whereas association relies on the presence and structure of Linkage Disequilibrium (LD), which reflects distant shared ancestry and therefore many recombination events, both current and historic, providing a much higher resolution than linkage. LD is the non-random association of alleles at two closely-linked loci within a random-mating population. Recombination seems to be the major cause of LD breakdown, since LD patterns mirror recombination (Maniatis et al., 2002). However, natural selection, genetic drift, population subdivision and population bottlenecks are all factors that influence LD structure (Kong et al., 2010). Historically recent mutations are likely to be
in high LD with the surrounding SNPs, even in regions of recombination, but are likely to be rare unless selection or demographic processes have increased their frequency.

The extent of LD can be measured using several metrics although the most common include the covariance ($D$), the ratio of $D$ to its maximum possible absolute value ($D'$), association ($\rho$), correlation ($r$) and correlation coefficient ($r^2$) (Tapper, 2007) (see Appendix I for formulae). Most of these metrics heavily rely on allele frequencies with the exception of $D'$ and $\rho$ (Morton et al., 2001; VanLiere and Rosenberg, 2008), which are less sensitive to variations in allele frequencies (Morton et al., 2001). $r^2$ has more power for selecting tagging SNPs than $D'$ but is less good at signaling lack of recombination of low frequency alleles. It gives a value of 1 where the allele frequencies of the SNPs are the same and there is no recombination, but lower values where one of the two SNPs is rare. $r^2$ has been extensively used in GWA studies, for example in defining LD intervals in meta-analyses.

Each individual has two homologous chromosomes, one inherited from each parent. Therefore, since genotyping platforms are so far unable to assign SNP alleles to their respective homologues, the genotyped SNPs need to be phased. Phasing is the determination of which SNP allele belongs to the maternal or paternal homologue, which is in turn required in order to determine haplotype blocks. Haplotype blocks are genomic regions that...
contain markers exhibiting strong LD with one another and thus tend to be inherited together from generation to generation. With the increasing technological advances and decreasing cost of SNP genotyping, haplotype inference and phasing using statistical approaches has become one of the major areas of statistical methodological expansions. Expectation Maximization (EM) is an algorithm that can be used or underlies many statistical approaches used for haplotype inference. EM utilizes an iterative approach in order to infer the haplotype phase, which maximizes the likelihood, or in other words best describes, the data observed. EM works well for a limited number of SNPs, generally ten, but haplotype phase accuracy declines with a greater number of SNPs and the process becomes computationally costly (Browning and Browning, 2011).

In such cases, Coalescent-based models, such as Approximate Coalescent models and Hidden Markov Models (HMM), provide more accurate haplotype phasing as haplotype frequencies are better modeled \textit{a priori} (Browning and Browning, 2011). The Approximate Coalescent Model assumes the ancestral convergence of alleles back in time, for which the parameters are sometimes estimated using a stochastic EM framework to explore all possible solutions or by Markov Chain Monte Carlo (MCMC) methods (Browning and Browning, 2011).
Although HapMap contains a reference panel of over three million SNPs, the current genotyping platforms used in GWASs only contain a subset of this reference panel. In fact, in some cases the SNPs only partially overlap between different genotyping arrays. Nevertheless, indirect association can still be observed if the typed SNP is in LD (high $r^2$ value) with the putative causal agent. The power to detect the untyped putative causal agent depends on the allele frequency, and its effect size, as well as the strength of LD with the genotyped SNP. Meta-analyses combine several different GWASs, often carried out using different SNP genotyping arrays, which despite some overlap, by design they contain different SNPs making the combination of test statistics for the same SNPs across the genome difficult among the different studies. Therefore, imputation has been suggested as a way to create a homogenous subset of SNPs to meta-analyse the different independent GWASs. Imputation is an inference method which takes advantage of association between the genotyped SNPs and untyped SNPs. Genotypes of untyped SNPs are inferred by reference to a panel of densely-typed individuals (Guan and Stephens, 2008) (e.g. HapMap database, 1000 Genomes Project). The imputed genotypes are obtained using a Bayesian approach that uses a predicted distribution that is based on haplotype inference from the observed genotypes (Sterne et al., 2009). Imputation has been used universally in GWASs, meta-analyses and other epidemiological studies and introduces small approximations in regions of conserved LD, but can potentially introduce significant bias and inaccuracies in regions of LD breakdown. Imputation algorithms are generally user-defined for each particular dataset in order to carefully model the distribution of each variable.
with missing values. Even so, imputation remains an approximation technique. In fact, in a published cardiovascular risk prediction tool that was developed using imputation to handle missing data, it was initially reported that cardiovascular risk was unrelated to cholesterol (Sterne et al., 2009) (Hippisley-Cox et al., 2007). It was however subsequently clarified that when the analysis was carried out using only individuals without missing data, a clear association between cardiovascular risk and cholesterol was observed (Sterne et al., 2009), which highlights the limitations of using imputation for missing data.

In addition to these potential inaccuracies in the meta analyses, the lack of power in detecting genome-wide association could be due to the unrealistic assumption that one of the SNPs on the genotyping platform is either causal or in almost complete LD, as defined by $r^2$, with the putative causal agent. This would not be the case for rare variants nor in regions of breakdown of LD. In fact it is now widely accepted that the currently used standard methods of analysis are underpowered for detecting rare variants, which could be responsible for substantial allelic heterogeneity in complex diseases (Li and Leal, 2008).

Secondly, another reason for the lack of power comes from the stringent significance thresholds required as a result of multiple testing. Additionally, the P-value for each individual SNP across datasets does not need to reach
nominal statistical significance across all the independent GWASs in order for the P-values in the datasets to be meta-analysed. Another problem of the meta-analysis approach is that it inevitably leads to the pooling of several phenotypic subgroups, as well as different ages of onset (early-onset and adult-onset) as well as ethnicities in order to increase the sample size and hence power to detect association.

iii. Crohn’s Disease and Ulcerative Colitis GWASs

The relatively large λs makes CD a good case for genetic studies. In fact, initial studies focused more on CD than UC. One of the first large-scale GWAS was conducted by The Wellcome Trust Case Control Consortium (WTCCC), which analysed ~14,000 cases of seven common diseases, including CD (WTCCC, 2007). The UK WTCCC Phase I CD GWAS analysis identified an initial 9 CD susceptibility loci using ~2,000 cases (WTCCC, 2007). Several other GWASs investigated CD associations in different Caucasian populations, including Belgian (Libioulle et al., 2007), German (Hampe et al., 2007) and USA (McGovern et al., 2010), as well as different ethnicities, namely Jewish and Non-Jewish from North America (Rioux et al., 2007). The largest CD association study to date consisted of a meta-analysis of six of the available independent GWAS datasets, one of which only consisted of early-onset CD patients (Imielinski et al., 2009), combining 6,333 cases and 15,056 controls (Franke et al., 2010). This meta-analysis identified
and confirmed a total of 71 intervals (loci) for CD susceptibility. However, despite the large sample size, only \textit{NOD2} was detected on 16q, despite expectations of other loci on that chromosome. Additionally, in several cases, the LD intervals were quite large (over 1 Megabase) with several suggested genes within them. Despite the international efforts, the confirmed 71 CD loci found up until that time through the several GWASs and meta-analyses were reported to account for only 23.2\% (Franke et al., 2010) of the genetic contribution, suggesting that there were many more loci to be found and that further research is required to fully understand the genetics of CD.

Following the WTCCC Phase I studies that encompassed CD, the WTCCC Phase II data generation extended the list of phenotypes under investigation, and now incorporated UC as one of the datasets. The WTCCC Phase II UC data consisted of a larger sample size than the WTCCC CD data, which is more convenient for detecting association in situations like UC, where the genetic contribution is lower than for other complex conditions like CD (Consortium et al., 2009). Several other GWASs from a variety of geographic locations, including Germany, Belgium, Japan and Korea were carried out (Anderson et al., 2011; Asano et al., 2009; Consortium et al., 2009; Ellinghaus et al., 2013; Franke et al., 2008; Franke et al., 2010; Hampe et al., 1999; Haritunians et al., 2010; McGovern et al., 2010; Silverberg et al., 2009; Yang et al., 2013).
More recently, with the aim of expanding the knowledge of the aetiology of IBD, a large-scale genome-wide meta-analysis was carried out, combining data from 15 GWASs of CD and/or UC together with Immunochip genotyping data, where the latter genotyping platform consisted of specific SNPs within or in regulatory regions of immune-related genes. The sample size consisted of more than 75,000 cases and controls together, making this study the largest IBD meta-analysis to date (Jostins et al., 2012) and will be discussed in further detail in Chapter IV. This study identified and replicated 30 CD-specific, 23 UC-specific and 110 UC and CD shared susceptibility loci, resulting in 163 confirmed general IBD susceptibility loci (Jostins et al., 2012). In the European population, the total number of confirmed UC loci now stands at 59, explaining, it is claimed, approximately 16% of the genetic contribution (Jostins et al., 2012).
V. ANOTHER APPROACH- LINKAGE
DISEQUILIBRIUM UNIT MAPS

Another approach to association studies is to combine information from many adjacent markers, such as the multi-marker method developed by Maniatis et al (Maniatis et al., 2007; Maniatis et al., 2005). The power of this multi-marker method comes partly from the fact that it does not assume the putative causal agent to be in high LD, as measured by \( r^2 \), with the genotyped SNP since SNPs within a genomic window are simultaneously analysed within a composite likelihood framework, and partly from the fact that this method incorporates the structure of LD in the human genome by modeling on genetic distances in LD Units (LDUs) in contrast to physical location in kb.

LDU maps represent the genetic distance of SNPs, as opposed to their physical distance. Conventional genetic maps in centi Morgans (cM) are based on recombinants from family data. Such maps can only capture the recently-occuring recombination events since there are only a few generations involved in family data. The main limitation of genetic maps in cM is their relative low resolution since only informative, in other words markers exhibiting heterozygosity in relevant members of the pedigree, can be used for such maps. Microsatellite (STR) polymorphisms are ideal, but not frequent enough in the genome. The later genetic map is based on approximately 300,000 informative SNPs on Utah Residents samples with Northern and Western European ancestry from the Centre d’Étude du Polymorphisme.
Humain (CEPH) collection, together with families from the deCODE project (Kong et al., 2010). On the other hand, LDU maps provide information from both current and historic recombination events based on the shared ancestry of unrelated individuals and they can be constructed from millions of markers. LDU maps are generally constructed from SNP data using an adaptation of the Malécot model of isolation by distance, which describes the decline of pairwise SNP association as a function of physical distance as shown in Figure 4, with cumulative distances in LDU (Maniatis et al., 2002).

**Figure 4. The Relationship between LD and physical distance**
Illustrates the best-fit line of various estimates of the observed pairwise SNP associations ($\rho_{\text{obs}}$). $\varepsilon$ is the exponential decline in association $\rho$ as a function of increasing physical distance between pairs of SNPs. The greater the exponential decline $\varepsilon$ of pairwise SNP association, the faster the decay of LD (as shown at $\varepsilon=0.008$).
The methodology for constructing LDU maps is given by Maniatis et al. (Maniatis et al., 2002) using the LDMAP software (Lau et al., 2007) and is an extension of earlier work (Morton et al., 2007). It is based on the Malécot model that describes the expected decline of association $\rho_{\text{exp}}$ between any pair of SNPs as:

$$
\rho_{\text{exp}} = (1 - L)Me^{-\Sigma \epsilon_id_i} + L
$$

where $\rho_{\text{exp}}$ is the expected association, $M$ is the initial value of LD before decay begins, thus representing the intercept and $L$ is the asymptote. $M$ reflects the phylogenetic origin of haplotypes, where $M=1$ indicates a unique haplotype and hence a monophyletic origin, and $M$ less than 1 suggests a polyphyletic origin, and thus the presence of more than one ancestral haplotype (Collins and Morton, 1998). $L$ is the asymptote, which corrects for spurious associations at large distances. The exponential decline $\epsilon_i$ represents the decline of association as a function of physical distance ($d_i$) between a pair of SNPs, with $d_i$ representing the distance in kb between a marker $i$ and a neighbouring marker $i+1$. The product of $\epsilon_i d_i$ is analogous and more accurately known than the product of recombination $\theta$ and $t$ time in generations and hence $\epsilon_i d_i$ is a better metric for LD (Tapper, 2007). The observed pairwise SNP-by-SNP associations calculated using the parameter $\rho_{\text{obs}}$ are used to iteratively estimate, using Maximum Likelihood, the parameters $M$, $\epsilon$ and $L$. 


To do this, it is necessary first to assign phase, which is done using the Hill algorithm (Hill, 1974), which uses a maximum likelihood approach to infer phase for each pair of SNPs from the frequency of diploid genotypes. The 3-by-3 diplotype table can then be converted into a 2-by-2 table, from which the allele frequencies $Q$ and $R$ and the covariance $D$, are calculated. An example of the 2-by-2 haplotype table is illustrated in Table 3:

Table 3. 2x2 count of haplotype frequencies.

<table>
<thead>
<tr>
<th>SNP B</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNP</td>
<td>1</td>
<td>a = $f_{11}$</td>
</tr>
<tr>
<td>A</td>
<td>2</td>
<td>c = $f_{21}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R = $a + c$</td>
</tr>
</tbody>
</table>

$f$ is the frequency of the inferred haplotype and $(1-Q)$ and $(1-R)$ are the allele frequencies.

The covariance $D$ can then be calculated as follows:

$$D = f_{11}f_{22} - f_{12}f_{21}$$

The observed association $\rho_{(obs)}$ can then be calculated as follows:
\[ \rho_{(obs)} = \frac{(ad-bc)}{(a+b)(b+d)} \]

which is equivalent to:

\[ \rho_{(obs)} = \frac{D}{Q(1-R)} \]

where \( D \) is the covariance between the two markers, and \( Q \) and \( R \) are the allele frequencies calculated from the 2-by-2 haplotype table illustrated in Table 3. The difference between \( D \) and \( D' \) is that for the latter, \( D \) is normalized by the theoretical maximum and minimum for the observed allele frequencies relative to the value of \( D \), as is shown in Appendix 1.
Figure 5. Expected Pairwise Association per SNP interval. 
This figure illustrates the first five SNPs of a chromosome, with the first SNP interval composed of pairwise SNP association between SNP\(_1\)-SNP\(_2\), SNP\(_1\)-SNP\(_3\), SNP\(_1\)-SNP\(_4\), SNP\(_1\)-SNP\(_5\), which are used to estimate values of \(\varepsilon\).

Figure 5 illustrates the first five SNPs on a chromosome, where the first SNP interval is composed of pairwise associations between SNP\(_1\)-SNP\(_2\), SNP\(_1\)-SNP\(_3\), SNP\(_1\)-SNP\(_4\), SNP\(_1\)-SNP\(_5\) …SNP\(_1\)-SNP\(_n\). For each \(i\)th SNP interval, the Malécot model

\[
\rho = (1-L)Me^{-\varepsilon d_i} + L
\]

is subsequently used to iteratively estimate, using a maximum likelihood approach, the values of \(M\), \(\varepsilon\) and \(L\), by using all the observed pairwise association for the SNPs covering that specific interval, and their corresponding distances \(d_i\) in kb, weighted by the information \(K\rho\) for each interval (Tapper, 2007). This information is now used to construct LDU maps where:
\[ LDU = \varepsilon_i d_i \]

for every SNP interval.

These LDU maps can describe the underlying structure of LD (Maniatis et al., 2002) and are visualized by plotting marker locations in LDU against distances in kb, which demonstrate the non-linear relationship between physical distance and LD. These metric genetic maps are analogous to linkage maps in cM (Tapper et al., 2005). Blocks of conserved LD are areas of reduced haplotype diversity while steps represent LD breakdown most likely due to recombination as cross-over profiles agree with LDU patterns (Webb et al., 2008). Although patterns of LD are mainly a consequence of recombination (Jeffreys and Neumann, 2009), other factors, such as selection and genetic drift, as well as stochastic effects are important (Slatkin, 2008). HapMap Phase II data is used to obtain genetic distances in LDU since their estimation is based on a higher resolution as a result of a denser SNP coverage as opposed to HapMap III.

Subsequent to the construction of LDU maps, for each analytical window the same Malécot model is used to model the decline of affection-status-by-SNP association as a function of genetic distance in order to estimate the location of the putative causal agent. This will be discussed in more detail in Chapter II. One of the major advantages of using composite likelihood over
single-SNP testing is a greatly reduced number of tests and hence a less stringent multiple-testing correction. This method therefore addresses the current major problem of lack of power associated with single SNP testing and avoids the need for imputing as a result of analysing SNPs simultaneously in analytical windows. Other details are given in Maniatis et al (Maniatis et al., 2007), which provides evidence of the power and resolution of this approach over single SNPs.
VI. GENERAL AIMS OF STUDY

The overall aim of this study was to make progress on elucidating the complex genetics of IBD using the multi-marker LD mapping approach described in the previous section (Maniatis et al., 2007). The first step in this study was to re-analyse Chromosome 16q in relation to CD, on the publically available WTCCC CD data and the North American National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium CD data (IBDGC) as a replication sample, with the aim of identifying novel susceptibility genes on Chromosome 16q, other than NOD2. The goal of this part was to shed light on the possibility of genetic heterogeneity underlying the region of significant linkage on 16q in patients who do not carry the common NOD2 mutations.

The second step was to apply the same multi-marker approach to the whole genome using the same data (WTCCC and NIDDK) for CD. The first aim was to identify whether the 71 previously reported CD loci based on the meta-analysis of six GWASs, could be identified using only the WTCCC and NIDDK datasets. The second was to see whether this method would identify novel susceptibility loci for CD, since the 71 loci did not appear to account for the total genetic contribution.
Subsequently, the attention was shifted towards UC. The same method was applied to the WTCCC Phase II UC data and two NIDDK UC datasets as replication samples, in order to identify novel susceptibility loci for UC.
CHAPTER II. DISSECTING CHROMOSOME 16: GENETIC AND PHENOTYPIC STRATIFICATION PROVIDES INSIGHT INTO CROHN’S DISEASE.

I. INTRODUCTION

One of the major breakthroughs in CD genetics came in 2001 when three functional mutations within *NOD2* were identified, as a culmination of the previous work using family and association studies. *NOD2* encodes a protein that is responsible for recognizing pathogens through its Leucine Rich Repeats (LRRs) domain and hence this discovery provides a direct link to a genetically altered host immune system (Budarf et al., 2009; Hugot et al., 2001).

It was however subsequently reported that there is a lack of direct relationship between the prevalence of these three mutations (rs2066844, rs2066845, rs5743293, see Table 2 and Figure 3 in Chapter I) in the general population and CD frequency (Hugot et al., 2007). Indeed, *NOD2* mutations have not been found in all CD patients (Lesage et al., 2002), although this is not surprising in complex inheritance. It is also important to note that the
NOD2 mutations are also relatively frequent in healthy individuals in Central Europe, and the average frequency of these mutations in Caucasians is 4.3% for R702W (rs2066844), 1.2% for G908R (rs2066845) and 2.3% for the L1007fsinsC frameshift mutation (rs5743293) (Hugot et al., 2007). In addition, the linkage peak originally identified on chromosome 16 persisted even after the patients that were found to have the NOD2 mutations were removed from the data set, however in this case, the linkage peak shifted some 25cM downstream of the NOD2 gene (van Heel et al., 2003), suggesting the presence of other chromosome 16q susceptibility genes. Despite the shift in the linkage peak, no other signals on 16q have been found so far in published GWA studies. To add to the complexity, NOD2 mutations are associated with ileal CD but not with perianal or colonic disease (Ahmad et al., 2002), further suggesting the involvement of both genetic and phenotypic heterogeneity in relation to CD.

At the outset of this thesis work, the IBD Genetics Consortium had made significant progress in mapping genes involved in CD, and combined GWASs identified an initial 32 susceptibility loci (Barrett et al., 2008), which included NOD2 on chromosome 16q, followed by an additional 39 (Franke et al., 2010), making a total of 71. Several of these loci are implicated in other diseases involving inflammatory and immune dysregulation (thus, PTGER4 on Chromosome 5p, is common to CD, UC (Anderson et al., 2011) and multiple sclerosis). However, this study reported that the 71 loci account for only
23.2% (Franke et al., 2010) of the genetic risk a problem of so-called “missing heritability”.

In this chapter I describe how the GWA database was revisited using the multi-marker LD mapping approach mentioned in the Introduction (Maniatis et al., 2007). This first analysis focused on the previously identified IBD1 linkage region on Chromosome 16q (Cavanaugh, 2001), since the strong evidence for linkage in this region cannot be fully accounted for by NOD2 alone. Indeed, using this LDU multi-marker approach, several distinct association signals of high significance were identified on chromosome 16q alone. For this first step, I focused on three of these signals to study in detail. Each of the three signals was found in the WTCCC data and, quite independently, in the NIDDK dataset, which also contains information on Jewish ancestry as well as additional sub-phenotype data.

The work in this chapter has already been published (Elding et al., 2011) and contributions made by others are mentioned in the subsequent text.
II. METHODS

i. Subjects and Methods

2,009 cases of Crohn’s Disease and 3004 combined controls from the GWA scan of the UK WTCCC study (WTCCC, 2007) based on the Affymetrix 500K array, which contains approximately 500,000 SNPs, were analysed in this study. Half of the ~3,000 nationally-ascertained controls came from the 1958 British Birth Cohort collection and the remainder from the UK Blood Services Collection of Common Controls (WTCCC, 2007).

For this study, the quality control filtering was conducted by Winston Lau and the procedure that was followed is described in detail in the Methods section of Chapter IV. After quality control, a total of 1698 cases and 2948 combined controls were retained for analysis. The cases were confirmed patients of any subtype of CD using endoscopic, radiological procedures and histopathological criteria. The cases were not specifically enriched for early age of onset or family history and they were from a variety of IBD clinics. For the replication study, following quality control, 813 North American patients with CD and 947 controls made available by the NIDDK IBD Genetics Consortium (IBDGC) were analysed. The NIDDK IBDGC GWA scan was
based on the Illumina HumanHap300 array (Riouxf et al., 2007), consisting of approximately 320,000 SNPs, and has a smaller sample size and SNP set that only partially overlaps with the WTCCC SNP array. The WTCCC reports fewer phenotypic data than the NIDDK study does, and the latter includes information on the involvement of other intestinal locations.

ii. Genetic analysis

A high density LDU map for the whole of chromosome 16 had been previously constructed using the CEU (Utah residents with Northern and Western European ancestry) PHASE II data from the HapMap Project (Lau et al., 2007). See Chapter I for details about the construction of LDU maps.

The entire 16q was divided into non-overlapping windows based on the LDU map, with a minimum length of 10 LDU and a minimum number of 30 SNPs for each window (See Figure 6).
Figure 6. Partitioning the Chromosome.
The chromosome arm is partitioned into non-overlapping 10 LDU windows and a minimum of 30 SNPs in each 10 LDU window.

This resulted in 98 windows for 16q for both GWA datasets. For each window the LDU mapping method previously published by Maniatis et al (Maniatis et al., 2007) was used, which will be described in detail in this section. This method returns a P-value and an estimate of the causal location (Ś) using genetic locations derived from a high–resolution linkage disequilibrium (LD) map (Maniatis et al., 2002). The association mapping approach that was applied for each window was based on the same Malécot model but ρ was
replaced with \( z \), which reflects the association between the affection status and every SNP.

Table 4. A 3x2 table of Affection Status-by-genotype, converted into a 2x2 table of Affection Status-by-SNP alleles.

<table>
<thead>
<tr>
<th>Affection Status</th>
<th>Genotypes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>Aa</td>
</tr>
<tr>
<td>Affected</td>
<td>( n_{AA} )</td>
<td>( n_{Aa} )</td>
</tr>
<tr>
<td>Unaffected</td>
<td>( n_{AA} )</td>
<td>( n_{Aa} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Affection Status</th>
<th>Alleles</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>a</td>
</tr>
<tr>
<td>Affected</td>
<td>Count</td>
<td>( a = 2( n_{AA} ) + n_{Aa} )</td>
</tr>
<tr>
<td>Unaffected</td>
<td>Count</td>
<td>( c = 2( n_{AA} ) + n_{Aa} )</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>( R )</td>
</tr>
</tbody>
</table>

\( f \) is the frequency of the affected individuals and \( R \) is the allele frequency.

The observed association \( z_{(obs)} \) can then be calculated as follows (see Table 4):

\[
z_{(obs)} = \frac{(ad - bc)}{(a + b)(b + d)}
\]

Which is equivalent to:

\[
z_{(obs)} = \frac{D}{f (1 - R)}
\]
where $D$ is the covariance between the Affection Status and the marker alleles and $f$ is the frequency of affected individuals in the population and $R$ is the allele frequency.

The objective of this method is to estimate $\hat{S}$, which is the location of the causal variant on the HapMap LDU map. Therefore, the distance $d$ in the model is replaced with $|(S_i-\hat{S})|$ where $S_i$ is the LDU location of the $i$th marker within the window and $\hat{S}$ is the location estimate.

$$z_{(exp)} = (1 - L)Me^{-e[S_i-\hat{S}]} + L$$

Each window was tested for association with CD by using composite likelihood ($\Lambda$) that combines information from all single-SNP tests within each window, and therefore avoids undue multiple testing correction. $\Lambda$ is estimated as:

$$\Lambda = \sum k_i [z_{(obs)}_i - z_{(exp)}_i]^2$$

where $z_{(obs)}_i$ is the observed association between the affection status and every $i$th SNP and $z_{(exp)}_i$ is the expected association from the model, weighted for nominal information $K_i$. 
The significance of association for each window was obtained by calculating an F-statistic from the comparison between $\Lambda$ from the null model, assuming no association, and $\Lambda$ from the alternative, where the $\hat{\Sigma}$ is iteratively estimated. Since each window will contain a different number of SNPs, the P-value takes into account the different degrees of freedom for each window. Therefore, for convenience, the F-statistic is converted to a $\chi^2$ with 1 degree of freedom (Maniatis et al., 2007).

A Bonferroni threshold was calculated in order to account for multiple testing, using the following formula:

$$P - \text{value threshold} = \frac{\alpha}{\text{Number of tests}}$$

where $\alpha$ is the commonly accepted probability of a 5% false positive rate. The Bonferroni P-value threshold used was $5 \times 10^{-4}$. This P-value threshold corresponds to the 98 analytical windows on chromosome 16q that were tested for this analysis.

The 95% confidence interval (CI) for the estimated location $\hat{\Sigma}$ was obtained as:

$$\hat{\Sigma} \pm t(SE)$$
where $t$ is the tabulated value of Student's $t$-test and $SE$ is the Standard Error of the parameter $\hat{S}$. The predicted estimates of $\hat{S}$ and 95% CIs are obtained by fitting the LDU genetic distances since this approach increases the power of association (Maniatis et al., 2007). For convenience, these estimates are converted back to kb (NCBI build 37) by linear interpolation of the two flanking SNPs in HapMap. Therefore the 95% CIs measured in kb cannot be symmetrical because of the ‘block-step’ structure of the human genome. When $\hat{S}$ is in an LD block (horizontal line) then all markers within that block have the same LDU location. In such cases, the midpoint of that block was taken as an estimate of $\hat{S}$ in kb.

The significance around the $\hat{S}$ region was additionally analysed by calculating a curvature that reflects the likelihood surface. This curvature is based on $\chi^2_1$ estimates at fine resolution. Each $\chi^2_1$ is estimated in the same way as above but the model that estimates $\hat{S}$ is compared against a model, whereby $\hat{S}$ is fixed incrementally. These $\chi^2_1$ values are converted to $Z$ estimates using the following formula:

$$Z = \frac{\chi^2_1}{-2ln10}$$

Therefore, these logs of the likelihood odds ratios (LOD) provide a measure of confidence. All $Z$ estimates are plotted against the kb map in order to visualise the locations in the map that deviate from the maximum likelihood.
estimation ($\hat{S}$), as shown in Figure 7B and Figure 7C. The smaller the $Z$ estimate, the greater the maximum likelihood.

**iii. Genetic and Phenotypic stratification**

In order to stratify the data with respect to carrier status for the most common $NOD2$ mutations, in the absence of actual data on those mutations, linked SNPs were used. rs2076756 was used in the WTCCC dataset (G being the minor allele with a frequency of 0.24, in the controls, and 0.32 in the cases) and rs5743289 for the NIDDK dataset (T being the minor allele frequency of 0.17 in controls and 0.24 in cases). These SNPs, which are approximately a 100bp apart, are in a region of conserved LD that contains the three $NOD2$ mutations (see LDU map in Fig 6A; and as previously reported for rs2076756).

The WTCCC dataset contains patients of any subtype of CD but with no sub-classification available in the database. The NIDDK database on the other hand, contains additional information on disease, in particular that of possible extra-ileal intestinal involvement and also classifies the patients and controls according to ancestry (Jewish/Non-Jewish). Since there was prior expectation of genetic differentiation across these categories we exploited this
extra information to stratify the analyses of the CDH3, CDH1 and IRF8 regions.
III. RESULTS

Initially, using the WTCCC data for chromosome 16q, three major signals were identified, in the regions of NOD2/CYLD, CDH3/CDH1 and IRF8 (Tables 4, 6 and 7). The NIDDK GWAS data was then used to replicate this study.

I. NOD2 and CYLD region

Table 5 and Figure 7A show the significance and estimated locations (Ș) for the genomic region that harbours NOD2 and CYLD for both datasets. Two separate signals of association mapped to different locations in this region. Analysis of a window that included marker information from NOD2 but not CYLD yielded a highly significant association with CD for the WTCCC dataset, which was replicated using the NIDDK dataset. The estimated (Ș) location was identical for both datasets (50,749.2 kb, 95% CI for WTCCC: 50,707-50,766 kb and 95% CI for NIDDK: 50,708-50,839 kb), which is within an LDU block that spans 16 kb. The block includes exons 4 and 8, which harbour two of the most frequent functional mutations (rs2066844- R702W and rs2066845- G908R, respectively) within the NOD2 gene. The third most frequent mutation (rs5743293- L1007fsinsC) is on a neighbouring LD block with a very slightly different LDU location (see LDU block, Figure 7A).
The analysis of the WTCCC data for the adjacent window containing CYLD yielded an estimated location 11 kb (Ŝ: 50,847.3 kb, 95% CI: 50,839-50,851 kb) downstream of the gene (Figure 7A) and approximately 98 kb downstream of the NOD2 signal. This signal was replicated with the NIDDK data with an estimated location 234 base pairs downstream from the WTCCC Ŝ (Ŝ: 50,846.5 kb, 95% CI: 50,846-50,847 kb). For the CYLD window, the 95% CI was smaller than that obtained for the NOD2 window because there is less LD in the region.

Analysis of a window that included marker information from both NOD2 and CYLD (NOD2&CYLD window, see Table 5) yielded an estimated location Ŝ between NOD2 and CYLD for the WTCCC data, and the likelihood surface incorporated both genes (Figure 7A, 7B and 7C). The analysis of the same NOD2&CYLD window using the NIDDK data produced a very similar likelihood surface that incorporated both NOD2 and CYLD although the estimated location pointed within NOD2, very close to the three NOD2 mutations, as for the window that contained marker information for NOD2 alone (Figure 7A, 7B and 7C).
Table 5. Association statistics and estimated location of the causal variation for three different windows covering \textit{NOD2} alone (50,731-50,767 kb), \textit{CYLD} alone (50,776-50,836 kb) and \textit{NOD2} and \textit{CYLD} combined in relation to the locations one the human genome sequence.

<table>
<thead>
<tr>
<th>Data</th>
<th>Window*</th>
<th>Cases</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>Estimated Location (kb)</th>
<th>95% Confidence Interval CI (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTCCC</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>1698</td>
<td>79.7</td>
<td>$4\times10^{-19}$</td>
<td>50,802.5</td>
<td>50,701-50,846</td>
</tr>
<tr>
<td>NIDDK</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>813</td>
<td>31.9</td>
<td>$2\times10^{-08}$</td>
<td>50,749.2</td>
<td>50,708-50,839</td>
</tr>
<tr>
<td>WTCCC</td>
<td>\textit{NOD2}</td>
<td>1698</td>
<td>62.6</td>
<td>$3\times10^{-15}$</td>
<td>50,749.2</td>
<td>50,707-50,766</td>
</tr>
<tr>
<td>NIDDK</td>
<td>\textit{NOD2}</td>
<td>813</td>
<td>37.1</td>
<td>$1\times10^{-9}$</td>
<td>50,749.2</td>
<td>50,708-50,839</td>
</tr>
<tr>
<td>WTCCC</td>
<td>\textit{CYLD}</td>
<td>1698</td>
<td>54.4</td>
<td>$2\times10^{-13}$</td>
<td>50,847.3</td>
<td>50,839-50,851</td>
</tr>
<tr>
<td>NIDDK</td>
<td>\textit{CYLD}</td>
<td>813</td>
<td>12.5</td>
<td>$4\times10^{-4}$</td>
<td>50,846.5</td>
<td>50,846-50,847</td>
</tr>
</tbody>
</table>

*Window with marker information covering \textit{NOD2} or the adjacent window covering \textit{CYLD}.†A window $\chi^2$ using composite likelihood.

Figure 7A shows the estimates of $\hat{S}$ for the two different \textit{NOD2/CYLD} windows and datasets. For both datasets, the \textit{CYLD} window was significantly associated with CD ($2\times10^{-13}$ and $4\times10^{-4}$ for WTCCC and NIDDK respectively, Table 5).
Figure 7. LDU mapping of the associations detected in the NOD2, CYLD and combined windows.
Gold font relates to analysis results for the combined $NOD2$&$CYLD$ window. Maroon font illustrates results for the $NOD2$ window alone whereas green font represents results for the $CYLD$ window alone. [A] Analysis of all patients with SNP data grouped in two separate windows covering either $NOD2$ ($NOD2$ window) or $CYLD$ ($CYLD$ window), and analysis of all patients with SNP data grouped in a window combining marker information for both $NOD2$ and $CYLD$ ($NOD2$&$CYLD$ window). The vertical lines are the estimated locations ($\hat{s}$) for the $NOD2$ window, the $CYLD$ window and the $NOD2$&$CYLD$ window. The grey dashed line shows the LDU map constructed from the HapMap CEU data. [B] stratified data enriched for carriers of the most frequent $NOD2$ mutations. rs2066844, rs2066845 and rs5743293 are the three major $NOD2$ mutations. The dark blue line represents the likelihood surface for the NIDDK $NOD2$&$CYLD$ window analysis of the unstratified data. The gold line represents the likelihood surface for the WTCCC $NOD2$&$CYLD$ window analysis of the unstratified data. The magenta line represents the likelihood surface of the $NOD2$&$CYLD$ window analysis of the NIDDK patients who carry the $NOD2$ mutations. The light blue line represents the likelihood surface of the $NOD2$&$CYLD$ window analysis of the WTCCC patients who carry the $NOD2$ mutations. [C] stratified data enriched for non-carriers for the most frequent $NOD2$ mutations. The dark blue line represents the likelihood surface for the NIDDK $NOD2$&$CYLD$ window analysis of the unstratified data. The gold line represents the likelihood surface for the WTCCC $NOD2$&$CYLD$ window analysis of the unstratified data. The magenta line represents the likelihood surface of the $NOD2$&$CYLD$ window analysis of the NIDDK patients who do not carry the $NOD2$ mutations. The light blue line represents the likelihood surface of the $NOD2$&$CYLD$ window analysis of the WTCCC patients who do not carry the $NOD2$ mutations.
II. Genetic Heterogeneity within the $NOD2$ and $CYLD$ region

These results showed that the $NOD2$ region is more complex than previously thought. The two different $S$ locations within the $NOD2/CYLD$ region are an indication of the existence of different risk alleles in different patients. The three frequent causal $NOD2$ mutations (Hampe et al., 2001; Hugot et al., 2001; Hugot et al., 2007) were not included in the genotyping platforms for both WTCCC and NIDDK and hence the carriers of the mutations could not be identified. However, the data included known SNPs that are in strong LD with these mutations (i.e.: form part of the background haplotype on which the functionally significant mutations arose). The relationship between these two genes was therefore further investigated by analysing a window that included marker information from both $NOD2$ and $CYLD$, but stratifying the data according to specific SNPs. The stratification separated, as far as possible, (in the absence of data on the causative $NOD2$ mutations), patients without the main functional $NOD2$ mutations from those with greatest likelihood of carrying them.

The group that includes all the carriers of the disease-associated allele [heterozygous and homozygous for the minor allele, i.e. carriers with AG/GG or CT/TT genotypes for the rs2076756 (WTCCC) and rs5743289 (NIDDK) SNPs respectively] unsurprisingly yielded much higher significance levels than before, even though the number of patients was much smaller than that of the full dataset (Table 6). This confirms the notion that these two groups of patients included the majority of cases with the functional $NOD2$ mutations. In addition, the $S$ was
within NOD2 despite analysing both genes in the same window (NOD2&CYLD window, Table 6, Figure 7B). The position of $\hat{S}$ (50,749.2 kb) was exactly the same as for the NOD2 window in Figure 7A using the unstratified data.

The analysis of the non-carrier cases for the WTCCC (AA for rs2076756) and NIDDK (CC rs5743289), produced essentially identical results to each other, both, pointing towards a location approximately 11 kb downstream of CYLD (Table 6, Figure 7C). This genetic stratification reveals heterogeneity among patients with CD and suggests that a second locus in the vicinity of CYLD plays a larger role in patients who do not carry NOD2 mutations.
Table 6. Association statistics and estimated location of the causal variation for a window covering \textit{NOD2} (50,50,731-50,767 kb) and \textit{CYLD} (50,776-50,836 kb) in relation to the locations on the human genome sequence.

<table>
<thead>
<tr>
<th>Data</th>
<th>Window**</th>
<th>Cases</th>
<th>$\chi^2$†</th>
<th>P-value</th>
<th>Estimated Location (kb)</th>
<th>Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WTCCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>805</td>
<td>46.0</td>
<td>$1 \times 10^{-11}$</td>
<td>50,846.3</td>
<td>CYLD</td>
</tr>
<tr>
<td>AG*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>665</td>
<td>124.6</td>
<td>$6 \times 10^{-29}$</td>
<td>50,749.2</td>
<td>NOD2</td>
</tr>
<tr>
<td>GG*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>199</td>
<td>82.8</td>
<td>$9 \times 10^{-20}$</td>
<td>50,749.2</td>
<td>NOD2</td>
</tr>
<tr>
<td><strong>NIDDK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>482</td>
<td>13.5</td>
<td>$2 \times 10^{-4}$</td>
<td>50,846.3</td>
<td>CYLD</td>
</tr>
<tr>
<td>CT*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>266</td>
<td>60.5</td>
<td>$7 \times 10^{-15}$</td>
<td>50,749.2</td>
<td>NOD2</td>
</tr>
<tr>
<td>TT*</td>
<td>\textit{NOD2} &amp; \textit{CYLD}</td>
<td>60</td>
<td>103.3</td>
<td>$3 \times 10^{-24}$</td>
<td>50,749.2</td>
<td>NOD2</td>
</tr>
</tbody>
</table>

*Data stratified based on the AA, AG, GG genotypes for the rs2076756 SNP from the WTCCC data (50,756.9 kb) and CC, CT, TT genotypes for the rs5743289 SNP from the NIDDK data (50,756.8 kb). **Window with marker information from both genes. †A window $\chi^2$ using composite likelihood.

III. \textit{CDH3/CDH1} and \textit{IRF8}

Table 7 shows the significance and estimated locations for the \textit{CDH3/CDH1} and \textit{IRF8} windows. The original analysis of the WTCCC data had shown that both windows were significantly associated with CD ($1 \times 10^{-8}$ and $6 \times 10^{-9}$, respectively). Neither of these signals were however initially replicated with the NIDDK GWA scan of the full data-set but showed significant association when the windows were analysed based on a subset of the data, using phenotypic
information provided by the NIDDK IBDGC. This subset included patients with ileal CD who had involvement of at least one extra-ileal intestinal location, *i.e.* jejunal, colorectal or perianal. The signal near *CDH3/CDH1* was replicated using this subset of the NIDDK data despite the much smaller number of cases (Table 7). For both GWA scans, the estimated location $\hat{S}$ for the former window was between *CDH3* and *CDH1*, within an LDU block that spans 65 kb (Figure 8). The causal locus could be anywhere within that block, which encompasses the 3' region of *CDH3* through to *CDH1* intron 2 (Figure 8), but it also includes a functional promoter SNP rs16260 (Li et al., 2000) (Figure 8) previously associated with Irritable Bowel Syndrome (IBS).
Figure 8. Localisation within the CDH3/CDH1 region.
The LD map of the region is illustrated by the black line, which is obtained by plotting HapMap LDUs (Y axis) against kb (X axis). The red vertical arrow is the estimated location $\hat{S}$ for both data sets but because of the very long LD block, the causal location(s) could reside anywhere in this block. The rs16260 is a functional SNP within this block, which is located 365 nucleotides upstream of the transcription start site for CDH1. NIDDK Ileal+ data: ileal CD with involvement of at least one extra-ileal intestinal location. The blue horizontal dashed line shows the 95% Confidence Interval for the WTCCC CD dataset. The purple horizontal dashed line represents the 95% Confidence Interval for the NIDDK Combined Ileal+ data. The orange triangles represent the SNPs on the Affymetrix 500K genotyping array used in the WTCCC CD study. The blue diamonds represent the SNPs on the Affymetrix 500K genotyping array used in the WTCCC study. The orange triangles represent the SNPs on the Illumina HumanHap 300v.1 genotyping array used in the NIDDK study.
For the IRF8 window, the WTCCC data yielded an Ŝ location 29 kb downstream of the gene, within a small block that is flanked by LD breakdown (Figure 9). The analysis of the NIDDK data for patients with any extra-ileal intestinal involvement showed a signal, which is 1.7 kb telomeric to IRF8 within a region of LD breakdown (Figure 9).

Table 7. Association statistics and estimated location of the causal variation for two different windows covering CDH3 (68,678-68,733 kb), CDH1 (68,711-68,869 kb) and IRF8 (85,933-85,956 kb) in relation to the locations on the human genome sequence.

<table>
<thead>
<tr>
<th>Data</th>
<th>Window</th>
<th>Cases</th>
<th>$\chi^2$</th>
<th>P-value</th>
<th>Estimated Location (kb)</th>
<th>95% Confidence Interval CI (kb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTCCC</td>
<td>CDH3/CDH1</td>
<td>1698</td>
<td>32.6</td>
<td>$1 \times 10^{-8}$</td>
<td>68,746.1</td>
<td>68,682 – 68,836</td>
</tr>
<tr>
<td>NIDDK*</td>
<td>CDH3/CDH1</td>
<td>315</td>
<td>6.2</td>
<td>$1 \times 10^{-2}$</td>
<td>68,746.1</td>
<td>68,684 – 68,836</td>
</tr>
<tr>
<td>WTCCC</td>
<td>IRF8</td>
<td>1698</td>
<td>34.7</td>
<td>$4 \times 10^{-9}$</td>
<td>85,982.3</td>
<td>85,982 – 85,984</td>
</tr>
<tr>
<td>NIDDK*</td>
<td>IRF8</td>
<td>315</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jewish§</td>
<td>IRF8</td>
<td>38</td>
<td>20.9</td>
<td>$5 \times 10^{-6}$</td>
<td>85,958.2</td>
<td>85,949 – 85,961</td>
</tr>
<tr>
<td>Non-Jewish</td>
<td>IRF8</td>
<td>277</td>
<td>5.3</td>
<td>$2 \times 10^{-2}$</td>
<td>85,958.2</td>
<td>85,935 – 85,961</td>
</tr>
</tbody>
</table>

*Ileal CD with involvement of at least one other extra-ileal intestinal location. §432 Jewish and 515 non-Jewish controls were used for these analyses. †A window $\chi^2$ using composite likelihood. Note that the 95% CI for IRF8 for the UK and North American data are non-overlapping suggesting heterogeneity of location of the causative change, i.e.: allelic heterogeneity.
Figure 9. Localisation within the *IRF8* region.
The LD map of the region is illustrated by the black line, which is obtained by plotting HapMap LDUs (Y axis) against kb (X axis). The red vertical arrow is the estimated location $\hat{S}$ for both data sets NIDDK Ileal+ data: ileal CD with involvement of at least one extra-ileal intestinal location. Two SNPs have been identified for UC and MS in GWA meta-analyses. The short light blue horizontal dashed line shows the 95% Confidence Interval for the WTCCC CD dataset. The purple horizontal dashed line represents the 95% Confidence Interval for the NIDDK Jewish Ileal+ data. The green horizontal dashed line represents the 95% Confidence Interval for the NIDDK Non Jewish Ileal+ data. The 95% CIs are non-symmetrical due to the block-step structure of the human genome. The blue diamonds represent the SNPs on the Affymetrix 500K genotyping array used in the WTCCC study. The orange triangles represent the SNPs on the Illumina HumanHap 300v.1 genotyping array used in the NIDDK study.
These two NIDDK datasets yielded essentially identical \( \hat{S} \) locations. The 95% CI for both the Jewish and non-Jewish data included part of the \( IRF8 \) gene with an estimated location 24 kb upstream of the WTCCC signal (Table 7, Figure 9), further suggesting allelic heterogeneity.

In this analysis 98 windows were tested. Statistical significance observed in the WTCCC data passed the Bonferroni threshold calculated based on these 98 tests (See Methods Section of this chapter). These signals were replicated using the NIDDK data with its smaller sample size and SNP coverage.
IV. DISCUSSION

Here, using the multi-marker genetic mapping approach on the available WTCCC, three novel significant signals of association with CD were found on chromosome 16q alone, all of which were replicated using the NIDDK GWAS data supporting the presence of genetic heterogeneity on chromosome 16q.

Evidence is presented for the first time that there is an independent involvement of a locus in the vicinity of \textit{NOD2}, near the neighbouring gene \textit{CYLD}. The pattern of association shows clear evidence of an independent signal but does not formally show that the \textit{CYLD} gene is involved. A distant enhancer affecting \textit{NOD2} expression could be implicated but other evidence suggests that \textit{CYLD} itself may be important.

First, in support of this notion, genome-wide cDNA microarray analysis demonstrates that \textit{CYLD} gene expression is down-regulated in CD (Costello et al., 2005). \textit{NOD2} interacts with Nuclear Factor-κB (NF-κB) signalling in a complex way, which includes involvement of ubiquitinylation (Abbott et al., 2004). Functional studies have so far provided conflicting evidence on the effect that the three \textit{NOD2} mutations have with respect to inflammation and bacterial recognition (Eckmann and Karin, 2005). On the one hand, it was reported that upon bacterial LPS stimulation, the three mutant \textit{NOD2} alleles result in the
ablation of the NOD2 Peptidoglycan-sensing activities and the failure to activate NF-κB (Bonen et al., 2003). On the other hand, a mouse-model of the frameshift 3020insC mutation showed increased levels of the cytokine IL-1β, which is a pro-inflammatory cytokine, after stimulation with MDP (Maeda et al., 2005). It is of interest that CYLD is a deubiquitinating (removal of ubiquitin) enzyme which has been shown to regulate cell proliferation, cell survival and inflammatory responses (Brummelkamp et al., 2003) and is also involved in NF-κB signalling. Dysregulation of NF-κB signalling leads to a defective immune system causing an immunodeficient or autoimmune phenotype depending on whether NF-κB function is impaired or persistent (Courtois and Gilmore, 2006).

**CYLD** is important in immune homoeostasis since it prevents the spontaneous activation of NF-κB in peripheral T and B lymphocytes. The peripheral T-cells from CYLD-deficient mice have increased sensitivity and a heightened response to T-Cell Receptor (TCR) stimulation, which leads to spontaneous inflammation in the colon (Reiley et al., 2007), and colitis-associated tumorigenesis (Zhang et al., 2006). Inflammation is the major underlying phenotype of CD and some Crohn’s Disease patients develop colon cancer at a later stage in life. In this study a causal locus downstream of **CYLD** was mapped, which lies 2kb upstream of a putative gene regulatory element (Pennacchio et al., 2006) and approximately 7kb upstream of a Leprosy susceptibility GWAS SNP (Zhang et al., 2011). The element is located in an LD block spanning 8.3kb (Figure 7A, B). This regulatory element could potentially be an enhancer for **CYLD**, especially since **CYLD** expression has been found to be downregulated in CD. However, the estimated
location of the putative causal agent in this possible regulatory region could also be pointing to a mutation in which acts as a distant element in relation to *NOD2*.

The lower significance in the NIDDK data, as compared to the WTCCC result, is probably not only due to the difference in sample size but also because the phenotypic classifications were different in the two studies. The WTCCC included any subtype of CD and not just the ileal form of the condition. The 95% Confidence Interval (CI) for the *CYLD* window is very narrow for both datasets because the $S$ is within a region of LD breakdown caused by a recombination hot spot.

Unfortunately, the data analysed in this study did not contain the actual *NOD2* mutations and the results are therefore based on data stratified according to a SNP, which is in complete LD with the three common *NOD2* mutations. Subsequent to publishing the Chromosome 16q study (Elding et al., 2011), a meta-analysis on Leprosy (Zhang et al., 2011) identified a susceptibility GWAS SNP closely located to the *CYLD* signals identified in this Chapter using the LDU multi-marker mapping approach. This is of interest since both CD and Leprosy display common immunologic characteristics, which include a Th1-cell response with granuloma formation (Zhang et al., 2009). It is also suggested that some CD cases might have a common mycobacterial cause as seen in Leprosy (Schurr and Gros, 2009). Additionally, the ENCODE (ENCyclopaedia Of DNA Elements) Consortium subsequently published a comprehensive list of all the DNA functional elements in the human genome, including Transcription Factor Binding
sites and their respective Transcription Factors as well as DNAse I Hypersensitive site, which are sites that are commonly found in transcriptionally active genes. It was interesting to find that the estimated location of the putative causal agent and the 95 % CI for the CYLD signal that was identified in this Chapter contained several transcription factor binding sites. Indeed the estimated location of the putative causal agent mapped precisely upstream of a binding site for the transcription factor CEBPB, in a DNase I Hypersensitive Site. The gene that codes for this transcription factor is essential in the regulation of genes that are implicated in inflammatory and immune responses (Boi et al., 2012; Mayer et al., 2013). The IBDase FP7 European consortium performed an independent conditional analysis where they stratified patients based on the actual NOD2 mutations and subsequently identified the involvement of CYLD independently from that of NOD2 in patients that do not carry the common NOD2 mutations (I. Cleynen, 2011), which to an extent re-enforces the findings presented here. Indeed, CYLD is known to be modulated by some bacteria and viruses and as introduced in Chapter I of this thesis, the gut microbiota are known to play a significant role in IBD aetiology.

The second and third region were identified using the phenotypically stratified data that contained patients with ileal as well as extra-ileal involvement demonstrating that considering phenotypic heterogeneity is clearly important. The second region covers the genes CDH3 and CDH1 encoding cadherin proteins that participate in cell recognition, signalling, morphogenesis and tumour progression. CDH1 encodes an epithelial cadherin (E-Cadherin) expressed in the intestine with essential functions in intestinal homeostasis (Schneider et al.,
2010). The loss of E-cadherin expression leads to apoptosis and shedding of cells and to disruption of the maturation of Paneth and Goblet cells, important in the innate immune system and microbial defence (Schneider et al., 2010). E-cadherin helps to maintain the intestinal epithelial defence system, and reduced $CDH1$ expression is a feature of CD and UC patients with an inflamed intestinal epithelium (Gassler et al., 2001). A genome-wide linkage analysis on CD reported evidence of linkage on 16q, some 25cM downstream of $NOD2$, in families that did not carry the $NOD2$ mutations (van Heel et al., 2003). Notably, $CDH3$ and $CDH1$ are at that linkage peak, approximately 25Mb downstream of $NOD2$. However, GWA studies and meta-analyses on CD did not detect these genes despite the large number of samples and imputation based on the latest HapMap samples. A GWA study on Ulcerative Colitis on the other hand, did report $CDH1$ as a new susceptibility locus (Barrett et al., 2009), with the most significant SNP for UC 180kb upstream of the gene, which will be further discussed in Chapter IV. Although $CDH1$ has not been reported for CD by others to date, this analysis demonstrates that the most likely location of the causal variant is within an interval that is flanked by $CDH3$ and $CDH1$. This interval is an LD block that includes a functional promoter variant (rs16260; Figure 8) (Li et al., 2000) that is also associated with IBS (Villani et al., 2010), a chronic inflammatory condition involving recurrent abdominal discomfort. $CDH1$ was also detected in a GWA meta-analysis for colorectal cancer and the reported SNPs fall within our confidence interval (Houlston et al., 2008). $CDH3$, which encodes Placental-
Cadherin (P-cadherin), is also implicated in colorectal carcinomas (Milicic et al., 2008).

The third region became statistically significant after separating the data further into Jewish and non-Jewish patients and this effect shows the importance of considering heterogeneity of ancestry. The third region covers the IRF8 gene, which encodes the transcription factor also known as Interferon Consensus Sequence-Binding Protein, which plays a negative regulatory role in cells of the immune system. Using a subset of the NIDDK data (Jewish patients with ileal CD plus additional extra-ileal involvement) yielded an estimated causal location 24 kb away from the estimate obtained using the WTCCC data. The difference in localisation may reflect allelic heterogeneity.

The significant association in the IRF8 region on chromosome 16q was originally identified in a meta-analysis on Multiple Sclerosis (MS) (De Jager et al., 2009), which was shortly followed by a meta-analysis that identified an association between the region harbouring IRF8 and UC (Anderson et al., 2011), the other sub-type of IBD. However, the latest association studies on CD failed to reveal any CD-specific associations on Chromosome 16q other than NOD2. Thus, the analysis presented here, together with other GWASs, confirm the continually emerging evidence for the presence of shared loci among different immune and inflammatory-mediated complex diseases. IRF8 has been additionally implicated in Systemic Lupus Erythematosus (SLE) (Lessard et al., 2012) as well as MS (De Jager et al., 2009), UC (Anderson et al., 2011) and CD
(Elding et al., 2011) (Figure 9). This greatly suggests the implication of shared pathways between these diseases, and hence calls in the need for pathway analysis in complex diseases. *IRF8* expression is crucial in bone metabolism, with *IRF8*-deficient mice displaying extensive osteoporosis, one of the extra-intestinal manifestations associated with CD (Zhao et al., 2009).

This analysis provided a novel insight into the genetic and phenotypic heterogeneity of CD and demonstrates that the approach taken in this part of the project may be a promising way forward to study other frequent and complex diseases. Following the results that were obtained from this hypothesis-driven part of this project, the next step was to perform a hypothesis-free GWAS, using the LDU multi-marker mapping approach to the WTCCC and NIDDK CD datasets, which will be explored in the next chapter.
CHAPTER III. NOVEL GENE REGIONS IDENTIFIED FOR CROHN’S DISEASE.

I. INTRODUCTION

The analysis of chromosome 16q using only two GWASs described in Chapter II was very encouraging and illustrated how this LDU multi-marker approach can provide additional study power and highlighted the importance of genetic heterogeneity (i.e. the involvement of different risk genes in different patients) as well as that of phenotypic heterogeneity. This paved the way to studying the whole genome.

The purpose of the next part of the project was thus to analyse the whole genome using the same approach, and exploiting the positive experience of the use of phenotypic sub-classification, in order to see whether it was possible to find additional susceptibility disease genes (see the Methods section of Chapter II for further details). The work described in this chapter has been published (Elding et al., 2013).
II. METHODS

i. Genetic Analysis

As in the previous chapter, a total of 1,698 cases of CD and 2,948 ethnically matched controls were analysed from the UK WTCCC GWAS data (WTCCC, 2007) and the GWAS replication data consisted of 813 North American CD patients and 947 ethnically matched controls from the NIDDK IBDGC. Data quality control was carried out by Winston Lau as described in the previous Chapter.

Each chromosome arm was divided into non-overlapping analytical windows for both the WTCCC and the entire NIDDK GWA data-sets, as described in the Methods section of Chapter II. For each window along the whole genome, a composite-likelihood ($\Lambda$) test was used, in which all the SNPs within a window were tested simultaneously (see previous chapter for more details about the methodology used). The method returned a P-value together with an estimated location ($\hat{S}$) of the putative causal agent and the LDU estimation of $\hat{S}$ for each window is converted back to kb (NCBI build 37) by using linear interpolation of the two flanking SNPs in HapMap. In cases where $\hat{S}$ mapped to the end of a window, the window was extended in that direction to capture SNPs on the far side to improve the accuracy of location.
ii. Phenotypic Stratification

The previous analysis (See Chapter II) showed that stratifying the analysis according to the occurrence of extra-ileal intestinal involvement as opposed to ileal inflammation alone (a subdivision of which appears to be linked with genetic stratification) increased the power of detecting association of the 16q windows. Since the NIDDK GWAS data contains a detailed description of the location of patients’ intestinal inflammation, the NIDDK data was stratified according to this information. For all the analytical windows that showed nominal statistical evidence of association using the WTCCC data, we analysed the same windows using the entire NIDDK data and also using a subset of the NIDDK data containing CD cases that reported extra-ileal in addition to ileal inflammation. Unlike the controls, the vast majority of cases in this subdivision were non-Jewish. We therefore analysed only non-Jewish patients with extra-ileal inflammation and non-Jewish controls. This subdivision reduced the sample size from 813 to 277 CD cases and from 947 to 515 controls. Preliminary analyses showed that fewer signals were obtained by doing this, as might be expected because of the reduced power, but our aim was to reduce as far as possible false positives obtained as a result of ethnic stratification.
iii. Previously reported and novel significant gene-regions

The first part of this analysis was to look for signals within the previously published intervals from the recent meta-analysis (Franke et al., 2010) and present P-values for the relevant data sets (See Table 8). For the novel discovery analysis a Meta-analysis P-value is presented for each analytical window that shows a) evidence of nominal statistical significance for both data samples and b) the $\hat{S}$ estimate for both samples are within 150 kb of one another. These criteria were used in order to reduce the possibility of detecting more than one signal, as a result of heterogeneity, and thus facilitate the meta-analysis of shared locations.

iv. Meta-analysis of shared locations

The significant P-values obtained from the independent datasets were combined using Fisher’s combined probability test. For $k$ independent tests, where each independent test of the null hypothesis results in a P-value, the P-values for each independent test can be combined as follows:

$$
\chi^2 = -2 \sum_{i=1}^{k} \ln(P)
$$

where the $\chi^2$ has $2k$ degrees of freedom.
In order to account for multiple testing, we used a Bonferroni P-value threshold of $1 \times 10^{-5}$, which corresponds to the total number of analytical windows and the additional analyses performed for the NIDDK data using the extra-ileal subgroup. In order to capture replications of slightly lower significance but with more precisely agreeing $\hat{S}$ values, a second threshold was used in which the $\hat{S}$ for both datasets had to lie within 80 kb of each other to be considered a replication and with a Meta P-value within the range of $1 \times 10^{-3}$ and $1 \times 10^{-5}$.

v. Significant gene-regions and Gene Ontology

For each of the replicated windows, the closest gene within a maximum distance of approximately 300 kb of the estimated location $\hat{S}$ for each sample was retrieved and then listed in the tables (See Tables 8 and 9). In the case where the closest gene was more than $\sim$300kb away, the estimated location $\hat{S}$ is listed as being ‘intergenic’. Using BioMart, the Gene Ontology (GO) annotations attributed to each gene were retrieved and the results are shown in Appendix II.
III. RESULTS

iv. Identifying the previously reported CD intervals

The first goal was to determine whether the LDU mapping method could detect the 71 loci previously identified from the most recent large meta-analysis of six independent datasets. Our aim was to consider the reported intervals rather than focusing on the specific genes flagged in the Consortium study. Table 8 presents the statistical evidence and location estimates, for signals within these 71 intervals (Franke et al., 2010). Since the majority of these intervals (approximately 80%) were more than 150 kb in length (defined around the most significant SNP using LD information), it was difficult to meta-analyse the results obtained using the multi-marker mapping procedure used in this analysis, since there was a risk of combining independent signals. The P-values obtained from WTCCC and NIDDK are therefore presented separately. Using the multi-marker mapping approach, a total 66 out of the 71 intervals (loci) were identified in one or both of these data sets using an uncorrected significance threshold of $P<0.05$. Only five intervals showed no evidence of association for either WTCCC or NIDDK using the LDU method. The majority of these 66 signals (88%) were identified with the larger WTCCC data with the remaining 8 intervals (12%) showing nominal evidence of association for the smaller NIDDK data set alone. Interestingly, these eight (12%) include regions (e.g. 10q22, 16p11 and 19q13)
that have previously been implicated for paediatric IBD patients (Imielinski et al., 2009). This is consistent with the fact that the NIDDK dataset probably includes a larger number of patients with early onset CD (~37%) than WTCCC, where this information is not recorded. It is worth noting that one of the 6 contributory data sets to the most recent meta-analysis also included entirely paediatric IBD patients (Franke et al., 2010). The first published results by the WTCCC (WTCCC, 2007) reported 9 loci but Table 7 shows 28 signals for WTCCC alone that passed the genome-wide significance threshold of $1 \times 10^{-5}$.

v. Genetic Heterogeneity within the previously reported CD intervals

Unlike the recent meta-analysis, where a particular gene or genes within these intervals was identified through a series of in silico analyses, the genes closest to the location estimates are presented here (Table 8). In several cases these agree with the previously identified genes (e.g. STAT3, IL23R), but in other cases there are differences. For several regions two different estimates of localisation ($\hat{\beta}$) were obtained for WTCCC and NIDDK, both within the same interval. Heterogeneity in some regions is expected but location estimates can help identify this. For example for the interleukin-rich interval (2q12.1), the WTCCC dataset yielded an estimate within IL18RAP but for NIDDK the $\hat{\beta}$ is within IL1RL1. Both genes have been previously suggested as candidates within the 2q12.1 interval (Franke et al., 2010) but an independent fine mapping study has shown strong association to the IL18RAP rs917997 SNP for both CD and UC.
(Zhernakova et al., 2008), which is approximately 10 kb away from WTCCC Ŝ (Figure 10). A recent study (Rivas et al., 2011) using deep sequencing identified a rare coding variant (V527L) of possible functional significance within *IL18RAP*, which is only 8 kb away from the WTCCC location, though it is probable that other functional variants are also involved. As far as the second gene is concerned, the importance of *IL1RL1* to inflammatory processes has also been documented (Akhabir and Sandford, 2010) for a variety of human pathologies including celiac disease (Amundsen et al., 2010). The LDU map clearly shows that there are several recombination hot spots between *IL18RAP* and *IL1RL1* (Figure 10) making it likely that these two signals are independent and that there is genetic heterogeneity within these previously identified intervals. This is similar to that previously noted in the case of *NOD2* and *CYLD*, in the previous chromosome 16q study (Elding et al., 2011), as described in Chapter II.
vi. 134 novel gene-regions identified

In addition to the 66 localization estimates obtained, 134 novel signals were identified. Table 7 shows the list of 78 of the 134 novel signals that passed the genome-wide significance threshold of $1 \times 10^{-5}$. Here the distance between the locations of each signal does not exceed 150 kb, so the meta-analysis P-value is provided (as outlined in methods). Approximately 78% of the WTCCC signals were replicated using the complete NIDDK data set. However, in a third of these,
the association was significant in the complete but also in the smaller subset of the data. In this third, the smaller NIDDK extra-ileal subset showed higher significance despite the substantial decrease in the number of cases and controls. Furthermore 22% of the WTCCC signals were only replicated using this subset of the NIDDK data.

Figure 11. Localisation within the ERBB4 region. LD map of the region is shown by plotting HapMap Regional LDUs (Y axis) against kb (X axis). The red vertical arrows are the estimated locations Ŝ for the WTCCC and NIDDK datasets. The red diamonds represent the SNPs found in this region on the WTCCC Affymetrix 500K genotyping array whereas the blue diamonds represent the SNPs found in this region on the NIDDK Illumina HumanHap 300 genotyping array.
For the majority (74%) of the 78 signals, the location estimates from both datasets point to the same gene, with approximately half of the signals being intragenic and half intergenic locations (gene with asterisk implies that at least one of the signals is within the gene (Table 9 and 10). In all cases, including the ~50% that reside outside of genes, the closest gene is considered as a candidate. It should however be noted that in some cases long range cis-elements may be involved, which regulate genes far outside the 150 kb distance, with other genes intervening, or regulatory elements may exist within an intron of an adjacent gene (Jones and Swallow, 2011). Indeed, cis-acting gene expression Quantitative Trait Loci (eQTL) have been implicated in both Mendelian and complex disorders. eQTLs are loci in the genome that control mRNA expression levels. There have been several efforts in correlating GWAS disease-risk loci with eQTL genes in an attempt to further explain the missing heritability that is very common to complex conditions, including CD. In fact, some GWAS CD susceptibility SNPs have been shown to be associated with variable expression levels of PTGER4, CARD9, ERAP2, TNFSF11 in Epstein-Barr Virus (EBV) transformed Lymphoblastoid Cell Lines (LCLs) (Libioulle et al., 2007; Montgomery and Dermitzakis, 2011).

Several of the novel genes have been reported to be involved in inflammatory/immune dysregulation conditions (e.g. DOCK8, ITGA9). In other cases the genes have been previously implicated in colonic inflammation or colonic cell morphology based on functional studies. By way of illustration, Figure 11 presents an example of the estimated locations (Ŝ) for the genomic region that harbours ERBB4 (2q34 window). For both datasets, this window was significantly
associated with CD with a Meta P-value of $3 \times 10^{-6}$ (Table 9). Figure 11 shows the LDU map starting from the 3' region and spanning half way down the gene, which stretches across more than 1 Megabase. The map shows numerous short LD blocks across the region. However, despite the large LD breakdown in the area, both estimates of $\hat{S}$ are close to each other and within the same intron.

Table 10 shows the list of 56 of the 134 novel signals that showed association with CD where the P-values ($1 \times 10^{-3} - 1 \times 10^{-5}$ range) based upon meta-analyses were below the Bonferroni threshold but estimates of localization in the two data sets were not more than 80 kb apart from each other. Most of the signals (96%) in Table 10, give estimates of $\hat{S}$ for the same gene.
IV. DISCUSSION

Using the LD approach 66 of the 71 previously reported loci from meta-analysis were confirmed and 134 novel gene regions that are associated with Crohn’s Disease have been identified, providing evidence for 200 gene regions that include CD susceptibility loci. More precise location estimates are provided for the 66 previously published intervals, as well as locations for the 134 new signals. The very large numbers of genes listed in Table 9 and 10 support the idea that CD is truly polygenic and complex in nature and that much of this complexity is genetic in origin. Many genes show functions that are compatible with involvement in immune/inflammatory processes as well as integrity of the intestinal epithelium and differentiation.

In the CD analysis described in this chapter, many of the replicated signals were identified only, or more strongly, using a subset of the NIDDK data, which contained patients with ileal CD who had involvement of at least one extra-ileal intestinal location. Despite the substantial decrease in sample size, analysis of this sub-phenotype using this method yielded much higher power than the analysis of the full data. This indicates that phenotypic heterogeneity is clearly important and that accurate as well as detailed phenotype information is crucial in genetic studies, especially when assessing a trait showing clinical variation.
Rather than mapping to LD intervals around the most significant SNP, this method provides estimated locations of the putative causal agents. These location estimates are of great importance since they do not only pinpoint precise locations but also provide the possibility of detecting possible heterogeneity, as shown with the example of *NOD2/CYLD* on chromosome 16q described in the previous Chapter and with the example of *IL1RL1/IL18RAP* on chromosome 2q identified here.

Several of the genes that were identified in this part of the analysis had been previously implicated in IBD through functional studies. An example is *ERBB4* (which encodes Receptor protein-tyrosine kinase erbB-4) on 2q34 (See Table 9). *ERBB4* is expressed at high levels in the inflamed colonic mucosa of CD patients (Frey et al., 2009). Using adult mouse colon, it was also shown that ERBB4 is an important regulator in the epithelial response to inflammation and injury (Frey et al., 2009). *ERBB4* expression has been linked to a number of cellular processes such as cell survival, proliferation and tumorigenesis in different tissues (Erlich et al., 2001; Starr et al., 2006). A recent study suggested that this elevated *ERBB4* expression could lead to colitis-associated development of colorectal tumours (Frey et al., 2010). *ERRB4* has also been implicated, together with E-cadherin (encoded by *CDH1* on 16q22.1, previously identified as a risk gene for CD and ulcerative colitis), in the suppression of anoikis (Kang et al., 2007) (programmed cell death as a result of cell detachment from the extracellular matrix), suggesting that there may be interaction between these two genes. Despite the fact that *ERBB4* is a very large gene (>1 Mb), the estimated locations of the putative causal agent for both datasets (WTCCC and NIDDK) are very close and within
the same intron, making it an excellent target for follow-up fine mapping studies and re-sequencing.

Several of the genes listed in Table 10, which presents 56 gene regions with lower confidence of association, but with very close location estimates between the two datasets, are also very interesting. For example, the window harbouring the BTLA gene gave location estimates that are just 2 kb apart. A study using a mouse model of colitis has shown functional evidence of BTLA involvement in colitis (Steinberg et al., 2008). Box 1 illustrates a functional overview of some genes of interest that were identified in this part of the project. The molecular and functional attributes of all the genes identified in this chapter are illustrated in Appendix II.

The LDU multi-marker mapping approach successfully identified many additional novel CD susceptibility loci by re-analysing publically available GWAS data. The next step would be to shift the focus towards UC and identify whether, using the LDU multi-marker mapping approach, more loci could be detected for this-subtype, which is known to have a lower genetic contribution than UC.

**Box 1: Functional overview of some genes of interest identified.**
**ERBB4:** (v-erb-a erythroblastic leukemia viral oncogene homologue 4). This gene is a member of the Tyrosine protein kinase family and the Epidermal Growth Factor receptor subfamily. ErbB4 is a TNF-inducible receptor and has been found to regulate repair in response to injury and inflammation. Activation of E-Cadherin (encoded by CDH1—See Table 3) which suppresses anoikis (a type of apoptosis involving detachment from the extracellular matrix) activates ErbB4 receptor tyrosine kinase and subsequent activation of PI3 Kinase pathway leading to cell proliferation.

**BTLA:** (B and T Lymphocyte Associated). BTLA is a member of the immunoglobulin superfamily containing a single Ig domain. It is also a receptor that relays inhibitory signals to suppress the immune response. BTLA engagement is required to prevent colitis acceleration in a mouse model. The expression of TNFSF14 and BTLA on both adaptive and innate cells strongly indicates that this ligand-receptor system could play several roles in immunity and inflammation. Mutations in this gene have been associated with an increased risk of Rheumatoid Arthritis.

**ITGA9:** (integrin alpha 9). This gene encodes an alpha integrin. Integrin are heterodimeric integral membrane glycoproteins composed of an alpha chain and beta chain that mediate cell-cell and cell-matrix adhesions. ITGA9 is normally active in colonic epithelia. Alpha-9 deficient bone marrow cells in mice show a marked decrease in STAT3 phosphorylation (See Table 1 on chromosome 17q) after G-CSF stimulation in granulopoiesis.

**DOCK8:** (dictator of cytokinesis 8). This gene encodes a member of the DOCK180 family of Guanine Nucleotide Exchange Factors. Mutations in this gene result in the autosomal recessive hyperimmunoglobulin E (hyper-IgE) syndrome characterized by immunodeficiency, lack of connective tissue and recurrent infections among other symptoms. DOCK8 is most highly expressed in B and T lymphocytes and mutations in DOCK8 diminish clonal expansion of both CD4 and CD8 T cells after engagement of TCR and co-stimulatory molecules. It was found that patients with large homozygous deletions in DOCK8 had IBD or suggestive IBD. DOCK8 is also required to form a normal T-cell immune-synapse with antigen-presenting Dendritic Cells (DCs).

**BRD7:** (bromodomain containing 7). The product of this gene has been identified as a component of one form of SWI/SNF chromatin remodeling complex which also interacts with p53. BRD7 depletion delays replicative senescence and extends cellular life-span.

**TEC:** (Tec protein tyrosine kinase). Tec is part of the Tec family non-receptor protein tyrosine kinases. Tec kinase is an central component of T-cell signaling and has a distinct role in T cell activation. This gene plays a role in Calcium influx, apoptosis, gene expression, actin re-organisation as well as cell-adhesion and migration and is found to be activated by bacterial Lipopolysaccharide (LPS).

**USP1:** (ubiquitin-specific peptidase 1). This gene encodes a member of the ubiquitining specific processing (UBP) family of proteases that is a deubiquitinating (DUB) enzyme. PCNA (a central component of the ubiquitin-based molecular switch dictating error-free versus error-prone DNA repair) polyubiquitination is negatively regulated by USP1 in the absence of DNA damage.
Table 8. Whole-genome association statistics and closest gene to the
estimated location Ŝ of the causal variant for the previously reported 71 LD
intervals.
Chr

Reported
Interval (Mb)

WTCCC Ŝ

1p31.3

67.36 - 67.77

67,684.8

1p13.2

113.95 - 114.62

1p36.23

7.74 - 7.97

NIDDK Ŝ

NIDDK Pvalue

-11

67,707.3

3.0x10

-03

114,108.3

5.0x10

-

-

7,801.1

2.2x10

-03

160,837.3

5.8x10

114,560.3

WTCCC Pvalue

2.1x10
1.4x10

1q23.3

160.69 - 162.47

160,887.0

2.6x10

1q25.1

172.66 - 172.95

172,891.9

3.6x10

1q32.1

200.85 - 201.06

200,877.3

3.0x10

1q22

154.97 - 156.13

-

1q31.3

197.32 - 197.95

197,786.1

1q32.1

206.80 - 207.03

2p23.3

25.45 - 25.60

2p23.3

27.39 - 27.86

-13

-

-14

200,957.2

-10
-03
-05
-03

-02

1.5x10

Gene (WTCCC/
NIDDK If different)

IL23R*
OLFML3/MAGI3*
CAMTA1*
ITLN2/CD244
TNFSF18
C1orf106*/KIF21B*

-

-

-

-

-04

-

-

DENND1B

-

-

-

-

-

25,389.2

3.5x10-02

-

-

POMC*

27,697.4

5.4x10-04

27,619.3

2.3x10-11

IFT172*/PPM1G*

-05

43,581.0

1.1x10-02

THADA*

1.2x10

2p21

43.45 - 43.95

43,840.8

2.0x10

2p15

60.92 - 61.89

61,395.5

1.9x10-05

-

-

C2orf74

2q37.1

234.15 - 234.57

234,144.8

5.6x10-25

234,171.9

2.2x10-09

ATG16L1*

2q12.1

102.80 - 103.30

103,059.8

1.8x10-08

102,951.7

1.7x10-05

IL18RAP*/IL1RL1*

-02

198,205.8

1.1x10-03

PLCL1*/ANKRD44

2q33.1

198.14 - 198.96

198,957.7

1.6x10

2q37.1

231.05 - 231.23

231,109.3

2.8x10-05

-

-

SP140*

3p21.31

48.18 - 51.75

49,743.9

1.7x10-31

48,818.0

3.3x10-19

RNF123*/PRKAR2A*

3p24.3

18.60 - 18.88

18,707.0

5.3x10-03

18,629.1

2.6x10-05

SATB1

-51

40,288.0

2.7x10-07

PTGER4

5p13.1

39.84 - 40.96

40,447.1

6.0x10

5q31.1

129.38 - 132.02

131,748.2

2.7x10-22

131,631.4

8.9x10-07

C5orf56*/SLC22A4*

-09

-

-

IRGM

5q33.1

150.03 - 150.40

150,230.7

3.6x10

5q33.3

158.50 - 158.95

158,825.7

5.6x10-06

158,826.0

3.5x10-02

IL12B

5q13.2

72.45 - 72.58

72,465.4

5.8x10-03

-

-

TMEM174

5q15

96.08 - 96.42

96,372.2

1.3x10-08

-

-

LNPEP

5q31.3

141.41 - 141.64

141,480.3

1.3x10-02

-

-

NDFIP1

5q35.2

173.22 - 173.54

-

-

173,417.9

6.7x10-03

C5orf47*

-03

CDKAL1*/E2F3*

6p22.3

20.49 - 21.14

20,559.3

4.3x10

20,433.1

2.8x10-03

6p21.32

31.38 - 32.87

32,720.6

1.2x10-27

32,193.4

1.6x10-07

HLA-DQB2

3,417.6

-07

-

-

SLC22A23*

-

-

106,421.7

4.0x10-02

PRDM1

167,441.4

-09

167,355.9

8.5x10-03

FGFR1OP*/RNASET2*

6p25.2
6q21
6q27
6q15

3.41 - 3.47
106.39 - 106.56
167.34 - 167.55
90.80 - 91.08

1.5x10
3.3x10

-

-

-

-

-

6q25.3

159.34 - 159.54

159,539.7

1.2x10-03

-

-

FNDC1

7p12.2

50.25 - 50.33

50,255.3

9.4x10-04

-

-

C7orf72

8q24.13

126.47 - 126.58

126,544.1

4.5x10-05

-

-

TRIB1

8q24.21

129.49 - 129.60

129,567.2

1.3x10-04

129,570.7

2.9x10-03

intergenic

9p24.1

4.94 - 5.30

5,274.6

1.4x10-04

5,270.3

5.4x10-03

RLN2

-04

-

-

TNFSF15
SNAPC4*/SDCCAG3*

9q32

117.43 - 117.70

117,555.6

3.9x10

9q34.3

139.13 - 139.42

139,280.8

2.3x10-05

139,299.7

2.6x10-03

-29

-

-

CCNY*

6,165.5

1.2x10-08

PFKFB3*/RBM17

10p11.21

35.18 - 35.90

35,554.8

3.4x10

10p15.1

6.03 - 6.17

6,189.9

3.6x10-03

10q21.2

64.30 - 64.76

64,448.3

1.2x10-18

-

-

ZNF365

10q24.2

101.27 - 101.34

101,324.7

1.2x10-32

101,274.6

2.3x10-02

NKX2-3

10q21.1

59.83 - 60.14

59,892.8

9.3x10-09

59,893.1

1.6x10-02

IPMK

10q22.3

81.00 - 81.10

-

-

81,019.8

1.5x10-02

ZMIZ1*

11q13.5

76.02 - 76.36

76,304.4

4.4x10-10

-

-

C11orf30

11q12.2

61.52 - 61.68

61,680.2

3.4x10-02

-

-

RAB3IL1*

11q13.1

63.82 - 64.29

64,027.0

5.8x10-03

64,137.4

3.2x10-02

PLCB3*/RPS6KA4*

-02

12q12

40.13 - 41.02

40,598.3

3.0x10

40,368.0

1.7x10-03

LRRK2/SLC2A13*

13q14.11

44.23 - 44.64

44,491.1

6.6x10-12

44,607.7

3.0x10-02

LACC1/LINC00284

13q14.11

42.82 - 43.10

43,022.6

1.3x10-07

-

-

TNFSF11

97


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<th>WTCCC P-value</th>
<th>NIDDK Ŝ</th>
<th>NIDDK P-value</th>
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**Bold** denotes that the signal is replicated using the data taken only from the Non-Jewish 'ileal' patients who also had extra-ileal inflammation; *at least one of the estimated locations Ŝ is located within the identified gene.
Table 9. Whole-genome association statistics and the closest gene to the estimated location \( \hat{S} \) of the causal variant for the convincingly confirmed 78 gene-regions.

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<tr>
<th>Chr</th>
<th>WTCCC ( \hat{S} )</th>
<th>NIDDK ( \hat{S} )</th>
<th>Gene (WTCCC/NIDDK if different)</th>
<th>Meta-P-value</th>
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### Table 9 continued

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**Bold** denotes that the signal is replicated using the data taken only from the Non-Jewish 'ileal' patients who also had extra-ileal inflammation; *at least one of the estimated locations Š is located within the identified gene;§ the signal is significant in the Pooled NIDDK data as well as the stratified Non Jewish ileal and extra-ileal dataset.

**Table 10.** Whole-genome association statistics and the closest gene to the estimated location Š of the causal variant for the confirmed 56 gene-regions (P-value 10^{-3}-10^{-5}).

<table>
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<th>Chr</th>
<th>WTCCC Š</th>
<th>NIDDK Š</th>
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<th>Meta-P-value</th>
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<tr>
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<td>4p15.33</td>
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<td>WTCCC Š</td>
<td>NIDDK Š</td>
<td>Gene (WTCCC/NIDDK if different)</td>
<td>Meta-P-value</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>---------</td>
<td>----------------------------------</td>
<td>--------------</td>
</tr>
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<td>1,539.0</td>
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<td>12,331.6</td>
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</tr>
<tr>
<td>14q31.1</td>
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<td>50,171.3</td>
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<td>76,275.6</td>
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</tr>
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<td>intergenic</td>
<td>7.3x10⁻⁵</td>
</tr>
</tbody>
</table>

**Bold** denotes that the signal is replicated using the data taken only from the Non-Jewish ‘ileal’ patients who also had extra-ileal inflammation; *at least one of the estimated locations Š is located within the identified gene; ⁵the signal is significant in the Pooled NIDDK data as well as the stratified Non Jewish ileal and extra-ileal dataset.
CHAPTER IV. NOVEL GENE REGIONS IDENTIFIED FOR ULCERATIVE COLITIS.

I. INTRODUCTION

Following the success in identifying novel genes for Crohn’s disease using the LDU mapping approach, the attention was shifted towards Ulcerative Colitis. The progress in identifying genetic risk factors for UC has been slower than that for CD. This is mainly attributable to the fact that much of the attention for association studies was initially given to CD because it has a higher genetic contribution than UC.

However, early linkage analyses had been successful in identifying UC-specific linkage peaks, as well as highlighting the similarities between CD and UC. Interestingly, Giallourakis et al identified an IBD risk haplotype at the \textit{IBD5} locus, which harbours a cytokine cluster, as a general IBD susceptibility factor, with an added epistatic effect between the \textit{IBD5} risk haplotype and the \textit{NOD2} mutations in the case of UC despite the fact that \textit{NOD2} is not a risk factor for UC (Giallourakis et al., 2003). Additionally, the shared \textit{IBD2} locus on chromosome 12 shows much stronger linkage for UC than for CD (Parkes et al., 2000).
The initial UC association analyses involved testing hits that were previously identified and confirmed for CD in UC datasets. Subsequently, genome-wide analysis of larger UC cohorts were carried out, where novel UC loci were identified, owing to the much larger sample sizes and hence higher power than could be envisaged just a few years before. These novel genes provide invaluable insight into the pathogenesis of UC. For instance, \textit{CDH1}, \textit{ECM} and \textit{LAMB1} are all implicated in the correct functioning of the gut's mucosal barrier, which is at the forefront of IBD pathogenesis. In this context it is noteworthy that \textit{CDH1}, encoding the E-Cadherin protein, was identified for the first time in this project as a susceptibility gene for CD, as is described in Chapter II of this thesis. In fact, \textit{CDH1} is an interesting finding since it provides a direct link between UC and colorectal cancer, which is known to be more prevalent among UC cases. The promoter region of \textit{CDH1} has been shown to be hypermethylated in colon cancer, which is an epigenetic mark commonly associated with gene silencing and thus, in this scenario, reduced expression of \textit{CDH1}. This reduced expression could provide a tumour cell sufficient selective advantage for outgrowth (Wheeler et al., 2001). It has additionally been reported that a loss of E-Cadherin function displays preferential right-sided tumorigenesis as opposed to left-sided pathogenesis (Porter et al., 2002). Upon investigation of this left-side protection, it has been functionally shown that P-Cadherin, encoded by \textit{CDH3} (See Chapter II), is expressed very early in colorectal dysplasia (Hardy et al., 2002) and an increase in P-Cadherin, which can substitute for many E-Cadherin functionalities, compensates for the down-regulation effect of E-Cadherin, namely decreased cell-adhesion and facilitation of cell migration (Porter et al., 2002).
Independently of *CDH1*, the risk of colorectal cancer in UC patients increases with disease duration as well as extent of disease, severity of inflammation and early onset of UC. This increased risk of colorectal cancer in UC patients could also in part be explained by the fact that premature telomere shortening, which is often associated with cancer, is observed in the colonic cells of UC patients (Risques et al., 2008).

The largest UC-specific GWAS carried out to date consisted of a meta-analysis of six GWASes containing approximately 6,687 cases and 19,718 controls as a discovery panel and 9,628 cases combined with 12,917 controls as a replication dataset. This study successfully increased the number of UC loci from 29 to 47. Subsequently, an IBD meta-analysis identified 12 new additional UC-specific loci. However, the total disease variance explained by these loci remains at 7.5%. The problem of missing heritability thus applies to UC as well.

Since the LDU mapping approach demonstrated a higher power to detect association and discover more susceptibility loci for CD, as described in Chapters II and III, the aim of the analysis that will be described in this chapter was to re-analyse the WTCCC Phase 2 UC dataset, followed by replication, in an attempt to unearth novel susceptibility loci for UC.
II. METHODS

i. Subjects

The UK WTCCC Phase II Ulcerative Colitis case-control dataset used in this part of the project consisted of 2,869 Ulcerative Colitis cases, and 5,986 nationally-ascertained controls prior to quality control. 2,988 control samples came from the National Blood Services (NBS) Collection of common controls and 2,998 control samples came from the 1958 British Birth Cohort (BC). The diagnosis of Ulcerative Colitis cases was done using standard endoscopic, radiologic and histopathological criteria and the samples were recruited from ten centres within the United Kingdom (Cambridge, Oxford, London, Newcastle, Sheffield, Edinburgh, Dundee, Manchester, Torbay and Exeter) (Consortium et al., 2009). The cases and the controls were genotyped on the high-resolution Affymetrix 6.0 array, containing approximately 1 million SNPs.

In order to replicate the findings, two replication datasets were used. Prior to quality control filtering, the first replication dataset consisted of 538 control samples, which came from a Parkinson’s Disease GWA study and 487 Ulcerative Colitis cases came from a subset of the NIDDK International IBD Genetics Consortium UC data. All the NIDDK UC cases were reported to have the disease extending beyond the rectum (Silverberg et al., 2009). Both the cases and the controls for this replication dataset were genotyped on the Illumina 550v.3
genotyping platform consisting of approximately 550,000 SNPs. The samples for this case-control dataset were of white European, non-Hispanic ancestry (Silverberg et al., 2009).

The second replication dataset consisted of the other subset of the NIDDK UC cases containing 540 UC cases genotyped on the Illumina HumanHap 300v.2 genotyping platform. The ethnically-matched controls used were 515 Non-Jewish controls, which are a subset of the NIDDK CD GWAS described in Chapter II and III, genotyped on the Illumina HumanHap 300v.1 platform. Both the Illumina HumanHap 300v.1 and 300v.2 contain approximately of 320,000 SNPs. Different sets of control data were used since the NIDDK UC data did not have matching controls and therefore, ethnically-matched control data (PD GWAS Controls and NIDDK Non-Jewish CD GWAS Controls) genotyped on similar platforms were used in order to facilitate the merging of genotype data between the cases and controls. Table 11 summarises the data sets used in this part of the project, including the number of samples used after quality control, where the latter will be discussed in detail in the following section.
Table 11. Summary of datasets used for the UC GWAS.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>Sample Size</th>
<th>Genotyping Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTCCC2 UC</td>
<td>WTCCC2 NBS and 1958BC</td>
<td>Controls: 2,705 (1958BC) 2,674 (NBS)</td>
<td>Affymetrix 6.0 (~ 1 million SNPs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases: 2,361</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total 7,740</td>
<td></td>
</tr>
<tr>
<td>NIDDK UC IBDO§</td>
<td>Parkinson’s Disease GWAS Controls</td>
<td>Controls: 534 Cases: 126 (UC IBDO) 359 (UC GRU)</td>
<td>Illumina HumanHap550v.3 (~ 550,000 SNPs)</td>
</tr>
<tr>
<td>NIDDK UC GRU§</td>
<td></td>
<td>Total 1,019</td>
<td></td>
</tr>
<tr>
<td>NIDDK UC GRU§</td>
<td>NIDDK CD Non-Jewish Controls</td>
<td>Controls: 503 Cases: 534</td>
<td>UC Cases: Illumina HumanHap300v.2 CD Controls: Illumina HumanHap300v.1 (~ 320,000 SNPs)</td>
</tr>
</tbody>
</table>

§ IBDO samples are patients that gave consent for their DNA to be used for IBD Research Only whereas GRU samples gave consent for their DNA to be used for General Research Use.
ii. Quality Control- WTCCC 2 UC Case-Control Dataset

The WTCCC provided quality control exclusion lists for both the SNP data as well as the sample data for each of the UC, NBS and 1958BC data-sets. Before carrying out any quality control analyses myself, the data were filtered according to these lists. The SNP exclusion list contained 5 exclusion criteria for each SNP, namely Minor Allele Frequency (MAF), information, Hardy Weinberg Equilibrium (HWE) test, missingness and plate effect. If a SNP failed to pass any one of these criteria, it was advised that the SNP should be excluded from the data. The exclusion thresholds that the WTCCC used for each of these criteria will be explained in more detail below.

For this WTCCC SNP exclusion list, the MAF threshold used for each SNP was 1%. Therefore, any SNP where the MAF falls below 1% was included in the exclusion list. The information criterion is a measure of statistical information about allele frequency in the genotype data, ranging from 0 to 1 and reflects the level of certainty regarding the called genotype, where 0 denotes complete uncertainty and 1 complete certainty. In order for SNPs to be retained in the data, the information had to be higher than 0.975. The HWE test is a measure of deviation from HWE in the general population. This test is generally carried out in controls since true association in cases can distort HWE tests. Since in most cases deviation from HWE generally reflects poor genotyping, or copy number variation for which the analysis would be confusing, HWE testing is routinely done for quality control prior to association studies. The P-value threshold used
by the WTCCC for the HWE test for each SNP was $1 \times 10^{-20}$ and therefore, any SNPs with a lower P-value was incorporated in the exclusion list. The missingness relates to the proportion of genotypes, which fail to reach the maximum call probability threshold of 0.90. If this missingness proportion is higher than 0.02, the SNP is marked for exclusion. The plate criterion is introduced because cases and controls were plated on different plates and consists of a P-value of a $n$-degree of freedom test of plate association. If the P-value is lower than $1 \times 10^{-05}$, the SNP is marked for exclusion.

The WTCCC sample exclusion list considered six criteria for quality control, namely SNP missingness across a sample, relatedness of samples, ancestry, gender, channel and identity. If a sample failed to pass any one of these criteria, it was suggested that the sample should be excluded from the data.

The missingness criterion can be subdivided into two sub-criteria. Firstly, the individuals were compared on the basis of a fraction of successfully called SNPs that were heterozygous, and then on the proportion of SNPs where the maximum call probability did not meet the 0.90 threshold. If any individuals were outlying in either sub-criteria, they were listed in the exclusion list. The individuals in the data were tested for relatedness by the WTCCC by running a Hidden Markov Model (HMM), which identifies the proportion Identity-by-Descent (IBD) between pairs of individuals. In this analysis, if two individuals were more than 5% identical by descent, the individual with the lowest genotype call rate was marked for exclusion from the data. For the ancestry analysis, the individuals were projected onto the first two principal components of a Principal Components Analysis (PCA)
of HapMap individuals. If any individuals were shown to differ from the remaining individuals in the dataset in terms of ancestry, they were flagged for exclusion in the WTCCC exclusion list provided. The WTCCC inferred the gender from the intensities of the A-allele probes on the X chromosome, which were normalized against the intensities of the autosomal SNPs. If certain individuals showed discrepancies between the gender supplied and the inferred gender, or if the gender could not be inferred from the intensities, these individuals were listed in the exclusion list. The channel criterion consisted of excluding individuals where the mean of their A and B allele intensities from 10,000 SNPs on chromosome 22 was outlying when compared to the sample at large. The identity analysis that the WTCCC carried out checked the genotype concordance of approximately 30 SNPs that were previously genotyped using the Sequenom at the Wellcome Trust Sanger Institute (WTSI) and the genotypes obtained for the Affymetrix 6.0 platform for these SNPs for each individual. If the concordance between the two platforms was lower than 90%, the individual was marked for exclusion from the data.

After filtering the data for these SNP and individual exclusion criteria, the routine and widely-applied GWAS quality control outlined in the next section was carried out. Appendix III and IV illustrate flowcharts outlining the steps carried out for the data manipulation of the WTCCC2 and NIDDK Data.
a. Principal Components Analysis

After removing SNPs and individuals that were indicated in the sample exclusion lists provided by the WTCCC, Principal Components Analysis (PCA) was carried out to detect possible outliers in the dataset. In order to perform the PCA, any SNPs with a Minor Allele Frequency (MAF) smaller than 0.05, missing rate of more than 5% and an LD $r^2$ threshold larger than 0.2 were removed. The LD pruning was done in order to avoid a heavy influence from clusters of SNPs in LD with each other for both the PCA and Relatedness analysis described below. The PCA was carried out in the publically available software R using the packages gdsfmt and SNPRelate (Zheng et al., 2012). The first step was to calculate the genetic covariance matrix from the genotype data, as well as the correlation coefficients between the sample loadings and the SNP genotypes, followed by the calculation of SNP eigenvectors (Zheng et al., 2012). The PCA results, as illustrated in Figure 12, showed that there were two outliers, one in each of the 1958BC and NBS datasets. Despite previous filtering for identity by descent outliers using the WTCCC exclusion lists, subsequent analysis of these two individuals showed that they were almost certainly the same individual or identical twins, since visual inspection of the data showed that the SNP genotypes were the same for both individuals, with the only difference in the genotypes due to missingness. This could be due to the fact that separate WTCCC exclusion lists were provided for the two control groups (1958BC and NBS) thus suggesting that QC was carried out on the two data separately, which would have missed identifying these two related individuals. Therefore, the sample that had most missing genotypes was removed from the data before further proceeding with the quality control analysis.
Figure 12. Principal Components Analysis of WTCCC Phase II Case-Control Dataset.
The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The blue triangles represent the sample loadings for the WTCCC UC Cases, the black diamonds the sample loadings for the WTCCC 1958BC Controls and the red squares the sample loadings for the WTCCC NBS controls. The samples circled in red are the outliers identified in this analysis and the outlier with most missingness was removed from the data.

The PCA procedure was repeated using the WTCCC2 UC Case-Control Data merged with the HapMap 3 dataset. This was done in order to see how the WTCCC2 UC Case-Control dataset clusters with respect to the populations in HapMap 3 (See Figure 13). Since the two datasets came from different studies, the strand orientation was not the same for all SNPs. To overcome this problem, the data were merged in PLINK, which flags any SNPs found to be in opposite strand orientation between both datasets, followed by flipping the strand for the
SNPs in question in the WTCCC2 UC Case-Control data to match that in HapMap3. Additionally, since the Affymetrix 6.0 genotyping platform contained palindromic SNPs (A/T or G/C SNPs), these needed to be removed from the data for the quality control analysis only, prior to merging with the HapMap 3 data as the strand orientation of these SNPs between two different datasets cannot be determined.

As expected, the data cluster with the European population CEU, which consists of Utah residents with Northern and Western European ancestry from the CEPH (Centre d’Étude du Polymorphisme Humain) collection and with the Tuscan population from Italy, (TSI).
Figure 13. Principal Components Analysis of merged HapMap3 and WTCCC2 UC Case-Control Datasets.
The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The data points on the plot illustrate the sample loadings. The WTCCC Case-Control data cluster with the CEU and TSI, as expected.
b. Relatedness Analysis- Identity-by-Descent and Identity-by-State Analysis

The relatedness analysis was equally carried out in R using the packages gdsfmt and SNPRelate.

The Identity-by-Descent (IBD) analysis using the PLINK Method of Moments (MoM) was carried out in order to identify whether any individuals in the UC case-control data set were related after the initial individual filtering. As expected, since the related individuals had already been removed, the results of this analysis showed no significant relatedness between the individuals, as shown in Figure 14.

The Identity-by-State (IBS) analysis was done by creating a $n \times n$ matrix containing genome-wide average IBS pairwise identities, followed by a Multidimensional Scaling (MDS) analysis, which allowed the visualisation of similarities and differences in the individuals under study. The IBS and MDS analyses were carried out on the HapMap3 dataset merged with the WTCCC2 UC Case-Control data, as was done for the PCA described in the previous section. The results of the MDS analysis, as illustrated in Figure 15, demonstrate that no outliers were detected and also that allele sharing was, as expected, highest between the WTCCC UC Case-Control dataset, the CEU and TSI since all three are European populations.
Figure 14. Identity-by-Descent Analysis of the merged WTCCC2 UC Case-Control Dataset based on pairwise kinship coefficients. The Y-axis represents the k1 pairwise IBD coefficients, which are probabilities of sharing one IBD. The X-axis represents the k0 pairwise IBD coefficients, which is the probability of sharing zero IBD. The red dashed line represents the expected IBD. The black circles represent the samples in the WTCCC UC Case-Control data. The results show that there is no relatedness among the samples in the WTCCC Case-Control data.

c. SNP filtering and individual missingness

In order to minimize false positive associations due to artifacts in the data the quality control was made more stringent. SNPs with a MAF lower than 0.03, HWE test P-value lower than $1.57 \times 10^{-3}$ and a missing rate greater than 20% were further excluded from the data. The final sample count is listed in Table 11.
CHB: Han Chinese in Beijing, China
CHD: Han Chinese in Denver, Colorado
JPT: Japanese in Tokyo, Japan

GIH: Gujarati Indians in Houston, Texas
MEX: Mexican Ancestry in Los Angeles, California

ASW: African Ancestry in Southwest USA
LWK: Luhya in Webuye, Kenya
MKK: Maasai in Kinyawa, Kenya
YRI: Yoruba in Ibadan, Nigeria

CEU: Utah Residents with Northern and Western European Ancestry from the CEPH Collection
TSI: Toscani in Italy

WTCCC2 NBS Controls
WTCCC2 1958 BC Controls
WTCCC2 UC Cases
Figure 15. Multidimensional Scaling Analysis, based on IBS distances of the merged HapMap3 and WTCCC2 UC Case-Control dataset.
The Y-axis represents the second vector of the MDS and the X-axis the first vector. The data points on the plot represent the HapMap3 and WTCCC Case-Control samples. No outliers were detected in this analysis.
iii. Quality Control Analysis- NIDDK UC datasets

For the additional two Ulcerative Colitis Datasets, the same quality control procedure outlined in section II.ii.a-c of this Chapter was carried out. However, prior to combining the UC Cases with the Controls, the PCA was carried out on the separate datasets, since no prior exclusion lists were given for the separate data unlike for the WTCCC2 UC described before. The NIDDK UC IBDO Cases (See Table 11) showed no outliers (See Figure 16) but GRU Cases genotyped on the Illumina HumanHap550v.3 (See Table 11) showed 1 major outlier, as shown circled in Figure 17. This was expected, as in the NIDDK data release notes it was noted that after the original analysis of this data it was subsequently identified that one of the samples was Trinidadian. Similarly, the Parkinson’s Disease Control data also showed four outliers (See Figure 18).
After removing the outliers from both datasets, the Parkinson’s Disease GWAS controls were merged with the NIDDK UC IBDO and GRU cases genotyped on the Illumina HumanHap550v3. Again, since the two datasets came from different studies, there were differences in strand orientation for certain SNPs, despite being genotyped on the same platform. Therefore, in order to merge the two datasets, the same procedure in PLINK was followed as described earlier. However, in this case, the Illumina HumanHap550v3 did not contain any palindromic SNPs. After the Cases and Controls were successfully merged, the
Case-Control dataset was then merged with the HapMap 3 data, after flipping the strand orientation to match that of HapMap 3, and the PCA was carried out (Figure 19).

Figure 17. Principal Components Analysis of NIDDK GRU UC Cases genotyped on the Illumina HumanHap 550v.3 platform. The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The black diamonds represent the sample loadings for the NIDDK GRU UC Cases. The samples circled in red represents the outlier identified in this analysis, which was removed from the data. The NIDDK GRU UC Cases are patients who gave consent for their DNA to be used for general research use.
Figure 18. Principal Components Analysis of Parkinson's Disease GWAS Control data genotyped on the Illumina HumanHap 550v.3 platform. The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The blue triangles represent the sample loadings for the PD GWAS Controls. The samples circled in red are the outliers identified in this analysis, which were removed from the data.

Despite the previous filtering, additional outliers could still be detected when the NIDDK IBDO and GRU UC Cases genotyped on the Illumina HumanHap 550v.3 were merged with the PD GWAS Control data and with the HapMap3 data (Figure 19). Two outliers were found in the NIDDK UC GRU cases and one in the Parkinson’s Disease GWAS controls. These three outliers were also detected in the IBS-based MDS analysis (Figure 20) but no outliers were visible in the IBD analysis (Figure 21).
Figure 19. Principal Components Analysis of NIDDK IBDO and GRU UC Cases merged with Parkinson’s Disease GWAS Controls genotyped on the Illumina HumanHap 550v.3 and HapMap3 data.

The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The data points on the plot represent the sample loadings for the HapMap3, PD GWAS Controls and NIDDK UC data. The samples circled in red are the outliers identified in this analysis, which were removed from the data.
Figure 20. Multidimensional Scaling Analysis based on IBS distances of NIDDK IBDO and GRU UC Cases merged with Parkinson's Disease GWAS Controls genotyped on the Illumina HumanHap 550v.3 platform and HapMap3 data.
The Y-axis represents the second vector of the MDS and the X-axis the first vector. The data points on the plot represent the HapMap3, the PD GWAS controls and NIDDK UC Data. The samples circled in red represent the outliers identified in this analysis, which are the same as those illustrated in Figure 19. The samples were removed from the data.
Figure 21. IBD analysis of the merged Parkinson’s Disease GWAS Controls and NIDDK IBDO and GRU UC Cases genotyped on the Illumina HumanHap 500v.3 platform based on pairwise kinship coefficients. The Y-axis represents the k1 pairwise IBD coefficients, which are probabilities of sharing one IBD. The X-axis represents the k0 pairwise IBD coefficients, which is the probability of sharing zero IBD. The red dashed line represents the expected IBD. The black circles represent the samples in the PD GWAS controls and NIDDK IBDO and GRU UC Cases. The results show that there is no relatedness among the samples analysed.

The final step in the quality control filtering of this case-control dataset, SNPs with a MAF higher than 0.03, HWE test P-value lower than $1.57 \times 10^{-3}$ and a missing rate greater than 20%. The final SNP and individual count is listed in Table 11.

The same quality control procedure was carried out for the remaining NIDDK GRU UC Cases, which were genotyped on the Illumina HumanHap300v.2 platform and the NIDDK Non-Jewish CD Controls dataset, genotyped on the
Illumina HumanHap300v.1 (See Table 11). Although both datasets were genotyped on the Illumina HumanHap300, they were genotyped on different versions of the platform and therefore they did not contain the same set of SNPs. Therefore, prior to merging the NIDDK UC GRU Cases and the NIDDK Non-Jewish CD Controls, the SNPs that were not present on both platforms were removed. Subsequently, merging of the dataset was carried out in PLINK, as described earlier, after the necessary strand orientation flipping was done. After the successful merging of the cases with the controls, the quality controls analysis described in II.ii.a-c was carried out.

Figure 22. Principal Components Analysis of merged NIDDK Non-Jewish CD Controls genotyped on the Illumina HumanHap 300v.1 and NIDDK GRU UC Cases genotyped on the Illumina HumanHap 300v.2 platform. The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The red squares represent the sample loadings for the NIDDK GRU UC Cases and the black diamonds represent the sample loadings for the NIDDK Non Jewish CD Controls. The samples circled in red are the outliers identified in this analysis, which were removed from the data.
The PCA revealed six outliers in the data, all of which came from the NIDDK Non-Jewish Control data, as shown circled in red in Figure 22. After these six outliers were removed from the data and the data were merged with the HapMap3 data, five outliers in the NIDDK GRU UC cases and four outliers in the NIDDK Non Jewish CD Controls were detected in a PCA analysis (Figure 23), as well as in the MDS analyses based on IBS distances (Figure 24). These individuals were removed from the data prior to proceeding with the quality control analysis.
ASW: African Ancestry in Southwest USA
LWK: Luhya in Webuye, Kenya
MKK: Maasai in Kinyawa, Kenya
YRI: Yoruba in Ibadan, Nigeria

CEU Utah Residents with Northern and Western European Ancestry from the CEPH Collection
TSI: Toscani in Italy

GIH: Gujarati Indians in Houston, Texas
MEX: Mexican Ancestry in Los Angeles, California

CHB: Han Chinese in Beijing, China
CHD: Han Chinese in Denver, Colorado
JPT: Japanese in Tokyo, Japan

NIDDK UC GRU Illumina 300v2
NIDDK CD Controls Illumina 300v1
Figure 23. Principal Components Analysis of merged NIDDK Non-Jewish CD Controls (Illumina HumanHap 300v.1), NIDDK GRU UC Cases (Illumina HumanHap 300v.2) and HapMap3 data.

The Y-axis represents the first Principal Component and the X-axis represents the second Principal Component. The data points on the plot represent the sample loadings for the HapMap3, NIDDK Non Jewish CD Controls and NIDDK GRU UC Cases. The samples circled in red are the outliers identified in this analysis, which were removed from the data.
Figure 24. Multidimensional Scaling Analysis of merged NIDDK Non-Jewish CD Controls, NIDDK GRU UC Cases and HapMap3 data, based on IBS Distances.

The Y-axis represents the second vector of the MDS and the X-axis the first vector. The data points on the plot represent the HapMap3, the NIDDK Non Jewish CD Controls and NIDDK GRU UC Data. The samples circled in red represent the outliers identified in this analysis, which are the same as those illustrated in Figure 19. The samples were removed from the data.
The subsequent IBD analysis also revealed two pairs of related individuals (Figure 25). The first pair consisted of two Non-Jewish CD controls whereas the second pair consisted of a Non-Jewish CD control and a GRU UC Case. One member of the first pair was removed and the NIDDK Non Jewish CD control was removed from the second pair.

![IBD analysis of the merged NIDDK Non-Jewish CD Controls and NIDDK GRU UC Cases based on pairwise kinship coefficients.](image)

**Figure 25.** IBD analysis of the merged NIDDK Non-Jewish CD Controls and NIDDK GRU UC Cases based on pairwise kinship coefficients. The Y-axis represents the k1 pairwise IBD coefficients, which are probabilities of sharing one IBD. The X-axis represents the k0 pairwise IBD coefficients, which is the probability of sharing zero IBD. The red dashed line represents the expected IBD. The black circles represent the samples in the NIDDK Non Jewish CD Controls and NIDDK GRU UC Cases. The results show that there are two pairs of related individuals in the merged data. A member from each pair was removed from the merged data.
iv. Genetic Analysis

The LDU mapping approach described in the Methods section of Chapter II was applied to the WTCCC2 Ulcerative Case-Control dataset, the merged NIDDK IBDO and GRU UC Cases and PD GWAS controls genotyped on the Illumina HumanHap550v.3 platform, and finally the merged NIDDK Non-Jewish CD controls and NIDDK GRU UC Cases genotyped on the Illumina HumanHap300v.1 and Illumina HumanHap300v.2 platforms respectively.

Each chromosome was divided into approximately 10 LDU non-overlapping windows for each dataset. Approximately the same LDU locations for the boundaries used for the Crohn’s Disease analyses described in Chapters II and III were used for the UC datasets. This was done in order to facilitate the comparison of significant gene regions between the two subtypes IBD subtypes, which was to be our next aim. All the SNPs within a window were simultaneously tested within a composite likelihood (Λ) framework. The P-value was obtained, together with the estimated location Š of the putative causal agent in LDU. The latter was then converted into kb by linear interpolation of the two flanking SNPs in HapMap.
v. Replications and meta-analysis of shared locations

The meta-analysis of the P-values was carried out if the analytical windows showed nominal statistical significance for at least 2 datasets and the estimated locations $\hat{S}$ for these nominally significant windows were within 80 kb of one another, which is a more stringent distance threshold for replication than was used for the CD GWAS described Chapter III since the UC data contain a greater SNP density.

The meta-analysis of the significant P-values obtained from the independent datasets was done using Fisher’s combined probability test (see Methods section of Chapter III). The P-value for each test was combined as follows in order to produce a meta-analysis $\chi^2$ with $2k$ degrees of freedom for $k$ number of tests:

$$\chi^2 = -2 \sum_{i=1}^{k} \ln(P)$$

A Bonferroni threshold was calculated as follows in order to account for multiple testing (see Methods section of Chapter II):

$$P-value\ threshold = \frac{\alpha}{Number\ of\ tests}$$

where $\alpha$ is the commonly accepted probability of 5% false positive rate. The Bonferroni P-value threshold used was $1 \times 10^{-5}$. This P-value threshold
corresponds to the total number of genome-wide analytical windows that were carried out for this analysis.

**vi. Significant gene-regions identified**

As described in Chapter III, the gene closest to the estimated location $\hat{S}$ was retrieved from a list of genome-wide RefSeq genes for each of the replicated analytical windows. If the distance between the gene retrieved and the estimated location $\hat{S}$ was larger than 300 kb, the estimated location $\hat{S}$ is listed as being “intergenic”. Using BioMart, the Gene Ontology (GO) annotations attributed to each gene were retrieved and the results are shown in Appendix V.
III. RESULTS

i. Identifying the previously reported UC intervals.

As for the GWAS described in Chapter III of this thesis, the first step was to identify whether the LDU mapping method could detect the 59 previously reported loci. 47 of these 59 loci had been identified in a meta-analysis that consisted of six independent GWAS data and approximately 1.4 million autosomal markers. The remaining 12 loci were identified in the latest IBD meta-analysis, which consisted of fifteen GWAS data on CD and/or UC, as well as Immunochip data for approximately 75,000 cases and controls. In order for a previous locus to be considered as replicated using the LDU mapping method, the estimated location $\hat{S}$ or the 95% CI had to lie within, or overlap in the case of the 95% CI, the reported LD interval. This approach was taken since the genes represented in both published studies are the result of \textit{in-silico} analyses that aimed to identify positional candidate genes of interest, rather than the certain causal location with direct evidence from functional studies. Out of the 59 previously identified loci, 53 were also found in at least one dataset within this study using an uncorrected significance threshold of P-value lower than 0.05. Six intervals showed no evidence of association with any of the three independent data sets. The statistical evidence and location estimates for the 53 loci are illustrated in Table 12. Most of the signals were identified in the larger WTCCC UC data set (49 out of 53 signals) and 65% of these (32 of the 49 signals)
survived the genome-wide significance Bonferroni threshold of $1 \times 10^{-5}$. 40% of the signals (21 out of 53) replicated in two datasets and 8% (4) replicated in all three datasets, with an estimated location $\hat{S}$ within 80 kb between all three datasets. Three of the 53 signals were replicated in the NIDDK IBDO + GRU dataset genotyped on the Illumina HumanHap 550v.3 (referred to as NIDDK 550 in Table 12) alone. In most cases, the previously reported intervals were quite large in size and the estimated locations $\hat{S}$ in the replication data sets were not within 80 kb of the other signal(s). In those cases it was thus not possible to meta-analyse the $P$-values for the individual datasets and the individual $P$-values for the datasets are shown in Table 12. Indeed, differences in estimated locations $\hat{S}$ larger than 80 kb could suggest the presence of more than one signal. This could be the case for the signal on Chromosome 11q (Table 12), shown in Figure 26. The previously reported interval spanned half a megabase in size and the LDU mapping approach further refined this interval with the identification of two signals using the WTCCC UC data within this interval and one using the NIDDK UC 550 data. The estimated locations for both datasets are located immediately upstream or within $MAML2$ and in a region of LD breakdown (Figure 26). Considering the LD breakdown in the region, the dense SNP coverage in both datasets, and that none of the 95% CI overlap between the different datasets, it is unlikely that these signals represent one location and could be an indication for the presence of allelic heterogeneity. In such a case, meta-analysing $P$-values would imply the presence of only one signal and thus mask the presence of heterogeneity.
For 49% of the 53 loci identified (26 out of 53), the estimated location Ŝ is within a gene. The Consortium had reported positional candidate genes for 33 loci out of the 59 identified loci and 62% (16 out of 33 loci) of the genes illustrated in Table 12 match the genes reported by the Consortium for these intervals.

Since the reported LD intervals are quite large, in the instances where replication points to more than one gene it is difficult to determine whether this could be attributable to genuine genetic heterogeneity or simply an artifact of SNP resolution between the datasets. In Table 12 it can be seen that although some signals were identified using more than one dataset, the estimated location Ŝ for the datasets points to the same gene. 19 of the intervals shown in Table 12 have also been found to be shared with CD (Anderson et al., 2011) (see Table 12).
Table 12. Whole-genome association statistics and closest gene to the estimated location Ŝ of the causal variant for the previously reported UC loci.

<table>
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<th>Reported LD Interval (Mb)</th>
<th>WTCCC Ŝ (kb)</th>
<th>WTCCC P-value</th>
<th>NIDDK 550 Ŝ (kb)</th>
<th>NIDDK 550 P-value</th>
<th>NIDDK 300 Ŝ (kb)</th>
<th>NIDDK 300 P-value</th>
<th>WTCCC UC- NIDDK 550 Ŝ difference (kb)</th>
<th>WTCCC UC- NIDDK 300 Ŝ difference (kb)</th>
<th>NIDDK 550- NIDDK 300 Ŝ difference (kb)</th>
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§ Indicates SNPs with p-value < 5x10⁻⁵.
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<th>WTCCC P-value</th>
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<th>NIDDK 550 P-value</th>
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<th>NIDDK 300 P-value</th>
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<th>WTCCC UC- NIDDK 300 Ŝ difference (kb)</th>
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<td>NIDDK 550 P-value</td>
<td>NIDDK 300 Ŝ (kb)</td>
<td>NIDDK 300 P-value</td>
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<td>WTCCC UC- NIDDK 300 Ŝ difference (kb)</td>
<td>NIDDK 550- NIDDK 300 Ŝ difference (kb)</td>
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<td>PIM3</td>
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</table>

* denotes that at least one of the estimated locations Ŝ is located within the identified gene. The intervals highlighted in blue correspond to the loci previously identified in the IBD meta-analysis that also used the Immunochip genotyping array (Jostins et al., 2012). The intervals highlighted in grey correspond to loci that have been found to be shared with CD (Anderson et al., 2011). § The Meta P-value is only provided in instances where the Ŝ difference is less than 80 kb between datasets.
Figure 26. Localisation within the *MAML2* region.
The Y-axis represents genomic LDU distances and the X-axis represents physical distances in kilobases. The solid black line represents the LDU map of the region constructed from the HapMap CEU data. The red vertical arrow is the estimated location Ŝ of the causal variants. The blue diamonds show the SNPs found in this region on the WTCCC UC Affymetrix 6.0 array. The light green horizontal dashed lines represent the 95% CIs of the estimated locations Ŝ. The orange triangles are the SNPs on the NIDDK UC Illumina HumanHap 550v.3 array in this region.
i. 138 novel gene-regions identified

The second step was to determine whether the LDU mapping method would be able to detect novel signals using the three UC case-controls datasets. For this a meta-analysis approach was used in which the maximum distance between the estimated \( \hat{S} \) locations was set at 80kb. 138 novel gene-regions that passed the Bonferroni genome-wide significance threshold of \( 1 \times 10^{-5} \) were identified. Since the distance between the estimated locations \( \hat{S} \) was less than 80 kb, the meta-analysis P-value is provided for these replications. 10 of these 138 gene-regions replicate with all three datasets, with a meta P-value surviving the Bonferroni genome-wide significance threshold. One of these ten replications, the \( \text{ERAP1} \) gene-region, is illustrated in Figure 27. For this region, the estimated \( \hat{S} \) locations for the WTCCC UC and NIDDK UC Illumina HumanHap 550v.3 datasets lie within intron 17 of the \( \text{ERAP1} \) gene whereas, although still very close, the estimated \( \hat{S} \) location of the NIDDK UC Illumina HumanHap 300v.1 & v.2 dataset lies downstream of the gene. The estimated locations \( \hat{S} \) and their 95% CI are illustrated in Figure 27.

The remaining 128 novel gene-regions were replicated in two out of three datasets, with a meta P-value surviving the Bonferroni genome-wide significance threshold.

Out of these 138 gene regions, 12 signals were intergenic locations, where the closest gene was further than 300kb from the estimated locations \( \hat{S} \). Of the
remaining 126 gene-regions, 57% of the signals were intragenic locations, with the estimated location $\hat{S}$ being within a gene for at least one of the datasets. Additionally, in 75% of the 126 gene-regions, the estimated locations $\hat{S}$ for the datasets point to the same gene.

Table 13. Whole-genome association statistics and closest gene to the estimated location $\hat{S}$ of the causal variant for the 10 novel gene-regions that replicate in all three datasets with estimated locations $\hat{S}$ within 80 kb of each other.

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<th>NIDDK IBDO + GRU Illumina 550v.3</th>
<th>NIDDK GRU UC Illumina 300</th>
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<th>Gene</th>
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<td>30,277.9</td>
<td>9.3x10^{-07}</td>
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<td>2.1x10^{-09}</td>
<td>BPIFB3/BPIFB4*</td>
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</table>

* denotes that at least one of the estimated locations $\hat{S}$ is located within the identified gene. Genes in bold are genes that have been identified in Chapter III for CD. The gene region highlighted in grey is included in this table even though the estimated locations are further than 80 kb from one another because all the estimated locations for this gene-region are genetically very close as measure in LDU, due to its occurrence within a long region of very high LD).
Figure 27. Localisation within the *ERAP1* region.
The Y-axis represents genomic LDU locations whereas the X-axis represents genomic physical locations in kilobases. The solid black line represents the LDU map of the region constructed from the HapMap CEU data. The red vertical arrows are the estimated locations $\hat{S}$ of the causal variants. The dark green lines highlight the exons of the *ERAP1* gene. The dark blue bashed line represents the 95% CI for the WTCCC UC estimated location $\hat{S}$. The light blue dashed line represents the 95% CI for the NIDDK UC Illumina HumanHap 550v.3 estimated location $\hat{S}$. The grey dashed line represents the 95% CI of the NIDDK UC Illumina HumanHap 300v.1&v.2 estimated location $\hat{S}$. The light blue diamonds show the SNPs found in this regions on the WTCCC UC Affymetrix 6.0 array, the dark blue circles represent those on the NIDDK UC Illumina HumanHap 550v.3 array and the red triangles represent the SNPs in this regions that are common to both the NIDDK Illumina HumanHap 300v.1 and Illumina HumanHap 300v.2 arrays.
Table 14. Whole-genome association statistics and closest gene to the estimated location $\hat{S}$ of the causal variant for the 128 novel gene-regions that replicate with two datasets with an estimated location $\hat{S}$ within 80 kb between datasets. a) Whole-genome association statistics and closest gene to the estimated location $\hat{S}$ of the causal variant for the 108 novel gene-regions that replicate with two datasets with an estimated location $\hat{S}$ within 80 kb for WTCCC UC and NIDDK UC 550 or WTCCC UC and NIDDK UC 300 datasets. b) Whole-genome association statistics and closest gene to the estimated location $\hat{S}$ of the causal variant for the 20 novel gene-regions that replicate with two datasets with an estimated location $\hat{S}$ within 80 kb for NIDDK UC 550 and NIDDK UC 300 datasets.

Table 14 a)

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<th>UC Replication (Signal 1/Signal 2)</th>
<th>Signal 1</th>
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<td>WTCCC/NIDDK 550</td>
<td>26,833.1</td>
<td>26,770.9</td>
<td>3.5x10^{-17}</td>
<td>LINC00158*</td>
</tr>
<tr>
<td>22q</td>
<td>WTCCC/NIDDK 550</td>
<td>34,860.0</td>
<td>34,784.2</td>
<td>9.7x10^{-07}</td>
<td>intergenic</td>
</tr>
</tbody>
</table>

* denotes that at least one of the estimated locations Ŝ is located within the identified gene. Genes in bold are genes that have been identified in Chapter III for CD.

Table 14 b)

<table>
<thead>
<tr>
<th>Chr</th>
<th>UC Replication (Signal 1/Signal 2)</th>
<th>Signal 1</th>
<th>Signal 2</th>
<th>Meta P-value</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>177,964.6</td>
<td>178,030.4</td>
<td>8.7x10^{-06}</td>
<td>LOC730102</td>
</tr>
<tr>
<td>1q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>226,845.3</td>
<td>226,846.9</td>
<td>5.6x10^{-06}</td>
<td>ITPKB-IT1*</td>
</tr>
<tr>
<td>2p</td>
<td>NIDDK 550/NIDDK 300</td>
<td>29,978.8</td>
<td>29,979.3</td>
<td>2.6x10^{-07}</td>
<td>ALK*</td>
</tr>
<tr>
<td>2q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>134,975.7</td>
<td>135,031.4</td>
<td>4.1x10^{-10}</td>
<td>MGAT5*</td>
</tr>
<tr>
<td>2q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>137,187.7</td>
<td>137,187.0</td>
<td>8.0x10^{-27}</td>
<td>CXCR4</td>
</tr>
<tr>
<td>2q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>181,752.0</td>
<td>181,676.6</td>
<td>1.2x10^{-07}</td>
<td>UBE2E3</td>
</tr>
<tr>
<td>3q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>114,511.3</td>
<td>114,511.1</td>
<td>1.5x10^{-07}</td>
<td>ZBTB20*</td>
</tr>
<tr>
<td>4p</td>
<td>NIDDK 550/NIDDK 300</td>
<td>38,734.2</td>
<td>38,707.6</td>
<td>1.6x10^{-19}</td>
<td>KLF3</td>
</tr>
<tr>
<td>4q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>148,723.6</td>
<td>148,722.9</td>
<td>3.6x10^{-07}</td>
<td>ARHGAP10*</td>
</tr>
<tr>
<td>5p</td>
<td>NIDDK 550/NIDDK 300</td>
<td>30,570.2</td>
<td>30,547.0</td>
<td>3.3x10^{-07}</td>
<td>intergenic</td>
</tr>
<tr>
<td>5q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>170,170.2</td>
<td>170,212.3</td>
<td>3.5x10^{-06}</td>
<td>KCNIP1/GABRP*</td>
</tr>
<tr>
<td>5q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>176,784.7</td>
<td>176,827.1</td>
<td>2.2x10^{-07}</td>
<td>RGS14/PFN3*</td>
</tr>
<tr>
<td>10q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>52,198.4</td>
<td>52,261.6</td>
<td>1.4x10^{-08}</td>
<td>SGMS1*</td>
</tr>
<tr>
<td>12q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>1,495.7</td>
<td>1,509.9</td>
<td>1.3x10^{-06}</td>
<td>ERC1*</td>
</tr>
<tr>
<td>12q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>119,858.9</td>
<td>119,858.9</td>
<td>3.8x10^{-06}</td>
<td>CCDC60*</td>
</tr>
<tr>
<td>15q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>72,677.4</td>
<td>72,710.7</td>
<td>3.4x10^{-12}</td>
<td>HEXA-AS1/TMEM202</td>
</tr>
<tr>
<td>16q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>82,279.3</td>
<td>82,278.8</td>
<td>4.6x10^{-08}</td>
<td>MPHOSPH6</td>
</tr>
<tr>
<td>18q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>41,809.4</td>
<td>41,810.7</td>
<td>4.8x10^{-08}</td>
<td>intergenic</td>
</tr>
<tr>
<td>18q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>59,990.6</td>
<td>60,005.0</td>
<td>2.8x10^{-09}</td>
<td>TNFRSF11A*</td>
</tr>
<tr>
<td>20q</td>
<td>NIDDK 550/NIDDK 300</td>
<td>54,350.0</td>
<td>54,421.0</td>
<td>8.3x10^{-06}</td>
<td>CBLN4</td>
</tr>
</tbody>
</table>
From the 128 novel gene-regions illustrated in Table 14 a) and b), 68% of the signals have an estimated location $\hat{S}$ less than 50 kb apart in the two datasets and 40% had an estimated location $\hat{S}$ within less than 25 kb of each other. An example is shown in Figure 28, which illustrates the $MMP27$ gene-region. The estimated locations $\hat{S}$ for the WTCCC UC data and the NIDDK UC Illumina HumanHap 500v.3 data are identical for this region and are located in a small block of LD. Additionally, 7 of the 138 novel gene-regions were also identified in the CD analysis carried out in Chapter III, as shown in bold in Table 13 and 13. The molecular and functional attributes of all the genes identified in this chapter are shown in Appendix V.
Figure 28. Localisation within the *MMP27* gene-region.
The Y-axis represents genomic LDU locations whereas the X-axis represents genomic physical locations in kilobases. The solid black line represents the LDU map of the region constructed from the HapMap CEU data. The red vertical arrow is the estimated location Ŝ of the putative causal agents. The dark green lines highlight the exons of the *MMP27* gene. The light blue triangles show the SNPs found in this region on the NIDDK UC Illumina HumanHap 550v.3 array and the dark blue diamonds are the SNPs on the WTCCC UC Affymetrix 6.0 array in this region.
IV. DISCUSSION

In this Chapter, the LDU multi-marker mapping approach successfully identified, with the additional provision of location estimates rather than LD intervals, 53 out of 59 previously reported UC loci. There could be several reasons for the failure in replicating the six remaining previously identified intervals. One reason could be the discrepancy in SNP resolution between the study carried out here and the meta-analysis that originally identified these intervals, since imputation was used in the meta-analysis, which greatly increased the SNP resolution. Additionally, the original meta-analysis contained six GWAS datasets and therefore there is missing SNP data in the study carried out in this chapter, which solely made use of the WTCCC and NIDDK UC data. However, imputation was not carried out for the UC GWAS described in this chapter. Additionally, their efforts to combine data for the purpose of power may have increased heterogeneity within the dataset. Unlike in the case of the NIDDK CD dataset, there is lack of information on the UC phenotype. Based on the results from Chapters II and III, we can only predict that this increase in heterogeneity may translate to missing information.

In addition, 138 novel gene-regions were identified, with a closer replication of location estimates between the UC datasets. For the previously identified intervals, most of the signals were identified using the WTCCC UC data alone using this method and thus were not meta-analysed. The previously reported intervals together with the novel loci identified in this project increases the

159
number of UC loci found to date to 197, which is quite a substantial number considering that although polygenic, UC has been judged to have a lower genetic contribution than CD. It could be argued that even if some of these signals are false positives, many of the putative causal agents involved in UC are thus likely to be of low effect size. However, in the presence of disease heterogeneity, some of the signals could have a larger effect size in fewer people.

Previous genetic and animal studies have provided evidence for the involvement of a defective epithelial barrier in the gut (Consortium et al., 2009; Gitter et al., 2001; Schmitz et al., 1999). In the current study, several genes involved in cell motility, cell-cell junction and cell adhesion were identified. Examples of such genes are $CTNNA2$, $TLN2$, $FLRT2$, $FLRT3$ and $PKP2$. Box 2 provides functional information on selected genes from Tables 13 and 14 a) and b). The molecular and functional Gene Ontology terms attributed to all the novel genes that were identified in this Chapter are given in Appendix V.

It is also interesting that some of the genes identified here are involved in peptidase activity, such as $ERAP1$, $USP3$, $USP35$ and $TRHDE$. $ERAP1$ (Endoplasmic Reticulum AminoPeptidase 1), illustrated in Figure 27, is a zinc metallopeptidase known to be implicated in the processing of antigenic peptides prior to presentation on the Major Histocompatibility Complex (MHC) Class I molecules (Agrawal and Brown, 2014). It is also involved in the regulation of the adaptive immune response and the inhibition of $ERAP1$ has been found to increase the presentation of cell surface antigens as well as that of cytotoxic T-
cell responses (Zervoudi et al., 2013). \textit{ERAP1} has also been previously identified as a general IBD susceptibility locus in the latest IBD meta-analysis, with the reported SNP located approximately 100 kb downstream of the estimated locations presented here (Jostins et al., 2012).

Some of the genes that encode proteins with peptidase activity also form part of the proteinaceous \textbf{Extra-Cellular Matrix} (ECM), for example \textit{MMP27} and \textit{NAV2}. For instance, \textit{MMP27} is a very interesting candidate that has been found for the first time here, with identical estimated \hat{S} locations between the WTCCC UC and NIDDK Illumina HumanHap 500v.3 data, located in intron 17 of the \textit{MMP27} gene. \textit{MMP27} is part of the \textbf{Matrix MetalloProteinase} (MMP) family (Figure 28).

\textit{MMPs} are involved in the degradation of components of the ECM, such as collagen, which is an important process that contributes to processes such as cell survival, cell growth, as well as cell migration and cell invasion (Noel et al., 2012). MMPs are secreted as inactive proteins, which then become activated after cleavage by extracellular proteinases. Proteinases like MMPs disrupt the physiological barriers in order to facilitate the migration of cells and the release of chemotactic and growth factors from the ECM. Dysregulation of MMPs contributes to cancer, as well as ulcer formation, which is central to the phenotype of UC (Nagase et al., 2006). Dysregulation of MMPs has also been identified in coronary pathology, such as \textbf{Myocardial Infarction} (MI) and \textbf{Coronary Artery Disease} (CAD), where both conditions exhibit inflammatory features. However, although the chicken MMP27 protein has been found to digest gelatin
and casein and causes autolysis of the MMP27 enzyme, little information is available on the mammalian MMP27 enzyme (Nagase et al., 2006).

Another interesting candidate identified in this part of the project is the Ubiquitin Specific Protease \textit{USP3}, which is a hydrolase enzyme that deubiquitinates monoubiquitinated target proteins. Two of its target proteins are H2A and H2B, which are proteins involved in DNA-Damage Repair (DDR) check-point of the mitotic cycle. Thus, USP3 is essential for the proper progression through S phase and subsequent mitotic entry (Nicassio et al., 2007). As mentioned in the introduction of this chapter, studies have shown that improper cell-cycling is exhibited in UC patients. Indeed, it was found that the cell-cycle of colonic cells in UC patients progresses faster than that of colonic cells in healthy controls, which suggests a role for a dysregulated cell-cycle in UC and possibly why the progression to colorectal cancer is frequent among UC patients. \textit{USP3} has also been found to be associated with both CD and UC in an association study that targeted genes encoding proteases that also identified \textit{CYLD}, as discussed in Chapter II (Cleynen et al., 2014).

Other genes involved in the cell cycle have been identified in the UC meta-analysis described here, namely \textit{MPHOSPH6}, which is a protein phosphorylated in the M-Phase of the cell cycle, and \textit{PPP3CA}, a Serine/Threonine protein phosphatase, thus similar to cyclin-dependent kinases (cdks) and \textit{RGS14}, which has also been found to be required for phagocytosis (Lim et al., 2013).
In summary, using the LDU mapping approach, many novel signals have been identified, within or close to genes that are functionally relevant to the UC phenotype, as well as that of colorectal cancer. However, it is important to note that the genes presented here are the genes which are closest to the location estimate obtained and therefore are not necessarily causal since long-acting cis elements may be involved. Also, promoters and enhancers located within one gene but regulate a more distant gene are also known to exist and this cannot be identified with the LDU mapping approach or other association testing methods.
**TRHDE**: (Thyrotropin-Releasing Hormone-Degrading Enzyme). TRHDE is an extracellular peptidase, a member of the peptidase M1 family that specifically cleaves and inactivates the neuropeptide thyrotropin-releasing hormone. This gene was also identified in a GWA study of Rheumatoid Arthritis and in a study on Grave’s Disease where both diseases display a huge involvement of a dysregulated immune system.

**CTNNA2**: (Catenin, alpha-2). CTNNA2 is also known as Cadherin-associated protein as a result of the physical interaction between CTNNA2 and Cadherins. Catenins anchor Cadherins to the cell’s cytoskeleton. Together with CDH1, which encodes E-Cadherin (See Chapter II), CTNNA2 was found to be a mutator driver gene involved in gastric cancer (Wang et al., 2014).

**ERAP1**: (Endoplasmic Reticulum Amino-Peptidase 1). Like TRHDE, ERAP1 is a member of the M1 family of zinc metalloproteinases. ERAP1 is involved in the processing of immune-related receptor ligands, such as HLA-B27 ligands, via peptide trimming. Upon LPS stimulation, it has been demonstrated that the secretion of ERAP1 is mediated by Toll-Like Receptors (TLRs) through intermediate cytokines such as IFN-β and TNF-α that ultimately results in the activation of processes that mediate inflammation. ERAP1 was also found to be associated with Ankylosing Spondylitis, Psoriatic Arthritis and Bechet’s Disease, which are all conditions with an inflammatory aetiology.

**PKP2**: (Plakophilin 2). PKP2 is a protein located in the desmosomes, which are cellular structures that link cells together, as well as in the cell nucleus. PKP2 is essential in bridging the cytoplasmic end of Cadherin proteins, such as E-Cadherin, with cytoskeletal intermediate filaments. PKP2 may be involved in the re-organisation of actin leading to the assembly of desmosomes.
i. The story so far.

Disease-gene mapping using linkage analyses has a long history, but association mapping was still emerging when techniques that allow high-throughput SNP genotyping were being developed. The success of GWAS as a method of gene-mapping has been surrounded by skepticism from much of the scientific community since although many loci have been identified, a substantial number of cases and controls (75,000 cases and controls combined in the latest IBD meta-analysis) were needed to achieve these results and the genetic contribution that these loci explain remains low. Another factor that contributed to this skepticism is the fact that the genes that have been identified in GWAS have been done so by in silico analyses of LD intervals. Indeed, in the case of large LD intervals or LD-intervals which are gene-rich, many candidate genes have been reported and thus it is not known which are the actual putative causal agents within these intervals.
a. Genetic and phenotypic heterogeneity.

In this project it was firstly shown that with detailed phenotypic information, one can detect a greater proportion of the genes involved, as well as phenotypic and genetic heterogeneity, even with the use of smaller data sets, and thus sample sizes. By scanning the genome using a method based on composite likelihood that takes directly into account the underlying LD structure in the genome, more information than previously reported was extracted from these publically available GWAS datasets without recourse to enormous meta-analyses. In addition, the estimated locations of the putative causal agents that this LDU mapping method provides is essential in narrowing down the locations of the potential putative causal agents. The location estimates provide a starting point for targeted functional analyses and sequencing. Another major advantage of location estimates of the putative causal agents is the ability to more easily identify the possible presence of genetic heterogeneity, which is known to be involved in the aetiology of many complex diseases (Silverman and Palmer, 2000). Previous studies by our group and others have already reported the increased power of using composite likelihood, rather than single-SNP testing and modelling on LDU distances as opposed to physical locations in kb (Andrew et al., 2008; Maniatis et al., 2007; Politopoulos et al., 2011). The work presented in this thesis, part of which is published, illustrates this further by extending to genome-wide data (Elding et al., 2011, 2013).
In Chapters III and IV a large number of signals associated with CD and UC were identified, which mainly identify single genes with confirmation in independent cohorts, making it likely that most are real. In some cases they may have a large effect and in some cases only a small effect on the risk of CD or UC. Since the location of the causal variant is based on an estimation within a 95% confidence interval, the actual causal variant or variants that are in direct LD are still to be found and it is thus not possible to measure the effect size or indeed the direction of effect of the causal variant. Critically, as also demonstrated in the second chapter, it is likely that different risk genes are involved to a greater or lesser extent in different patients. The genomic locations that are provided in this project are estimates of the positions of the variants of functional significance assuming a mono-phylogenetic origin and thus no substantial allelic heterogeneity. Previous studies demonstrated the greater power of using LDU as compared to physical maps for detecting association and refining location using the same multi-marker methodology (Andrew et al., 2008; Gibson et al., 2008; Politopoulos et al., 2011). The close distance between the location estimates for many of the signals in the two different cohorts analysed in Chapter III and IV suggests that these allelic variants will often be the same, but in some cases there are clear indications of independent allelic variants, perhaps controlling the expression of the same gene (in cis). Genetic heterogeneity can also be attributed to unlinked loci.

It has been previously found that the reported NOD2 mutations determine ileal disease only and that disease heterogeneity may be genetically determined, coupled with the fact that ileal disease is generally associated with an early age
of diagnosis (Ahmad et al., 2002). This therefore demonstrates the importance of considering phenotypic subgroups of CD and hence collecting more accurate phenotypic description of patient data for GWAS, especially since it is well established that response to treatment in CD patients is somewhat dependent on the disease location rather than disease behaviour (Weiss et al., 2010). The 95% CIs of the estimated locations $\hat{S}$ can help in pin-pointing such cases where independent allelic variants are likely to play a role. An example is the case of $IRF8$ described in Chapter II (Figure 9) where although the SNP coverage in the region is quite similar between the two datasets, the estimated locations have non-overlapping 95% CIs. Although this could be attributable to the only partially-overlapping genotyping arrays used in both studies, it could also be an indication of the involvement of independent allelic variants at that locus. In either case this method offers greater precision for future in-depth analysis using bioinformatics and re-sequencing.

One major problem is that phenotypic heterogeneity is currently under-studied, especially in large-scale genetic studies. For instance, the prevalence of CD among Ashkenazi Jews is higher than that for non Jewish Europeans, but surprisingly, in 1996 it was shown that no linkage is observed on chromosome 16q in Ashkenazi Jewish families (Ohmen et al., 1996). Also, as discussed in Chapter I, no linkage was ever observed on chromosome 16q in UC families (Ohmen et al., 1996), which was one of the first lines of evidence for the presence of genetic heterogeneity between the two sub-types of IBD. Additionally, although there is a substantial overlap in susceptibility loci between early-onset and adult-onset, there is also a degree of heterogeneity. For instance,
the signal on Chromosome 16p (Table 8 and 15) was found to be associated in early-onset CD patients (Imielinski et al., 2009). Indeed, in this thesis work, the signal on Chromosome 16p was identified using the NIDDK CD dataset only (Table 8 and 15), which contains patients with early-onset CD, but not in WTCCC. Despite this knowledge, disease phenotype is not well recorded in the publically available data-bases and heterogeneity for neither CD or UC has been studied in detail to date. The focus has been toward large meta-analyses combining different sub-types and age of onset.

The main reason for the limited study of heterogeneity is because the main concern has been to increase the sample size and hence power to detect association. The extent to which the meta-analysis approach results in a gain in power is variable since combination of groups of patients who have been ascertained by different criteria and from different geographic locations will mean that variants that only apply to a specific sub-group will go unseen. Here I show that stratifying the data based on subtypes of CD proves to be more beneficial in dissecting the underlying genetic heterogeneity involved in CD, in contrast to increasing the sample size, at least with the method reported here. It will be important in the future to reconsider the collection of clinical data and attempt to record more complete information.

The previous linkage peaks significant for IBD (Cavanaugh, 2001; Cavanaugh et al., 1998; Hampe et al., 1999; Hampe et al., 1999; Hugot et al., 1996; Ohmen et al., 1996; Parkes et al., 2000; Satsangi et al., 1996) have all been identified in
GWAS, with the exception of *IBD4* in relation to CD and *IBD6* on Chromosome 19p13 in relation to UC, as shown in Table 15. In the linkage study that identified *IBD6*, it was reported that there was substantial heterogeneity in relation to CD with respect to significance of linkage and the carrier status of the *NOD2* mutations in CD patients. The same study did not find significant linkage at the *IBD4* locus (van Heel et al., 2003). Indeed, the *IBD6* locus was only identified after the patients with the *NOD2* mutations were removed from the data, suggesting the presence of genetic heterogeneity. Since the same study detected evidence for the presence of epistatic interactions between the *IBD5* and the *IBD6* loci, the authors hypothesized that the Canadian study that detected linkage at the *IBD6* locus could be explained by the fact that their study showed a stronger *IBD5* linkage signal than the one reported by van Heel *et al.* and could thus facilitate the detection of linkage at the *IBD6* locus in the Canadian families. The *IBD8* UC linkage peak is identified in a GWAS for the first time in the work described in Chapter IV of this thesis.
Table 15. Follow up of significant IBD linkage peaks in GWAS.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Chr</th>
<th>Linkage Significance</th>
<th>CD Confirmed from previous Meta-Analyses</th>
<th>Newly reported in this thesis</th>
<th>UC Confirmed from previous Meta-Analyses</th>
<th>Newly reported in this thesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD1</td>
<td>16q12</td>
<td>CD</td>
<td>NOD2</td>
<td>CYLD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD2</td>
<td>12p13.2-q24.1</td>
<td>CD and UC</td>
<td>LRRK2/SLC2A13</td>
<td>ANO4</td>
<td>C12orf74</td>
<td>IFNG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMEM117</td>
<td>CCDC91</td>
<td>PKP2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAND1</td>
<td>IFNG</td>
<td>TRHDE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>KITLG</td>
<td>IFNG</td>
<td>WSCD2/CMKLR1</td>
</tr>
<tr>
<td>IBD3</td>
<td>6p21.3</td>
<td>CD and UC</td>
<td>HLA-DQB2</td>
<td></td>
<td>TAP2/LA-DQB-2</td>
<td>HLA-DPB1/HLA-DOA</td>
</tr>
<tr>
<td>IBD4</td>
<td>14q11-q12</td>
<td>CD</td>
<td>Not identified in GWAS</td>
<td></td>
<td>Not identified in GWAS</td>
<td>NOVA1/MIR4307</td>
</tr>
<tr>
<td>IBD5</td>
<td>5q31</td>
<td>CD</td>
<td>C5orf56/SLC22A4</td>
<td></td>
<td>C5orf66</td>
<td>HSPA4/FSTL4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NRG2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YIPF5</td>
</tr>
<tr>
<td>IBD6</td>
<td>19p13</td>
<td>CD and UC</td>
<td>SBNO2</td>
<td>PDE4A</td>
<td>Not identified in GWAS</td>
<td></td>
</tr>
<tr>
<td>IBD7</td>
<td>1p36</td>
<td>CD and UC</td>
<td>CAMTA1</td>
<td></td>
<td>OTUD3/RNF186</td>
<td>CATSPER4</td>
</tr>
<tr>
<td>IBD8</td>
<td>16p</td>
<td>CD and UC</td>
<td>CD19</td>
<td>RBFOX1</td>
<td>Not identified in GWAS</td>
<td>GPR139</td>
</tr>
</tbody>
</table>

Genes separated by “/” represent one signal from the same window but estimated locations Ŝ of the causal variant for the discovery and replication dataset(s) point to different genes. Red font implies that although linkage has been observed, no signal has been detected in previous GWAS or in this thesis work. Blue font represents significant linkage peaks that have not been detected by previous GWAS but association in the linkage region has been identified in this thesis work. The significance and estimated locations Ŝ for these signals are illustrated in Tables 8, 9 and 10 for CD and in Tables 12, 13 and 14 for UC.
It is also of interest to consider our GWAS results described in Chapters III and IV in relation to previous candidate gene studies. Like single-SNP analysis, the LDU mapping approach still failed to replicate some genes that had been reported to be associated from single gene studies. For instance \textit{IL16}, \textit{TLR4} and \textit{MUC3A} (Franchimont et al., 2004; Glas et al., 2003; Kyo et al., 2001; Ouburg et al., 2005) are among the examples of genes that were good functional candidates in early candidate gene studies but were never identified in GWA studies. In the case of \textit{IL16}, functional analysis revealed the involvement of a polymorphism located in promoter region of \textit{IL16} in CD patients only (Glas et al., 2003) and an amino acid substitution (Asp299Gly) polymorphism in the \textit{TLR4} gene was reported to be involved in both CD and UC (Franchimont et al., 2004). Apart from possible ethnic or disease sub-group differences, the failure to replicate these loci could be simply due to the fact that these loci might have been false-positives in the previous studies. Another reason for failing to replicate true susceptibility loci in functionally implicated genes could be the low SNP coverage or problems with these regions affecting the current genotyping platforms. In the case of \textit{MUC3}, the Genome Browser sequence is still incorrectly annotated and fails to detect that it is a duplicated gene (Gum et al., 2003; Kyo et al., 2001; Pratt et al., 2000), suggesting that the LDU map is also inaccurate, since an error in the physical map will be reflected in the genetic map.
b. Interactions and Epistatic effects.

Aside from the impact of accurate phenotypic description and that of heterogeneity, another complication in identifying susceptibility loci for IBD, or complex diseases in general, arises from the presence of interactions or epistasis between loci. Indeed, this could be another reason behind the failure in replicating findings from functional candidate gene studies in association studies and meta-analyses. *DMBT1*, a scavenger and antibacterial pattern recognition receptor, was never identified in GWASes and is an example of such interaction. A candidate gene study had identified an association between a deletion variant of the *DMBT1* allele and and increased risk for CD (Renner et al., 2007). More recently functional and epistatic analyses have shown evidence of interaction. *DMBT1* is a target gene of the *IL-22* cytokine, which is in turn modulated by CD-risk variants in *IL23R*, an established IBD susceptibility locus (Zervoudi et al., 2013). The risk variants in *IL23R* have also been shown to modulate the expression of *DMBT1* in the intestines of CD patients (Zervoudi et al., 2013).

Another example comes from *NOD2*. As mentioned in the introduction of Chapter IV, it had already been established that *NOD2* is a CD-specific risk factor but although linkage and association analyses failed to identify *NOD2* in relation to UC, it was still shown that there is a possible epistatic interaction between the cytokine cluster-containing *IBD5* locus and the *NOD2* mutations and that these two loci could interact in a synergistic way to contribute towards the onset of UC (Giallourakis et al., 2003). In fact, the same study also reported that
much of the significance of the *IBD5* association signal arose from UC patients that carried the *NOD2* mutations (Giallourakis et al., 2003).

In addition to epistatic effects, gene-environment interactions are of great importance in complex conditions and can have a considerable impact on the development of the phenotype. In fact, an individual can inherit the predisposing factors to a particular disease but never develop the disease itself unless exposed to an environmental factor. Therefore, the analogy that “genetics loads the gun but the environment pulls the trigger” perfectly captures the complex interplay between host genetics, including gene-gene-interactions, and disease onset (Olden, 2006; Ramos and Olden, 2008). After all, autoimmune or immune deficiency diseases like IBD involve the host’s response to an environmental stimulus. Thus, in a genetically susceptible host, this gene-environment interaction can lead to the onset of disease. Indeed, the term gene-environment interaction can be defined as the environment’s impact on the direction and degree of a genetic variant’s effect on phenotype (Ramos and Olden, 2008). In the case of IBD, it is well established that diet and the gut microbiota composition of an individual are major environmental factors that play a role in the onset of IBD. In addition, smoking is an environmental factor which shows different directions of effect with respect to CD and UC, with smoking apparently being ‘protective’ for UC. Gene-environment interaction studies have so far been hampered by the fact that studies in experimental models they have to be done in model animals or cell lines and are usually limited to one environmental component, which may not be sufficient to show what occurs *in vivo*.
Further epidemiological and genetic association studies that contain data on environmental factors are needed. These will provide information that will eventually help in elucidating the mechanisms and pathways involved in disease onset as well as in providing the opportunity for possible intervention prior to disease onset, where predisposing genetic factors are known to be involved.

**ii. Considerations for future work involving the LDU mapping approach**

Although the LDU mapping method used in this project shows several advantages over other types of association methods, there are limitations that need to be considered. As for the case with other association testing methods, this method is not immune to false-positive results. A Bonferroni threshold was used throughout this project in an attempt to account for false-positives arising purely by chance due to multiple testing. Bonferroni correction is known to be a very conservative method to account for multiple testing, which makes it a difficult case to find a fine balance between eliminating false-positives and reducing false-negatives as a result of multiple testing corrections in association studies. However, false-positives could also arise due to the presence of population sub-structure in the datasets. For all the datasets that were analysed in this project, the data were projected on the first two Principal Components of HapMap3 data in order to detect any genome-wide population sub-structure within the GWAS
data. This method for detecting structure is routinely done in association studies and is thought to work well on a genome-wide level. Indeed, in the quality control analyses of previously published GWAS, as well as in the quality control that was carried out in this thesis work population outliers that were known to exist within the data were successfully identified. However, what if the data exhibits hidden sub-structure, such as locus-specific effects which reflect very subtle differences in recent ancestry?

In recently admixed populations, such as in African Americans, two or more populations would have been mixing for a short amount of time thus leading to a new population (Glas et al., 2003). The ancestry of this new population can be accounted for by the different proportions from the original populations. Unlike in non-admixed populations, where the whole genome is representative of the population under study, in these recently admixed populations the genome is subdivided, due to recombination, into short sections of differing ancestry, which makes it difficult to identify the ancestral genetic information of such individuals (Glas et al., 2003). Although the scenario of such admixture is highly unlikely to apply to the datasets used in this thesis work, independent work carried out on UK samples as part of the People of the British Isles (PoBI) project identified the presence of population structure within the UK when surnames were taken into account and the data were modeled using a simple point admixture approach based on maximum likelihood (Winney et al., 2012). This fine population structure within the UK was never detected when traditional methods, such as PCA or Fst, were carried out. However subtle stratification due to difference in the representation of geographic regions in the UK is masked in the PCA since there
are only short segments of the genome that differ, in other words there is the presence of locus specific differences in ancestry. One of the factors that contributes to these regions of local ancestry is natural selection. Indeed, IBD is an immune-mediated disease and natural selection has played a significant role in shaping host immune defence by acting on immune-related genes (Barreiro and Quintana-Murci, 2010). Natural selection on immune related genes, whether negative, positive or balancing selection, reflects past infectious epidemics and thus past population demographics. The effect of this selection on host immunity could hence partly contribute to the differences in prevalence of certain diseases in different populations (McEvoy et al., 2009). Locus specific ancestry differences could thus be one of the causes of spurious association with any association testing methods used in complex disease genetics.

Another issue to be considered when using the LDU mapping method is the selection of the difference in distance between the estimated locations Ŝ between datasets in order for a location to be considered a replication. In fact, for the main CD meta-analysis carried out in Chapter III the difference in distance between the estimated locations Ŝ, for the locations where the meta P-value survived the Bonferroni threshold, was set to lie within 150 kb between the WTCCC CD and NIDDK CD datasets, but the majority fell within 80kb. Since the UC SNP data had a much higher SNP resolution (1 million SNPs) I used the more stringent estimated location Ŝ difference threshold of 80 kb. However, making the decision about this difference threshold is rather arbitrary. Another approach would be to use a LDU cut-off for distance difference thresholds or to take into account the 95% Confidence Intervals of the estimated locations Ŝ. Clearly, the difference in
SNP content and resolution in the different datasets that are meta-analysed may affect the estimations of \( \hat{S} \). A computational approach to resolving this dilemma would be complicated.

This highlights the problem of the heterogeneity introduced into the datasets by the difference in SNP coverage on the platforms used at different times by the various investigators. A solution that investigators have used to overcome this problem has been to impute genotypes in order to homogenise the set of SNPs that are being tested in the different datasets. Imputation could also potentially be used in conjunction with the LDU mapping approach, in order to meta-analyse the same set of SNPs across datasets. However, the advantage of the LDU mapping approach is that comparisons can be made across data sets even with very different SNP coverage.

A high-resolution, homogeneous subset of SNPs across datasets, together with better refined phenotypes should reduce the complications that heterogeneity brings to disease-gene mapping.

iii. Future work- Inflammatory Bowel Disease meta-analysis and beyond.

The work that was carried out during the course of this thesis focused on CD and UC specific analyses. The next step would be to conduct an analysis specifically for IBD. There are two possible approaches that could be taken in
order to carry out this work. The first method would involve the meta-analysis of the location estimates that are close to each other from the nominally significant windows in the CD and UC datasets independently and subsequently meta-analysing the P-values and applying a Bonferroni correction for multiple testing. Taking this approach will involve the careful consideration about what difference in distance between the estimated locations obtained by the CD and UC datasets should be used, especially in the light of the considerations that have been discussed above, since genetic heterogeneity involving the same genetic region will become more likely when considering CD and UC together.

The second approach would be to combine the genotype data for both diseases, for example combining the WTCCC CD with WTCCC UC as one data set and combining the NIDDK CD together with the NIDDK UC datasets as a replication data set. The major problem with this approach is that all the CD and UC datasets are genotyped on different genotyping platforms. Therefore the direct concatenation of datasets will not be possible, and SNPs that are not common to the genotyping platforms of the data being concatenated will be lost, thus leading to a loss in SNP resolution. However, these SNPs could perhaps be imputed, without having a huge impact on the LDU mapping approach since much of the power of this approach comes from the LDU maps, which are obtained using the HapMap data. This approach would also overcome the issue that the NIDDK CD Controls would need to be used twice if the UC and CD datasets were to be analysed separately, since the NIDDK CD Controls were used in Chapters II, III and IV. Indeed, both approaches could be carried out and the results can be compared, although in my opinion, the second approach would
be best as it would require less decision-making about distance threshold for estimated locations that could affect the final results and it also provides the opportunity to increase the sample size for each CD-UC dataset, which will lead to an increase in power to detect association pertaining to IBD, given that in this case only loci that are in common between the disease categories are of interest. Thus, the second approach seems to provide a better balance between Type I (False Positives) and Type II errors (False Negatives).

In the meantime, it is worthwhile to look at the genes that have been identified in both disease sub-types independently, in the work described in Chapters III and IV. Table 16 illustrates the genes that are common to both CD and UC and were found independently in Chapter III (Tables 8 and 9) and Chapter IV (Table 14).
### Table 16. Genes common to both CD and UC identified in this thesis work.

| Chr | LD Interval (Mb)§ | WTCCC CD $|$ | NIDDK CD $|$ | WTCCC UC $|$ | NIDDK UC 550 $|$ | NIDDK UC 300 $|$ | Overlap in 95% CI of significant estimated locations $|$ | Gene |
|-----|------------------|-------------|----------|-------------|--------------|--------------|----------------------|-------|
| 1p  | 67.53-67.77      | 67,864.8    | 67,707.3 | 67,769.1    | -            | 67,741.5    | WTCCC CD/NIDDK CD/NIDDK UC 300 | IL23R* |
| 2q  | -                | 170,038.8   | 170,037.2| 169,969.0   | 170,001.5    | -            | None                             | LRP2* |
| 2q  | -                | 226,258.2   | 226,258.4| 226,257.7   | 226,231.6    | -            | WTCCC CD/NIDDK CD/WTCCC UC      | NYAP2 |
| 5p  | 40.28-40.81      | 40,447.1    | 40,288.0 | -           | 40,617.6     | -            | WTCCC CD/NIDDK UC 550           | PTGER4|
| 5q  | 158.53-158.93    | 158,825.7   | 158,826.0| 158,825.8   | -            | -            | All                               | IL12B |
| 7p  | -                | 41,898.3    | 41,939.6 | 41,923.9    | -            | 41,941.0    | All                               | GL3   |
| 9q  | 117.44-117.70    | 117,555.6   | -        | 117,559.8   | -            | -            | All                               | TNFSF15*|
| 10p | 35.18-35.90      | 35,554.8    | -        | 35,554.4    | -            | -            | All                               | CCNY* |
| 10q | -                | 63,604.2    | 63,553.3 | 63,552.9    | 63,553.5     | -            | NIDDK CD/WTCCC UC/ NIDDK UC 550 | C10orf107 |
| 10q | -                | 90,787.7    | 90,787.7 | 90,739.8    | 90,787.4     | -            | WTCCC CD/NIDDK CD/NIDDK UC 550  | FAS   |
| 10q | 101.26-101.34    | 101,324.7   | 101,274.6| 101,754.7   | 101,342.5    | -            | None                             | NKK2-3|
| 11q | 76.04-76.34      | 76,304.4    | -        | 76,303.3    | -            | -            | All                               | C11orf30|
| 12p | -                | 28,744.32   | 28,741.7 | 28,6769.5   | 28,595.9     | 28,309.1    | NIDDK CD/WTCCC UC/NIDDK UC 300 | CCDC91*|
| 16q | -                | 85,982.3    | 85,958.0 | 85,996.3    | -            | -            | WTCCC CD/WTCCC UC                | IRF8* |
| 20p | -                | 15,802.7    | 15,876.4 | 14,314.2    | 14,352.4     | -            | None                             | MACROD2*|
| 20q | -                | 62,19-62.51 | 62,327.9 | -           | 62,326.9     | -            | All                               | RTEL1* |
| 21q | 16.70-16.85      | 16,841.4    | -        | 16,818.4    | 16,802.9     | -            | All                               | USP25 |
| 21q | 45.59-45.70      | 45,609.1    | -        | 45,608.8    | -            | -            | All                               | ICOSLG|

* denotes that at least one of the estimated locations $|$ is located within the identified gene. § LD interval if the signal was reported in the published meta-analysis previous to this thesis work. – means no significant signal detected within the datasets. Signals highlighted in green represent the signals that have been identified in this thesis work.
In the CD analysis, approximately half of the signals that were identified in this thesis work, highlighted in dark green in Table 16, were replicated using the smaller NIDDK CD dataset containing ileal patients that exhibited extra-ileal manifestations and half using the NIDDK Pooled dataset (Table 9 and Table 10). In 5 of the 7 shared genes shown in Table 16, the difference in location estimates between both the CD datasets and the UC datasets is less than 70kb, but not for the remaining two signals. In the case of CCDC91, shown in Figure 29, the difference in location estimates was larger than 400 kb but genetically, the location estimates lie close to one another, being within approximately one LDU of each other. CCDC91 is an interesting finding since although not much in known about this gene, Ph.D. thesis work carried out by Tao Jiong at the National University of Singapore that focused on looking at genomic copy number alterations identified a deletion of the CCDC91 gene region in a gastric cancer cell line (Jiong, 2011). In addition, independent studies have identified this region as a CNV region, where both amplification and deletion of the CCDC91 gene and the surrounding region have been detected in cancer cell lines (Bignell et al., 2010; Johnson et al., 2010; Shih Ie et al., 2011). In the case of MACROD2, the location estimates between CD and UC were approximately 1,500 kb apart, but the location estimates for all the CD and UC datasets lie within the MACROD2 gene. MACROD2 is also located at a site of genomic instability, with recurrent microdeletions being reported within the MACROD2 gene locus, both in the general population and in patients of colorectal carcinomas (Linnebacher et al., 2013). The genomic instability of these two regions, and possibly that of other regions along the genome, could explain the
difficulty in obtaining close location estimates between different datasets, since this instability is also very likely to be reflected in the LDU map of the region.
Figure 29. Localisation within the *CCDC91* gene-region.
The Y-axis represents genomic LDU locations whereas the X-axis represents genomic physical locations in kilobases. The solid black line represents the LDU map of the region constructed from the HapMap CEU data. The red vertical arrows are the estimated locations Ŝ of the putative causal agents for the UC data. The blue vertical dashed arrows are the estimated locations Ŝ of the putative causal agents for the CD data.
Other future work would also be to combine the results from GWAS with intestinal expression data.

The co-localisation of eQTL loci with some of the estimated locations outside exonic regions obtained in this project would help to narrow the region housing the likely causal variants involved in regulation. This co-localisation could also be done in conjunction with ChIP-Seq (ChIP-Sequencing) analysis, and other functional annotations from the ENCODE project, which can be used to point to DNA-protein binding sites, especially for the identified regions that do not harbour any genes and could thus represent non-coding regulatory SNPs. This co-localisation approach is illustrated in Figure 30. Technological advances in Next-Generation Sequencing paved the way to RNA-Seq (RNA-Sequencing), or “Whole-Transcriptome Shotgun Sequencing”, which is one way of carrying out expression analysis. One application of RNA-Seq is to explore the RNA levels from a genome at a given time. This tissue-specific expression information, together with the results from previous meta-analyses and the estimated locations identified in this thesis work could be consolidated in order to pinpoint the genes involved in CD and UC.

Considering that complex diseases, such as IBD, result from the contribution of both environmental and genetic factors, investigating the impact of the interactions between environmental factors and regulatory SNPs will also be a crucial element in dissecting the environmental triggers that contribute to the onset of IBD as well as in identifying the mechanisms and pathways that lead to
the disease phenotype. In fact, interactions between the environment and regulatory SNPs affecting Allele-Specific Expression (ASE) has already been demonstrated in a study that looked at monozygotic twins (Buil et al., 2014).

Figure 30. A co-localisation approach for future studies of possible regulatory regions.

Genetic variation in regulation does not necessarily involve the closest gene. ASE can be conducted on biopsy material from patients.
Another approach will be the investigation of gene-gene interactions, which as discussed in this Chapter, are known to contribute to the onset of IBD. For example, the approach of stratifying the data by NOD2 could be used to explore the effect on unlinked associations, perhaps by examining loci flagged in the literature or perhaps genome-wide.

From the studies carried out on the gut microbiota in relation to IBD pathogenesis, no causal bacterial agent has been identified so far and it is still unclear whether the dysbiosis observed is the result of, or indeed precedes, the onset of IBD, leading to the chicken and the egg dilemma—which of the two comes first? The improvements in techniques for microbial community profiling, such as the advent of Next-Generation Sequencing, opened the doors to high-throughput analyses of genomes of entire communities, in other words, metagenomic analyses, including previously unculturable organisms. The aim of metagenomics analyses is to determine the role that the microbes play in human health as well as in the onset of diseases. Indeed, the Human Microbiome Project (HMP) was conceived, which started in 2007 with the aim of developing the necessary tools and datasets in order to study the role that microbes play in relation to human health and disease. The project is currently in its second and final phase, generating datasets that integrate the biological properties from both microbiome and host from studies related to microbiome-associated diseases and is expected to end in 2015. Such datasets could be exploited in order to unravel the host-microbiota interactions that take place in the pathogenesis of IBD and elucidate whether microbiota dysregulation takes place prior to or after the onset of IBD. The data generated from such studies could be used as phenotypes in...
GWA studies in order to identify possible association between a particular microbiota species and disease outcome. Another approach would be to assess the clustering of the microbiota composition of CD or UC patients according the specific sub-phenotypes (e.g.: ileal only disease for CD and proximal versus distal colonic inflammation in UC). Depending on the findings, this would also provide the opportunity for therapeutic development and possibly prevention of dysbiosis in genetically susceptible hosts.

From previous association studies, as well as from the work presented in this thesis, it can be concluded that with increasing bioinformatics and statistical advances, association studies are identifying many loci at a much faster pace than can be functionally tested, not only for IBD, but for complex diseases globally. It is only very recently that functional techniques such as RNA-Seq are scaling up to genome-wide level. Combining the ever increasing statistical tools together with the emerging functional techniques, including the human microbiome data, could thus open the door to unraveling the mechanisms behind IBD and ultimately target the relevant pathways in the specific CD and UC subgroups for sub-phenotype stratified treatment.


association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. Nat Genet 41, 1330-1334.


scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nature genetics 39, 207-211.


WTCCC (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447, 661-678.


Appendix I- Different LD metrics

**Formula for Covariance $D$:**

$$D = f_{11}f_{22} - f_{12}f_{21}$$

where $f$ is the frequency of the inferred haplotype.

**Formula for $D'$:**

When $D$ is negative, $D' = \frac{|D|}{\min[QR, (1 - Q)(1 - R)]}$

When $D$ is positive, $D' = \frac{|D|}{\min[Q(1 - R), R(1 - Q)]}$

**Formula for association $\rho$:**

$$\rho = \frac{D}{Q(1 - R)}$$

where $D$ is the covariance and $Q$ and $R$ are the allele frequencies.

**Formula for correlation $r$:**

$$r = \frac{D}{\sqrt{Q(1 - Q)R(1 - R)}}$$

where $D$ is the covariance and $Q$ and $R$ are the allele frequencies.
Formula for correlation coefficient $r^2$:

$$r^2 = \frac{D^2}{Q(1-Q)R(1-R)}$$

where $D$ is the covariance and $Q$ and $R$ are the allele frequencies.
Appendix II- BioMart Analysis from the Crohn’s Disease GWAS described in Chapter III.

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<th>GO Term Accession</th>
<th>GO Term Name</th>
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Appendix III- WTCCC Phase II Ulcerative Colitis Cases, NBS Controls and 1958BC Controls- Quality Control and Data manipulation prior to analysis flowchart.

**STEP 1 - SENDING A REQUEST TO DOWNLOAD THE DATA & A REQUEST FOR ENCRYPTION KEYS TO BE SENT VIA POST**

**STEP 2 - DECRYPTION OF DATA**
Download Gpg4Win from [http://www.gnupg.org](http://www.gnupg.org)

**STEP 3 - CONVERT FROM OXSTAT TO PLINK FORMAT**
Download the static executable version of GTOOL from [http://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html](http://www.well.ox.ac.uk/~cfreeman/software/gwas/gtool.html). The GTOOL program will be fed the extracted CHIAMO.gen file (genotype calls) for each Chromosome and the sample file.

**STEP 4 CONVERTING ‘NN’ FOR ‘00’ FOR MISSING GENOTYPES**

**STEP 5 - DATA FILTERING ACCORDING TO PROVIDED SNP EXCLUSION LISTS**
**STEP 5- PERFORMING QUALITY CONTROL USING R SNPRelate AND GDSFMT PACKAGEs**
This step was carried out using the instructions here: [http://corearray.sourceforge.net/tutorials/SNPRelate/](http://corearray.sourceforge.net/tutorials/SNPRelate/)
Analysis carried out: Principal Components Analysis, IBD Method of Moments, and Multi-Dimensional Scaling Analysis using IBS distances. QC filtering used for snps: MAF cut-off = 0.05, missing rate cut-off= 0.05 and ld.threshold = 0.2

**STEP 6- REMOVING OUTLIERS EMERGING FROM STEP 5**

**STEP 6- CONVERT PLINK TO LDU MAPPING APPROACH FORMAT**

**STEP 6- CONCATENATION OF CONTROL AND CASES DATASETS**

**STEP 7- DATA GENOTYPE ENCODING (AA, AT…→ 11, 12, …)**
Encoding all the genotypes (A A, A C…) into number codes (1 1, 1 2 …). This step also produces details about the MAF (details_genotype.txt) and Hardy Weinberg (fulldetails_genotype.txt- also for MAF).

**STEP 8- DATA SNP FILTERING - IN HOUSE QC**
Filtering of the SNPs which fail HWE test, have a low MAF (<0.03), HWE Chi Squared test >10 or have a percentage missingness > 20%. this information is provided in a file in the previous step (fulldetails_* file). This is only done on the id filtered concatenated controls dataset.
Appendix IV- NIDDK Ulcerative Colitis Cases and Crohn’s Disease Controls- Quality Control and Data manipulation prior to analysis flowchart.

**STEP 1- DOWNLOAD THE DATA**

**STEP 2- DECRYPTION OF DATA**

**STEP 3 RECODING PLINK FILES IN PED AND MAP AND SPLITTING THESE GENOME WIDE FILES BY CHROMOSOME**

**STEP 4 CONVERTING ‘NN’ FOR ‘00’ FOR MISSING GENOTYPES AND ASSIGNING AFFECTION STATUS**

**STEP 5- PERFORMING QUALITY CONTROL USING R SNPRelate AND GDSFMT PACKAGEs**
This step was carried out using the instructions here: [http://corearray.sourceforge.net/tutorials/SNPRelate/](http://corearray.sourceforge.net/tutorials/SNPRelate/)
Analysis carried out: Principal Components Analysis, IBD Method of Moments, and Multi-Dimensional Scaling Analysis using IBS distances. QC filtering used for snps: MAF cut-off = 0.05, missing rate cut-off= 0.05 and ld.threshold = 0.2 (see pages 22-66 of Lab book Volume 3)

**STEP 6- REMOVING OUTLIERS EMERGING FROM STEP 5**
This is done by identifying the individual ID in the previous step and writing a perl program, which identifies the ID in the dataset and removes it- still to be optimised!

**STEP 7- CONVERT PLINK TO LDU MAPPING APPROACH FORMAT**

**STEP 8- GENOTYPE ENCODING**
Encoding all the genotypes (A A, A C…) into number codes (1 1, 1 2 …). This step also produces details about the MAF (details_genotype.txt) and Hardy Weinberg (fulldetails_genotype.txt- also for MAF)-

**STEP 9- DATA SNP FILTERING -IN HOUSE QC**
Filtering of the SNPs which fail HWE test, have a low MAF (<0.03), HWE Chi Squared test >10 or have a percentage missingness > 20%. this information is provided in a file in the previous step (fulldetails_* file). This is only done on the id filtered concatenated controls dataset.
### Appendix V- BioMart Analysis from the Ulcerative Colitis GWAS described in Chapter IV

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