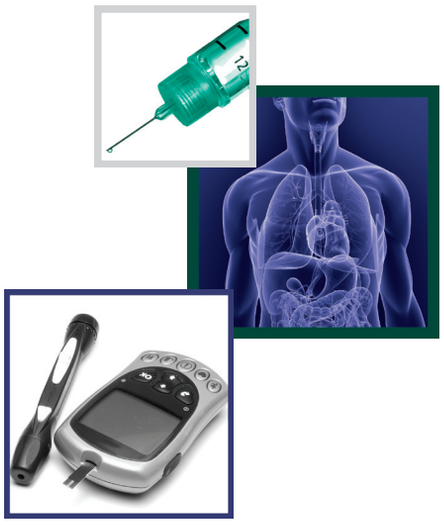
REVIEW

Obesity: is Type II diabetes a foregone conclusion or further dependent on genetic susceptibility?



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Practice Points

- Genetics of obesity:
  - To date, 32 loci are shown to be significantly associated with BMI and account for 1.45% of the total variation in BMI.
  - A proportion of the BMI risk loci are highly expressed in the brain and highlight the importance of energy regulation in overall obesity.
- Genetics of body fat distribution:
  - To date, only 1.03% of the variance in waist:hip ratio (WHR), independent of BMI, is explained by the 14 associated loci.
  - The 14 WHR-associated loci contain variation associated with cholesterol, insulin and insulin resistance, all linked to the development of Type 2 diabetes (T2D), and half of these loci show sex-specific effects.
  - The overlap of loci that are associated with both WHR and T2D suggest a link between specific patterns of body fat, independent of overall obesity, and the development of T2D.
- Role of obesity in T2D:
  - While not all obese individuals develop T2D, obesity generally increases the risk of insulin resistance, and consequently, increases the risk of developing T2D.
  - While increased intra-abdominal fat is associated with increased T2D risk, the accumulation of gluteal fat is shown to decrease T2D risk; emphasizing the important role of body fat distribution in the development of T2D.
- Conclusion & future perspective:
  - Both overall obesity and fat distribution patterns are linked to metabolic disturbances and T2D.
  - There is a clear need to improve our understanding of the genes involved in obesity, body fat distribution and T2D.
  - Fine mapping, sequencing and functional studies may be required to clarify the exact biological mechanisms for the implicated loci.
  - Therapeutic targets may benefit from the incorporation of knowledge regarding the genes that control body fat distribution in addition to overall obesity and T2D.

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SUMMARY Obesity results from an excess accumulation of body fat and is a major risk factor for Type 2 diabetes (T2D). Common, overall obesity is a complex trait influenced by both genetic and environmental factors. Recent genome-wide association studies have identified robust associations at 32 loci with overall obesity as well as 14 with body fat distribution. While overlapping evidence from both genetic and epidemiological studies suggests a link between obesity and T2D, specific fat distribution patterns, independent of overall adiposity, may play an equally important role in T2D risk. Understanding the etiological link between obesity, fat distribution and T2D presents new opportunities for the management, and ultimately treatment, of these diseases.

Obesity and being overweight result from a positive, overall energy balance, which occurs when a person's caloric intake exceeds their caloric expenditure [1]. The prevalence of common forms of obesity that affect the general population, have shown a marked increase over the last 30 years – generally attributed to an 'obeseogenic environment', such as decreased physical activity and high fat diet choices [2]. Obesity and overweight are usually defined using the BMI, calculated as weight (in kilograms) divided by height in meters squared (kg/m^2) [3]. Individuals with a BMI >25 kg/m^2 are classified as overweight, while those with a BMI >30 kg/m^2 are considered obese [4]. The obesity epidemic is growing at an alarming rate, and by 2015, it is estimated that 2.3 billion adults worldwide will be overweight and more than 700 million will be obese [5].

The increasing prevalence of global obesity is believed to be a major contributor to the rising incidence of the metabolic syndrome, which encompasses risk factors such as hypertension, cardiovascular disease, insulin resistance (IR) and Type 2 diabetes (T2D) [6–9]. The increased rate of T2D has been specifically tied to the growing obesity epidemic [10], but the link between these two traits remains unclear and strong evidence suggests an important contribution of genetic mechanisms to T2D [11]. Indeed, while the majority of individuals with overall obesity do develop metabolic complications, which may be partly mediated by the correlation between obesity and IR, approximately 10–25% remain insulin sensitive and metabolically healthy [12]. Interestingly, detailed physiological studies point to the fact that the majority of currently known variants that influence T2D risk operate through effects on β-cell function rather than insulin sensitivity [13]. However, for the purpose of this article, we will focus on the component of T2D that is associated with obesity and fat distribution.

Body fat distribution has also been established as an important determinant of metabolic health [14,15]. Central obesity (intra-abdominal fat accumulation) is more strongly associated with the risk of metabolic diseases, such as T2D, than common overall obesity [16–18]. Studies in South Asian populations have also demonstrated a significant association between thicker truncal subcutaneous adipose tissue, independent of total body fat, and the metabolic syndrome [19,20]. Furthermore, the accumulation of gluteal fat (fat accumulation around the hips and thighs) has been shown to confer a protective effect against the risk of developing T2D [21,22]. While BMI is a useful surrogate measure of overall obesity and fat percentage [4], it does not account for regional differences in body fat at the same BMI, which can be influenced by ethnicity, age and gender, and can have important consequences for T2D risk [23]. Therefore, measurements that consider abdominal and gluteal fat distribution, such as waist circumference (WC) and waist–hip ratio (WHR), have become key in the classification of obesity and obesity-related metabolic risk factors such as T2D [24–26], since these measurements are better estimates [18,23], and consequently better risk factors, of central fat distribution.

As specific fat distributions contribute significantly to T2D risk, and obesity remains the largest modifiable risk factor of metabolic diseases, understanding both the genetic and environmental causes of overall obesity, as well as individual patterns of fat distribution, may clarify the etiological link between these traits.

Genetics of obesity

Twin and adoption studies have shown that genetic effects account for between 60–90% of the BMI variance within a population [27]. Similarly, heritability estimates of obesity-related measures (BMI, WC, WHR and total fat mass), range from 40 to 70% [28–30]. While the exact biological mechanisms that underlie human obesity remain elusive, the ongoing discovery of genes involved in various forms of obesity, has provided valuable insight into both the molecular and functional aspects of the disease.

Extreme monogenic forms of obesity & fat distribution

Both monogenic and syndromic forms of obesity are very rare and appear to be largely controlled by highly penetrant genetic effects, making them suitable for detection in family-based linkage studies [31]. Single genes responsible for monogenic forms of obesity were initially discovered by family-based linkage and candidate gene studies [32]. These include mutations in the leptin [33,34] and melanocortin pathways [35], both involved in energy homeostasis, which resulted in extreme forms of the disease [36,37]. Interestingly, all of the single gene mutations (~20 genes) that have been identified and shown to cause monogenic forms of the disease, do so through exerting their action on the control of energy balance [38]. Since energy intake in individuals with monogenic forms of obesity is often elevated, while their energy expenditure generally remains unchanged, a positive overall energy balance, and ultimately obesity, ensues. Chromosomal abnormalities were also found to cause syndromic obesity, such as Prader-Willi syndrome, characterized by decreased satiety response to food intake and increased risk of severe obesity [39]. Despite an increase in the overall adiposity, the specific reduction in central adiposity in patients with Prader-Willi syndrome appears to confer a protective effect against obesity-related metabolic complications [40]. This again emphasizes the importance of body fat distribution in metabolic health. Additionally, genes underlying rare syndromic lipodystrophies have been discovered and provide further evidence for the role of genes involved in fat distribution. Lipodystrophies are characterized by the decreased ability to store fat in adipose tissues and subsequent accumulation of ectopic fat stored in the liver and muscle [41]. This commonly results in the development of severe IR and T2D [42,43] and again emphasizes the importance of fat distribution in metabolic health.

Common, complex obesity

In the case of common obesity, however, each risk allele is responsible for only a small portion of the overall genetic variation of the obesity phenotype [44,45] and these effects are further confounded by their interactions with environmental factors. Therefore, the relatively low power of linkage studies (a consequence of their small sample sizes) to detect the small effect alleles underlying common forms of the disease, resulted in the limited identification of common obesity-risk alleles. Therefore, the focus shifted to genome-wide association (GWA) studies, which involve the population-wide examination of whole genomes, to identify specific genetic variation associated with common diseases [46]. This strategy provides a powerful, hypothesis-free method of detecting moderate–small effect alleles that predispose individuals to common obesity [44,47–50].

The identification of the genetic risk factors in GWA studies for common, overall obesity has followed four stages of discovery [44,45,47,48,50–53], where each successive stage is characterized by a significant increase in power and, as a result, the detection of novel obesity-susceptibility loci.

The first gene to be robustly associated with common obesity and related traits was identified by the Wellcome Trust Case Control Consortium, in a study designed to search for T2D risk alleles in 1924 cases and 2938 controls [51]. Single nucleotide polymorphisms in the first intron of the fat-mass and obesity-associated (*FTO*) gene were found to be significantly associated (p value < 5×10^{-8}) with the T2D phenotype [51]. However, this signal was completely abolished when adjusted for BMI in the replication samples, suggesting that the single nucleotide polymorphisms in the *FTO* gene were risk alleles for obesity rather than T2D [47]. This association has since been extensively replicated [44,48–50,54,55]. To date, the *FTO* locus explains the largest proportion of inter-individual variation in BMI [44], such that people carrying two copies of the *FTO* risk allele are, on average, 3 kg heavier than those with no copies [47].

The initial success of GWA studies in detecting the first obesity-susceptibility locus, provided the impetus that we needed to re-evaluate study designs and increase the power to detect more of the small-effect alleles affecting common, overall obesity. This lead to the second stage of GWA discovery, which saw data from various cohorts being combined, in a process known as meta-analysis, in order to achieve increased study power. A meta-analysis of 16,876 samples was carried out to search for genetic variants associated with BMI [50]. Despite the vast increase in sample size, only one novel locus, situated 188 kb downstream of the *MC4R* gene (near-*MC4R*), was identified as being significantly associated with BMI [50] and it was evident that even larger sample sizes would be needed to identify further susceptibility loci.

So followed the third stage of GWA studies, where a collaborative meta-analysis of 32,387 individuals identified six novel loci associated with obesity **(Table 1)**, as well as confirming the already known obesity-associated loci *FTO* and near-*MC4R* [48]. These six loci include near neuronal growth regulator (*NEGR*)*1*, near transmembrane protein (*TMEM*)*18*, in SH2B adaptor protein (*SH2B*)*1*, near potassium channel tetramerization domain containing 15 (*KCTD15*), near glucosamine-6-phosphate deaminase *(GNPDA)2*, and in mitochondrial carrier homolog *(MTCH)2*. At the same time, Thorleifsson *et al.* identified eight loci significantly associated with BMI and replicated the signals previously seen in the *FTO* and near-*MC4R* loci, based on a sample of 34,416 individuals [49]. Of the eight additional loci, four (near-*NEGR1,* near-*TMEM18, SH2B1* and near-*KCTD15*) had also been identified by the previous study [48], whereas four loci were new. These were *SEC16B*, between *ETV5* and *DGKG*, *BDNF*, and between *BCDIN3D* and *FAIM2* **(Table 1)**.

Despite the success of these large studies, the ten aforementioned obesity susceptibility loci explain only a small proportion of the variation in BMI [44] and power calculations indicated that even larger samples may be needed to detect the additional small effect alleles contributing to the risk of common, overall obesity [48]. Therefore, the fourth stage of discovery followed, and the largest study to date (249,769 individuals) was designed to search for further associations with BMI [44]. Owing to the dramatic increase in power of this study, a total of 32 BMI-associated loci were confirmed **(Table 1)**. Thus, the number of loci robustly associated with common, overall obesity was increased from ten to 32 and genes in some of the newly identified loci are hoped to provide important information regarding body weight regulations [44].

Despite the success of GWAS, only 1.45% of the total variation for BMI is currently accounted for [44] and extensive efforts will be needed to further explain genetic predisposition to overall obesity. These genetic discoveries are only the first step in understanding the underlying disease mechanisms involved in obesity, since known susceptibility variants may map to a number of different genes that could potentially contribute towards obesity [10]. Despite this possible ambiguity, the discovery of obesity risk loci has successfully highlighted some of the biological pathways involved in obesity risk. To date, a large proportion of common obesity loci implicated by GWA studies are highly expressed in the brain and, therefore, thought to emphasize the importance of energy regulation in overall adiposity [36,48–50,52]. However, these genes offer little insight into the individual patterns of body fat distribution and studies were therefore designed to pinpoint loci specifically involved in the control of fat distribution and related metabolic disease risk [53].

Genetics of body fat distribution

Increasing evidence suggests that genetic variation significantly influences patterns of body fat distribution [56]. The deposition of central adiposity has a significant genetic component and after correcting for BMI, which is closely correlated, heritability estimates of WC and WHR remain at 0.6 and 0.45, respectively [57]. Furthermore, extreme forms of body fat distribution seen in patients with lipodystrophy, confirm that genetic mutations can result in the loss of subcutaneous adipose tissue and increased intra-abdominal fat [58]. Finally, sex-specific genetic effects have been shown to control the sexual dimorphism observed in body composition traits, such as fat percentage, lean mass and fat distribution [59]. The clear genetic contribution towards individual variation in fat distribution, together with the known adverse effects of visceral (central) adiposity on metabolic diseases such as T2D, have lead to the analysis of traits specifically associated with measures of body fat distribution (WC and WHR). The genes identified in these studies followed similar stages of discovery to those found to be associated with common, overall obesity.

In 2008, a GWA study identified a polymorphism near the *MC4R* locus that was significantly associated with WC, and found that individuals homozygous for this risk allele, have approximately 2 cm increased WC [52]. This discovery provided further evidence of the genetic control of body fat distribution, independent of overall adiposity, and lead to the formation of collaborative studies aimed at detecting additional loci involved in fat distribution.

A large meta-analysis was carried out for adult WC and WHR and discovered two novel loci significantly associated with WC **(Table 2)**; namely transcription factor AP-2β (*TFAP2B*) and methionine sulfoxide reductase A (*MSRA*). While overall obesity-susceptibility genes are

Table 1. Four stages of discovery for the genes associated with overall obesity (BMI).

Stage	Date	SNP	Chr	Effect allele	Nearest gene	Study size	Major ethnic group	Ref.
Stage 1	2007	rs9939609	16	a	*FTO*	4862	British	[47]
Stage 2	2008	rs1121980	16	a	*FTO*	16,876	European	[50]
		rs17782313	18	c	Near-*MC4R*			
Stage 3	2009	rs9939609	16	a	*FTO*	32,387	European	[48]
		rs17782313	18	c	Near-*MC4R*			
		rs2815752	1	a	*NEGR1*			
		rs6548238	2	c	*TMEM18*			
		rs7498665	16	g	*SH2B1*			
		rs11084753	19	g	*KCTD15*			
		rs10938397	4	g	*GNPDA2*			
		rs10838738	11	g	*MTCH2*			
Stage 3	2009	rs1558902	16	a	*FTO*	34,416	Icelandic	[49]
		rs571312	18	c	Near-*MC4R*			
		rs2568958	1	a	*NEGR1*			
		rs7561317	2	g	*TMEM18*			
		rs7498665	16	g	*SH2B1*			
		rs29941	19	c	*KCTD15*			
		rs10913469	1	c	*SEC16B*			
		rs4923461	11	a	*BDNF*			
		rs7647305	3	c	*ETV5-DGKG*			
		rs7138803	12	a	*BCDIN3D-FAIM2*			
Stage 4	2010	rs543874	1	g	*SEC16B*	249,769	European	[44]
		rs987237	6	g	*TFAP2B*			
		rs7138803	12	a	*FAIM2*			
		rs10150332	14	c	*NRXN3*			
		rs713586	2	c	*RBJ*			
		rs12444979	16	c	*GPRC5B*			
		rs2241423	15	g	*MAP2K5*			
		rs2287019	19	c	*QPCTL*			
		rs1514175	1	a	*TNNI3K*			
		rs13107325	4	t	*SLC39A8*			
		rs2112347	5	t	*FLJ35779*			
		rs10968576	9	g	*LRRN6C*			
		rs3810291	19	a	*TMEM160*			
		rs887912	2	t	*FANCL*			
		rs13078807	3	g	*CADM2*			
		rs11847697	14	t	*PRKD1*			
		rs2890652	2	c	*LRP1B*			
		rs1555543	1	c	*PTBP2*			
		rs4771122	13	g	*MTIF3*			
		rs4836133	5	a	*ZNF608*			
		rs4929949	11	c	*RPL27A*			
		rs206936	6	g	*NUDT3*			

Chr: Chromosome; SNP: Single nucleotide polymorphism.

known to affect the hypothalamus, *TFAP2B* is thought to act directly on adipocyte response to a positive energy balance [53]. Another locus, lysophospholipase-like (*LYPLAL*)1, was found to be associated with WHR in women only and provides evidence of the sexual dimorphism of fat distribution – adding to evidence of the intrinsic genetic contribution [53].

In a subsequent, even larger study, 31,373 individuals were analysed for associations with WC [60]. Apart from confirming associations with *FTO* and *MC4R*, the study also identified a new locus, *NRXN3*, previously implicated in the control of addiction and reward behavior, and found it to be significantly associated with WC (Table 2). However, after adjustment for BMI,

Table 2. Loci associated with measures of body fat distribution (waist:hip ratio, adjusted for BMI).

Date	SNP	Chr	Effect allele	Nearest gene	Phenotype	Major ethnic group	Ref.
2008	rs12970134	18	a	*MC4R*	WC†	South Asian‡	[52]
2009	rs987237	6	g	*TFAP2B*	WC†	European	[53]
	rs7826222	8	g	*MSRA*	WC†		
	rs4846567	1	g	*LYPLA1*	WHR		
2009	rs10146997	14	a	*NRXN3*	WC†	European	[60]
2010	rs4846567	1	g	*LYPLA1*	WHR	European	[45]
	rs9491696	6	g	*RSPOS*	WHR		
	rs6905288	6	a	*VEGFA*	WHR		
	rs984222	1	g	*TBX15-WARS2*	WHR		
	rs1055144	7	t	*NFE2L3*	WHR		
	rs10195252	2	t	*GRB14*§	WHR		
	rs1011731	1	g	*DNM3-PIGC*	WHR		
	rs718314	12	g	*ITPR2-SSPN*	WHR		
	rs1294421	6	g	*LY86*	WHR		
	rs1443512	12	a	*HOXC13*	WHR		
	rs6795735	3	c	*ADAMTS9*¶	WHR		
	rs4823006	22	a	*ZNRF3-KREMEN1*	WHR		
	rs6784615	3	t	*NISCH-STAB1*	WHR		
	rs6861681	5	a	*CPEB4*	WHR		

†Likely to be mediated through BMI.
‡Overweight and obesity, as defined in this study, are based on the European criteria of BMI >25 kg/m^2 and BMI >30 kg/m^2, respectively.
§Associated with insulin levels.
¶Type 2 diabetes susceptibility locus.
Chr: Chromosome; SNP: Single nucleotide polymorphism; WC: Waist circumference; WHR: Waist:hip ratio.
Data taken from [4].

the signal for WC was rendered insignificant, implying the involvement of this locus in overall adiposity, rather than central fat deposition [60]. This reflects the much higher correlation between WC and BMI (r^2 = ~0.9) compared with WHR and BMI (r^2 = ~0.6) [53] and lead to the focus on WHR, adjusted for age, gender and BMI, which appears as a measure for fat distribution, independent of overall adiposity [45].

Thus, in another wave of discovery, measures of body fat distribution were examined in data from 77,167 participants [45]. After adjusting for BMI, they found 13 new loci in or near genes not previously associated with WHR or other measures of adiposity **(Table 2)**. The WHR-associated *LYPLAL1* locus was replicated in this study and together, these 14 loci explain 1.03% of the variance in WHR (after adjustment for BMI, age and sex). The independent genetic processes that influence body fat distribution and the risk of obesity were further highlighted by the sexual dimorphism seen in the variants associated with WHR in a sex-specific meta-analysis. Heid *et al.* showed that the WHR-increasing allele at all 14 body fat distribution loci in women are associated with increased WC, while only six of these loci are associated with increased WC in men [45]. Furthermore, sex-specific effects are evident from the vastly different effect sizes at seven of the 14 WHR-associated loci. The heterogeneity observed across these loci between men and women is a reflection of the differential sex effects that influence specific patterns of fat distribution.

In the same study, the 14 WHR-associated loci were further evaluated for their relationship with other metabolic traits. These results show a directionally consistent enrichment of associations of WHR loci to increased triglycerides, cholesterol, fasting insulin and IR and emphasize the extensive genetic overlap underpinning various metabolic traits. Additionally, three WHR-associated loci, mapping to *ADAMTS9*, *NISCH-STAB1* and *ITPR2-SSPN*, were associated with T2D with nominal significance and 11 of the 14 loci showed directionally consistent T2D associations [45].

The overlap of loci associated with both WHR and T2D presents an important possibility for an etiological link between fat distribution, independent of overall obesity and T2D risk. Since higher WHR is associated with a higher risk of diabetes [61,62] and a larger hip circumference is

associated with a lower risk of diabetes [21], the importance of the genes controlling fat distribution, rather than general obesity, in the etiology of T2D is intriguing.

The role of obesity in T2D

Epidemiological studies have shown that one of the major health consequences associated with obesity, is the development of T2D [63,64] and obesity has been shown to significantly increase the rates of mortality from diabetes [65]. This is further supported by the fact that changes in lifestyle resulting in weight loss, have been shown to notably reduce the incidence of diabetes [66]. However, our understanding of the physiological systems underlying obesity and T2D, and the ongoing detection of genes implicated in both diseases suggest that the link between them is complex and may also be driven by specific patterns of fat deposition, rather than overall obesity alone.

The major physiological basis for the link between obesity and the onset of T2D is the ability of obesity to give rise to IR [7,67,68]. Obesity has been shown to cause an increase in the amount of triglycerides stored outside of adipose tissue, at sites such as skeletal muscle, heart, kidneys and liver [69]. As a consequence of this, the level of circulating free fatty acids is increased and IR may occur in these tissues as a result of the elevated exposure to lipid levels. Initially excess insulin is produced to compensate for the body's resistance to it, but eventually this compensation is no longer adequate and diabetes can result [63].

Indeed, several genetic studies also support the epidemiological and physiological link between overall obesity and T2D [45,47]. Five of the loci that have been found to be significantly associated with common, overall obesity, have also been shown to increase the risk of T2D and appear, like *FTO*, to be mediated through BMI [70]. Distinct patterns of body fat distribution, independent of overall adiposity, also have a marked effect on IR and T2D risk [71]. An extreme example of this can be seen in patients with lipodystrophy, where it is the specific distribution of fat around the liver and pancreas that leads to IR in liver and muscle, rather than overall accumulation of fat [42]. Adding to this, studies have shown that increased abdominal adiposity and IR are characteristic features of first-degree relatives of patients with T2D [72,73], suggesting an overlap in the genes that control fat distribution and those that influence the development of T2D.

This is further supported by genetic studies that have identified WHR-associated loci that control both T2D and IR [45]. WHR-increasing variants at the *GRB14* locus were shown to be significantly associated with IR [45]; a result supported by animal models that suggest that *GRB14* is a tissue-specific modulator of insulin action [74]. Furthermore, the signal near *ADAMTS9* associated with WHR, overlaps a known T2D-suceptibility locus [75]. The effect of *ADAMTS9* on T2D risk may, to an extent, be mediated through decreased insulin sensitivity in peripheral tissues [76] and thus emphasizes the primary effect of this locus on fat distribution.

Despite the inextricable link between these diseases, T2D is not an inevitable consequence of obesity. Certainly, the accumulation of abnormal amounts of intra-abdominal fat is specifically associated with T2D [16,17], but this accumulation of central adiposity is not merely a consequence of being overweight and/or obesity. In fact, significantly larger amounts of abdominal fat has been observed in individuals with IR, independent of total fat mass [12]. Furthermore, individuals who are predisposed to gluteal fat accumulation exhibit a decreased T2D risk [22]. Therefore, genetic risk factors involved specifically in fat distribution may have important consequences for both obesity and T2D.

Conclusion

The underlying biological mechanisms of both obesity and T2D remain unclear. Overlapping genetic variation associated with BMI and T2D is proof of the genetic link between the two diseases, but many obesity-susceptibility variants remain independent of T2D risk. Indeed, there are also genes that predispose individuals to T2D that are independent of obesity and not all obese patients develop T2D, making the development of T2D in obese individuals unpredictable. Body fat distribution has shown to play a more important role in T2D risk than general obesity, and many of the genetic factors influencing these patterns of distribution, are independent of overall adiposity. Additionally, because only a small fraction of the heritability of BMI and body fat distribution is accounted for hereto, and since environmental factors are known to have a significant effect on both obesity and T2D risk, the impact of the genetic link between these two traits remains to be evaluated.

Future perspective

Although large meta-analyses have had some success in unraveling the genetic susceptibility of common obesity and body fat distribution, there is still a long way to go to fully understanding the mechanisms that contribute to these phenotypes. Importantly, an improved understanding of the entire allele spectrum underlying both overall obesity and fat distribution could potentially shed light on their contribution to T2D risk.

Despite the success of GWA studies in the identification of common disease alleles, a large portion of common disease heritability remains unaccounted for. So far only 1.45 and 1.03% of the variance in BMI and WHR, respectively, has been explained. One reason for this could be that the statistically significant signals identified in GWA studies, may be located at some distance from the genes involved in obesity. Thus, candidate genes, currently hypothesized to play a role in the obesity etiology, may not be the actual causative genes. It has also been suggested that a large portion of the unexplained variance of these traits, could be driven by both rare and structural variants, as well as complex gene–gene and gene–environment interactions, that cannot be detected in current GWA studies. Clearly, the identification of obesity-associated loci is merely the first step towards understanding the disease and improved genotyping technology, and intense sequencing and fine-mapping studies are likely to be required in order to elucidate the actual causal variants at these loci.

Finally, therapeutic targets aimed at ameliorating the effects of common obesity have had little impact so far, but perhaps, shifting the attention to drug-development based on the genes that influence patterns of fat distribution in particular, will prove to be more suitable in the fight against obesity and obesity-related metabolic disorders.

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