Revealing the genetic roots of obesity and type 2 diabetes
Vliet-Ostaptchouk, Jana Vladimirovna van

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 1

General introduction
The genetics of obesity and type 2 diabetes
“Make no mistake: the dread obesity epidemic that is everywhere in the news is not restricted to any race, creed, ethnicity or slice of the socioeconomic supersized pie. As recent studies reveal, virtually every group known to demography is getting fatter.

The poor are getting fatter and the well-to-do are getting fatter. The old are getting fatter, baby boomers and Generation Xers are getting fatter, children too young to have a category are really getting fatter. People are broadening abroad as well – in Europe, Australia, South America, Africa, Russia, the Middle East. Asians once seemed blessed with magic anti-adipose devices, but they, too, are getting fatter.

Even in the poorest nations, where hunger and famines are still part of the landscape, obesity rates are climbing.”

The prevalence of overweight and obesity has developed at an alarming rate worldwide over the past two decades. There are more overfed people on the planet now than underfed people. In the United States alone, at least two-third of the adult population are officially overweight, and about half of them are obese. The American magazine *Time Online* already in 2004 reported that the total effects of individual weight problems in the population have risen to the level of a national crisis.

The consequences are dramatic and sometimes even preposterous. For example the ongoing heated debates in mass media about how airlines should deal with the increasing amount of severely overweight passengers. Those debates started after some cases, like the Barbara Hewson one, a Welsh woman, who was recently paid US$ 20,000 by Virgin Atlantic in compensation for being crushed and injured by an obese person sitting next to her on a transatlantic flight. Lately, Air-France KLM announced that obese people who are unable to squeeze into a single plane seat will have to pay nearly double. In contrast, producers of safety seats for children are starting to make bigger models because too many children age 6 and under are too fat to fit into regular ones.

The U.K. government has recently banned the word ‘obese’ to describe overweight children (August 2008). The term was considered to ‘shut people down’. Civil servants decided to introduce the term ‘very overweight’ instead, which they consider to be less offensive.

Meanwhile, liposuction was the second most popular cosmetic surgery in the US in 2008, topped only by breast enlargement. Total spending on this procedure amounted some 3 billion dollar, which is half a billion more than the USA spent on world wide food aid in that year.

But the ‘Big Fat problem’ is not simply an aesthetic inconvenience. Both overweight and obesity are medical conditions characterized by abnormal or excessive fat accumulation that affect people throughout society. They present not only a serious risk to public health on their own account (i.e. by increasing both morbidity and mortality), but especially because they also trigger the development of type 2 diabetes, a disease associated with the body's ineffective use of insulin, which in turn results in multiple

---

1 http://www.time.com/time/subscriber/covers/1101040607/article/how_we_grew_so_big_diet01a.html
2 http://news.bbc.co.uk/2/hi/uk_news/wales/2346319.stm
4 http://www.msnbc.msn.com/id/12122212/
5 http://www.timesonline.co.uk/tol/life_and_style/health/child_health/article4458852.ece
6 http://www.oregonlive.com/health/index.ssf/2009/05/cosmetic_surgery_numbers_sag_b.html
7 http://www.ers.usda.gov/amberwaves/november08/Findings/USFoodAid.htm
severe health complications. Experts in the field of healthy aging consider both obesity and type 2 diabetes key problems that need to be solved first. But to be able to solve the problems we have to understand its underlying roots and processes. So if we like to live long and healthy, then we should understand the origin of obesity first.

**BMI and the definition of obesity**

According to World Health Organization (WHO) guidelines, the major definition of overweight and obesity is body mass index (BMI), a simple measurement comparing weight and height (BMI=weight (kg)/height (m)^2), that classifies a person to be overweight (pre-obese) or obese when their BMI is equal to or more than 25 or 30, respectively. As a clinical tool, BMI is easy to calculate, inexpensive, and a well-defined criteria for the diagnosis of the severity of obesity in adults, as it is independent from sex and age (1). However, BMI should be considered as a surrogate measure of total body fat as it is does not directly incorporate body fat or fat distribution levels and, thus, it may not reflect the same degree of fatness in different individuals (2). Also, association of BMI with percentage of body fat and body fat distribution differs across populations (3). For example, on the basis of the available data in Asia, the WHO expert consultation concluded that Asians generally have a higher percentage of body fat than Caucasians of the same age, sex, and BMI (3). Moreover, the proportion of Asian people with elevated risk factors for type 2 diabetes and cardiovascular disease is substantial even below the existing WHO BMI cut-off point of 25. Therefore, in the current WHO classification additional BMI cut-off points associated with increased health risk are suggested (Table 1).

In addition to BMI, there are other measures commonly used in obesity research, such as waist circumference and waist-to-hip circumference ratio. Both measures are related to abdominal or visceral obesity, e.g. body fat stored around the stomach and abdomen, and skinfold thickness quantifying subcutaneous fat which is located just beneath the skin. Furthermore, computed tomography or magnetic resonance imaging are available to quantify central fat mass and visceral fat, but these methods are expensive and time-consuming and therefore unsuitable for routine clinical screening. In Table 2 a summary on the different measures and methods is shown, as well as an estimation of costs and difficulties of measuring body fat distribution.

In recent years much evidence has accumulated that abdominal obesity, independent of total fatness, is directly related to a number of metabolic parameters associated with the obesity-related diseases (4). As waist circumference is the most practical tool to estimate an individual’s abdominal fat, the National Heart, Lung, and
Blood Institute guidelines recommended to use this measure as a predictor of a high health risk defined as above 102 cm in men and above 88 cm in women (Table 1) (5). For Asian people, these waist circumference cut-off values suggested to be higher than 90 cm in men and higher than 80 in women (6).

**Table 1:** Classification of adult overweight and obesity by BMI, waist circumference, and associated disease risk for type 2 diabetes, hypertension and cardiovascular disease.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Disease risk relative to normal weight and waist circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Principal cut-off points</td>
<td>Additional cut-off points</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50 - 24.99</td>
<td>18.50 - 22.99</td>
</tr>
<tr>
<td>Overweight Pre-obese status</td>
<td>≥25.00</td>
<td>≥25.00</td>
</tr>
<tr>
<td></td>
<td>27.50 - 29.99</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>≥30.00</td>
<td>≥30.00</td>
</tr>
<tr>
<td></td>
<td>35.00 - 39.99</td>
<td>35.00 - 39.99</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>≥40.00</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>


¹ In the Asian population: in men ≥ 90 cm and in women ≥ 80
² Additional BMI cut-off points associated with increased health risk in the Asian population

The prevalence of obesity

The WHO has recently proclaimed that obesity has reached epidemic proportions globally (Figure 1): in 2005 33% of the world’s adult population (1.3 billion people) were estimated to be overweight (BMI≥25) or obese (BMI≥30) (7). Obesity was once considered a problem of economically developed countries but the number of overweight and obese people is now dramatically increasing in low- and middle-income countries at a rate never before seen in developed countries. In addition, obesity is also becoming a leading threat to the health of children and adolescents: according to the WHO estimations at least 20 million children under the age of five are overweight worldwide (1). As the majority of these kids become overweight or obese adults, the
Table 2: Measures and methods of estimating body fat phenotypes that are commonly used in obesity research.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Measurement method</th>
<th>Ease of use</th>
<th>Related costs</th>
<th>Accuracy</th>
<th>Measures fat distribution</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Scale</td>
<td>Easy</td>
<td>$</td>
<td>High</td>
<td>No</td>
<td>Total weight</td>
</tr>
<tr>
<td>Body Mass Index (BMI, kg/m²)</td>
<td>Scales to measure weight and height</td>
<td>Easy</td>
<td>$</td>
<td>High</td>
<td>No</td>
<td>Total body fat</td>
</tr>
<tr>
<td>Waist circumference, waist-to-hip circumference ratio</td>
<td>Tape measure</td>
<td>Easy</td>
<td>$</td>
<td>Moderate</td>
<td>Yes</td>
<td>Total and visceral fat</td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>Skin calipers</td>
<td>Easy</td>
<td>$</td>
<td>Low</td>
<td>Yes</td>
<td>Subcutaneous fat</td>
</tr>
<tr>
<td>Central or visceral body fat</td>
<td>DEXA</td>
<td>Moderate</td>
<td>$$</td>
<td>High</td>
<td>Yes</td>
<td>Distribution of central or visceral body fat</td>
</tr>
<tr>
<td>Body fat distribution</td>
<td>Computed tomography</td>
<td>Difficult</td>
<td>$SS$$</td>
<td>High</td>
<td>Yes</td>
<td>Distribution and amount of central or visceral body fat</td>
</tr>
<tr>
<td></td>
<td>Magnetic resonance imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
future prognosis does not look optimistic. If recent trends continue unabated, by 2030 the absolute numbers could rise to a total of 2.16 billion overweight and 1.12 billion obese individuals, or 38% and 20% of the world’s adult population, respectively (7).

![Worldwide age-standardized prevalence of overweight and obesity in adults (20 years and older) by country in 2005. Adapted from Kelly et al., with permission, from Int. J. Obes. REF. (7). © (2008) Macmillan Publishers Ltd.](image)

**Figure 1:** Worldwide age-standardized prevalence of overweight and obesity in adults (20 years and older) by country in 2005. Adapted from Kelly et al., with permission, from Int. J. Obes. REF. (7). © (2008) Macmillan Publishers Ltd.

The global obesity epidemic is also occurring in the Netherlands: during the period 1981-2004, the prevalence of overweight increased from 35.7% to 48.3% among men and from 27.1% to 38.3% among women. Similarly the prevalence of obesity increased from 3.9% to 8.7% among men and from 6.1% to 11.5% among women (8). Alarmingly, the number of overweight and obese children is rising at an even faster rate as the prevalence of overweight (including obesity) Dutch children and adolescents aged 0-20 almost tripled from 1980 to 2003 (9).
How does obesity impact health?
Scientists and medical doctors compare obesity with a health time bomb (10). This is not surprisingly because of obesity’s many serious comorbidities which also put a large financial burden on the economy. As raised body weight leads to adverse metabolic effects on insulin resistance, blood pressure, cholesterol and triglycerides, overweight and obesity are strongly associated with a higher risk for multiple diseases, including type 2 diabetes, hypertension, cardiovascular disease (mainly heart disease and stroke), certain types of cancer, gallbladder disease and also mortality (1, 11, 12). As a result, obesity accounts for an estimated 2-6% of total health care costs in developed countries. However, the true costs are undoubtedly much higher as not all obesity-related conditions are included in the calculations (1, 13).

Obesity and type 2 diabetes: the twin epidemics
The twin epidemics of obesity and diabetes already represent the biggest public health challenge of the 21st century: the epidemic of obesity is mirrored by the rapidly rising incidence of type 2 diabetes. According to the WHO, more than 220 million people worldwide have type 2 diabetes (14). As discussed below, the major effect of overweight and obesity on an individual’s health is the development of insulin resistance that over time may lead to type 2 diabetes (Box 1). Indeed, approximately 60% of all type 2 diabetes cases are directly attributed to weight gain (1), and many experts believe that “obesity has become to diabetes what tobacco is to lung cancer” (13).

The pathophysiological road from obesity to metabolic syndrome
The mechanisms leading from obesity to all these various chronic diseases are complicated and not fully elucidated. Nevertheless, there is substantial evidence that obesity, especially excess visceral fat accumulation, is an important predictor of insulin resistance (15) and may partly be a cause of the so-called “metabolic syndrome” (16). Despite the controversy and concerns over the conceptual definition of metabolic syndrome (17), many agree that it is a condition commonly associated with clustering of metabolic abnormalities, including abdominal or visceral obesity, elevated glucose level or insulin resistance, increased triglycerides, low high-density lipoprotein (HDL) cholesterol level, and arterial hypertension, that together promote the development of diabetes and cardiovascular disease (CVD) (16-18).
Box 1: Type 2 diabetes – a short summary

Type 2 diabetes is a chronic disease caused by complex interactions of genetic and environmental factors. The disease is characterized by elevated plasma glucose levels arising from the body’s inability to respond to insulin it produces, i.e. insulin resistance, combined with impaired β-cell function to produce enough insulin to keep blood glucose levels normal, i.e. insulin deficiency. Type 2 diabetes is diagnosed according to the WHO recommendations from 1999: a fasting plasma glucose level >7.0 mmol/l or 2-hour post glucose load glucose levels >11.1 mmol/l (91).

The main risk factor for type 2 diabetes is overweight combined with physical inactivity, i.e. according to the WHO estimations about 60% of diabetes globally can be attributed to weight gain. In additions, a family history of diabetes, age and ethnic background are known to be important risk factors for the disease and are known to contribute to disease predisposition (91).

The concordance rate for type 2 diabetes is higher in monozygotic than in dizygotic twins. Also, the sibling recurrence risk ratio for the disease (or relative risk for a relative of diabetic patients compared with population risk) is estimated to be around 3.5 in the European population. These figures indicate a substantial role for heredity in determining the risk of type 2 diabetes calculated to be 30-70%. Until recently, the search for type 2 diabetes genes was not very successful due to both its polygenic and heterogeneous nature and due to the limitations of the approaches used in the pre-genome-wide association (GWA) era. To date, almost 20 robustly replicating type 2 diabetes loci have been identified in GWA studies.

The WHO type 2 diabetes facts for “dummies”.

- At least one in ten deaths among adults between 35 and 64 years old is attributable to diabetes.
- In developed countries most people with diabetes are above the age of retirement, whereas in developing countries those most frequently affected are aged between 35 and 64.
- In developing countries the number of people with diabetes will increase by 150% in the next 25 years.
- The global increase in diabetes will occur because of population ageing and growth, and because of increasing trends towards obesity, unhealthy diets and sedentary lifestyles.
Proposed mechanisms, by which visceral adiposity could be linked to the metabolic abnormalities, are summarized in Figure 2. The excess of the visceral fat, which shows insulin resistance due its biochemical features, will lead to the higher concentration of free fatty acids (FFA). Chronically elevated blood FFA concentration is associated with peripheral insulin resistance and alteration in lipolysis (i.e. reduced production of the “good cholesterol” HDL lipoprotein and increased production of the “bad cholesterol” LDL lipoprotein, that increase risk for CVD), and also affects metabolic processes in liver resulting in hepatic hyperinsulinemia, increased glucose production and overproduction of very low-density lipoprotein (VLDL) (18). Next, the adipose tissue is an endocrine organ releasing numerous proinflammatory molecules, adipokines, such as interleukin (IL)-6 and tumour necrosis factor-α (TNF-α), and also the hormone adiponectin, that stimulates hepatic glucose usage and reduces FFA levels. Thus, the result of visceral fat accumulation is a proinflammatory and hypertensive state accompanied by elevated levels of adipokines and reduced levels of adiponectin, both these conditions contribute to insulin resistance (15). In addition, there is another complementary mechanism proposed by Despres, in which subcutaneous adipose tissue acts as an ‘energy sink’ in case of a positive energy balance when an individual has to handle a calorie surplus (19). Thus, the accumulation of intra-abdominal fat may be a marker of the relative inability of subcutaneous adipose tissue to play a role as a depot buffering the energy excess, which leads to the accumulation of fat at undesired sites such as liver, heart, pancreas or skeletal muscle (19).

Altogether, it is likely that the obesity status mediates various metabolic abnormalities via complex mechanisms that increase the risk to develop type 2 diabetes and CVD.

What causes overweight and obesity?
Since the fundamental cause of obesity and overweight is an energy imbalance between calories consumed on the one hand and calories expended on the other hand, increases in rates of obesity must reflect a state of positive energy balance which is very likely a result of the profound changes in society and in behavioral patterns of populations over recent decades. Indeed, it is widely accepted that multiple factors contribute to this epidemic, including economic growth, modernization, urbanization and, most important, changes in our lifestyle: eating habits have shifted to greater consumption of energy-dense foods that are high in fats and sugars while, at the same time, physical activity has decreased (1, 20).
Although it is clear that the rising prevalence of obesity is related to recent environmental changes, the relationship is not a simple one. Not all people are affected equally by the obesogenic environment, and under similar conditions of overfeeding
and sedentary lifestyle different individuals are responding with different gains in weight (21). Such individual variability in the predisposition for obesity may be due to genetic susceptibility. Indeed, many twin-, adoption- and family studies have indicated a significant contribution of genetic factors to obesity pathogenesis (21-26). For example, in the most recently published twin study by Wardle et al. (n=5,100) the heritability of both BMI and waist circumference was estimated to be 77% (24), meaning that around 77% of the individual variation in adiposity between persons is apparently due to genetic factors. Comparable heritability estimates were reported for body fat content and total and regional fat distribution, ranging between 50% and 85% (25, 26). In addition, it appears that some people may have inherited a greater susceptibility to gain body fat or to store excess energy as abdominal fat deposits when challenged by chronic overfeeding.

Thus, even in a presence of strongly obesogenic environment, the hereditary factors remain important contributors to the disease etiology, and many experts agree that the current obesity epidemic is most likely the result of a complex interplay between multiple genetic, behavioral and environmental factors that affect energy balance and, thus, body weight regulation (27-30). In addition, many hypotheses explaining the origin of this epidemic were proposed, a summary of which is shown in Box 2.

**Biological factors in the etiology of obesity – the neuroendocrine control of energy homeostasis**

Since inherited factors are playing an important role in obesity, they must be operating through physiological systems, e.g. the systems that match energy intake with energy expenditure resulting in energy balance to maintain a stable body weight. Recent evidence suggests a key role for the region of the brain known as the hypothalamus in the regulation of energy homeostasis in mammals (31, 32). In short, the hypothalamus receives multiple adiposity- and nutrient-related signals from peripheral systems that reflect the energy status of the body, interprets these signals and transmit the information to (1) changes in behavior, including appetite, satiety, food intake and physical activity and (2) changes in the neuroendocrine system that regulates energy expenditure and metabolic processes, including secretion of different hormones (e.g. growth and sex hormones, thyroid, cortisol and insulin) (31, 32). As a result, in most people, body weight remains remarkably stable most of the time despite the wide variations in daily energy intake and expenditure.

Also, the regulation of appetite and satiety is strongly influenced by genetic factors as the heritability of individual difference in eating behaviors is estimated to range from
about 20% to 40% (33). Interestingly, animal and human studies demonstrate a plausible bias in the regulation of energy balance towards a negative energy balance. In other words, this system is biased towards preservation of energy storage for future possible food shortage, and therefore, overfeeding leads to much less compensatory change in energy expenditure than food restriction (27). These observations suggest a presence of the “default setting” in our physiology to protect more strongly against weight loss than against weight gain. Thus, in the presence of the obesogenic environment certain heritable neurobehavioral traits, especially those influencing eating patterns, such as hunger, satiety or food intake, combined with the physiological “default setting” may be very important drivers of the individual’s predisposition to become obese (34).

**Box 2: Main hypotheses explaining the origin of obesity**

**The thrifty gene hypothesis**

In 1962, James Neel suggested that ‘thrifty’ genes would have been advantageous in periods of famine during human evolutionary history resulting in selection pressures (92). Neel postulated the existence of metabolically thrifty genes: these permit more efficient food utilization, fat deposition and rapid weight gain at occasional times of food abundance, thereby making the gene-bearer more able to survive a subsequent famine. Examples of thrifty genes would include those resulting in high levels of insulin or of leptin, or in hair-triggered insulin release (93). However, in modern society with food overabundance and sedentary lifestyle, this thrifty genotype, that ‘prepares’ individuals for a famine that never comes, is suggested to lead to metabolically disadvantageous phenotypes. The result is the obesity epidemic and obesity related health problems such as type 2 diabetes. Although the thrifty genes hypothesis is popular and frequently cited, it is also controversial and has been discussed for decades in many scientific papers.

**The ‘predator release’ hypothesis**

According to Speakman (94) the mortality rates in famine do not appear high enough to select for thrifty genes, and the difference in survival per generation between obese and non-obese subjects, as a consequence of famine exposure, is insufficient to generate the observed genetic background to the current epidemic. He suggests that our body fatness was historically regulated by a system that involves upper and lower intervention limits. The lower intervention limit is set by the risk of reduced fertility and starvation (i.e. too thin individuals would not tolerate periods of food shortage), and the upper intervention limit is set by the risk of predation (i.e. our heavier ancestors were at greater risk of being
predated upon). Over the past 2 million years our ancestors developed weapons and fire and were released from heavy predation pressure. As a result, the genes defining the upper intervention point have been subject to random mutation and drift. These mutations would only be exposed as giving their bearers a predisposition to obesity, for example, in modern societies where energy is freely available, resulting in a pattern of susceptibility of obesity we observed today.

**Obesity as a heritable neurobehavioral disorder strongly influenced by environment**

Recently, O’Rahilly and Farooqi proposed a new hypothesis that explains the current obesity epidemic. Based on the observations from the studies of monogenetic forms of obesity they suggested that hereditary factors could have their major impact on the regulation of appetite and satiety defined by the ‘hypothalamic set point’ (34). Since human appetite varies markedly between individuals, this variation may underlie differences in inter-individual susceptibility to obesity. As suggested by Speakman (94), until recently a naturally occurring shift toward an upward drift in adipose stores may rarely have actually manifested themselves as obesity because of the high energy cost of obtaining food during most of human evolution. So, according to O’Rahilly and Farooqi, due to the remarkable change in our society over the last 50 years or so, the large part of the human population is now living in the ‘toxic’ environment (i.e. too much food and too little physical activity) where excessive energy storage is not required for survival. As a result, individuals who are genetically predisposed to overweight and adiposity have finally had an opportunity to reach their ‘obesity potential’, while other groups of individuals whose hypothalamic set points have not randomly moved upwards through ‘genetic drift’ remain lean in the presence of the ‘toxic’ environment.

**The thrifty phenotype or metabolic programming hypothesis**

The thrifty phenotype hypothesis, introduced by Hales and Barker in 1992 (95), proposed the concept that environmental factors acting in early life, in particular poor nutrition, produces permanent changes in glucose-insulin metabolism that might influence the later risk for metabolic syndrome and type 2 diabetes. In this model, malnutrition at different stages of fetal life and infancy acts not as a selection pressure over many generations to alter the genetic make up of the population, but rather as an early environmental influence acting in an individual to increase risk of disease. Today this hypothesis is known as ‘the metabolic programming’ theory. Recent investigations highlight that adaptations made by the nutritionally manipulated fetus may lead to a long term re-setting of cellular energy homeostasis, most probably via epigenetic modification of genes involved in a number of key regulatory pathways (96).
The genetics of obesity and type 2 diabetes

Obesity is a complex disease caused by the interaction between multiple genetic and environmental factors. Over the past few decades, numerous research groups have been involved in the search for obesity associated genes using different strategies. To provide an overview of studies relevant to the genetics of obesity, the Obesity Gene Map (OGM) database was developed (http://obesitygene.pbrc.edu/). Between 1996 to 2005, OGM has extensively evaluated all published results including monogenic forms of obesity, transgenic and knockout animal models, quantitative trait loci (QTL) from animal cross-breeding experiments, linkages from genome scans, and association studies with candidate genes (35). More recently, OGM was replaced by the Human Genome Epidemiology Network (HuGENet), a continuously updated knowledge base of published, population-based epidemiologic studies of human genes extracted and curated from PubMed, that includes information on population prevalence of genetic variants, gene-disease associations, gene-gene and gene-environment interactions (http://hugenavigator.net/) (36). At the moment of writing this chapter (January 2010) 591 candidate genes for obesity and 630 genes for type 2 diabetes were reported in the database.

Approaches in genetic studies of complex diseases
There are numerous strategies to identify the genetic determinants of complex disorders. The methods commonly used in obesity genetics include studies of severe forms of obesity, linkage or genome scan studies, candidate gene analyses and genome-wide association studies (Table 3). Similar methods are used to unravel the genetics of type 2 diabetes. A summary of the different studies is listed below.

Studies of monogenic forms of obesity and type 2 diabetes
The first approach is focusing on rare forms of obesity or diabetes which are usually caused by a mutation in a single gene and display a Mendelian pattern of inheritance. Although the majority of these mutations are rare by definition, they often have a strong effect and frequently lead to severe phenotypes, such as manifestation in childhood. From these studies we have learned that human obesity can result from a multiplicity of defects in the leptin-melanocortin pathway within the brain (37). These alterations include mutations in the leptin LEP and leptin receptor LEPR gene that lead to hyperphagia as a result of the absence of food intake control. Also, there are mutations in the genes highly expressed in the brain (particularly in the hypothalamus)
such as the POMC gene, the melanocortin 4 receptor MC4R gene (coding mutations in this gene are the most frequent cause for severe obesity with prevalence varying from 0.5%-1% in obese adults to 6% in subjects with early-onset obesity), the brain derived neurotrophic factor BDNF, and prohormone convertase 1 PCSK1. Both POMC and MC4R play a key role in the regulation of food intake and energy metabolism, PCSK1 also regulates the energy metabolism, and BDNF is involved in multiple processes related to stress response, mood disorders, hyperactivity and also eating behavior.

In addition to monogenic forms of obesity, there are also about 30 syndromic forms of obesity in which obesity is a clinical feature, often associated with mental retardation, dysmorphic features, and organ-specific developmental abnormalities. The most common syndromes are Prader-Willi syndrome (PWS), characterized by obesity, short stature, mental retardation and hyperphagia, and caused by a deletion on the paternal chromosome 15 (15q11.2-q12), and Bardet-Biedl syndrome (BBS), characterized by obesity, pigmentary retinopathy, polydactyly, mental retardation and hypogenitalism, and which is linked to at least seven genomic loci (37).

Importantly, the studies on severe forms of obesity suggest that the physiological systems regulating eating behavior might be highly important in the obesity pathogenesis, since most of the genes discovered so far have their principal impact on hunger, satiety and food intake.

The genetic studies of monogenic forms of diabetes which account for 2-5% of the disease have led to the identification of a few genes in which rare major mutations result in pancreatic β-cell dysfunction associated with a stable or progressive distortion of insulin secretion. Well known examples are the KCNJ11 gene encoding the ATP-sensitive potassium channel KIR 6.2 which is involved in neonatal diabetes, the peroxisome proliferator-activated receptor gamma (PPARG) gene and the Wolfram syndrome 1 (WSF1) gene involved in severe insulin resistance, and the hepatocyte nuclear factors 4-alpha and 1-beta (HNF4a and HNF1β, also known as transcription factor-2 TCF2) genes discovered in patients with maturity onset diabetes of the young (MODY) (38). All these genes have been convincingly associated with type 2 diabetes in candidate genes studies (39, 40), supporting the hypothesis that more subtle genetic changes affecting the functions of these genes might play a role in determining susceptibility to more common multifactorial forms of the disease.

**Genome-wide linkage studies**

This approach is used to identify loci containing genes that influence the phenotype or a trait of interest. Based on the assumption, that disease-influencing variants are
co-segregating within families, this method involves the genotyping of polymorphic markers, positioned across the whole genome at 1-10 cM intervals, in a large number of related individuals and a further analysis of linkage between markers and phenotype or disease status (41). In fact, this method has been very successful for mapping loci or genes underlying monogenic “Mendelian” diseases, because of the high penetrance of the disease-causing variants.

To date, more than 60 genome-wide scans for obesity-related phenotypes have been published, with a variety of loci and genes being identified. Around 250 QTLs have been found which are distributed over all chromosomes except the Y chromosome (35). Results that have been replicated in at least three genome-wide linkage scans include loci on chromosomes 2p, 3q, 5p, 6p, 7q, 10p, 11q, 17p and 20q. However, a recent large meta-analysis that combined 37 genome-wide linkage scans data encompassing more than 10,000 families and over 31,000 individuals, failed to find strongly positive loci for BMI (42). The lack of success can be attributable to multiple factors, such as the presence of considerable locus heterogeneity, a low coverage of the often used microsatellite markers in the majority of the studies; the imprecise definition of obesity phenotype; and an inadequate statistical power of the linkage studies to detect genes with modest effects on the disease. In addition, the collection of families necessary for conducting genome-wide scans requires finding a large number of families with individuals possessing the disease phenotype and using strict ascertainment criteria to exclude families with different environmental exposures and genetic or ethnic backgrounds - factors that could lead to reducing power of the study (41, 42). Hence, so far the genome-wide linkage scan has not been an effective method to identify genetic variants that contribute to common obesity.

More then 30 genome wide linkage scans for type 2 diabetes have been carried out to date. However, no susceptibility variant that can reliably account for any of the replicated T2D-linkage peaks has been identified (43). Recently published large meta-analyses of the International Type 2 Diabetes Linkage Analysis Consortium data (a total of 23 genome scans were included), failed to confirm the previously reported disease peaks on chromosomes 1q, 2q, 3p, 3q, 8p, 12q, 18, and 20q and suggested evidence for linkage on regions of chromosomes 4, 10, 14, and 16 for type 2 diabetes, with no signal reaching genome-wide significance (44). However, another meta-analysis that included 52 genetic linkage scans for type 2 diabetes and for its precursor quantitative traits (e.g. plasma glucose or insulin levels) suggested locations for type 2 diabetes susceptibility genes based on clusters of replicated results indicating that there are major genes for type 2 diabetes on 1q, 2q, 6q, 8p, 9q, 17pq, 18p, 19q and 20q (45). Some of these peaks
are overlapping with the previously reported original disease susceptibility loci. The observed inconsistency in the results may be due to the different genome-wide scans included in the meta-analysis and to the different analytic compilations of the linkage data used for the meta-analyses. Also, phenotypic heterogeneity of type 2 diabetes and an insufficient sample size of many scans to detect a linkage signal for locations where the genetic effect is weak might be possible explanations of these results.

Interestingly, one of the first successes in the genetics of diabetes – the identification of transcription factor 7-like 2 (TCF7L2) gene – was discovered in the follow-up fine mapping study of the indicative linkage locus on chromosome 10q (46). However, the common variants driving the association with type 2 diabetes do not explain the originally observed linkage suggesting a presence of yet undiscovered rare causal variants. Thus, it might possible that the fine mapping studies have concentrated on evaluating the role of common polymorphisms while most original linkage signals reflect the actions of multiple rare variants (47). In this case, deep sequencing of the loci targeting low frequency polymorphisms should lead to the identification of additional diabetes susceptibility variants with larger effect size.

**Candidate gene association studies**

This approach is very straightforward as it aims to detect association between a particular genetic variant and a disease (or a trait), assuming that a “causal” variant is more frequent in persons with the disease than in those without it. In the past, association studies focused on functional candidate genes, i.e. genes known to be involved in the disease related physiological pathways or identified in animal studies or through genome-wide scans (48).

Despite the numerous reports on candidate gene association studies in obesity, a relatively small number of genes were proven to be associated: 22 genes were consistently associated with obesity-related phenotypes in at least five studies, and only 12 genes have more than 10 replications (35). Among these genes are genes involved in the regulation of energy expenditure and lipid and adipose tissue metabolism (PPARG (30 studies), ADRB3 (29), ADRB2 (20), GNB3 (14), UCP3 (12), ADIPOQ (11), UCP2 (11), NR3C1 (10) and UCP1 (10)) and genes involved in the regulation of food intake (LEPR (16 studies), LEP (11), and HTR2C (10)) (35). Only recently large-scale or meta-analyses studies for obesity candidate genes were performed (49, 50). From the above mentioned list of the genes only ADRB3 was confirmed in a large meta-analysis of 97 studies, involving almost 45,000 individuals: the Trp64Arg ADRB3 variant was found to be associated with BMI in East Asians, but not in Europeans (51). Also, three
other genes – BDNF (52), MC4R (53) and PCSK1 (54) have been robustly associated with obesity in large-scale or meta-analysis studies (49, 50). Interestingly, mutations in these genes are also known to cause severe or early-onset obesity. This provides evidence of possible overlap between monogenic and complex forms of the disease.

In spite of the numerous research publications on candidate gene studies in type 2 diabetes, only four genes have been shown to be robustly associated with the disease: PPARG (55), KCNJ11 (56), WFS1 (57), and TCF2 (57). As discussed previously, all these genes are also involved in monogenic forms of diabetes. Next, TCF7L2 gene variants have been established as one of the major determinants of disease risk (58). Compared with non-carriers, heterozygous and homozygous carriers of the TCF7L2 at-risk alleles (38% and 7% of the population, respectively) have relative risks of 1.45 and 2.41 respectively. This corresponds to a population attributable risk of 21% (46). The precise mechanisms by which TCF7L2 polymorphisms increase risk are not well understood, although various functional studies suggest that they may exert their effect on insulin secretion, reduced β-cell proliferation, hepatic glucose production, or adipocyte function (39).

The major problem that has plagued the candidate gene approach for both obesity and type 2 diabetes is the nonreplication of previously reported associations (59). In part this nonreplication may be caused by heterogeneity within an individual, both with respect to the alleles contributing to disease as well as to the variable combinations of genetic risk factors influenced by environmental factors during a person’s lifetime (60). Also, given a large number of “small effect” genes for any complex disease, many studies have limited power because of small sample size (n<1000). In other words, the smaller the effect of the disease-influencing genetic marker and the lower its minor allele frequency, the larger the sample size required to detect an association between this variant and disease risk with sufficient power. Therefore, with a small sample size, positive results do not prove and negative results do not disprove true association.

**Genome-wide association studies**

Genome-wide association studies (GWAS) combine the latest advances in genotyping technology with a comprehensive catalogue of common genetic variants based on single-nucleotide polymorphism (SNP) catalogued by the International HapMap project (61). These studies use high-density, genome-wide arrays to assay hundreds of thousands of SNPs that capture the majority of common variation in the human genome, and relate these variants to diseases or specific traits. GWAS is a hypothesis-free approach with respect to the underlying cause of disease. In the last few years, GWAS have led
to breakthrough progress in our understanding of the genetic determinants of many different common diseases: over 530 variants or regions associated with more than 115 complex diseases or traits have been identified and replicated in diverse population samples (62). Data from these GWAS are summarized in the catalog of Genome-Wide Association Studies (http://www.genome.gov/26525384) (63).

Most GWAS for obesity have examined the association with BMI, as it is a good indicator of adiposity available in many studies, or with early-onset or severe obesity, assuming that the populations of the morbidly obese patients might be enriched for the variants also predisposing to common obesity. The first wave of the GWAS for obesity have led to the most important discovery in obesity genetics so far – the fat mass and obesity associated gene \textit{FTO} (49, 50). Interestingly, \textit{FTO} was identified through a genome-wide association study for type 2 diabetes (64). However, after adjusting for BMI, the association with type 2 diabetes was completely abolished, indicating that the \textit{FTO} – type 2 diabetes association was mediated through BMI. Subsequently, the \textit{FTO} effect on BMI has been replicated in multiple populations of different ethnicities, as well as in all the recently published GWAS for obesity. The frequency of the \textit{FTO} risk variant with a per-allele effect size of 0.40-0.66 kg/m\textsuperscript{2} BMI units, is high in populations of European decent: 63% carry at least one risk allele and 16% are homozygous. The population attributable risk for obesity (about 20%) and overweight (about 13%) is also relatively high, however the \textit{FTO} variants explain only 1% of the variance in BMI (65).

To date, in genome wide association studies around twenty genes or loci were reported to influence body weight - \textit{BDNF, CTNNBL1, ESR, ETV5, FTO, GNPDA2, INSIG2, KCTD15, LYPLAL1, MC4R, MSRA, NEGR, NPC1, NRXN3, PFKP, PPARG, PTER, SH2B1, TFAP2B, and TMEM18} (47, 64, 66-74). In this overview on the GWAS results we have focused on large-scale high-density studies only that also included a replication stage, and the summary on the identified loci is shown in Table 3. Notably, the majority of associated loci highlight genes that are highly expressed in the brain (and particularly in the hypothalamus), suggesting a key role for genes involved in regulating energy balance over those involved in metabolism (75).

So far, 19 type 2 diabetes susceptibility variants have been reported in GWAS, among which five loci (\textit{PPARG, KCNJ11, WSF1, TCF2} and \textit{TCF7L2}) were the confirmation of the previously reported genes and fourteen loci were novel. Among the newly discovered regions (Table 3) near \textit{CDKN2A/B, CDKAL1, SLC30A8, IGF2BP2, HHEX/IDE, FTO} and \textit{KCQ61} genes have been identified through individual GWA studies for type 2 diabetes carried out in European (76-82) and in Japanese populations (\textit{KCQ61}) (83, 84);\textit{ NOTCH2, CDC123/CAMK1D, ADAMTS9, THADA, TSPAN8/LGR5, and JAZF1} – through the
meta-analysis of GWA data that had greater power to detect the genes with modest or small effects (85); and the \textit{MTNR1B} gene was found through the GWA analysis for the association with fasting glucose concentration or insulin secretion (86-88). Since many of these novel loci contain or are close to genes that are highly expressed in the pancreatic \(\beta\)-cells, it has been concluded that impaired \(\beta\)-cell function has a more essential role in the etiology of type 2 diabetes than insulin resistance. However, it is important to keep in mind that the true type 2 diabetes genes may be located at some distance from the association signals. The recent GWA scans were all focused on overt type 2 diabetes and, thus, biased towards finding genes involved in \(\beta\)-cell defects, since ultimately all forms of diabetes could be considered as having relative insulin deficiency. Other studies that investigated the relationship between insulin sensitivity and genotypes in the prediabetic state (i.e. before the onset of overt hyperglycemia) may lead to the identification of new genes acting through other physiological pathways (39).

The main findings of the GWAS indicate that there is hardly any overlap with the linkage or candidate gene studies. Such results may be explained by the limitations of the last two methods mentioned earlier, as well as by the overestimation of the effect sizes due to its lower significance thresholds compared with the very strict requirements for the GWAS. In general, the recently identified loci for common obesity have very modest effects on disease risk and explain only a small proportion of overall variance for BMI – the combined effect of all obesity-associated variants explains less than 5% of BMI heritability. In case of type 2 diabetes, the currently known susceptibility variants explain only 5-10% of the inherited predisposition. These results may be an indication of the major GWAS limitations: (1) a bias towards common variants (i.e. with minor allele frequency >5%) and lack of power for identifying associations with rare variants; (2) absence of good coverage for all the common variations in the human genome even by high-density SNP chips (estimated coverage is \(\sim 80\%\)) leading to false-negative results; (3) too stringent control for false-positive findings that results in the reduced power to detect genes with small effect size; (4) requirement for extremely large sample sizes; and (5) possible biases due to case and control selection and genotyping errors (89). Finally, it is important to keep in mind that many of the susceptibility variants identified in the GWA studies are located in intergenic regions and are not directly pinpointing to plausible causal variants.
### Table 3: The established disease susceptibility loci identified in genome-wide association studies.

<table>
<thead>
<tr>
<th>Chr</th>
<th>Nearby gene</th>
<th>Gene symbol</th>
<th>Gene function</th>
<th>Odds ratio</th>
<th>Frequency of risk allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q25</td>
<td>SEC16B</td>
<td>SEC16 homologue B</td>
<td>Unknown function</td>
<td>1.11</td>
<td>0.25</td>
</tr>
<tr>
<td>1p31</td>
<td>NEGR1*</td>
<td>Neuronal growth regulator 1</td>
<td>Neuronal outgrowth</td>
<td>1.05 - 1.07</td>
<td>0.64</td>
</tr>
<tr>
<td>2p25</td>
<td>TMEM18*</td>
<td>Transmembrane protein 18</td>
<td>Neural development</td>
<td>1.19 - 1.41</td>
<td>0.85</td>
</tr>
<tr>
<td>3q27</td>
<td>ETV5*</td>
<td>Ets variant gene 5</td>
<td>A transcription factor</td>
<td>1.11</td>
<td>0.80</td>
</tr>
<tr>
<td>4p13</td>
<td>GNPDA2*</td>
<td>Glucosamine-6-phosphate deaminase 2</td>
<td>Unknown function, expressed in the hypothalamus</td>
<td>1.12 - 1.20</td>
<td>0.45</td>
</tr>
<tr>
<td>10p12</td>
<td>PTER*</td>
<td>Phosphotriesterase-related gene</td>
<td>Highly expressed in the hypothalamus, have a role in apoptosis</td>
<td>1.3</td>
<td>0.91</td>
</tr>
<tr>
<td>11p11</td>
<td>MTCH2</td>
<td>Melanin-concentrating hormone receptor</td>
<td>Promotes food intake</td>
<td>1.03</td>
<td>0.36</td>
</tr>
<tr>
<td>11p14</td>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
<td>Regulation of development, stress response, mood disorders, involved in eating behaviour and body weight regulation, expressed in the hypothalamus</td>
<td>1.11</td>
<td>0.77</td>
</tr>
<tr>
<td>12q13</td>
<td>FAIM2 *</td>
<td>Fas apoptotic inhibitory molecule 2</td>
<td>Involved in apoptosis</td>
<td>1.14</td>
<td>0.35</td>
</tr>
<tr>
<td>16p11</td>
<td>SH2B1</td>
<td>SH2-B homolog</td>
<td>Implicated in leptin signaling,</td>
<td>1.08 - 1.11</td>
<td>0.38</td>
</tr>
<tr>
<td>16q12</td>
<td>FTO</td>
<td>Fat mass and obesity-associated gene</td>
<td>Highly expressed in the hypothalamus, involved in regulation of energy balance (food intake)</td>
<td>1.27 - 1.67</td>
<td>0.46</td>
</tr>
<tr>
<td>16q23</td>
<td>MAF*</td>
<td>v-mafmucosapineurotetic fibrosarcoma oncogene homologue</td>
<td>Involved in developmental and cellular differentiation processes, notably of the immune system, pancreas and adipose tissue</td>
<td>1.12 - 1.39</td>
<td>0.56</td>
</tr>
<tr>
<td>18q11</td>
<td>NPC1</td>
<td>Niemann-Pick disease, type C1</td>
<td>Highly expressed in the hypothalamus, involved in lipid transport in the central nervous system, liver and macrophages</td>
<td>1.12</td>
<td>0.53</td>
</tr>
<tr>
<td>Chr</td>
<td>Nearby gene</td>
<td>Gene symbol</td>
<td>Gene function</td>
<td>Odds ratio</td>
<td>Frequency of risk allele</td>
</tr>
<tr>
<td>------</td>
<td>--------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>18q21</td>
<td>MC4R *</td>
<td>Melanocortin-4 receptor</td>
<td>Inhibits food intake and increases metabolic rate</td>
<td>1.12 - 1.30</td>
<td>0.28</td>
</tr>
<tr>
<td>19q13</td>
<td>KCTD15*</td>
<td>Potassium channel tetramerisation domain containing 15</td>
<td>Unknown function, expressed in the hypothalamus</td>
<td>0.96 - 1.10</td>
<td>0.69</td>
</tr>
<tr>
<td>1p12</td>
<td>NOTCH2</td>
<td>Notch 2 preproprotein</td>
<td>Transmembrane receptor implicated in pancreatic organogenesis</td>
<td>1.13</td>
<td>0.11</td>
</tr>
<tr>
<td>2p21</td>
<td>THADA</td>
<td>Thyroid adenoma-associated gene</td>
<td>Unknown; associates with PPARG</td>
<td>1.15</td>
<td>0.90</td>
</tr>
<tr>
<td>3p14</td>
<td>ADAMTS9*</td>
<td>Disintegrin-like and metalloproteinase with thrombospondin type 1 motif</td>
<td>Proteolytic enzyme regulating extracellular matrix, expressed in muscle and pancreas</td>
<td>1.09</td>
<td>0.76</td>
</tr>
<tr>
<td>3p25</td>
<td>PPARG</td>
<td>Peroxisome proliferator activating receptor gamma</td>
<td>Transcription factor receptor involved in adipocyte development</td>
<td>1.17</td>
<td>0.85</td>
</tr>
<tr>
<td>3q28</td>
<td>IGF2BP2</td>
<td>IGF2 mRNA-binding protein 2</td>
<td>Growth factor binding protein, pancreatic development</td>
<td>1.14</td>
<td>0.29</td>
</tr>
<tr>
<td>4p16</td>
<td>WFS1</td>
<td>Wolfram syndrome 1</td>
<td>Endoplasmic reticulum transmembrane protein</td>
<td>1.11-1.15</td>
<td>0.60</td>
</tr>
<tr>
<td>6p22</td>
<td>CDKAL1</td>
<td>CDKS regulatory subunit associated protein 1-like 1</td>
<td>Presumed regulator of cyclin kinase; islet gluco toxicity sensor</td>
<td>1.0-1.20</td>
<td>0.31</td>
</tr>
<tr>
<td>7p15</td>
<td>JAZF1</td>
<td>Juxtaposed with another zinc finger gene 1</td>
<td>Zinc-finger protein of unknown function, associated with prostate cancer</td>
<td>1.10</td>
<td>0.50</td>
</tr>
<tr>
<td>8q24</td>
<td>SLC30A8</td>
<td>ZNT8</td>
<td>Zinc transporter 8; a possible role in insulin storage and secretion</td>
<td>1.18</td>
<td>0.65</td>
</tr>
<tr>
<td>9p21</td>
<td>CDKN2A/CDKN2B *</td>
<td>Cyclin-dependent kinase inhibitor and p15</td>
<td>Cyclin-dependent kinase; tumor suppressor; islet development</td>
<td>1.20</td>
<td>0.83</td>
</tr>
<tr>
<td>Chr</td>
<td>Nearby gene</td>
<td>Gene symbol</td>
<td>Gene function</td>
<td>Odds ratio</td>
<td>Frequency of risk allele</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------</td>
<td>------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>10p13-p14</td>
<td><em>CDC123</em>/CAMK1D*</td>
<td>Cell division cycle protein 123 homolog / Calcium/calmodulin-dependent protein kinase i-delta</td>
<td>Cell cycle, protein kinase entry of the cell cycle, mediator of chemokine signal transduction in granulocytes</td>
<td>1.11</td>
<td>0.18</td>
</tr>
<tr>
<td>10q23-q25</td>
<td>HHEX*</td>
<td>Hematopoietically expressed homeobox</td>
<td>Homeobox transcription factor involved in pancreatic development</td>
<td>1.13</td>
<td>0.53</td>
</tr>
<tr>
<td>10q25.3</td>
<td>TCF7L2</td>
<td>Transcription factor 7-like 2</td>
<td>Transcription factor; transactivates proglucagon and insulin genes</td>
<td>1.31-1.71</td>
<td>0.26</td>
</tr>
<tr>
<td>11q21</td>
<td>MTNR1B</td>
<td>Melatonin receptor 1B</td>
<td>Possibly mediates the inhibitory effect of melatonin on insulin secretion</td>
<td>1.10</td>
<td>0.30</td>
</tr>
<tr>
<td>11p15</td>
<td>KCNQ1</td>
<td>Potassium voltage-gated channel, KQT-like subfamily, member 1</td>
<td>A role in the electrical depolarisation of cell membrane in the heart and presumably in pancreas beta cells</td>
<td>1.23</td>
<td>0.21</td>
</tr>
<tr>
<td>11p15.1</td>
<td>KCNJ11</td>
<td>Kir6.2 K⁺ channel</td>
<td>Inwardly rectifying potassium channel; risk allele impairs insulin secretion</td>
<td>1.14</td>
<td>0.47</td>
</tr>
<tr>
<td>12q21</td>
<td>TSPAN8*</td>
<td>Tetraspanin 8</td>
<td>Cell surface glycoprotein; implicated in gastrointestinal cancer</td>
<td>1.09</td>
<td>0.27</td>
</tr>
<tr>
<td>16q12</td>
<td>FTO</td>
<td>Fat Mass-and Obesity-Associated Gene</td>
<td>Alters BMI in general population</td>
<td>1.27</td>
<td>0.38</td>
</tr>
<tr>
<td>17q21</td>
<td>TCF2</td>
<td>Transcription factor-2 (or HNF1β)</td>
<td>Transcription factor, associated with pancreatic atrophy, neonatal diabetes</td>
<td>1.12</td>
<td>0.47</td>
</tr>
</tbody>
</table>

* Nearest gene in the region (except where there is a very strong positional candidate).
Overlap between obesity and type 2 diabetes susceptibility loci

As many obese individuals (around 90%) develop type 2 diabetes, this may indicate a commonality of predisposing genetic factors for these two diseases. In a recent study comparing all of the published genome-wide linkage scans for type 2 diabetes and obesity, five overlapping chromosomal regions for both diseases were identified. These five susceptibility loci contain 27 functional candidate genes that are involved in eating behavior, metabolism and inflammation (90). So far, GWAS for obesity and type 2 diabetes have shown only one overlap, i.e. the FTO gene. Although it is clear that the FTO association with diabetes is due to its primary effect on BMI and obesity (64).

Since not all obese people develop diabetes and not all diabetic patients are obese, it is important to investigate which sets of genes are involved with both diseases and which sets are driving each illness separately (compare and contrast). The identification of these different genetic backgrounds might reveal a molecular link between the two disorders and may also direct efficient patient’s treatment strategies. For example, physicians could distinguish individuals of normal weight who might go on to develop diabetes regardless of changes in body weight, or overweight individuals who might be able to prevent obesity and type 2 diabetes through the adjustments in diet and changes in life style.

Concluding remarks

Taking together the physiological mechanisms involved in the regulation of body weight and in the development of obesity and type 2 diabetes, the genetic components that determine an individual’s predisposition to disease and the changes in the environment associated with a modern lifestyle, the following questions should be addressed to further our understanding of the underlying causes of obesity and diabetes.

Does the increase in obesity rates reflect a failure of the biological system for regulating body weight in the presence of an “obesogenic” environment?

Are people with a genetic predisposition to store more body fat and/or with certain food preferences and eating habits, more prone to become obese under these circumstances?

Which of the individuals with a genetic predisposition to store more body fat and/or to have certain food preferences and eating habits will develop type 2 diabetes?
Is there any common pathophysiological mechanism that defines the development of both diseases, and which mechanisms are specific to each of them?

How can we identify the genes that increase the risk for obesity and type 2 diabetes?

**Aim and outline of this thesis**

Obesity and type 2 diabetes are two complex multifactorial diseases with common metabolic features. The high co-occurrence rate of both diseases all over the world may indicate the presence of shared predisposing genetic factors for these disorders. The central aim of this thesis was to gain insight into the genetic susceptibility to both obesity and type 2 diabetes. We investigated different candidate genes for the predisposition for both these diseases, in order to further our understanding of the genetic architecture of obesity and type 2 diabetes.

Recent evidence suggests a key role for the region of the brain known as the hypothalamus in the control of energy homeostasis in mammals. In chapter 2 we summarize current knowledge on the physiological role of the hypothalamus in body weight regulation and describe the results of a large-scale literature review we performed to examine the contribution of genetic variants in the hypothalamic regulatory pathways to obesity. Several important issues that should be considered in genetic studies on obesity are discussed, such as the definition of the obesity phenotype and statistical strategies to analyze the relationship between genetic variants and complex diseases.

Chapter 3 presents a study in which we provide evidence that the TUB gene might be a novel candidate gene for common obesity. In this study TUB was selected as a relevant candidate gene for obesity and/or type 2 diabetes from a locus on chromosome 11p15 which was previously identified in a linkage scan for obesity-driven type 2 diabetes in a defined Dutch population. In a follow-up study involving fine mapping of the gene and its flanking regions, the association of common variants in TUB with both diseases was examined. While we observed no effect of the genotyped polymorphisms on type 2 diabetes risk, we did observe a correlation between TUB variants and both increased body mass index and obesity. This finding was confirmed in a replication set from a general population.

In chapter 4 we validate our TUB results in a large population-based study and also explore possible mechanisms underlying the observed association of TUB with
body weight. We investigated the relationship between TUB variants and different anthropometric and food intake data. The analysis confirmed the association of TUB with different measures of body composition and also revealed that the individuals carrying the at-risk alleles for obesity had certain food preferences in their daily diet, e.g. eating more sugar. These results led us to the conclusion that the TUB gene may be related to eating behavior in humans.

In chapter 5 the association was studied between the transcription factor 7-like 2 (TCF7L2) gene and type 2 diabetes in a Dutch population. Our data provided evidence that TCF7L2 variants strongly contribute to the risk of type 2 diabetes with the population-attributable risk of 10% in the Dutch population.

In chapter 6 we examine whether SNPs near the hematopoietically expressed homeobox (HHEX) gene identified in a genome-wide association study, contribute to type 2 diabetes risk in a Dutch population. We were able to confirm the association between HHEX variants and type 2 diabetes.

Chapter 7 describes major challenges and future perspectives for further research on the genetics of both obesity and type 2 diabetes.
References


76. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007 Jun 7;447(7145):661-78.


