Genotype-phenotype relationships and their clinical implications in inflammatory bowel disease and type 2 diabetes
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Chapter 1
General Introduction
The era of genome-wide association studies and impact on complex disease

Many people die each year as a result of disease complications and poor response to treatment, which could be due to multiple factors, including disease determinants, environmental exposures and genetic factors in complex diseases. For the most part, complex diseases such as inflammatory bowel disease (IBD) and type 2 diabetes (T2D) are caused and influenced by a combination of genetic, environmental, and lifestyle factors, most of which have not yet been identified. Linkage analysis and the candidate gene approach linked genotype to phenotype before the development of genome-wide association studies (GWAS).

The general goals of GWAS are to identify genetic risk factors, candidate genes and regions that are associated with disease phenotype and disease-related complications to better understand the underlying biology of disease. A significant breakthrough in understanding the genetic basis of complex traits including IBD and T2D was facilitated by the arrival of GWAS. Advances in genetic studies have identified large numbers of genetic factors associated with disease phenotypes, providing important insights into disease pathogenesis, and raised the prospect of using genetic testing to provide personalized treatment for patients. Many novel
genetic associations in the field of IBD and T2D have been described recently. This success has led to the hope that the findings will translate into improved clinical care for the increasing numbers of patients with these two complex diseases.

One important clinical translation of genetic information is to predict an individual’s risk of developing the complex disease. Since many genetic variants have small effect sizes and each accounts for a small part of disease heritability, genetic risk scores (GRSs) have been used that summarizes the overall genetic risk across the genome by aggregating information from multiple risk alleles of single nucleotide polymorphisms (SNPs).

Recently, the GRS approach has been used to predict the incidence of disease. GRS present more information about the genetic background of complex disease than candidate SNP associations alone. Recent genetic studies have also contributed to explaining the underlying biology of disease associated with disease-related sub-phenotypes and disease complications. Another potential area of clinical translation includes the association between genetic variants and (poor) response to pharmaceutical therapy (i.e., pharmacogenetics), and the development of novel therapeutics. Identification of genetic variants, increasing susceptibility to disease and its combined information might aid in the personalized prediction of disease risk and disease course.

GWAS have facilitated a substantial and rapid rise in the number of novels confirmed genetic susceptibility variants implicated in the development of IBD and T2D enabling a better understanding of disease mechanisms and identifying novel targets with the potential to facilitate personalized medicine and clinical care. In addition, genetic studies have been used to understand the link between T2D, and its comorbidities. Furthermore, recent pharmacogenetic studies have also confirmed the association between genetic variants, poor response to therapy and the link between genotype and disease comorbidities in T2D. Evidence suggests opportunities for patient classification using genetic plus non-genetic information to improve prevention/management of IBD.

Although many new and interesting susceptibility loci have been identified, it is challenging to translate them into clinical practice. Their effectiveness to predict risk, comorbidities and response to treatment remain limited. Therefore, more powerful strategies are needed to overcome these difficulties.

**General aim and outline of the thesis**

This thesis aims to investigate whether genetic variants may influence and explain disease sub-phenotypes, disease course and disease complications of IBD and T2D. Accordingly, this thesis is divided into two parts focusing on IBD and T2D, respectively.
Part 1: Epidemiology of IBD, the role of genetic variants in disease phenotypes and prediction

Inflammatory bowel disease (IBD) is a diverse group of gastrointestinal disorders with complex pathogenesis which comprises two immune-mediated conditions: Crohn’s Disease (CD) and Ulcerative Colitis (UC). It is a heterogeneous disease without identifiable causes at the clinical level, which confers a significant burden for the patient. The symptoms of IBD are associated with substantial morbidity. CD and UC share several disease susceptibility loci, many of which are implicated in other immune-mediated diseases.

CD is characterized by chronic inflammation of any part of the gastrointestinal tract, has a progressive and damaging course and is increasing in incidence worldwide. CD can cause transmural lesions and has long been recognized as a disabling, progressive disease, leading to high costs and a substantial quality-of-life burden. The majority of CD patients develop complications necessitating hospitalization or surgery. Earlier, more aggressive treatment can change the natural history of the disease and decrease complications and the need for hospitalization and surgery. CD is a complex disease, and treatment should in future be more personalized to address the underlying pathogenetic mechanism.

UC is causing more superficial lesions that are limited to the colon, and its progressive and disabling nature often may be underestimated. The possibility of colectomy always has been considered as a cure, and the burden is lower than in CD. UC is more common in developed countries.

IBD is composed of chronic, relapsing intestinal inflammatory diseases and is thought to arise from inappropriate activation of the intestinal mucosal immune system in response to commensal bacteria in a genetically susceptible individual after exposure to environmental triggers. The majority of patients are diagnosed early in life and the incidence continues to rise, therefore, the effect of IBD on health-care systems will raise exponentially.

It is now clear that IBD has evolved into a global emergency with rising prevalence worldwide. For example, IBD has shown rising prevalence in newly industrialized countries of Asia attributed largely to adoption of Westernized lifestyles and other associated environmental factors. The number of patients with IBD in this part of the world is expected to grow exponentially in the next decade.

IBD has been studied in great detail regarding the composition of its sub-phenotypes, its course and complications. In the past few decades, epidemiological studies have been involved in establishing the differences in the incidence of IBD throughout developing countries. IBD has significant morbidity rate but limited excess mortality.

Recent studies suggest mortality rates seem higher than previously reported.
Understanding the epidemiological patterns of IBD that result in hospitalizations, its high costs, morbidity and mortality over a period of time, in addition to its trends is necessary and valuable information for health policy makers and clinicians.

Differences in epidemiology of IBD between the newly industrialized countries and Western world are primarily explained by differences in genetic and environmental factors involved in disease development. Although, it is believed that environmental factors are important to cause the disease, an underlying genetic susceptibility is also required. IBD is thought to have a strong genetic component, since family history of IBD is the greatest risk factor for disease at all ages. GWAS studies have identified over 240 genetic variants linked to IBD, largely in individuals of European descent and some in Asian and African-American populations. GWAS have highlighted genetic similarities and differences between ethnicities, as well as between the IBD subtypes, CD and UC.

Identified variants have provided biological insights into the disease mechanisms conferring differential susceptibility to CD and UC and affecting host–microbe interactions among the IBD subtypes. Information on identified SNPs has been combined into GRSs representing the genetic background of the disease. Understanding the role of GRSs in predicting disease may improve the identification of high-risk individuals in the general population for whom preventive interventions will be needed to prevent occurrence of the disease. The role of GRSs in predicting disease phenotypes in IBD has been extensively investigated. However, the validity of GRSs in prediction of IBD, CD, and UC occurrence in populations from East and Central Asia has not been tested.

In chapter 2, I sought to study and report the outcome of IBD in the context of other gastrointestinal disease, as these diseases are among the most common causes of morbidity throughout the world. Such information can help to generate new hypotheses for scientists in this field and lead to further relevant research and preventive measures. To conduct this project, I analyzed and compared the final diagnosis according to International Classification of Diseases (ICD-10) about 5880 admitted patients in a typical tertiary referral hospital for two 5-year time periods during 2000-2004 and 2005-2009. The result of the study gave an overview of the rate of admission for CD and UC patients.

In chapter 3, I aimed to evaluate and interpret epidemiological characteristics, clinical presentation, and risk factors of UC to provide a complete overview of the evidence available to date on the epidemiological features of UC in a wide geographical and ethnically varied population during a long period of time. I performed a systematic literature search for the epidemiology of UC using a prede-
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In chapter 4, I aimed to identify new IBD risk loci and compare the genetic architecture of IBD susceptibility across ancestrally divergent populations. The evidence of shared IBD risk loci across diverse populations suggests that combining genotype data from cohorts of different ancestry will enable the detection of additional IBD-associated loci. In this study, I contributed to the aggregation of genome-wide or immunochip genotype data from 96,486 individuals of European and non-European ancestry.

In chapter 5, I subsequently aimed to investigate the predictability and occurrence of IBD (CD and UC) by means of GRS for up to 201 known shared genome-wide significant IBD associated variants, in yet unaffected high risk individuals from East and Central Asia. I aimed to understand accountable variance of IBD explained by GRS for IBD, CD, and UC in East and Central Asians where the clinical implication of genetic findings in IBD is a matter of persistent debate as the prevalence of IBD is rising. This trans-ethnic study included 9,698 subjects of three East Asian (Japan, South-Korea and China) and two Central Asian countries (India and Iran).

Part 2: Role of genetic variants in disease complications and hyperglycemic control in T2D.

One of the most studied complex diseases with respect to genetic analysis and response to medications is T2D. The etiology of T2D is a combination of beta-cell dysfunction and insulin resistance, which is promoted by either genetic or environmental factors (e.g., obesity, westernized diet, and life style). T2D and its complications have contributed massively to the burden of mortality and disability worldwide. There are currently about 420 million people living with T2D. Up to 80 percent of patients with diabetes experience higher rates of morbidity and premature mortality due to microvascular and macrovascular complications of diabetes, such as cardiovascular disease (CVD), nephropathy, retinopathy and neuropathy. Evidence suggests that early glycaemic control in patients with T2D is associated with a reduction in complications of diabetes. Glycemic control may be achieved by adherence to a healthy lifestyle and using hypoglycemic agents.

The goal of all treatment strategies for T2D is lowering blood glucose concentrations to levels approximately in the normal range and to reduce the effects of chronic hyperglycemia while avoiding serious hypoglycemic events. A commonly used measure of average blood glucose control is measuring glycated hemoglobin.
(HbA1c), which reflects plasma glucose control over the previous two to three months. HbA1c has been shown to be strongly related to the occurrence of complications in T2D patients in prospective observational studies\textsuperscript{35}. T2D is treated with nine major classes of oral and injectable approved drugs.

Even though many cases of T2D could be prevented by maintaining a healthy body weight and changing to a healthy lifestyle, some individuals are more susceptible to T2D than others, which suggest that individual differences in response to lifestyle interventions exist. Significant evidence from twin and family studies has suggested a genetic source of T2D\textsuperscript{36}. Although the current rise in prevalence of T2D is driven mainly by changes in lifestyle, genetic determinants are widely considered to contribute to susceptibility to this disease\textsuperscript{37}. Inter-individual variation in developing complications of diabetes is attributed to differences in patients’ demographics, lifestyle factors, medication adherence, and genetic factors\textsuperscript{38}.

T2D and its related comorbid diseases are caused by the interplay of both genetic and environmental factors over the lifespan\textsuperscript{39}. GWAS have facilitated an extensive and prompt extension in the number of confirmed genetic susceptibility variants for T2D. Over the past decade, successive GWAS have identified 243 genetic loci associated with T2D, representing the complex polygenic nature of T2D\textsuperscript{40}. In part two I looked at the pharmacological treatment of T2D and the association of genetic variants with respect to disease course or complications.

In chapter 6, I sought to identify which genetic variants are associated with the incidence of the major comorbid diseases related to T2D including cardiovascular disease, cancer, nephropathy, retinopathy and neurologic diseases in patients with T2D within the framework of the Utrecht Cardiovascular Pharmacogenetic studies with long-term follow-up data.

In chapter 7, I aimed to determine the relation between hypoglycemic agents and the level of HbA1c over time after diagnosis of T2D with a long-term follow-up by the means of a historical cohort analysis of Medicare registry data within the framework of the Utrecht Cardiovascular Pharmacogenetic studies.

Finally, I presented the main findings of the previous chapters and put them into a broader perspective. In chapter 8, I discussed the implications of this thesis for clinical practice and provide suggestions for future research directions.
REFERENCES


Part 1

Epidemiology of IBD, role of genetic variants in disease phenotypes and prediction