Gene Variants for Obesity and Type 2 Diabetes – A Shared Aetiology?

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Abstract

The incidence of type 2 diabetes is rising rapidly worldwide, mainly due to the increase in the incidence of obesity. Both obesity and type 2 diabetes are complex genetic traits, but they share some non-genetic risk factors. Hence, it is tempting to speculate that susceptibility to type 2 diabetes and obesity may also involve shared underlying genetic factors acting on common molecular mechanisms. Recent genome-wide association (GWA) studies identified 17 common loci for obesity and 19 common loci for type 2 diabetes. This article explores whether the susceptibility loci for type 2 diabetes and obesity can indicate potential overlapping mechanisms in the disorders. In addition, we touch on the challenges regarding follow-up of confirmed GWA signals, as well as alternative approaches to analysing GWA data to a fuller potential.

Keywords

Genetics, type 2 diabetes, diabetes genes, obesity genes, genome-wide association studies, complex genetic traits

The incidence of type 2 diabetes is rising rapidly worldwide, and there are already more than 180 million diabetic subjects. Type 2 diabetes risk factors include ethnic background, age, hypertension, overweight, increased abdominal fat and lack of physical exercise. Obesity is considered to be the most important risk factor for type 2 diabetes and the main factor driving the current epidemic, as 90% of type 2 diabetes patients are obese. Worldwide, obesity has also reached epidemic proportions, with 300 million adults classified as clinically obese (based on data from the World Health Organization). Up to 50% of these obese individuals will develop type 2 diabetes at some stage in their life, depending on the age at which they became obese.

Type 2 diabetes and obesity are multifactorial disorders in which both genetic and non-genetic (environmental and lifestyle) factors play a role. Although the lifetime risk for type 2 diabetes in the western world is around 10%, first-degree relatives of patients have a 20–40% risk of the disease, and concordance rates for identical twins have been estimated to be 57% or higher (up to 90%) for type 2 diabetes in male twins.[1] These observations clearly indicate that there is a genetic component to the disease. However, the model seems to be more complex, involving multiple genes and environmental factors.

Common obesity and type 2 diabetes share some non-genetic factors, as both are influenced by diet and physical inactivity. Both conditions are characterised by insulin resistance, suggesting a shared pathology. It has been proposed that susceptibility to developing type 2 diabetes and obesity is, in part, due to shared underlying genetic factors involved in common molecular mechanisms. This article explores the genes recently identified for type 2 diabetes and obesity by genome-wide association studies (GWAS) and evaluates their functions in an effort to determine whether there is any support for the hypothesis that type 2 diabetes and obesity share some underlying mechanism(s).

Common Type 2 Diabetes and Obesity Susceptibility Loci

Before the era of GWAS, genes were prioritised as candidate disease genes because of their function and/or position, and they were then studied for association with obesity and type 2 diabetes. These approaches had limited success, as replication of associated genes proved possible only for variants in or near *PPARG, KCNJ11, TCF2* and *WFS1* with type 2 diabetes[2] and for variants in or near *BDNF, MC4R* and *SH2B1* with obesity. Recently, a number of GWAS have identified 17 common loci for obesity and 19 common loci for type 2 diabetes (see *Tables 1* and *2*).[3–14] An interesting finding is that the results of GWAS often point towards genes with currently unknown or poorly described functions. This is one of the reasons why the previous approaches to gene hunting had limited success. Most of the recently identified genes were not tested for association simply because their biological functions were unknown and they were not therefore suspected of being involved in the disease.

GWAS further indicate that associated common markers have only a minor impact on disease susceptibility. The known risk variants for type 2 diabetes are all relatively common in the population,

Table 1: Overview of Genetic Variants Associated with Type 2 Diabetes and Their Putative Role in Disease Pathogenesis

Marker	Chr	Closest Gene(s)	Putative Mechanism in T2D
rs7578597	2	THADA	Apoptosis of β cells
rs10010131	4	WFS1	Apoptosis of β cells
rs10923931	1	NOTCH2	β-cell growth and development
rs4402960	3	IGF2BP2	β-cell growth and development
rs10946398	6	CDKAL1	β-cell growth and development
rs1111875	10	HHEX-IDE	β-cell growth and development
rs7901695	10	TCF7L2	β-cell growth and development
rs4430796	17	TCF2	β- cell growth and development Cell cycle
rs864745	7	JAZF1	Cell cycle
rs10811661	9	CDKN2A-2B	Cell cycle
rs12779790	10	CDC123-CAMK1D	Cell cycle
rs13266634	8	SLC30A8	Insulin secretion
rs2237892	11	KCNQ1	Insulin secretion
rs5215	11	KCNJ11	Insulin secretion
rs10830963	11	MTNR1B	Insulin secretion
rs17036101	3	SYNC, PPARG	Unknown
rs4607103	3	ADAMTS9	Unknown
rs1153188	12	DCD	Unknown
rs7961581	12	TSPAN8	Unknown

Chr = chromosome, T2D = type 2 diabetes.

Table 2: Overview of Genetic Variants Associated with Obesity and Their Putative Role in Pathogenesis

Marker	Chr	Closest Gene(s)	Putative Mechanism in Obesity
rs4074134	11	BDNF	Energy homeostasis
rs7498665	16	SH2B1	Energy homeostasis
rs9939609	16	FTO	Energy homeostasis
rs17782313	18	MC4R	Energy homeostasis
rs1805081	18	NPC1	Lipid transport
rs2815752	1	NEGR1	Neural development
rs6548238	2	TMEM18	Neural development
rs10838738	11	MTCH2	Satiation signalling
rs10913469	1	SEC16B	Unknown
rs7647305	3	ETV5	Unknown
rs10938397	4	GNPDA2	Unknown
rs2844479	6	NCR3	Unknown
rs4712652	6	PRL	Unknown
rs10508503	10	PTER	Unknown
rs7138803	12	BCDIN3D	Unknown
rs1424233	16	MAF	Unknown
rs11084753	19	KCTD15	Unknown

Chr = chromosome.

ranging from 0.26 for *TCF7L2* to 0.85 for *PPARG* in the European population, and have a low effect size with odds ratios (ORs) ranging from 1.10 (confidence interval [CI] 1.07–1.14) for *TCF2* to 1.37 (CI 1.31–1.43) for *TCF7L2*. For obesity, each of the associated variants has a very modest effect, ranging from $0.06\,kg/m^2$ for *KCTD15* to $0.33\,kg/m^2$ for *FTO* per allele change in body mass index (BMI). All these variants together can explain only a small percentage of the genetic susceptibly of type 2 diabetes and

obesity. However, these variants are generally not the causal variants. The ORs of the causal variants should be higher and will presumably explain a larger percentage of the genetic susceptibility to these two conditions. In addition, it is likely that many more genes contribute a similar or smaller effect.

Functions of Type 2 Diabetes and Obesity Genes

The susceptibility loci for obesity and type 2 diabetes can provide insight into the aetiology of the traits, yet it is difficult to link genetic associations to biological mechanisms. It is important to keep in mind that most of the observed associations are located in non-coding regions of the genome and that the presented type 2 diabetes and obesity genes are mostly genes near the associated markers. We assume that at least some of these nearby genes are truly involved in the traits as we discuss the function of these genes to gain more insight into the disease pathology.

Type 2 Diabetes

The main feature of type 2 diabetes is the inability of an individual to maintain proper blood glucose levels. The key player in this homeostasis is the peptide hormone insulin, which is produced in the β cells of the pancreas. After a meal this hormone is released into the bloodstream and transported to its several target tissues, where it diminishes hepatic glucose output and triggers glucose uptake and storage as either fat or glycogen. Type 2 diabetes starts

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with the failure of several tissues, such as adipose tissue and muscle, to respond to the stimulus of insulin (this is often referred to as insulin resistance). As a result, insulin levels rise and it is presumed that, after a certain time, β cells are not able to keep up with the growing demands for insulin release. At this point a (second) vicious cycle of higher blood glucose levels and a higher demand for insulin is entered, which increases the strain on the β cells and leads to β-cell apoptosis and, ultimately, a complete inability to produce insulin.[15]

The type 2 diabetes risk variants currently pinpointed appear to act through interference with β-cell insulin secretion rather than through insulin sensitivity of insulin target tissues. This indicates that disturbances in β-cell function are ultimately decisive for the actual development of type 2 diabetes. The known type 2 diabetes genes can be classified into subgroups for their potential role in β-cell function based on what is known about their molecular function.[15] It has been proposed that *KCNJ11*, *KCNQ1*, *MTNR1B* and *SLC30A8* are involved in insulin secretion; *CDKAL1*, *IGF2BP2*, *HHEX-IDE*, *NOTCH2*, *JAZF1*, *TCF7L2* and *TCF2* in β-cell growth and development; *TCF2*, *CDKN2A-2B*, *CDC123* and *JAZF1* in the cell cycle; and *THADA* and *WFS1* in the apoptosis of β cells.

Obesity

Overweight and obesity result from a long-lasting imbalance between food intake and energy expenditure, leading to storage of excess calories as body fat. Control of energy balance involves the integration of satiety signals from the gastrointestinal tract, adipose tissue and nutrient-related signals. Adiposity signals provide feedback information from body energy stores to various

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hypothalamic regions and are mediated via the circulating hormones leptin and insulin and others. As a result, bodyweight remains remarkably stable most of the time in most people, but any defects in this system can lead to a deregulation of bodyweight. It is known that hypothalamic defects in either insulin or leptin signalling are associated with increased food intake and/or heavier bodyweight.[16,17]

Many of the recently established obesity susceptibility loci are located near genes that are highly expressed in the brain and/or have been shown to have a function in neuronal development or activity. These suggest a key role for the hypothalamic pathways in regulating food intake and energy homeostasis in the architecture of obesity. The role of *BDNF*, *MC4R* and *SH2B1* genes in obesity pathogenesis is well known from functional studies. *MC4R* is the key signalling neuropeptide, inhibiting food intake and increasing metabolic rate.[18] *BDNF* decreases food intake in response to nutritional status and *MC4R* signalling.[19] Studies show that *SH2B1* regulates energy balance, bodyweight, peripheral insulin sensitivity and glucose homeostasis, at least in part by enhancing hypothalamic leptin sensitivity.[20] The roles of the other recently identified loci in obesity pathogenesis are not yet clear. *FTO* is suggested to participate in the central control of energy homeostasis, where it is regulated by feeding and fasting.[21] *NEGR1* and *TMEM18* are involved in neural development,[11,13] whereas *NPC1* is involved in endosomal cholesterol trafficking in the central nervous system, liver and macrophages.[22]

Because satiation signals influence how many calories are eaten during individual meals, it is interesting to further explore the effect of obesity susceptibility variants on total and nutrient-specific dietary intake. Although total energy intake is a vital aspect of food intake, macronutrient composition or diet patterns may be equally important factors underlying the development of obesity. Common variants near the *FTO* and *MC4R* genes were recently found to be associated with total energy intake, and a variant near *MC4R* was also found to be associated with dietary fat.[23–25] In addition, in a study population of 1,700 Dutch females, the susceptibility loci near *NEGR1*, *TMEM18*, *BDNF*, *MTCH2* and *SH2B1* showed association with macronutrient intake.[26] It can be argued that the genes associated with food intake play a role in satiation signalling.

Further insight into the function of these genes may yield valuable clues for lifestyle intervention and therapeutics.

Genome-wide Association Studies Give Insight into Shared Disease Aetiology

So far, results from the recent GWA studies do not point towards obesity and type 2 diabetes having an increased risk from shared disease susceptibility loci. It seems that the susceptibility genes for obesity are involved at the start of the trait (energy imbalance) and those for type 2 diabetes at a later stage of the disease (β-cell defect).

The initial finding of association between the *FTO* gene and type 2 diabetes was subsequently shown to be entirely due to an obesity risk. The gene was found to be highly associated with type 2 diabetes in several study populations[27] but failed to replicate in studies where they matched the cases and controls on BMI or selected relatively lean cases.[7,9] The loci near *GNPDA2*, *BDNF* and *TMEM18* that were associated with obesity were also found to be weakly associated with type 2 diabetes.[11,13] Follow-up studies should explore whether these associations with type 2 diabetes mainly act through an effect on weight regulation. They need to take into account not only BMI but also other measures of obesity. Recently, it has become clear that not only is the amount of body fat important but especially its distribution in determining disease risk. Independently of BMI, a larger waist circumference (as a measure of abdominal obesity) is related to chronic disease risk, such as type 2 diabetes.[28] However, because there are still many more obesity and type 2 diabetes genes to discover, we cannot rule out that the susceptibility for developing type 2 diabetes and obesity is partly due to shared underlying genetic factors.

In a previous study we compared all the published genome scans for type 2 diabetes and obesity and identified five overlapping chromosomal regions for both entities.[29] However, the shared genetic effect may be smaller than we initially thought, or obesity could simply be a non-genetic risk factor for type 2 diabetes because it provokes insulin resistance.

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Follow-up of Confirmed Associations and Alternative Gene-hunting Approaches

The next challenge is to go from the statistical association of the markers to a functional link between the genomic region and type 2 diabetes and obesity. The associated single nucleotide polymorphism (SNP) will either be the disease-causing variant or strong linkage disequilibrium (LD) with the causal variant, i.e. the associated SNP and the causal variant are inherited together. Re-sequencing of the susceptibility loci is needed to establish the causal genes. This will be a daunting task because the LD blocks can

be extensive. In GWAS, allele frequencies of approximately 300,000–500,000 common SNPs across the human genome are compared one by one between patients and healthy controls. Although this approach successfully identified new type 2 diabetes and obesity genes, a large part of the GWA data have not yet been analysed to their full potential.

It is possible that single-locus methods do not reflect the correct underlying model of association. There is growing evidence that gene–gene and gene–environment interactions contribute to complex diseases rather than single genes.[30] Several models for epistasis (i.e. gene–gene interactions) have been proposed,[31] including those in which the genes alone have no effect on disease aetiology but where their interaction modifies disease risk. In addition, it is likely that genetic variation contributes to disease risk through complex biological pathways. It is unlikely that the genes involved in these pathways will be picked up using traditional single-locus analyses, and different methods will be needed to extract this information from GWA data sets.[32]

Conclusion

Common obesity and type 2 diabetes share some non-genetic factors, as both are influenced by diet and physical inactivity. Both conditions are characterised by insulin resistance, suggesting a shared pathology. However, results from recent GWAS do not point towards shared disease susceptibility loci with an increased risk of both obesity and type 2 diabetes.

Currently, it seems that the susceptibility genes for obesity are involved at the start of the trait (energy imbalance), and those for

type 2 diabetes are involved at a later stage of the disease (β-cell defect). It is suggested that the shared genetic effect may be smaller than we thought, or obesity could simply be a non-genetic risk factor for type 2 diabetes because it provokes insulin resistance. Discovering more obesity and type 2 diabetes genes will provide a broader insight into the shared disease pathology. ■

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