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REVIEW

From monogenic to polygenic obesity: recent advances

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Abstract The heritability of obesity and body weight in general is high. A small number of confirmed monogenic forms of obesity—the respective mutations are sufficient by themselves to cause the condition in food abundant societies—have been identified by molecular genetic studies. The elucidation of these genes, mostly based on animal and family studies, has led to the identification of important pathways to the disorder and thus to a deeper understanding of the regulation of body weight. The identification of inborn deficiency of the mostly adipocyte-derived satiety hormone leptin in extremely obese children from consanguineous families paved the way to the first pharmacological therapy for obesity based on a molecular genetic finding. The genetic predisposition to obesity for most individuals, however, has a polygenic basis. A polygenic variant by itself has a small effect on the phenotype; only in combination with other predisposing variants does a sizeable phenotypic effect arise. Common variants in the first intron of the 'fat mass and obesity associated' gene (*FTO*) result in an elevated body mass index (BMI) equivalent to approximately $+0.4$ kg/m^2 per risk allele. The *FTO* variants were originally detected in a genome wide association study (GWAS) pertaining to type 2 diabetes mellitus. Large meta-analyses of GWAS have subsequently identified additional polygenic variants. Up to December 2009, polygenic variants have been confirmed in a total of 17 independent genomic regions. Further study of genetic effects on human body weight regulation should detect variants that will explain a larger proportion of the heritability. The development of new strategies for diagnosis, treatment and prevention of obesity can be anticipated.

Keywords Heritability · Genome wide

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Introduction

Obesity is a complex disorder that is caused by several genetic and non-genetic risk factors [1]. The causes of obesity have been perceived differently over the past 100 years; both biological and psychological explanations have emerged. In the early part of the twentieth century, pituitary/hypothalamic dysfunction was assumed to lead to obesity [2]. From the 1940s through to the 1970s it was thought that psychological and psychodynamic aspects played the most prominent role [3, 4]. Prader, Labhart and Willi described the first syndromal form of obesity in 1956 [5]. From the 1970s on, pertinence of (psycho)social factors has been discussed [6–9]. Milestone twin and adoption studies at the end of the 1980s and during the early 1990s provided evidence that genetic factors play a considerable role in body weight regulation [10–12]. Cloning of the leptin gene in 1994 [13] led to a rapid expansion of biomedical research. Large scale molecular genetic studies ensued [summarized in: 14]. The successful treatment of children with leptin deficiency [15] with recombinant leptin [16–18] showed for the first time that mutations in a single gene could lead to hyperphagia and obesity. More recently support has increased for the hypothesis that

obesity is a neuroendocrine disorder in which environmental risk factors and a genetic predisposition act in concert [5, 19, 20]. Recent large scale molecular genetic studies have substantiated that the genetic predisposition is in many cases due to the combined net effect of polygenic variants.

Environmental changes affecting both energy intake and expenditure are assumed to underlie the recent obesity epidemic as the gene pool of a population is unlikely to have changed substantially within the past generation [21]. This is in accordance with the 'thrifty genotype hypothesis' [22]. This hypothesis implies that gene variants which result in an increased energy deposition as fat have accumulated over time to maintain reproductive function as long as possible and to enhance survival during famines. Undoubtedly, gene–environment interactions will prove to play an important role in the aetiology of obesity. Such interactions could for example be conveyed via changes in DNA methylation patterns [23].

Recent discussions concern the definition of obesity or a subtype(s) of obesity as a psychiatric disorder(s). Resolution of this question depends on whether or not obesity can be viewed as an eating disorder [24]. Undoubtedly, obesity frequently has a behavioural basis; in addition, recent biomedical research has indicated that the brain and in particular the hypothalamus figure prominently in the regulation of appetite, body weight and physical activity. The respective neurotransmitter and neuropeptide pathways overlap with pathways involved in mood regulation and other psychological traits. Within the context of this special issue, a focus on the genetics of obesity is particularly warranted because body weight represents a readily quantifiable phenotype, which is thus amenable to quantitative genetics. This is in contrast to the categorical approach frequently taken for psychiatric disorders; however, due to the fact that many psychiatric disorders can also be viewed dimensionally, the recent success pertaining to the elucidation of polygenic variants involved in weight regulation serves to illustrate this approach. It may be noted that this success rests on the analysis of DNA samples of tens of thousands of individuals [24].

Twin, family and adoption studies

The strongest risk factor for childhood and adolescent obesity is parental obesity [25]. The risk is especially elevated if both parents are obese [26]. Some studies have found a stronger effect of maternal than paternal obesity [27] which may reflect pre- and postnatal environmental factors and sex-dependent genetic mechanisms. Maternal weight gain in pregnancy is positively correlated with the child's BMI into adulthood [28].

Twin, family and adoption studies have led to the conclusion that the strong predictive value of parental BMI mainly stems from genetic rather than environmental factors [29, 30]. Twin studies, in comparison to family and adoption studies, have revealed that between 60 and 90% of the BMI variance within a population can be accounted for by genetic effects. In single comparatively small twin studies where the twins were reared apart, the heritability estimates proved to be similar to those where the twins were raised together [e.g. 12]. For example, maximum-likelihood model-fitting analyses and intrapair correlation coefficients for BMI of identical twins reared apart were approximately 0.7. This value was comparable to those for twins reared together. Non-additive genetic variance made a significant contribution to these estimates of heritability [12]. However, a substantial number of twin pairs reared apart were not separated immediately after birth, so that apart from intrauterine influences, a shared early postnatal environment could account for inflated heritability estimates [29, 31].

Age affects heritability estimates of BMI only to a minor degree. An exception is the newborn period, for which a substantially lower heritability (0.4) was calculated [32]. Intrauterine environment has a strong influence on birth weight. It is widely known that, especially for monozygotic (MZ) twins, other anthropometric measurements, like body height, also correlate less well in infancy than in childhood. A recent, large scale twin study (longitudinal sample of more than 3,500 twin pairs) indicated that the genetic influence on BMI became progressively stronger during childhood. Heritability estimates were shown to increase from 0.48 at age 4 years to 0.78 at age 11 [33]. According to one study [34], the heritability of BMI is highest during late adolescence ($\sim$0.9). However, one needs to be cautious with the interpretation of twin studies as they often underestimate shared environmental effects and tend to overestimate dominant genetic effects.

The pathophysiological and behavioural basis of obesity is complex and applies to ingestion, absorption, metabolism and energy expenditure. Both macronutrient intake [35] and activity levels [36] have been shown to be genetically determined. Restrained eating, drive for thinness and other eating behaviours show heritability estimates in the range of 0.20–0.55 [37]. It appears that even television viewing may have an, albeit small, heritable component [38].

Epigenetic considerations

Apart from variation at the DNA level, epigenetic events are also assumed to contribute to the obesity epidemic [39, 40]. Modern-day living could affect methylation patterns of specific genes which in turn increase the risk

of obesity. Fraga et al. [41] observed that during the early years of life MZ twins are epigenetically indistinguishable from each other. However, with increasing age remarkable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation (with an effect on gene-expression) become apparent. Such changes induced by the environment could have an influence on individual BMI. A recent comparison of epigenetic metastability of 6,000 unique genomic regions between matched MZ and dizygotic (DZ) twins delineated epigenetic differences in both the MZ and DZ twins. As expected these differences were much more pronounced in samples of buccal cells from DZ co-twins. The epigenetic differences between MZ twins were most pronounced in buccal cells, but were also observed in gut and blood cells. Whereas DNA sequence differences could underlie the higher epigenetic discordance in DZ twins, animal studies and in silico SNP analyses favour the hypothesis that it is due to epigenomic differences in the zygotes. Molecular mechanisms of heritability may thus not be limited to DNA sequence differences [42].

In conclusion, family, twin and adoption studies have provided ample evidence for moderate to high heritability of BMI. Whereas, current molecular research is focussing on variation at the DNA level, epigenetic research will likely add a novel dimension towards the explanation of intra-individual variance of body weight.

Monogenic obesity

The elucidation of the mutations underlying diverse rodent mouse models (monogenic and one transgenic) led to the identification of most of the currently known monogenic forms of obesity in humans [43]. Family studies and in particular those on consanguineous pedigrees based on individuals with extreme obesity and in most cases with additional characteristic phenotypic features, like red hair, hyperinsulinism and infertility, proved to be highly successful in detecting mutations in the homologous human genes [43, 44]. This work proved fundamental in the elucidation of the leptinergic–melanocortinergic system. Put simply, leptin is a mostly adipocyte-derived satiety hormone that is secreted into the blood. It signals the size of the fat depot via the nucleus arcuatus in the hypothalamus. Increased leptin levels are registered by the leptin receptor. The signal is than forwarded to the melanocortin 4 receptor (MC4R) in higher order neurons. The endogenous agonist alpha-melanocyte stimulating hormone (α-MSH; product of the pro-opiomelanocortin gene; *POMC*) induces a satiating effect via the MC4R. The brain derived neurotrophic factor (BDNF) is involved in weight regulation downstream of the MC4R. Mutations in single genes of the leptinergic–melanocortinergic pathway have been shown to have a monogenic effect on the development of obesity.

The modes of inheritance of most of the aforementioned genes are autosomal recessive and autosomal dominant. The term monogenic obesity requires some specification and discussion: a 'monogene' is by common textbook definition, a gene with a strong effect on the phenotype [Mendelian traits or Mendelian (single gene) conditions], giving rise to a (close to) one-to-one relationship between genotype and phenotype. A 'major gene' is defined as a gene harbouring, a variant which is associated with a high lifetime risk for a disease; modifier genes and environmental factors additionally play a role in the aetiology of the respective diseases [45–47].

The distinction between monogenic obesity and obesity due to a major gene effect may appear semantic. However, because BMI is a quantitative trait with obesity representing the right tail of the distribution, attempts to address this distinction are warranted.

Consider mutations in the *MC4R*, which have been reported to result in monogenic obesity [e.g. 48, 49]. In *Mc4r* knock-out mice the heterozygous animals have a body weight in between the wild-type and homozygous knockout mice [50]; body weight distributions of mice with heterozygous and wild-type genotypes overlap substantially, particularly in male rodents. The obese phenotype in the knock-out mice led to mutation screens of the human *MC4R*. The initial detections of human mutation carriers were all based on small pedigrees [51–53]. Subsequent studies revealed that mutation carriers are not necessarily obese [e.g. 54, 55]. An epidemiological study based on approximately 4,000 individuals assessed within the framework of a population-based study revealed that none of the 6 individuals with functionally relevant *MC4R* mutations were obese [56]. Finally, in an attempt to adjust for familial background genetic and environmental factors Dempfle et al. [57] analysed current BMI of mutation and wild-type carriers in pedigrees based on index patients with *MC4R* mutations. The differences amounted to 4.5 and 9.5 kg/m^2 in males and females, respectively [57]. Accordingly, instead of using the term monogenic obesity, we consider it more appropriate to think of *MC4R* mutations as resulting in strong effect sizes conveying a high lifetime risk for obesity. The effect sizes of these mutations are lower than those of the leptin or leptin receptor gene mutations [43]. In contrast, the few individuals who were found to be homozygous or compound heterozygous for functionally relevant *MC4R* mutations were all extremely obese [55, 58].

Over the past 10–15 years mutations in several genes such as those coding for leptin (*LEP* [15, 59]), leptin receptor (*LEPR* [60]), prohormone convertase 1 (*PC1*

[61, 62]) and pro-opiomelanocortin (*POMC* [63, 64]) have been shown to lead to autosomal recessive forms of obesity [14]. These mutations are all rare and lead, apart from extreme obesity with an early onset, to additional phenotypical manifestations, including red hair (*POMC*), reduced or impaired fertility (*PC1*, leptin and *LEPR*), adrenal insufficiency (*POMC*), and impaired immunity (*LEP*) [16, 43, 65]. The pleiotropic effects warrant the consideration that these recessive disorders are classified as syndromal forms of obesity—similar to the Bardet–Biedl, Prader–Willi and other genetic syndromes associated with obesity [43, 66]. The pleiotropic Bardet–Biedl syndrome, of which obesity is one of the main clinical features, has been shown to have an oligogenic basis [14, 19, 43]. It was expected that the syndromic forms of obesity could help to unravel novel genes relevant for idiopathic obesity. However, although the genes for several of the syndromic forms have been detected, the relevance of these genes for general obesity is still unclear [14].

Both young [16, 17] and adult [67] individuals with inborn leptin deficiency have been treated successfully with recombinant leptin; weight loss (primarily fat mass) was shown to be substantial. Farooqi et al. [16, 18, 68, 69] described the rapidly altered eating behaviour upon initiation of treatment with recombinant leptin; food ingestion ceased to be the major focus of daily (and nightly) activity of the thus treated children [16, 18, 68, 69]. This is the first and until now only genetic form of human obesity that is amenable to successful pharmacological treatment.

The *MC4R* has been shown to comprise mutations entailing a substantially elevated body weight (see above) and two polymorphisms, which both have a small protective effect for the development of obesity (see below; e.g. [70, 71]. Currently, over 130 functionally relevant mutations have been detected in the human *MC4R* gene [72]. About 2–6% of extremely obese children and adolescents harbour such mutations. Among obese adults the prevalence is seemingly lower (1–2%). Approximately 0.5% of the normal weight population also harbour such mutations [56]. In vitro analyses have shown that most of these mutations lead to either total or partial loss of function [73, 74]. Thus, the endogenous agonist alpha-melanocyte stimulating hormone (α-MSH) is not able to induce its satiating effect to a full extent. Children with *MC4R* mutations have been shown to eat larger meals [58]. A negative effect of the mutations on energy expenditure also appears likely [75].

Phenotypical effects of *MC4R* mutations other than obesity have been shown to encompass hyperinsulinemia, elevated growth rate and higher bone density [58]. An initial report that *MC4R* mutations induce binge eating was not confirmed in subsequent investigations [19, 76–79].

Statistical approaches

To detect new obesity gene variants, different approaches have been employed [80]:

(1) Association studies

Several candidate genes have been analysed because of a priori biological, physiological or pharmacological evidence of their involvement in central or peripheral pathways controlling energy intake or expenditure [14]. A large number of conventional association studies involving obese cases and normal weight and/or lean controls, or less frequently studies of families have been performed [14]; meta-analyses have been reported for only a small number of such identified genetic variants. Unfortunately, classical candidate gene studies have proven largely unsuccessful in reliably detecting novel genetic variants relevant for obesity. Identification of a candidate gene can also rely on its location within a linkage region or a region identified via genome wide association studies (GWAS). In GWAS up to 2,000,000 genetic variants can currently be analysed for association with a given phenotype. This approach has been extremely successful for various phenotypes [81]. As the effect sizes are usually small, large groups need to be screened. Because in the pre-GWAS era sample sizes rarely exceeded 1,000 cases and 1,000 controls and in light of the small effect sizes of polygenic variants detected recently in GWAS, it must be concluded that most classical candidate gene studies were underpowered. It remains to be seen to what extent such genetic variants (and subsequently candidate genes) will be picked up in future large scale GWAS meta-analyses.

(2) Genome wide approaches

(a) Genome wide linkage studies aim to identify chromosomal regions harbouring one or more genes relevant for a respective phenotype by making use of linkage data. Those regions underlying linkage peaks are narrowed down by fine mapping, so that candidate gene analyses can be pursued. Although more than 40 microsatellite-based genome wide linkage scans have been performed and single candidate genes have been detected, none of the results have been validated unequivocally [82]. This supports the contention that the effect sizes of genes influencing adiposity are small and/or that substantial heterogeneity exists [83].

(b) GWAS provide a better design to identify common variants with low to moderate penetrance which are relevant as risk factors for the trait of interest. Within a short time span, GWAS have proven to be very successful for the detection of polygenic variants. The production of high density SNP-chips has made GWAS feasible, which only recently have led to the identification of a number of

confirmed genes for different complex disorders, thereby revolutionizing the molecular genetic analyses of complex disorders [81]. Stringent efforts to confirm (or reject) an original finding are absolutely crucial; due to the low effect sizes and possible gene–environment interactions it is to be expected that not every study will be able to confirm a true positive finding; meta-analyses are required. GWAS performed for obesity or body mass index (see Table 1) have already documented that this approach is extremely powerful to detect genetic variants relevant for the analysed phenotype(s). Currently known polygenic variants have a mean effect on BMI of approximately 0.03–0.5 kg/m^2; it appears reasonable that these effect sizes represent the upper limit of such common variants [84–86]. Independent gene variants with small but replicable effects on body weight have been identified unambiguously in 17 gene regions so far [86].

Polygenic obesity

Some traits can be due to the simultaneous presence of DNA variation in multiple genes. Any of a group of alleles at distinct gene loci that collectively control the inheritance of a quantitative phenotype or modify the expression of a qualitative character are termed 'polygenic' variants. It is generally assumed that for quantitative traits, each allele has a small effect and the allelic effects can be additive or non-additive. Potentially, many such polygenic variants play a role in body weight regulation. It is estimated that the total number of genes with a small effect most likely exceeds 100. The lower limit of effect sizes will most likely be well below 100 g. If an individual harbours many polygenic variants that increase body weight, obesity can ensue. Any single variant will have a higher frequency in obese than in normal weight and lean individuals [83]. A polygenic basis of obesity implies that the specific set of polygenic variants relevant for obesity in one individual is unlikely to be the same in another obese subject.

Melanocortin-4 receptor gene (MC4R)

The coding region of the *MC4R* harbours, in addition to the 'obesity mutations' mentioned above, two polygenic variants for weight regulation: the minor alleles of the polymorphisms coding for isoleucine instead of valine at amino acid position 103 (103I) and for leucine instead of isoleucine at position 251 (251L) of the receptor protein are negatively associated with obesity [70, 71, 87–89], the mean BMI of such carriers is slightly reduced in comparison to homozygous carriers of the major allele. Heterozygosity for the I103 variant was found in 2–9% of subjects from different populations [70]. A family-based association test (TDT) in 520 trios ascertained via a young obese offspring originally revealed under-transmission of the allele coding for the I103 variant. A first meta-analysis comprising 7,713 cases and controls substantiated the evidence for a negative association of the I103 variant with obesity (odds ratio: 0.69). An effect estimate of −0.48 kg/m^2 was calculated for I103 carriers [70]. This negative association of I103 with obesity was subsequently confirmed in a single large epidemiological study group comprising 7,937 individuals [87] and two further meta-analyses encompassing a total of 55,195 individuals [88, 89]. The MC4 receptor variant harbouring I103 revealed a modest (twofold) decrease in antagonist hAGRP(87–132) potency [90], which is consistent with the obesity protective effect conferred by this variant.

The influence of the second non-synonymous coding polymorphism (I251L; rs52820871) on body weight was detected in 16,797 individuals of European origin from nine independent case–control, population-based studies and family cohorts. A consistent negative association of the L251 variant (minor allele frequency in cases and controls ranged from 0.41 to 1.21%) with both childhood and adult extreme obesity (odds ratio ranging from 0.25 to 0.76) was detected in eight of the nine studies; the variant was also associated with reduced BMI in population-based samples. A meta-analysis supported the evidence of the obesity protective effect of MC4R L251 (OR = 0.52) [71].

Most recently, SNP rs17782313 188 kb downstream of *MC4R* was detected via a large scaled GWAS [85], thus further substantiating the important contribution of genetic variation at the *MC4R* locus to inter-individual differences in BMI. For the first step, GWAS data from seven studies including 16,876 European individuals had been analyzed jointly. The second strongest association signal ($p = 2.9 \times 10^{-6}$, after *FTO*, see below) was at rs17782313. Due to its position downstream of the *MC4R* its influence on weight regulation is likely to be mediated through effects on *MC4R* expression. The finding was confirmed in 60,352 adults and 5,988 children and 660 German nuclear families encompassing one or more obese offspring and both parents. Each copy of the rs17782313 C-allele was associated with a mean difference in BMI of approximately +0.22 kg/m^2 (+760 g). One copy of the C-allele resulted in an 8 and 12% increased odds ratio for overweight and obesity, respectively; no significant gender differences were detected. The effect on weight was disproportionately due to fat mass.

The effect of the C-allele was not detectable in children at birth and up to 42 months of age in the *Avon Longitudinal Study of Children and Parents* (almost 6,000 children) [85]. However, the effect size of one C-allele in children aged 7–11 was twice the amount observed in adults. Interestingly, in adults—but not in children—one copy of the C-allele also resulted in a higher mean height (0.21 cm) implying that this SNP [or the functionally

Table 1 Genetic variants with a polygenic effect on body weight in humans

SNP	Chr	Position	Nearest gene	Sample size in the original publication[a]	Frequency of the risk allele (risk allele)	Effect on BMI in the original publication	References
rs2815752	1	72,524,461	*NEGR1*	32,387	62% (A)	+0.10 kg/m^2 per A allele[b]	[92]
rs2568958	1	72,537,704	*NEGR1*	25,344	58% (A)	+0.43 kg/m^2 for AA genotype[c]	[84]
rs10913469	1	176,180,142	*SEC16B, RASAL2*	25,344	20% (C)	+0.50 kg/m^2 for CC genotype[c]	[84]
rs6548238	2	624,905	*TMEM18*	32,387	84% (C)	+0.26 kg/m^2 per C allele[b]	[92]
rs7561317	2	634,953	*TMEM18*	25,344	84% (G)	+0.70 kg/m^2 for GG genotype[c]	[84]
rs7566605	2	118,552,495	*INSIG2*	9,881	37% (C)	+1.00 kg/m^2 for CC genotype	[121]
rs7647305	3	187,316,984	*SFRS10, ETV5, DGKG*	25,344	77% (C)	+0.54 kg/m^2 for CC genotype[c]	[84]
rs10938397	4	45,023,455	*GNPDA2*	32,387	48% (G)	+0.19 kg/m^2 per G allele[b]	[92]
rs4712652	6	22,186,593	*PRL*	2,796	41% (A)	+0.031 kg/m^2 per A allele in children[d]	[126]
rs10508503	10	16,339,956	*PTER*	2,796	8.5% (C)	+0.144 kg/m^2 per C allele in children[d]	[126]
rs6265 (V66M)	11	27,636,492	*BDNF*	25,344	85% (G)	+0.67 kg/m^2 for GG genotype[c]	[84]
rs10838738	11	47,619,625	*MTCH2*	32,387	34% (G)	+0.07 kg/m^2 per G allele[b]	[92]
rs7138803	12	48,533,735	*BCDIN3D, FAIM2*	25,344	37% (A)	+0.54 kg/m^2 for AA genotype[c]	[84]
rs7498665	16	28,790,742	*SH2B1*	32,387	41% (G)	+0.15 kg/m^2 per G allele[b]	[92]
rs7498665	16	28,790,742	*SH2B1, ATP2A1*	25,344	44% (G)	+0.45 kg/m^2 for GG genotype[c]	[84]
rs8050136	16	52,373,776	*FTO*	25,344	41% (A)	+1.07 kg/m^2 for AA genotype[c]	[84]
rs9939609	16	52,378,028	*FTO*	38,759	40% (A)	+0.40 kg/m^2 per A allele	[95]
rs9939609	16	52,378,028	*FTO*	32,387	41% (A)	+0.33 kg/m^2 per A allele[b]	[92]
rs1421085	16	52,358,455	*FTO*	2,796	40% (C)	+0.112 kg/m^2 per C allele[d]	[126]
rs1424233	16	78,240,251	*MAF*	2,796	43% (A)	+0.091 kg/m^2 per A allele in children[d]	[126]
rs1805081	18	19,394,429	*NPC1*	2,796	44% (A)	−0.087 kg/m^2 per A allele in children[d]	[126]
rs17782313	18	56,002,077	*MC4R*	16,876	24% (C)	+0.22 kg/m^2 per C allele	[85]
rs17782313	18	56,002,077	*MC4R*	32,387	22% (C)	+0.22 kg/m^2 per C allele[b]	[92]
rs17782313	18	56,002,077	*MC4R*	2,796	17,5% (C)	+0.097 kg/m^2 per C allele[d]	[126]
rs12970134	18	56,035,730	*MC4R*	25,344	30% (A)	+0.36 kg/m^2 for AA genotype[c]	[82]
rs52820871 (I251L)	18	56,189,806	*MC4R*	16,797	0.75% (251L)	−0.35 SD of their BMI *Z*-score per 251L allele	[71]
rs2229616 (V103I)	18	56,190,256	*MC4R*	7,713	2% (103I)	−0.48 kg/m^2 per 103I allele	[70]
rs29941	19	39,001,372	*CHST8, KCTD15*	25,344	70% (C)	+0.46 kg/m^2 for CC genotype[c]	[84]
rs11084753	19	39,013,977	*KCTD15*	32,387	67% (G)	+0.06 kg/m^2 per G allele[b]	[92]

[a] Either in the GWAS or the initial sample

[b] Reported in the population-based cohorts EPIC, FINRISK97, BPPP and METSIM (N = 18,812; [92])

[c] Reported for the Islandic sample (N = 25,344; [84])

[d] reported for children from the Northern Finland Birth Cohort (N = 5,291; [126]), adapted from [86]

NEGR1: neuronal growth factor regulator 1; SEC16B; cerevisiae, homolog of, B; RASAL2: RAS protein activator like 2; TMEM18: transmembrane protein 18, INSIG2: insulin induced gene 2, SFRS10: splicing factor, arginine/serine-rich, 10; ETV5: ets variant 5; DGKG diacylglycerol kinase, gamma, 90kD, GNPDA2: glucosamine-6-phosphate deaminase 2; PRL: prolactin; PTER: phosphotriesterase related; BDNF: brain derived neurotrophic factor; MTCH2: mitochondrial carrier homolog 2 (C. elegans); BCDIN3D: BCDIN3 domain containing; FAIM2: Fas apoptotic inhibitory molecule 2; SH2B1: SH2B adaptor protein 1; ATP2A1: ATPase, Ca++ transporting, cardiac muscle, fast twitch 1; FTO: fat mass and obesity associated; MAF: v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian); NPC1: Niemann-Pick disease, type C1; MC4R: melanocortin 4 receptor; CHST8: carbohydrate (*N*-acetylgalactosamine 4-0) sulfotransferase 8; KCTD15: potassium channel tetramerisation domain containing 15

relevant SNP(s) in linkage disequilibrium] also affects overall adult size. This finding has been replicated [91–94].

Fat mass and obesity associated gene (*FTO*)

FTO was among the genes highlighted in GWAS for type 2 diabetes mellitus (T2DM) [95, 96]. By adjustment for BMI it was [95] found that the association to T2DM was actually due to the higher BMI of diabetic cases in comparison to non-diabetic controls. Confirmation of this effect on body weight was obtained in 13 cohorts with a total of 38,759 individuals within a meta-analysis showing that the A-allele of the variant rs9939609 (intron 1) was associated with a 31% increased risk to develop obesity. Among the adults 16% were homozygous for this risk-allele. When compared with individuals harbouring no copy of the risk-allele, they had a 1.67-fold increased odds ratio for obesity; mean body weights of these two groups differed by approximately 3 kg.

The association of SNPs in intron 1 of *FTO* has been confirmed in all sufficiently sized subsequent replication studies [e.g. 97–99]. The first GWAS specifically designed with a primary focus on obesity was performed in 487 extremely obese German children and adolescents and 442 lean controls [99]. Six SNPs in *FTO* showed the strongest evidence for association with obesity, one of which remained significant after correcting for multiple testing. The odds ratios for obesity for heterozygosity and homozygosity for the risk allele were 1.67 and 2.76, respectively. A longitudinal study of children aged 7 months ($n = 640$) at baseline to 15 years, showed that the *FTO* effect became evident from age 7 years on. In this study, *FTO* variants were not associated with energy intake or physical activity [100]. However, association was found between *FTO* risk variants and increased energy intake in adults [101–103] and decreased satiety [103], but not for energy expenditure [101, 102] or physical activity [100, 104].

Among 190 children and adolescents, those with at least one *FTO* risk allele reported episodes of loss of control over eating more frequently than individuals homozygous for the non-risk allele. Additionally, those children with risk alleles selected foods with a higher fat content at a buffet meal [105]. A large scale study ($n = 4{,}839$ population-based adults) revealed that low physical activity and high-fat diets might be especially obesity promoting in *FTO* risk allele carriers [106]. *FTO* risk alleles did not predict weight loss in obese children undergoing a 1-year intervention or their baseline fasting levels of blood glucose, triglycerides and cholesterol [107]. However, within the 280 participants the homozygous carriers of risk variants of both *FTO* and *INSIG2* (insulin induced gene 2; see below) showed the lowest degree of overweight reduction [108]. As some of the studies mentioned above were rather small scale ($n < 500$ e.g. [100, 101, 105, 107–109], additional confirmatory studies are warranted.

The strong association of genetic variation within *FTO* to obesity has led to a series of functional studies: *FTO* expression in skeletal muscle and adipose tissue in humans is seemingly not influenced by this variation [110]. An age-dependent decline in *FTO* expression was found to concur with peripheral defects of glucose and fat metabolism [112]. One of the obesity SNPs in intron 1 was associated with a reduced insulin effect on beta activity measured by magneto encephalography, which implicates a lower cerebro cortical response to insulin. This might be a mechanism by which variation in FTO contributes to the pathogenesis of obesity [111]. Wåhlén et al. [112] suggested a role of the FTO in fat cell lipolysis, thus providing a functional link to body weight regulation.

Human FTO is apparently a member of the non-heme dioxygenase (Fe(II)- and 2-oxoglutarate-dependent dioxygenases) superfamily [113, 114]. Amino acid conservation patterns support this hypothesis [114]. FTO belongs to the AlkB-related protein family [Gerken]. Recombinant murine Fto catalyzes demethylation of 3-methylthymine and 3-methyluracil residues in single-stranded DNA and RNA in vitro, although the efficiency is poor. Consistent with a potential role in nucleic acid demethylation, Fto localizes to the nucleus in transfected cells. Initially, it was criticised that 3-methylthymine and 3-methyluracil residues were analysed although they are rather uncommon in humans. Later it was shown, that Fto was also working, although less actively, on the more common forms of methylated DNA base damage (1-methyladenine and 3-metylcytosine) [112, 115]. *Fto* messenger RNA (mRNA) is most abundant (in comparison to all analysed tissues) in mouse brain and in particular in hypothalamic nuclei governing energy balance. In the arcuate nucleus, *Fto* mRNA levels have been found to be regulated by feeding and fasting [113]. *FTO* is ubiquitously expressed in human embryonic and adult tissues [116, 117].

Recently, it was shown that the loss of *Fto* in mice leads to postnatal growth retardation and a significant reduction in adipose tissue and lean body mass [118]. The leanness of *Fto* deficient mice ($Fto^{-}/^{-}$) develops as a consequence of increased energy expenditure and systemic sympathetic activation, despite decreased spontaneous locomotor activity and relative hyperphagia. The heterozygous $Fto^{+}/^{-}$ mice have a reduced *Fto* expression leading to a significantly reduced weight gain after 12 weeks compared to wild-type mice. Thus, the animal model for the first time demonstrated that *Fto* is functionally involved in energy homeostasis by the control of energy expenditure [118]. A dominant point mutation induced by ENU (*N*-ethyl-*N*-nitrosourea) mutagenesis in the murine *Fto* gene also resulted in reduced fat mass and increased energy

expenditure. In this model, locomotor activity was unaltered. High-fat diet led to increased lean mass and reduced fat mass in comparison to controls [119]. Based on these findings it appears that the human FTO risk variants in intron 1 are associated with an increased expression of *FTO*.

FTO is essential for normal development of the central nervous and cardiovascular systems in humans as shown by individuals with loss of function mutations in *FTO*: Boissel et al. [117] ascertained a large Palestinian Arab consanguineous multiplex family in which nine affected individuals presented with a novel polymalformation syndrome including postnatal growth retardation, microcephaly, severe psychomotor delay, functional brain deficits and characteristic facial dysmorphic features. Some patients also presented with structural brain malformations, cardiac defects, genital anomalies and cleft palate. Intercurrent infection or unidentified causes led to early lethality which occurred at 1–30 months of age. By linkage and sequence analyses a causative non-synonymous *FTO* mutation (R316Q) was detected homozygously in affected individuals. The mutation is located in an evolutionarily conserved region of *FTO* and leads to an inactivation of the enzymatic activity. Unfortunately, anthropometric data were not available for the unaffected family members; none of the heterozygous parents were clinically obese. Heterozygous carriers of loss of function mutations in *FTO* might be relatively resistant to become obese [117].

Recently, a large scale mutation screen in the coding region of *FTO* in 1,433 severely obese and 1,433 lean humans revealed novel mutations [120]. Functional in vitro studies showed that two of these mutations led to a reduced FTO function. Although the animal models implied that FTO deficiency should be related to leanness [118, 119] the two mutations were detected in both lean and obese individuals [120].

Insulin induced gene 2 (INSIG2)

The first GWAS for body weight (100k, Affymetrix) was conducted in 694 individuals from 288 families of the Framingham Heart Study [121]. In both children and adults, homozygosity for the minor allele of a common SNP (rs7566605) in the vicinity of *INSIG2* was found to be associated with obesity. The initial finding was confirmed in four of five separate samples comprised of individuals of Western European ancestry and African-Americans. Approximately 10% of the individuals harboured the obesity prone CC genotype, which conferred an average increase in BMI of approximately one BMI unit. A meta-analysis comprising all case–control samples showed that under a recessive model, the CC genotype was significantly associated with obesity (OR = 1.22) [121].

Several attempts to replicate the *INSIG2* finding have been undertaken. Both confirmations as well as negative findings have been reported [122–125]. *INSIG2* was not detected in any of the (joint) GWAS for obesity or BMI or in case–control studies [84, 86, 126]. A recent meta-analysis comprised data on a total of 74,345 individuals. Evidence for an overall association of rs7566605 with obesity was not detected. However, the data suggested an association with extreme degrees of obesity [127].

Other loci detected in genome wide association studies

Novel loci were identified by genome wide association studies in large study groups and via meta-analyses. Apart from the first large-scale meta-analysis mentioned above [85], three more recent GWAS reported novel obesity genes with small effects on human body weight [84, 92, 126]. A total of more than 150,000 individuals was analysed (Table 1).

A GWAS that was mainly based on individuals of the Icelandic population [84] resulted in a total of 29 variants in 11 chromosomal regions that reached genome wide significance, amongst them, variants located in seven new loci for obesity. Furthermore, *FTO* and *MC4R* were reconfirmed as well as the two obesity candidate genes brain derived neurotrophic factor gene (*BDNF*) and SH2B adaptor protein 1 gene (*SH2B1*) [84]. Four of the novel seven loci were not detected in the other two recent GWAS (see below and Table 1). Parallel to the Icelandic study [84], the meta-analysis of 15 GWAS for BMI ($n = 32{,}387$) was extended by the 'Genetic Investigation of ANthropometric Traits' consortium (GIANT) [92]; the study was also based on the GWAS data analysed by Loos et al. [85]. The best signals were now followed-up in 14 additional cohorts ($n = 59{,}082$). Again, strong confirmation was detected for *FTO* and *MC4R*. Additionally, six novel loci were identified (see Table 1).

Interestingly, for the first time a copy number variation (CNV) was described as potentially relevant for obesity [128] CNVs are by definition repeats of a size of 1 kb and more [129]. It is assumed that they might be involved in the regulation of neighbouring genes. The frequent 'obesity-CNV' (a 45-kb deletion) is located in a region near the neuronal growth regulator 1 gene (*NEGR1*). Further studies are required to unravel the underlying molecular mechanisms.

The newly detected variants lead to an increase of 0.06–0.33 kg/m^2 BMI units per allele. In adults with a height of 170 cm this corresponds to 173–954 g per allele. According to the recent GIANT study [92], the six newly discovered loci account for 0.40% and in combination with *FTO* and *MC4R* for a total of 0.84% of the BMI variance. The assessment of the combined impact of these loci on

BMI revealed that individuals with 13 or more obesity predisposing alleles across the eight loci were on average 1.46 BMI units (equivalent to 3.7–4.7 kg for an adult of average height) heavier than those individuals with less than three of these alleles [92]; the effects proved to be additive.

The third recent GWAS [126] comprising roughly 3,000 Europeans and a large confirmatory study group revealed, in addition to *FTO* and *MC4R*, significant association with obesity for three new risk loci (see Table 1). The polymorphism coding for 103I of the MC4R [e.g. 17] was also reconfirmed.

Conclusions and perspectives

Animal models and family studies led to the identification of rare monogenic forms of human obesity. The more common *MC4R* mutations in our opinion are more consistent with a 'major gene effect', as the near one-to-one relationship between genotype and phenotype is not evident among carriers of the risk allele. Instead, these individuals have a substantially increased risk of developing obesity. This initial work led to the discovery of the leptinergic–melanocortinergic pathway, which figures prominently in body weight regulation. Genome wide linkage and classical candidate gene studies were largely unsuccessful to identify obesity genes; these studies were underpowered. The emergence of GWAS has recently revolutionized the field in terms of detection of variants with small effect sizes.

Seventeen solidly confirmed polygenic variants for body weight regulation have been reported as of October 2009. It is obvious that more polygenic variants await detection; undoubtedly large scale GWAS will prove powerful for their elucidation. It will be interesting to determine if the effect sizes of the currently known polygenic variants represent the upper limit. Effect sizes of many as yet undetected variants could well be in the range of <50 g only. The detection of such variants will require meta-analyses based on hundreds of thousands of individuals. For those currently known polygenes, studies on gene–gene interactions can be undertaken. Finally, gene–environment interactions also become amenable to statistical analyses.

If a large number of genetic variants are detected in the future, prediction will potentially become feasible. In most cases, a straightforward but detailed family history would currently provide much more predictive power. However, the analysis of a family history cannot indicate the involvement of specific genetic or biochemical mechanisms. Hence, genetic tests could provide much more detailed data pertaining to the pathways predisposing to obesity within the analysed family.

As obviously only a small fraction of the variance of BMI can currently be explained by variation at the DNA level, one might speculate about the molecular mechanisms underlying the large proportion of as yet unexplained variance. As already pointed out, the effect sizes of gene variants might be very small. Another explanation is that obesity frequently results from infrequent variants with larger effect sizes; substantial heterogeneity might preclude their detection. Additionally, one has to bear in mind that the highly dense SNP-chips only cover a major part but not all the variation in the human genome. Furthermore, haplotypes instead of SNPs might prove more successful for unraveling novel genes for obesity. Complex gene–gene and gene–environment interactions may also contribute to the currently low explained BMI variance. If at any given locus relevant for body weight regulation, some SNPs lead to an elevated expression, others to a reduced expression, such loci might also escape detection using current technology. Finally the role played by CNVs in obesity requires scrutiny and the influence of epigenetic factors on the development of obesity merits close attention.

The future will show to what extent BMI variance at the population level can be explained at the molecular level [130]; this will have a profound impact as to the feasibility of diagnostic kits to detect obesity genes. The current obesity intervention programs are not very efficient, so that novel approaches for treatment have to be developed. Gene products of every detected polygene can be considered as a potential drug target for the treatment of obesity and associated disorders.

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