Summaries
Summary

Over the past two decades, we have observed an alarming escalation of the global prevalence of obesity that is mirrored by the rapidly rising incidence of type 2 diabetes. The high co-occurrence rate of these diseases is associated with serious health problems and mortality. Thus it puts a large financial burden on society and represents the biggest public health challenge of the 21st century. The twin epidemics of obesity and diabetes is mainly attributable to changes in our lifestyle, i.e. excessive consumption of foods that are high in fats and sugars combined with reduced physical activity, that lead to a chronic disruption of body weight regulation and to the development of metabolic disorders. In addition, family, twin and adoption studies indicate the significant role of genes in an individual’s predisposition to becoming obese. To date, most experts agree on that the recent upsurge in obesity is the result of a complex interplay between multiple genetic, behavioural and environmental factors, however the relative contribution of these causal factors remains unclear. The central aim of this thesis was to gain insight into the genetic susceptibility to both obesity and type 2 diabetes and to further our understanding of the genetic architecture of these complex diseases.

The introductory chapter 1 gives background information on obesity and type 2 diabetes in general (i.e. the definition and prevalence of both diseases, the underlying pathophysiological mechanisms and its complications) and provides an overview of the various approaches that can be used to identify the genetic determinants of complex disorders. In addition, the most important findings in the field of the genetics of obesity and type 2 diabetes are discussed here, with an emphasis on the established disease loci identified through recent genome-wide association studies.

In chapter 2, we examine the impact of genetic variation in the hypothalamus, the region of the brain known to play a key role in the control of energy homeostasis in mammals, in the aetiology of obesity. First, we describe the hypothalamic-signaling pathways, that regulates body weight, with focus on (i) the major neuropeptides involved in regulating food intake and on (ii) the receptors for the peripheral hormones involved in monitoring energy homeostasis. Next, we provide the results of a comprehensive literature review that was performed to investigate the contribution of genetic variants in the hypothalamic regulatory networks to obesity. Although, recent discoveries of novel obesity genes by genome-wide association studies as well as candidate gene and functional studies indicate a central role for the hypothalamic pathways in the genetic architecture of common obesity, the verdict still remains open on many promising candidate genes due to the lack of information. Finally, we discuss several important
issues in genetic studies on obesity which are often not recognized: better definition of obesity phenotypes, combined with detailed epidemiological data on lifestyle and dietary patterns, and the statistical approaches that allow to take the complexity of the hypothalamic system into account.

Chapter 3 presents a study in which we provide evidence that the \textit{TUB} gene is a novel candidate gene for common obesity. In this study \textit{TUB} was selected based on functional studies (e.g. the loss-of-function mutations in \textit{TUB} result in late-onset obesity and insulin resistance in mice) as a relevant candidate gene for obesity and/or type 2 diabetes from the chromosomal region 11p15. This locus was previously identified in a genome-wide linkage scan for obesity-driven type 2 diabetes in the Breda cohort. In the present follow-up study fine mapping of the gene and its flanking regions was performed and the association of common variants in \textit{TUB} with both diseases was examined. While no effect of the genotyped polymorphisms on type 2 diabetes risk was found, we did observe a correlation between \textit{TUB} variants and both increased body mass index (BMI) and obesity: the minor alleles of the variants rs2272382, rs2272383 and rs1528133 were associated with an average of 1.5 kg/m\textsuperscript{2} higher BMI, and were 1.3 times more frequent among obese people than lean individuals. This finding was confirmed in an independent replication set from a general Dutch population enriched for type 2 diabetes.

In chapter 4, we validate our original finding on the association of the \textit{TUB} gene with body weight in a large population-based study of 1680 middle-aged Dutch women and also explore possible mechanisms underlying the observed association. We investigated the relationship between \textit{TUB} variants and both anthropometry and macronutrient intake data. The analysis confirmed the association of \textit{TUB} with increased weight and BMI and, thus, showing that the relation of \textit{TUB} with body composition can be extended to a general population. Next, the analysis revealed that the individuals carrying the at-risk alleles for obesity had certain food preferences in their daily diet, in particular increased intake of mono- and disaccharides. In addition, we also found the positive association between these variants and glycemic load compared with non-carriers supporting the hypothesis that the effect of the \textit{TUB} gene on body composition might be explained by the increased intake of simple carbohydrates. These results led us to the conclusion that the \textit{TUB} gene may be related to eating behaviour in humans.

Chapter 5 describes the association study with the transcription factor 7-like 2 (\textit{TCF7L2}) gene and type 2 diabetes in a Dutch population. The \textit{TCF7L2} gene, a major determinant of type 2 diabetes susceptibility to date, was identified in a follow-up study of a previously-identified linkage signal on chromosome 10q in the Icelandic
population. Our data strongly confirmed that common variants of the TCF7L2 gene contribute to the risk of type 2 diabetes (each additional copy of the risk allele was associated with an odds ratio of ~1.5) with the population-attributable risk of 10% in the Dutch population.

In chapter 6, we examine whether single nucleotide polymorphisms near the hematopoietically expressed homeobox (HHEX) gene identified in a genome-wide scan study in French individuals as a type 2 diabetes susceptibility locus, contribute to the disease risk in a Dutch population. We were able to replicate the association between HHEX variants and type 2 diabetes.

Finally, in chapter 7, we discuss our current model of the genetic architecture of obesity and type 2 diabetes, the potential implications and limitations of these recent discoveries, and also provide future perspectives.

The main conclusions of this thesis

- The hypothalamic pathways play a central role in the genetic architecture of common obesity (chapter 2)
- The TUB gene is a novel candidate gene for common obesity (chapter 3)
- Genetic variation of the TUB gene is associated with both body composition and macronutrient intake, suggesting that TUB might influence eating behavior (chapter 4)
- Genetic variants of the TCF7L2 gene strongly modulate susceptibility to type 2 diabetes in a Dutch population (chapter 5)
- Common polymorphisms near the HHEX gene contribute to the risk of type 2 diabetes in a Dutch population (chapter 6)