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Genetic contribution to obesity: a literature review

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This investigation has been performed by order and for the account of Ministry of Public Health, Welfare and Sports, within the framework of project V/350020/07/AC, the genetic component of overweight.

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Abstract

Genetic contribution to obesity: a literature review

The risk of obesity is for a considerable part genetically determined. Which specific genetic factors are involved is yet unknown. Therefore, the use of genetic information for obesity prevention or treatment is currently unjustifiable. This is the conclusion of a literature review on the genetics of obesity conducted by the National Institute for Public Health and the Environment (RIVM) in order of the Dutch Ministry of Public Health, Welfare and Sports.

This study showed that about 40% of the total variation in body weight between individuals (expressed as the body mass index, BMI: weight / height^2) can be explained by genetic differences. Moreover, due to their genetic profile, individuals react differently on changes in energy intake and expenditure. For one out of ten cases with severe early onset obesity a rare mutation in a single gene is known. This is the case for at most 2.5% of the less extreme forms of obesity.

A lot of research has been carried out on gene variants that occur frequently in the population. For five of these gene variants there is convincing evidence supporting their involvement in determining BMI or obesity risk. They may explain 10% of the cases with overweight and 20% of the cases with obesity. However, genetic variation between individuals is more complex than previously thought. Therefore, the contribution of genetic factors to the onset of obesity is expected to be larger than currently known. This justifies current and future research in this area.

Key words: obesity, genetic factors, epigenetics, literature review

Rapport in het kort

De bijdrage van genetische factoren aan obesitas: een literatuurstudie

De kans op obesitas is voor een aanzienlijk deel erfelijk bepaald. Welke specifieke genetische factoren daarbij betrokken zijn, is nog niet bekend. Daarom is het op dit moment niet gerechtvaardigd om genetische informatie te gebruiken om obesitas te voorkómen of te behandelen. Dit is de conclusie van een literatuurstudie naar genetische factoren voor obesitas die in opdracht van het ministerie van VWS is uitgevoerd door het Rijksinstituut voor Volksgezondheid en Milieu (RIVM).

Het onderzoek heeft aangetoond dat ongeveer 40% van de variatie in het lichaamsgewicht tussen personen (uitgedrukt in de body mass index, BMI: gewicht / lengte^2) verklaard kan worden door genetische verschillen. Ook reageren mensen door hun erfelijk materiaal verschillend op veranderingen in energie-inname, -verbruik. Van een op de tien gevallen die op zeer jonge leeftijd extreem obees zijn, is een zeldzame genmutatie bekend. Van de minder extreme vormen van obesitas is hooguit 2,5% hiermee te verklaren.

Veel onderzoek is gedaan naar variaties in genen die bij veel mensen voorkomen. Van vijf genvarianten die bekend zijn, is overtuigend bewezen dat ze van invloed zijn op de BMI en het risico op obesitas. Zij verklaren mogelijk 10% van de gevallen met overgewicht en 20% van de gevallen met obesitas. De genetische verschillen tussen personen zijn echter complexer dan voorheen werd gedacht. Daarom is naar verwachting de genetische bijdrage aan het ontstaan van obesitas groter dan momenteel bekend is. Dit rechtvaardigt lopend en toekomstig onderzoek op dit terrein.

Trefwoorden: overgewicht, genetische factoren, epigenetica, literatuurstudie

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Summary

The prevalence of overweight and obesity continues to rise. World-wide about 1.6 billion people are overweight (BMI ≥25 kg/m^2) of which about 400 million suffer from obesity (BMI ≥30 kg/m^2). Overweight is the consequence of a long term disruption of the energy balance where daily energy intake exceeds daily energy expenditure. It is generally accepted that environmental and lifestyle factors are involved in the onset of obesity. In view of many overweight is the consequence of an individual's own behavior, and so far general recommendations are given to the public to prevent overweight and obesity. There is however evidence that in addition to lifestyle heredity plays a role in the development of human obesity. Advancing knowledge on the genetic component of overweight and obesity may make it necessary to change nutritional and overweight policies in the future. Therefore, a literature study was conducted commissioned by the Dutch Ministry of Public Health, Welfare and Sports, in order to get more insight into the current state of the art about the genetics of obesity.

A first indication that genetic factors contribute to obesity comes from the observation that obesity tends to run in families. Several approaches have been used to investigate the extent of the genetic contribution (heredity) (see chapter 2). Several twin studies, adoption studies and family studies have been carried out. While all found a heritable component for overweight or body mass index there is some disagreement about the magnitude of the effect. In general, twin studies reported the highest heritability estimates, adoption studies the lowest. Most recent reviews suggest that the heritability value for BMI seems to be 40%, which indicates that 40% of the total variance in BMI has a genetic origin.

The search for obesity genes at the start has been predominantly driven by research into monogenic obesity. Until 2005, 176 human obesity cases due to single-gene mutations in eleven different genes have been identified. Most of the identified genes are part of the leptin-melanocortin pathway which plays an important role in appetite regulation. Mutations in the MC4R gene explain 2.5% or less for moderate or severe obesity cases and up to 6% for more extreme forms of obesity (see chapter 3). Mutations in the LEPR and POMC gene may explain a small part (3% and ~1% respectively) of the severe early onset cases of obesity. Mutations in other genes explain only a few individual obesity cases. The contribution of these mutations to the overweight epidemic at the population level is therefore small.

Since monogenic obesity represent only a small fraction of all obesity cases, most cases are thought to result from the action of multiple genes (polygenic) and environmental factors. Until 2005, 426 positive associations between 127 genes and obesity related phenotypes, such as BMI, fat mass or waist circumference have been reported (see chapter 4). Overall, these associations are relatively small and the results are not very consistent. For only five genes (*ADRB3, PPARγ2, MC4R, TNFα* and *FTO)* there is convincing evidence from meta-analyses that they are associated with BMI or obesity. Single nucleotide polymorphisms in these genes may contribute to at least 10% of the overweight cases and 20% of the obesity cases at population level.

Until recently research on genetic determinants of obesity focused mainly on inheritable changes in the DNA nucleotide sequence (classic genetic variation), single nucleotide polymorphisms in particular. However, humans are genetically more diverse than previously thought, and therefore the genetic basis for common disease is likely to be more complicated. Epigenetic variation is another kind of genetic variation. In contrast to classic genetic variation it does not change the DNA nucleotide sequence itself, but influences the chromatin structure, i.e. the folding of the DNA. Variation in epigenetic modifications influences transcription control, the amount of protein produced and consequently a phenotype. Results from mouse models and syndromic obesity suggest that epigenetic variation influences body weight (see chapter 5). However, direct evidence demonstrating epigenetic variation to play a causal role in human obesity is yet to be uncovered. It would, however, be highly surprising if variation in the epigenome would not influence common disease susceptibility, including overweight and obesity. Also other forms of genetic variation have recently been discovered and the study into the relation with obesity has just been started. Therefore, the genetic contribution to obesity may be larger than currently envisaged.

Carrying a susceptibility allele predisposing for overweight or obesity does not necessarily lead to the disorder. Several genetic factors will act together and an environment that promotes obesity is necessary for its expression. A clear illustration of interaction between genes and environment can be derived from the Pima Indians (see chapter 6). Pima Indians living a traditional lifestyle in Mexico experience almost no obesity, while the prevalence of obesity is dramatically high among Pima Indians who live in the ‘obesogenic’ environment of Arizona, USA. Also twin studies have shown that in response to overfeeding or energy restriction some people are more likely to gain or lose weight than others. The differences between the twin pairs have a genetic basis. However, only few studies investigated specific gene-environment interactions in relation to obesity, and convincing evidence for a specific gene-environment interaction is lacking.

In summary, too little is known about specific genetic factors contributing to obesity to justify an integration of genetic information into public-health initiatives focused on promoting weight loss and preventing weight gain (see chapter 7). The observation that genetic variation between individuals is more complex than previously thought explains part of the disappointing results in the search for obesity genes. Additionally, it opens the way to new research lines for unraveling the genetic component of obesity. Epigenetic changes and copy number variation, among others, add more complexity to the genetic differences between people. Their implications for disease predisposition, including overweight and obesity, are promising. Therefore ongoing investments in research into genetic determinants of obesity are justified.

1 Introduction

The prevalence of overweight and obesity continues to rise. World-wide about 1.6 billion people are overweight (BMI ≥25 kg/m^2) of which about 400 million suffer from obesity (BMI ≥30 kg/m^2).[1] In the Netherlands, the situation is not very promising either. A survey carried out by the RIVM in the period 1998-2002 shows that 63% of Dutch men and 50% of Dutch women are overweight. The prevalence of obesity is 12% among men and 15% among women.[2] Although the prevalence of overweight in the Netherlands is comparable to the average prevalence within Europe, the prevalence of obesity is relatively low compared with other European countries.[3]
Overweight is the consequence of a long term disruption of the energy balance where daily energy intake exceeds daily energy expenditure.[4] The surplus of energy is mainly stored as fat. It is generally accepted that environmental and lifestyle factors are involved in the onset of obesity.[5] There is evidence that in addition heredity plays a role in the development of human obesity. All components of energy balance (energy intake, energy expenditure and energy storage) may be affected by genetic factors.

Nevertheless, the emerging obesity epidemic over the last four decades cannot be explained by changes in the genetic background of the population. After all, evolution is a slow process, so an increase in obesity causing gene variants during this period is highly unlikely. This observation has often been used as an argument against any role of genetic factors in the etiology of overweight and obesity. However, in our 'obesogenic' environment that promotes excessive calorie intake and discourages physical activity, genetic factors will actually determine who becomes fat or not.[5] Or in other words, based on their genetic predisposition, one individual will be more susceptible to become obese than another in similar environments and with comparable lifestyles. In line with this, there is a worldwide research interest in the interaction between genetic and lifestyle/environmental (dietary) factors in relation to overweight and obesity. Furthermore, genetic predisposition influences an individuals nutritional requirement.[6] Moreover, for a long time genetic effects have been only ascribed to changes in the DNA sequence (code), of which single nucleotide polymorphisms (SNPs) are the most studied. In this report we will call this classic genetic variation. However, nowadays there is a lot of interest in an other type of genetic variation, which is called epigenetic change. Epigenetic changes influence the structure (folding) of the DNA without changing the DNA sequence. Epigenetic changes are known to be influenced by the environment and lifestyle, but they also appear to be heritable from mother to daughter cell and across generations. It is thought that epigenetic changes may play an important role in determining the risk of future diseases.

In view of many overweight is the consequence of an individual's own behavior, and so far the Dutch government gives general recommendations to the public to prevent overweight and obesity. However, in view of the above, a part of the population may be highly susceptible to develop overweight, general dietary recommendations may be less effective for some individuals and more tailored advice may be necessary to prevent it. Therefore, advancing knowledge on the genetic component of overweight and obesity may make it necessary to change nutritional and overweight policies in the future. Therefore, we conducted a literature study commissioned by the Dutch Ministry of Public Health, Welfare and Sports, in order to get more insight into the current state of the art about the genetics of obesity.

The general evidence suggesting a genetic contribution to the etiology of obesity will be described in chapter 2. Chapter 3 describes the part of obesity prevalence explained by monogenic causes and gives a short overview of the most important genes involved. Chapter 4 describes obesity as a polygenic disorder where multiple genes are involved. Chapter 5 describes the knowledge about the contribution of epigenetic changes to obesity. Gene-environment interactions are described in chapter 6, followed by a general discussion (chapter 7) and conclusions (chapter 8).

2 General evidence for a genetic contribution to obesity

Obesity tends to run in families. Several approaches have been used to investigate the extent of the genetic contribution (heredity) to this familial aggregation of obesity, often measured by body mass index.

Parental, and particularly maternal, overweight has been found to be a risk factor for childhood overweight.[7] For example, young children, aged 5 to 7, with at least one overweight parent had a 2 to 3 times increased risk to become overweight themselves.[8] Children with two overweight parents had a 4.5 times increased risk, while children with two obese parents even had a 6 to 7 times increased risk to be overweight. These results show that the risk of childhood overweight rises when the severity of parental obesity increases and when both parents are overweight.

Data from large population based family studies (see Text box 1) showed that the risk of overweight (see Table 1) was not increased among relatives of overweight individuals.[9] However, the prevalence of moderate obesity was 1.5 times higher in first-degree relatives of moderately obese individuals than in the general population. Similar obesity risks were observed, however, for spouses of moderately obese individuals. This may suggest an environmental rather than a genetic explanation for the familial aggregation of moderate obesity. On the other hand, assortative mating - individuals tend to mate with individuals with comparable body size- can not be excluded.[9] The risk of severe obesity among family members of moderately to severe obese subjects was twice the general population risk.[9,10] For family members of extreme obese persons the risk of extreme obesity and very extreme obesity was even higher, i.e. four and seven times the general population risk, respectively.[10]

Text box 1: Family studies

Family studies can be used to explore similarities in BMI between family members and quantify the risk to become obese when a first-degree relative is overweight or obese (familial risk).

Table 1 Classification of overweight and obesity in adults, adapted from the WHO definition.[11]

BMI (kg/m^2)	Definition
<18.5	Underweight
18.5-24.9	Normal weight
25-29.9	Overweight
30-34.9	Moderate obese
35-39.9	Severe obese
40-44.9	Extreme obese
≥45	Very extreme obese

Overall, the findings from family studies show that familial risk increases when the level of obesity increases. Genetic factors seem to contribute to obesity, at least at BMI levels above 35 kg/m^2.[9,10] The genetic contribution to moderate obesity and overweight is less clear and the impact of shared environment can not be excluded.

Based on familial risks, *the extent* to which any observed familial aggregation may be caused by genes cannot be estimated.[12] More insight can be obtained from heritability estimates. They can be defined as the fraction of the variation in a trait (e.g BMI) within a population that is due to genetic effects, and have been obtained from twin, adoption and family studies.[13,14]

Text box 2: Twin studies

Monozygotic twins have 100% of their genes in common, while dizygotic twins have 50% of their genes in common. The premise behind twin studies is that because of this, greater similarity in a trait among monozygotic twins then among dizogotic twins may reflect a greater role of genetic factors.[14]

Studies among twins (see Text box 2) that were reared together showed that monozygotic twins have more similar body weights than dizygotic twins even after adjustment for height.[15,16] To better distinguish the importance of shared genes from shared environment studies have been conducted among identical twins that have been reared apart. They share their genes but not their environment. These type of studies showed similar heritability estimates as the more classic twin studies.[17-19] Overall, heritability estimates from twin studies range from 50% to 90% and cluster around 70% suggesting an important genetic influences on BMI.[13,19] The estimates tend to be higher for adolescent twins samples than for adult twins samples. This implicates that also environmental factors play a role.

Adoption studies compare the BMI of the adoptee to the BMI of both their biological (who share half of their genes) and their adoptive parents (who share their environment). Results from a large adoption study in 1986 from Stunkard and colleagues [20] showed that adopted children have body sizes that are more similar to that of their biological than that of their adoptive parents. Subsequent adoption studies reported heritability estimates clustering around 30% (range 20%-60%).[19,21,22]

Finally, heritability estimates can also be obtained from family studies. Parents and offspring as well as siblings share on average half of their genes, while spouses share their environment. Significant parent-offspring and sibling correlations but insignificant spouse correlations therefore suggest a genetic etiology. Significant spouse correlations suggest that part of the resemblance is due to shared environment. However, a role for genetic factors cannot completely be excluded due to assortative mating.[13] The large Quebec Family Study explored familial aggregation of BMI, waist circumference and sum of skinfolds. The results showed a heritability of 40% for all studied phenotypes.[23] This is in accordance with results from previous family studies with reported estimates ranging from 20% tot 80%.[19]

In summary, while it is generally accepted that BMI has an heritable component there is some disagreement about the magnitude of the effect. In general, twin studies reported the highest heritability estimates, adoption studies the lowest, while family studies reported intermediates values. Methodological advantages and disadvantages of each study design may explain the wide range in heritability estimates. Most recent reviews suggest that the most likely heritability value for BMI seems to be 40%, which indicates that 40% of the total variance in BMI has a genetic origin.[24,25]

3 Obesity prevalence explained by monogenetic disorders

At the start, the search for obesity genes has been predominantly driven by research into monogenic obesity. Until 2005, 176 human obesity cases due to single-gene mutations in eleven different genes have been identified.[26] All these genetic defects impair satiety and the observed obesity is often characterized by excessive hunger (hyperphagia). Most of the identified genes are part of the leptin-melanocortin pathway which plays an important role in appetite regulation.[13,27] To date, no monogenic forms of obesity due to reduced metabolic rate have been reported.

Mutations in the melanocortin-4 receptor gene (MC4R) are currently regarded as the most relevant genetic cause for extreme obesity. The MC4R is located in the hypothalamus and plays a key role in the regulation of food intake by integrating satiety and hunger signals.[28] To date, more than 70 different mutations in the MC4R gene have been associated with obesity in various study populations.[29] Remarkably, many mutations appeared unique for single patients, which underscores the rarity of individual mutations.[30] Table 2 shows the frequencies of pathogenic MC4R mutations in different European countries. The highest prevalences of MC4R mutations have been found in very obese children (BMI SDS > 4; see Text box 3 [31]) living in France, Germany and the United Kingdom (UK). Frequencies ranged from 5.3% till 6.3%.[32-34] Among extreme or very extreme obese adults coming from Finland, Switzerland and France MC4R mutation frequencies ranged from 0% till 4%. MCR4 mutation frequencies ranged from 0% till 2.5% among moderate and severe obese individuals from the UK, Germany, Italy and Denmark. Overall, the prevalences vary widely, suggesting that the frequency of MC4R mutations differs between European countries. Moreover, severe obesity and an early age of onset may be characteristic for carriers of MC4R mutations.

Text box 3: BMI Standard Deviation Score (SDS)

Among children, BMI varies strongly with age. Therefore their BMI values are often expressed as BMI standard deviation scores (SDS). BMI SDS represents the deviation from the BMI-distribution in children of the same age and gender. BMI SDS ≥ 1.1 corresponds to overweight, whereas a BMI SDS ≥ 2.3 corresponds to obesity.[31]

It is important to note that above mentioned cohorts are all selected for obesity. Therefore their results do not provide any information about the diagnostic interpretation of these variants, their prevalence and the relevance of MC4R mutations at the population level. Recently, two studies based on the general population have been reported. In a German general population sample with 23% of the participants being obese (BMI ≥30 kg/m^2), 0.15% (n=6) carried mutations affecting the functionality of MC4R.[35] However, none of those carriers were obese. Additionally, several mutations causing uncertain or unimpaired function were observed. Once again they were more frequent in non-obese (0.61%) than in obese individuals (0.21%). Therefore MC4R mutations that result in loss of function may not always lead to obesity. Another population based study among 1100 British subjects, detected a novel mutation leading to substantial loss of MC4R function in one out of the 203 obese persons (0.50%). However, this mutation was not found in another much larger sample (3525 subjects) of which a quarter had obesity.[36] Therefore, the mutation may be less frequent than expected.

Table 2 Frequencies of pathogenic MC4R mutations among obese subjects in different European countries

Study population	n	Country	BMI (kg/m^2)[1]	Age (years)[1]	Frequency % (n)	Ref
Children	63	France	4.6 ± 1.0[2]	11.6 ± 2.9	6.3 (4)	33
Children	500	UK	4.2 ± 0.8[2]	<10 yr[3]	5.8 (29)	34
Children and adolescents	808	Germany	32.5 ± 6.3	13.9 ± 2.7	5.3 (43)	37
Adults and adolescents	209	France	> 40	42 ± 12.0	4.0 (8)	38
Men with juvenile-onset obesity	750	Denmark	> 31	± 20 yr	2.5 (19)	39
Children	56	Finland	>98th percentile	13.6 ± 4.7	1.8 (1)	40
Adults	120	Italy	> 35	± 40 yr	1.7 (2)	41
Children and adolescents	172	France	4.3 ± 1.0[2]	12.6 ± 3.2	1.7 (3)	42
Adults and adolescents	469	Switzerland	44.1 ± 2.0	41.0 ± 0.5	1.3 (6)	43
Adults	159	Spain	>30	37.6 ± 5.8	0.6 (1)	44
Children and adolescents	208	Italy	3.6 ± 1.9[2]	10.5 ± 3.2	0.5 (1)	45
Children and adolescents	186	Germany	30.9 ± 5.8	13.2 ± 2.7	0.5 (1)	46
Adults	252	Finland	>40	48.6 ± 8.9	0.0 (0)	40
Adults	95	Belgium	47.9 ± 4.2	44.0 ± 11.4	0.0 (0)	47
Children and adolescents	123	Belgium	>95th percentile	16.6 ± 2.6	0.0 (0)	47
Men	40	UK	>35	not reported	0.0 (0)	48

[1] Presented as mean ± SD unless otherwise stated. [2] Presented as mean BMI SDS ± SD (see Text box 3). [3] Age of onset of obesity.

Monogenic obesity cases can also result from mutations in the gene coding for leptin (LEP) and its receptor (LEPR). Leptin is an hormone excreted by adipocytes which reports information about long term body fat storage to the brain. In the hypothalamus leptin acts to reduce energy intake through leptin receptors.[28] To date, in humans about nine patients with leptin deficiency and massive obesity due to a single mutation in the LEP gene have been reported.[49] Only three extremely obese relatives with a mutation in the LEPR gene were described.[49] More recently, in 2007, 300 individuals with severe childhood obesity (onset before 10 years of age) who lived in the UK were screened for LEPR mutations.[50] Eight of them carried LEPR mutations which implicates a prevalence of 3% in severe early onset obesity (age of onset < 10 years, BMI SDS >4). Information about the prevalence in other countries or among subjects with less severe forms of obesity is lacking.

Additionally, mutations in the gene encoding for pro-opiomelanocortin (POMC) may lead to monogenic obesity. POMC is a precursor of neuropeptides and acts in the hypothalamus trough the MC4R to reduce food intake. Approximately six patients with mutations in the POMC gene that caused congenital POMC deficiency and early onset obesity were reported.[49] In addition, a POMC mutation at position 236 has been discovered that results in the production of aberrant neuropeptides.[51] Pooling data from five studies revealed that this mutation was prevalent among 0.88% of subjects with early onset obesity (age ± 10 years and BMI >30 kg/m^2 or > 4 SDS) and among 0.22% of normal-weight controls.[51] Therefore, this mutation may be associated with early-onset obesity, but does not always lead to obesity as it has also been found in normal weight control subjects.

To date, only a few monogenic obesity cases that were caused by mutations in seven other genes (PCSK1, CRHR1, CRHR2, GPR24, MC3R, NTRK2, SIM1) have been described.[26] Based on current knowledge, the contribution of these mutations to the total obesity prevalence seems to be minimal.

For a long time, syndromic obesity, for which obesity is a clinical manifestation but not a dominant feature, was considered to be a monogenic disorder. However, advancing knowledge has revealed that multiple genetic factors are involved.[52] Today, there are at least 20 syndromes that are characterized by obesity, of which the Prader-Willi Syndrome is the most common (see also chapter 5). In the Netherlands, yearly 10 out of 200,000 newborns (0.005%) suffer from this syndrome. The Bardet-Biedl syndrome is another example of a disease that causes syndromic obesity with an estimated incidence of one per 160,000 births in Europe.[53] A clear mechanistic link between the product of the mutated gene and disturbed energy balance causing obesity has not been clarified for nearly all of the syndromic forms of obesity.[52] Since the prevalence of these syndromes is very low, they do not explain a significant part of the obesity cases at the population level.

In summary, mutations in the MC4R gene explain only a small part of the obesity cases, ranging from 2.5% or less for moderate or severe obesity and up to 6% for more extreme forms of obesity. Mutations in the LEPR and POMC gene may explain a small part (3% and ~1%, respectively) of the severe early onset cases of obesity. Mutations in other genes explain only a few individual obesity cases, while syndromic obesity is also too rare to contribute to the obesity epidemic.

4 Polygenic or complex obesity

Since monogenic and syndromic forms obesity represent only a small fraction of all obesity cases, most cases are thought to result from the action of multiple genes (polygenic) and environmental factors.[54] To date a lot of research has been carried out on candidate genes for obesity. Candidate genes are selected on the basis of their putative involvement in physiological pathways related to the regulation of energy balance or to adipose tissue biology.[13] Until 2005, 426 positive associations between 127 genes and obesity related phenotypes, such as BMI, fat mass or waist circumference have been reported.[26] Overall, these associations are relatively small and the results are not very consistent. Until now, twenty-two candidate genes have been repeatedly associated with obesity in at least five studies.[26] Among them, 12 genes showed replication in 10 studies and more (*ADRB2*, *ADRB3*, *UCP1*, *UCP2*, *UCP3*, *GRL* (energy expenditure), *LEP*, *LEPR*, *ADIPOQ*, *HTR2C* (energy intake), *PPARG*, *GNB3* (adipose tissue formation). However, for those genes also non-significant results have been published and these should also be taken into account when evaluating whether the observed association really exists. For this purpose, meta-analysis is a suitable tool (see Text box 4). Until 2006, meta-analyses have been conducted for single nucleotide polymorphisms (SNPs) in 10 promising obesity candidate genes (Appendix 1). For six genes there was no compelling evidence for an association between the SNP and obesity or related phenotypes after meta-analysis. Meta-analysis revealed a higher BMI in carriers of risk variants of the *ADRB3* and *PPARγ2* genes in comparison to non-carriers.[55,56] Risk variants of the *MC4R* and *TNFα* gene have been significantly associated with obesity through meta-analysis (Table 3).[57,58] However, the proportion of obesity cases that can be explained by specific gene variants depends both on the prevalence of the variant in the population (allele frequency) and the magnitude of risk. For example, when a gene variant increases the obesity risk fifty times, but one in a billion people carries the risk allele, the impact on population level is nil. Inversely, when a highly prevalent gene variant only modestly increases obesity risk, the contribution on a population level may be significant. Estimation of the contribution of genetic variants to the obesity epidemic can be done by calculating population attributable risks (see Text box 5). For the *TNFα* 308A variant which modestly increases obesity risk (1.26) but is present in a large fraction of the population (29.6%) the PAR is 7%. This means that 7% of the obesity cases may be due to this genetic variant.

Text box 4: Meta-analysis

Meta-analysis combine the results (positive, negative and null results) from all available studies on a specific topic and calculate an overall estimate from the individual estimates taking into account amongst others the sample size of the study.

Text box 5: Population attributable risk (PAR)

The PAR is an theoretical estimate of the proportion of a disease in a population due to exposure to a specific factor (eg. genetic variation, nutrition).

Ten years ago it became feasible to the study the whole genome at once by genome-wide scans. Since then several promising genes, for example *GAD2, ENPP1, SLC6A14, INSIG2,* have been reported.[53,59] Unfortunately, just as the results from candidate gene studies, it is very hard to replicate the findings from genome-wide scans. Recently, there has been some success in the discovery of the underlying genetic causes of obesity. Frayling and colleagues [60] observed a strong association between a variant in a gene called *FTO* (fat mass and obesity associated

gene) and childhood and adult obesity as a by product of an genome-wide scan aimed at diabetes. They replicated the finding in 13 cohorts with 38,759 participants. Individuals homozygous for the risk allele (16% of the population) weighted about 3 kilograms more and were 1.38 and more likely to be overweight than those not carrying a risk allele. Their risk of obesity was 1.67 times increased (Table 3). Herbert et al. [59] studied several SNPs in the FTO gene and calculated a population attributable risk. The results showed that 1 in 5 obesity cases or 1 in 10 cases of overweight may be related to this variant in the FTO gene. FTO may play some role in influencing how well the brain senses hunger and satiety, but the exact mechanism whereby it influences the risk of obesity still needs to be elucidated.[61]

Table 3 Gene variants that are significantly associated with BMI or obesity after meta-analysis

Gene (variant)	**Risk genotype**	**Frequency* %**	**Effect**	**Ref**
			Δ BMI	
ADRB3 (Trp64Arg)	Trp/Arg or Arg/Arg	26.5	Δ 0.30 (0.13-0.47)	55
PPARY2 (Pro12Ala)	Pr/Ala or Ala/Ala	23.2	Δ 0.87 (0.77-1.03)	56
			Odds ratios	
FTO (T/A)	Intron 1 A/A	16	1.67 (1.37-1.57)	60
MC4R (Val103Ile)	Val/Ile or Ile/Ile	3.3	0.82 (0.70 -0.96)	57
Tnf α (G-308A)	G/A or A/A	29.6	1.26 (1.06-1.49)	58

* Caucasian population

There is growing awareness that the failure to replicate findings from candidate gene studies and genome-wide scans may be due to underlying interactions between genes.[62] Unfortunately, it is difficult to detect gene-gene interaction in current association studies. One of the problems is that the sizes of the study samples are often underpowered to detect any gene-gene interaction. Until now, some examples of interactions between known obesity genes have been reported. For example, children and adolescents who carry both the risk variant of the *PPARY2* gene and the *ADRB3* gene were five times more likely to be obese than non-carriers.[63] The interaction between the *PPARY2* gene and the *ADRB3* gene was also observed among adults, with carriers of both risk alleles showing higher BMI than those with only the *PPARY2* variant.[64] These results illustrate the important role that gene-gene interactions may indeed play in obesity.

In summary, it is commonly accepted that obesity is a polygenetic disorder where multiple genes are involved. Despite the number of studies that has been done so far, for only five genes there is convincing evidence that they are associated with BMI or obesity. Single nucleotide polymorphisms may contribute to at least 20% of the obesity cases at population level. In addition, interactions between genes are thought to be involved in the etiology of obesity. However, large sample sizes are needed to discover these gene-gene interactions.

5 Epigenetic processes regulating body weight

Classic genetic variation has been defined as any inheritable change in DNA nucleotide sequence, such as a single nucleotide polymorphism (SNP), a deletion or an insertion. These classic genetic variations can change the function of the enzyme encoded, or the amount of enzyme produced. Epigenetic variation is another kind of genetic variation. In contrast to classic genetic variation it does not change the DNA nucleotide sequence itself, but influences the chromatin structure, i.e. the folding of the DNA.[65]

The genetic information available in the nucleus of every cell of the body comprises several billion (10^9) sequentially ordered base pairs. Subdivided over a number of chromosomes, these lengthy DNA stretches are wound, folded and organized into what is called the chromatin structure. The first level of chromatin organization is handled by histones, proteins around which the DNA is wound. Histones can be modified by the addition or removal of methyl, acetyl and phosphate groups by specialized enzymes. These modifications affect the density with which the DNA is wound around the histones. A tightly packed (closed conformation) region of the DNA is associated with transcriptional silencing and no gene product will be produced (see Text box 6). The open conformation of a loosely packed region is associated with transcriptional activity (See Figure 1).

Text box 6: Transcription

Process through which a DNA sequence is enzymatically copied to produce a complementary RNA. In the case of protein-encoding DNA, transcription is the beginning of the process that ultimately leads to the translation of the genetic code into a functional peptide or protein.

In addition, methyl groups can be added to (or removed from) the DNA itself. In particular the methylation of so-called “CpG-sites” (cytosine followed by a guanidine) is a reversible epigenetic variation influencing transcription. Frequently, CpG-rich clusters occur in and around promoters and other regulatory regions of genes. Methylation of CpG-sites is associated with transcriptional silencing, and the demethylated state with transcription activity.[65] Not all histones and CpG sites in a specific region need to have the same epigenetic marks, thereby allowing different transcriptional rates of the affected genes. It may range from totally silent to maximal transcription. Hence, variation in epigenetic modifications influences transcription control, the amount of protein produced and consequently a phenotype.

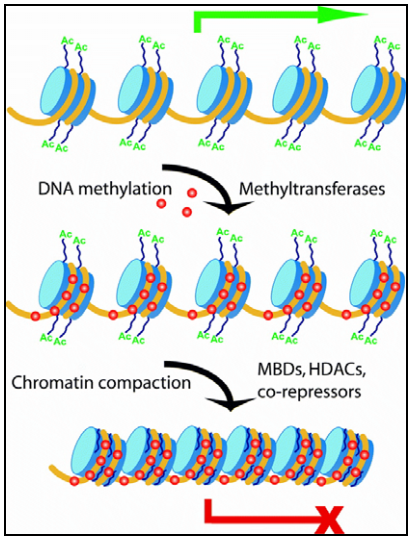

Figure 1. Epigenetic modifications in gene silencing.
A series of epigenetic modifications transforms transcriptionally active regions of DNA (top) into inactive compact chromatin (bottom).
Source: Cutfield et al.[65]

All epigenetic modifications within a given cell can be faithfully copied during DNA replication and repair, and cell division. Epigenetic modifications are heritable from mother to daughter cells and from generation to generation.[66] Nevertheless, the epigenome is not static, and is influenced by several cellular and environmental processes. First, epimutations may occur during DNA replication or repair, resulting in loss of the original epigenetic marks.[67] Second, epigenetic modifications occur and play a key role during development and cell differentiation.[68] Differential epigenetic marks allow individual cells to express the specific subset of genes required for the specialized function of a differentiated cell. Third, transcription factors, responding to cellular and environmental signals, attract cofactors that modify DNA methylation and histone acetylation. As a result transcription of their target genes is increased or decreased, orgastrating the appropriate cellular response (see Text box 7).[69] Fourth, environmental exposures, e.g. diets enriched with compounds/nutrients affecting the concentration of intracellular methyl donors, have been shown to influence epigenomes.[70-72] Even maternal care behavior (such as pup licking) was shown to modulate anxiety levels in offspring through reversible epigenome changes in rats.[71]

Text box 7: Transcription factors

Proteins regulating the transcription of (specific) genes

In a recent study using monozygotic twins, Fraga et al. [73] published a nice example of the population variation, heritability and environmental influences on the epigenome. They showed that the epigenome between pairs of monozygotic twins resembled each other much better than across pairs. This indicates that the epigenome varies within the population and has a certain amount of heritability. Furthermore, they showed that young monozygotic twin pairs were essentially indistinguishable in their epigenetic markings, whereas elderly monozygotic twin pairs had substantial differences in

several tissues, illustrating the influence of different environmental conditions with time on the epigenome.

The majority of the current knowledge and findings on epigenetic processes has been acquired using model systems (from single cells to animal models). That epigenetic changes also play a relevant role in humans is most obvious from cancer studies in which epigenetic changes in tumors have been investigated. Tumors frequently use epigenetic activation of oncogenes and/or deactivation of tumor suppressor genes to escape the cell division controls within the tumor cell and that of the surrounding tissue. Direct evidence that epigenetic variations play a role in human complex disease other than cancer is scarce, but widely presumed, as many recent reviews now suggest that the epigenome is involved in disease outcome. Studies implicating epigenetic regulation of body weight are shortly discussed below.

Firstly, evidence comes from animal models with obesity as a phenotype. In normal agouti mice the agouti gene is only expressed in the skin and the mice have a brown-black fur. In a mutant mouse model, viable yellow Avy/agouti (Avy) mice, the agouti protein is expressed in all somatic cells, causing yellow fur and obesity. Though the precise mechanism behind the obese phenotype is unknown, the overexpression of the agouti protein in the hypothalamus of Avy mice is thought to act as a melanocortin 4-receptor antagonist, leading to hyperphagia.[74]
The mutated gene carries multiple CpG-sites, and when methylated can suppress agouti expression. Indeed, CpG methylation correlates inversely with yellow fur and body weight.[70] Feeding diets supplemented with genistein, the major isoflavone in soy and soy products, to pregnant Avy dams induced CpG-methylation in their offspring. The pups' coat color shifted towards brown-black and they had a lean phenotype compared to pups from mothers on control diets. The lean phenotype and coat color of the genestein-exposed offspring were persistent during adult life, even though they received a standard diet without genistein after weaning.[75] These results clearly demonstrate that the exposure to dietary components in utero affects gene expression and alters susceptibility to obesity in adulthood by permanently altering the epigenome. Similar relationships in humans and normal mice, tying epigenetic changes to body weight, are yet to be revealed.

Secondly, evidence for the role of epigenetics in the etiology of obesity comes from studies on imprinting and syndromic obesity in humans. For imprinted genes only the maternal or paternal copy is expressed (see Text box 8). Epigenetic changes are involved in the imprinting of genes. Loss of imprinting or abnormal imprinting of these genes can result in several genetic diseases. For example, in humans a certain region of chromosome 15 carries differently imprinted genes on maternal and paternal chromosomes. Both imprintings are needed for normal development. Two syndromes are caused by a deletion of this chromosomal region.[76] One is the Prader-Willi syndrome (PWS). This syndrome is characterized by growth and mental retardation, obsessive-compulsive behavior, and marked obesity resulting from hyperphagia. The other is the

Text box 8: Genetic imprinting

For imprinted genes, gene expression occurs from only one allele. The expressed allele is dependent upon its parental origin. There are two major mechanisms that are involved in establishing the imprint; these are DNA methylation and histone modifications (epigenetic changes).

Angelman syndrome (AS). Class I patients are the most frequent and display the most severe phenotype of the five subclasses recognized, including severe developmental delay, impaired speech, movement and balance disorder, cognitive deficits, and unprovoked laughter, but no obesity. The difference is that for PWS the paternal chromosome caries the deletion, while for AS Class I the maternal chromosome is affected.

Thirdly, some indications that epigenetic processes may play a role in obesity comes from epidemiological studies among humans. Although any causal relationship between environmental exposures, epigenetic changes and obesity has not (yet) been demonstrated, epidemiological studies have demonstrated (sex-specific) transgenerational associations with nutrition and other lifestyle factors, such as smoking. For example, results from the Dutch famine cohort showed that famine exposure at different stages of gestation was variously associated with an increased risk of obesity, as well as dyslipidemia, and coronary heart disease.[77] In addition, the offspring of females exposed in the womb to famine in the first trimester did not have the expected increase in birth weight with increasing birth order.[78] Another example comes from the Avon Longitudinal Study of Parents and Children. In this study, early paternal smoking, starting before 11 years of age, was associated with greater BMI at age 9 years in sons, but not in daughters, after adjustment for possible confounding factors, such as education and maternal smoking.[79]
It is tempting to speculate that the altered phenotypes in the offspring according to exposure of the parents resulted from induced (and inherited) changes of the epigenome. However,.as mentioned before, direct evidence for this hypothesis is still lacking in humans.

In summary, direct evidence demonstrating epigenetic variation to play a causal role in human obesity is yet to be uncovered. However, results from mouse models and syndromic obesity suggest that epigenetic variation influences body weight. Therefore, it would be highly surprising if the epigenome does not add an additional level of complexity to common disease susceptibility, including overweight and obesity.

6 Gene-environment interaction in relation to obesity

The current obesity epidemic has developed during the past four decades and cannot be explained by changes in the DNA sequence of the population. Many generations are required to fix a new mutation in a significant portion of the population or alter the frequency of an "obesity-allele". In the last 40 years, however, our environment has dramatically changed to an environment that promotes excessive energy intake and discourages physical activity.[5] In this obesogenic environment some people maintain a normal weight whereas others become severely obese. Susceptibility for obesity is thought to be determined by the interaction between a persons genetic profile and environmental factors, such as diet and physical activity.[80] Loos et al. [13] suggested four levels of genetic susceptibility for obesity (see Table 4). The four levels are genetic obesity, strong predisposition, slight predisposition and genetically resistant. Genetic obesity is characterized by a single-gene mutation that leads to massive obesity irrespective of the environment (monogenic obesity; see chapter 3). Individuals with a strong predisposition are overweight in a non-obesogenic environment and obese in an obesogenic environment. Individuals with a slight predisposition are normal or overweight in a non-obesogenic environment but overweight or obese in an obesogenic environment. Genetically resistant individuals are characterized by normal weight even in an obesogenic environment.

Table 4 Four levels of genetic susceptibility for obesity in relation to different environmental conditions, as suggested by Loos et al.[13]

Level of genetic susceptibility	Body size in a non-obesogenic environment	Body size in an obesogenic environment
Genetic obesity	Massively obese	Massively Obese
Strong predisposition	Overweight	Obese
Slight predisposition	Normal weight / Overweight	Overweight / Obese
Genetically resistant	Normal weight	Normal weight

A clear illustration of interaction between genes and environment can be derived from the Pima Indians, a population very susceptible to obesity.[81] Pima Indians living a traditional lifestyle in the restrictive environment of the remote Mexico Sierra Madre mountains experience almost no obesity. In contrast, the prevalence of obesity is dramatically high among Pima Indians who abandon their traditional lifestyle and live in the 'obesogenic' environment of Arizona in the USA.
More evidence that genetic factors determine the response to lifestyle has come from long term studies on the response to changes in energy balance among identical twins. In 1990, twelve male monozygotic twin pairs were overfed by 1000 kcal per day, for 6 days per week during a 100-day period.[82] The excess energy intake over the entire period reached 84,000 kcal. At the end of the overfeeding period the mean body weight gain was 8.1 kg. However, the weight gain ranged considerably, i.e. from 4.3 kg to 13.3 kg. The weight gain varied at least three times more between twin pairs than within twin pairs. Analogously, in 1995, seven male monozygotic twin pairs were exposed to long term energy restriction. They increased their energy expenditure by exercising on cycle ergometers twice a day, for 9 out of 10 days over a period of 93 days while keeping their energy intake constant. The mean total

energy deficit caused by exercise over the entire period reached 58,000 kcal. The mean loss in body weight was 5.0 kg and ranged from 1.0 to 8.0 kg. Again, differences in the response to energy restriction within twin pairs were much smaller than differences between twin pairs.[83] These findings indicate that in response to overfeeding or energy restriction some people are more likely to gain or lose weight than others. Furthermore, the results show that the magnitude of one's response has a genetic basis.

Considering the complexity of biological pathways involved in energy intake, energy expenditure and formation of adipose tissue numerous genes are candidates for the study of genotype-environment interactions and obesity.[80] The potential role of various candidate genes in modulating the change in body weight in response to changes in diet or energy expenditure has however not been investigated frequently. Some examples are described here. Ukkola et al. investigated in the twin study mentioned above whether or not variation in 40 different genes contributed to the differences in weight gain as a result of overfeeding.[84] The results showed that a polymorphism in the beta-2 adrenergic receptor explained 7% of the variance in weight gain. A polymorphism in the beta-3 adrenergic receptor might influence the amount of weight loss during energy restriction in Japanese, but the results have not been conclusive.[80]
A relatively large study investigating gene-diet interactions is the NUGENOB study.[85] This study consisted of 549 adult obese women from eight European cities including Maastricht. The interaction between a total of 42 genetic variations located in 26 obesity candidate genes were and three dietary factors namely, dietary fibre intake, the ratio of polyunsaturated fat to saturated fat and the percentage of energy (en%) derived from fat, was studied. Of the 126 interactions tested, only one appeared to be consistently statistically significant among different models. Dietary fibre intake in interaction with a SNP in the hepatic lipase gene (*LIPC),* which is involved in lipid metabolism, was associated with obesity. Furthermore, a SNP in the adiponectin gene (*ADIPOQ*) and a SNP in the peroxisome proliferative activated receptor Gamma isoform 3 (*PPARG3)* gene might interact with dietary fat intake (en%). This study clearly showed the complexity of detecting gene-diet interactions in relation to obesity. In the future, larger studies are needed to discover such interactions.

In summary, interactions between genes and the environment play an important role in common obesity. Due to genetic predisposition, individuals react differently on changes in energy balance or dietary factors. To date, few studies investigated specific gene-environment interactions in relation to obesity. So far, convincing evidence for a specific interaction (in particular with macronutrients) is lacking.

7 Discussion

This review of the literature showed that there is clear evidence for a genetic contribution to obesity. BMI is an heritable trait and about 40% of its total variance can be explained by genetic variation. The contribution of genetic factors increases with increasing severity of overweight. This has been shown by indirect evidence from twin and family studies, but also by more direct evidence.
Single-gene mutations in MC4R, LEPR and POMC explain 0 - 2.5% of the less severe obesity cases but up to 10% of extreme obesity cases with an early age of onset. To date, it has shown to be difficult to identify the role of more common forms of genetic variation, such as single nucleotide polymorphisms, in overweight and obesity. Convincing evidence exists for only five specific polymorphisms. They may explain about 20% of the obesity cases at the population level. To what extent these findings may influence public-health initiatives focused on promoting weight loss and preventing weight gain, will be discussed below.

For a small number of individuals it is possible to determine the single-gene mutation causing their severe obesity. This may have a large impact for the individual, as effective therapies may be developed for the affected individuals. However, because of the small number of affected individuals, screening for these mutations among the general population is undesirable. Nevertheless, monogenetic forms of obesity have learned us a lot about the pathways involved in the regulation of energy balance. Mutations in the melanocortin-4 receptor gene (MC4R) are currently regarded as the most relevant genetic cause for extreme obesity. The MC4R is located in the hypothalamus and plays a key role in the regulation of food intake by integrating satiety and hunger signals.[28]

For most of the individuals with overweight or obesity it is difficult to assign the responsible genes. Carrying one susceptibility allele predisposing for overweight or obesity does not necessarily lead to the disorder. Several genetic factors will act together. In addition, an obesity promoting environment is necessary for the expression of obesity. Currently we live in an environment were everyone is exposed to abundant food supply. Therefore, it is very difficult to maintain a healthy body weight for individuals with a genetic predisposition, whereas genetic resistant individuals will hardly become obese. Genetic variation in the response to diet and lifestyle has been clearly demonstrated from twin studies (see chapter 6). This means that for a considerable number of subjects their overweight or obesity is not just the result of their (unhealthy) behavior, but also of genetic factors.

In theory, genetic information may help to develop individualized prevention programs. Individuals genetically predisposed to develop obesity may be identified and preventive action may be intensified for them. Furthermore, specific measures may be taken based on the individuals susceptibility to certain interventions, for example specific diets. Additionally, weight-loss treatment strategies could also be targeted towards the individual's genotype. However, specific gene-environment interactions have not been consistently reported. Therefore, the available data are far from sufficient to justify genetic screening and personalized advice based on the genetic background of the individual.

One of the reasons that the search for susceptibility genes and gene-environment interactions has been disappointing so far probably lies in the fact that larger studies are needed to study the small effects that

are expected. At the moment a lot of research efforts are going one that tackle this problem. One example, is the DIOGENES-project (Diet, Obesity and GENES, http://www.diogenes-eu.org/). DIOGENES is an integrated project of the EU Sixth Framework Programme for Research and Technological Development. One of the objectives is to investigate the role of gene-diet interactions in relation to weight gain among 12,000 participants. This number of subjects is better suited to disentangle the complex interactions that predispose to overweight and obesity.

The disappointing outcome of the search for genetic determinants of obesity so far, may also have other reasons. Until recently research focused mainly on classic genetic variation, single nucleotide polymorphisms in particular. However, humans are genetically more diverse than previously thought, and the genetic basis for common disease is likely to be more complicated than we had previously anticipated. There are other types of genetic variation between individuals that may influence susceptibility to disease. Copy number variation is an example of another type of genetic variation. As recently discovered, the number of copies for relatively large pieces of DNA at a given location in the genome can vary between individuals from zero to tens or even hundreds. At least 10% of the genome is subject to copy number variation. Many copy number variants include genes that result in differential levels of gene expression. Therefore copy number variation may account for a significant proportion of differences in gene expression between individuals and hence in normal phenotypic variation and disease susceptibility. Although the role of this type of genetic variation in the development of obesity remains to be determined, several other complex disorders, such as HIV-1 and Crohn's disease have already been associated with copy number variation.[86,87]

Even more (genetic) variation between individuals comes from epigenetic changes. Epigenetic changes do not change the DNA nucleotide sequence itself, but influence the folding of the DNA.[65] Epigenetic modifications are heritable from mother to daughter cell and across generations, and can also be influenced by the environment and lifestyle. These realizations yield two implications. First, our lifestyle does not only affect our own lives, but also the health risks of our offspring. And second, in contrast to genetic information we can influence the epigenetic information to prevent or cure common chronic diseases. Certain dietary habits and lifestyle choices, possibly during selected life stages, such as the reproductive period, pregnancy or specific stages of development, may program our epigenomes and that of future generations. Moreover, the flexible nature of the epigenome suggests a mechanism for fast evolutionary changes without the need for many generations required to fix a new mutation in a significant portion of the population. The amount of time needed for the latter (millennia) far exceeds the relatively recent onset of the threatening obesity epidemic (decennia), and has often been used as an argument against a genetic factor for the current health problem. Epigenetic changes due to environmental conditions and life-style choices may need only one or two generations to display an altered phenotype population wide. Epigenetics is an emerging research area that solicits future investments for the promising implications it may yield to affect disease predisposition, including overweight and obesity. Although direct evidence in humans is lacking, studies among mice and indirect indications from human studies suggest that epigenetic variation may indeed influence obesity risk (see chapter 5).

Because of the reasons described above, the genetic contribution to obesity may be larger than currently envisaged.

8 Conclusions

- Although there is sufficient evidence for a considerable genetic component to obesity, too little is known about specific genetic factors to justify an integration of genetic information into public-health initiatives focused on promoting weight loss and preventing weight gain.

- BMI is an heritable trait and about 40% of the total variance in BMI can be explained by genetic variation. The contribution of genetics to overweight and obesity increases as the severity of the disorder increases.

- Single-gene mutations explain at most 2.5% of less severe obesity cases and up to ~10% of extreme obesity cases with an early age of onset. Nearly all reported cases of monogenetic obesity are due to mutations in MC4R, LEPR or POMC genes, which play a role in appetite regulation.

- For five common genetic variants there is sufficient evidence supporting their role in determining BMI or obesity risk. These genetic variants may contribute to at least 10% of overweight and 20% of the obesity cases at the population level. The genes are involved in energy intake, energy expenditure as well as in adipose tissue formation.

- Due to genetic predisposition, individuals react differently on changes in energy balance or dietary factors. However, convincing direct evidence for specific gene-gene or gene-environment interactions is lacking to date. Larger studies are needed to discover these interactions in relation to obesity. Several of these studies are currently ongoing.

- Humans are genetically more diverse than previously thought. Epigenetic changes and copy number variation, among others, add more complexity to the genetic differences between people. Their implications for disease predisposition, including overweight and obesity, are promising.

- The genetic contribution to obesity may be larger than currently envisaged and ongoing investments in research into genetic determinants of obesity are justified.

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Appendix 1. Meta-analyses on candidate genes and obesity-related phenotypes

Gene[1]	SNP	Phenotype[2]	Study size[3]	Effect[4]	Ref
ADRB2: Adrenergic receptor β2	*Arg16Gly*	Obesity	NA	ns	88
	Gln27Glu	Obesity	12612	ns	
*ADRB3:*Adrenergic receptor β3	*Trp64Arg*	BMI	9,236	Increased BMI in Arg-carriers	55
*GRL :*Glucocorticoid receptor	*Asn363Ser*	BMI	5,909	Increased BMI in Ser-carriers	89
	Asn363Ser	Obesity	5,909	ns	
FTO: Fat mass and obesity associated gene	Intron 1 T/A	Overweight	38,759	Increased risk in A-carriers	60
	Intron 1 T/A	Obesity	38,759	Increased risk in A-carriers	
LEP: Leptine	*Ala19Gly*	Obesity	375	ns	90
LEPR: Leptine receptor	*Lys109Arg*	BMI/WC	2,498/NA	ns	90, 91
	Gln223Arg	BMI/WC	3,309/NA	ns	
	Lys656Asn	BMI/WC	2,886/NA	ns	
LPL: Lipoprotein lipase	*Asn291Ser*	BMI	3,233	ns	92
	Asn291Ser	WHR	1,473	ns	
MC4R: Melanocortin-4 receptor	*Val103Ile*	Obesity	29,563	Decreased risk in Ile-carriers	57
PPARγ2: Peroxisome proliferator -activated receptor-*γ*	*Pro12Ala*	BMI	19,699	Increased BMI in Ala-carriers	56
PPARGC1A: Peroxisome proliferator -activated receptor-*γ* co-actirvator-1α	*Gly182Ser*	BMI	8,536	ns	93
TNFα: Tumor necrosis factor α	*G-308A*	Obesity	3,119	Increased risk in A-carriers	58
	G-308A	BMI	5,009	Increased risk in A-carriers	
	G-308A	WHR	3,910	ns	

[1] Results among Causasians are presented as far as available.

[2] BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio.

[3] NA: not available.

[4] NS: not significant