From obesity genetics to the future of personalized obesity therapy

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Abstract | Obesity is a disorder characterized by an excess accumulation of body fat resulting from a mismatch between energy intake and expenditure. Incidence of obesity has increased dramatically in the past few years, almost certainly fuelled by a shift in dietary habits owing to the widespread availability of low-cost, hypercaloric foods. However, clear differences exist in obesity susceptibility among individuals exposed to the same obesogenic environment, implicating genetic risk factors. Numerous genes have been shown to be involved in the development of monofactorial forms of obesity. In genome-wide association studies, a large number of common variants have been associated with adiposity levels, each accounting for only a small proportion of the predicted heritability. Although the small effect sizes of obesity variants identified in genome-wide association studies currently preclude their utility in clinical settings, screening for a number of monogenic obesity variants is now possible. Such regular screening will provide more informed prognoses and help in the identification of at-risk individuals who could benefit from early intervention, in evaluation of the outcomes of current obesity treatments, and in personalization of the clinical management of obesity. This Review summarizes current advances in obesity genetics and discusses the future of research in this field and the potential relevance to personalized obesity therapy.

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Introduction

Obesity—clinically defined as a BMI above 30 kg/m^2—is placing an ever-increasing burden on public health worldwide. Individuals with obesity are at increased risk of several other health conditions including type 2 diabetes mellitus, hypertension, cardiovascular disease and osteoarthritis, as well as various forms of cancer.[1] Approximately 500 million people worldwide are estimated to have obesity (and 1.4 billion are estimated to be overweight), and this figure is expected to rise to 700 million by 2015.[2,3] Percentages of overweight and obese children are also rising rapidly, affecting over 40 million children worldwide.[3] Apart from medical repercussions, obesity is also an environmental and social challenge.

Almost certainly, the current worldwide obesity epidemic has, in concert with multiple other associated or causative factors, largely been driven by increased consumption of hypercaloric foods combined with a reduction in physical activity resulting in an imbalance between energy intake and expenditure.[4] However, a wide level of variability in obesity susceptibility is also observed among individuals, or communities, exposed to the same environmental risk factors. This observation suggests that genetic differences have an appreciable role in the observed individual variation in body weight and obesity susceptibility.[5] Such a genetic association is further supported by twin and family studies that have unanimously estimated the heritability of human corpulence and adiposity at between 40% and 70%.[6–11] However, this heritability is also modulated by environmental factors. Although a heritability of fat mass of up to 90% has been reported in Finnish twins who have low physical activity, this percentage is reduced to approximately 20% in the most active pairs of twins with the same ethnicity.[12] This finding indicates that the genetic influences on obesity are amplified in an obesogenic environment, and that intense and sustained physical activity is an effective method to counteract some of the deleterious effects of obesity susceptibility variants.[12]

In this article, we will review the key advances in the study of genetic factors that influence BMI variability and obesity risk among individuals, and provide an overview of promising areas of future research. We will also discuss how an increased understanding of hereditary factors influencing adiposity could contribute to personalized patient care. Given the recent technological advances in next-generation sequencing, this Review is particularly timely in allowing us to explore where the future might lead us in the quest to understand the genetics of this complex disorder, which is of increasing clinical importance.

Studies in monogenic obesity

Monogenic obesity is a collective term that refers to a number of rare forms of severe obesity that result from mutations of large effect size in an individual gene or

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chromosomal region. Despite the rarity of these monogenic forms of obesity, examination of their underlying genetic basis has made a substantial contribution to our understanding of the pathogenesis of obesity and has shed light on several pathways and mechanisms involved in the development of this condition.[13–16] Moreover, the study of monogenic forms of obesity has also altered our perception of obesity as an endogenous disorder by highlighting the contribution of neurological factors to its development.

Key points

- Individual susceptibility to obesity is strongly influenced by genetic factors
- Rare monogenic obesity variants of large effect size and common variants of small effect sizes collectively account for only a small proportion of the heritability of adiposity
- Several copy number variants, both common and rare, have been shown to contribute to individual variation in BMI and increased risk of obesity
- Genetic variants associated with BMI and obesity identified to date have increased our understanding of the underlying mechanisms by which obesity develops and is maintained
- Screening for monofactorial obesity variants can provide informed prognoses for patients and opportunities for early intervention and treatment of additional pathologies frequently associated with these forms of obesity
- Examination of clinical outcomes of interventions such as bariatric surgery in individuals with genetic susceptibility to obesity could permit personalization of obesity therapy in the future

The role of leptin

The first evidence of single-gene mutations that result in an increased susceptibility to obesity came from mouse studies. In 1994, the mutation responsible for the obese phenotype of the *ob/ob* mouse strain[17] was cloned and mapped to the leptin (*LEP*) gene.[18] Leptin is a hormone produced and secreted primarily by white adipose tissue.[18] Leptin is also produced in smaller concentrations in other tissues including brown adipocytes, the stomach, placenta, skeletal muscle and ovaries.[19–22] A mutation in the leptin receptor gene (*LEPR*) was subsequently identified as the causal mutation in the *db/db* mouse strain,[23–25] whose characteristic phenotype includes severe diabetes mellitus, obesity and dislipidaemia.[26,27]

Rare homozygous mutations in the leptin gene have also been identified in patients with severe early-onset obesity, which provided further evidence for the importance of the leptin–melanocortin pathway in hyperphagia and obesity susceptibility. To date, approximately 25 individuals carrying homozygous mutations in *LEP* that result in undetectable blood leptin levels have been identified.[28–34] Individuals with leptin deficiency develop severe early-onset obesity and extreme hyperphagia, as well as hyperinsulinaemia, hypothalamic hypothyroidism and hypogonadotropic hypogonadism (Table 1).[28–36] The discovery of mutations within the leptin gene resulting in severe obesity induced by leptin deficiency represents one of the key successes in obesity research, whereby exogenous administration of leptin to patients carrying homozygous *LEP* mutations results in reversal of the obesity phenotype in these individuals.[33,37] A wide range of clinical features have also been observed in patients with homozygous loss-of-function mutations in *LEPR*, including reduced insulin-like growth factor 1 (IGF-1) levels and growth abnormalities, as well as severe obesity with hyperphagia (Table 1).[38–40]

Table 1 | The genetic architecture of monogenic obesity[28–57]

Gene (gene symbol)	Chromosome position	Mode of inheritance	Associated phenotype
Leptin (*LEP*)	7q32.1	Autosomal recessive	Severe early-onset obesity Extreme hyperphagia Hyperinsulinaemia Hypothalamic hypothyroidism Hypogonadotropic hypogonadism
Leptin receptor (*LEPR*)	1p31.3	Autosomal recessive	Severe obesity with hyperphagia Delayed or absent puberty Reduced IGF-1 levels Growth abnormalities
Pro-opiomelanocortin (*POMC*)	2p23.3	Autosomal recessive	Severe paediatric-onset obesity Hyperphagia Red hair pigmentation Pale skin
Proprotein convertase subtilisin/kexin type 1 (*PCSK1*)	5q15	Autosomal recessive	Severe childhood obesity Abnormal glucose homeostasis Reduced plasma insulin with elevated proinsulin levels Hypogonadotropic hypogonadism Hypocortisolaemia
Melanocortin 4 receptor (*MC4R*)	18q21.32	Autosomal dominant/ recessive	Severe early-onset obesity Hyperphagia Highly elevated plasma insulin concentrations Increased BMD
Single-minded homolog 1 (*SIM1*)	6q16.3	Autosomal dominant	Early-onset obesity Hypotonia Developmental delay Short extremities

Additional leptin–melanocortin pathway genes

The results of the studies mentioned above provided the first indications of the anorectic effects of leptin and of the integral role that the leptin–melanocortin signaling pathway has in energy homeostasis and body weight regulation. These data led to an increased interest in genes that encode products acting within the leptin–melanocortin pathway, and a series of mutations that affect genes other than *LEP* and *LEPR* in this pathway have since been identified (Table 1). One such gene is the prohormone pro-opiomelanocortin (*POMC*) that is expressed in the arcuate nucleus of the hypothalamus. The gene product of *POMC* is cleaved to produce the melanocortin 4 receptor (MC4R) ligand alpha-melanocyte stimulating hormone (α-MSH),[41] and is thus an integral signal propagator of the leptin–melanocortin pathway. Loss-of-function mutations in *POMC* have been associated with severe early-onset obesity coupled with a characteristic red-hair pigmentation in affected individuals.[42–44] Additionally, both homozygous and heterozygous mutations have been identified in the *PCSK1* gene, which encodes the prohormone convertase 1 (PC1) enzyme responsible for post-translational processing of POMC, and these mutations result in partial or complete PC1 deficiency leading to monogenic early-onset obesity with hyperphagia.[45–48]

Box 1 | Study designs employed in complex disease genetics

Linkage analysis
Linkage analysis attempts to identify chromosomal regions co-segregating with a disease phenotype of interest in related individuals. This form of study takes advantage of the inverse relationship that exists between the frequency of recombination between any two loci and the physical distance between them. In this way, co-inheritance of genetic markers with a disease phenotype would suggest that the 'linked' genetic markers and the disease locus are in close proximity in the genome. Linkage analyses may be carried out using polymorphic markers such as microsatellites or single nucleotide polymorphism (SNP) panels, either on a genome-wide scale, or in candidate regions of interest.

Candidate gene studies
Candidate gene studies seek to detect association between genetic markers in predefined genes considered to be candidates for the phenotype of interest. These may be functional candidates, selected based on biological evidence implicating them in pathways relevant to the disease under study, or positional candidates mapping to genomic regions implicated through animal studies, linkage or association analyses, or from evidence of gene disruptions such as translocations or deletions segregating with the disease phenotype.[80] Candidate gene studies are hypothesis-driven, and, as would be expected, are reliant on the current state of knowledge in the field.[80]

Genome-wide association studies
Genome-wide association studies (GWAS) employ hypothesis-free methodologies to identify common variants associated with phenotypes of interest. In this form of analysis, allele and/or genotype frequencies at each SNP included in the study are tested for association with phenotypes of interest. GWAS rely on the premise that genotyped SNPs showing association with phenotypes of interest, although unlikely to be causal themselves, may be in linkage disequilibrium with the causal variants. Association studies of complex diseases frequently require large numbers of samples to provide sufficient power to detect associations of typically small effect size for common variants. Association studies for obesity-related traits may be subdivided into quantitative trait association analyses for BMI, and case–control studies of extreme obesity phenotypes.

MC4R is believed to propagate anorexigenic signals emanating from the leptin pathway through the paraventricular nucleus of the hypothalamus to downstream effectors. Consistent with this role, dominant and recessive loss-of-function mutations resulting in monogenic obesity have been identified in the *MC4R* gene.[49–53] Although frequency estimates of deleterious *MC4R* mutations have varied among studies, these mutations are thought to account for up to approximately 6% of childhood obesity and 2% of adult obesity cases.[49–53] One of the effectors thought to act both upstream and downstream of MC4R is encoded by the *SIM1* gene which, in addition to having an essential role in embryonic neurogenesis, is believed to contribute to the maintenance of energy homeostasis. Loss-of-function mutations in *SIM1* have been shown to result in severe hyperphagic obesity in both humans and mice.[54–59]

Studies in polygenic obesity

Polygenic obesity, also known as 'common obesity', is a form of obesity that is thought to result from the combined effect of variants in multiple genes acting in concert with environmental risk factors. Early studies investigating the genetic basis of common obesity relied on linkage analyses and candidate gene approaches (Box 1). However, the development of high-density single nucleotide polymorphism (SNP) genotyping arrays has expanded association analysis of common variants to a genome-wide scale, with the high-throughput nature of these technologies permitting genotyping of millions of SNPs in thousands of individuals. Multiple genomic loci have been shown to be associated with BMI and obesity, with several of these associations having been replicated in numerous studies (Figure 1 and Table 2).

Linkage analyses

To date, over 30 genome-wide linkage scans of BMI and obesity have been published. Although over 250 'positive' linkage results have been reported, with adiposity quantitative trait loci reported on every chromosome except the Y chromosome, little consistent replication has been observed among different linkage studies.[60] In a meta-analysis of 37 genome-wide linkage scans, researchers failed to find statistically significant evidence of linkage to any particular chromosomal region.[61] However, a few suggestive signals were observed at chromosome regions 13q13.2–13q33.1 and 12q23–12q24.3, as well as at the chromosome 16q12.2 region, which encompasses the fat mass and obesity-associated *FTO* gene.[61] Loci showing linkage to BMI and/or obesity, which have been replicated in multiple studies, include those on chromosome regions 1p36,[62–67] 2p21-2p23,[68–71] 2q14,[62,72,73] 3q27,[74–79] 6q21-6q23,[73,80,81] 7q31-7q32,[82–84] 10p11-10p12,[85–87] 11q14-11q24[80,88,89] and 20q11-20q13.[90–93]

Candidate gene studies

Several hundred obesity candidate gene studies have been carried out in the past two decades, with at least 127 candidate genes reported to be associated with obesity or obesity-related phenotypes.[60] The most widely replicated obesity and BMI candidate gene associations include *MC4R*,[94–101] brain-derived neurotrophic factor gene (*BDNF*),[102–105] *PCSK1*,[45,106] β-adrenergic receptor 3 gene (*ADRB3*),[107–111] and peroxisome proliferator-activated receptor γ gene (*PPARγ*).[112–114] However, evidence from many of the other candidate gene studies carried out to date has been conflicting, often due to differences in study power, sample size, patient recruitment, phenotyping and inclusion criteria.[115]

Nevertheless, candidate gene studies continue to contribute to our understanding of the genetic factors that influence obesity susceptibility. Given its role as a dietary fat sensor, the gene encoding G-protein coupled receptor 120 (*GPR120*) was considered a functional candidate gene for obesity. Mutations in *GPR120* have recently been shown to result in an elevated risk of obesity, combined with a reduced number of fat cells leading to increased fat storage in the liver.[116] Results of functional studies in mice provided further support for the role of GPR120 in energy homeostasis, with GPR120-deficient mice showing an increased susceptibility to obesity, fatty liver and impaired glycaemic control when exposed to a high-fat diet.[116] Acting as an environmental sensor, GPR120 provides a link between physiological response and dietary fat intake.[116] Environmental sensitivity genes are therefore particularly interesting candidate genes to study from a translational perspective, as action on both their biological pathways and on

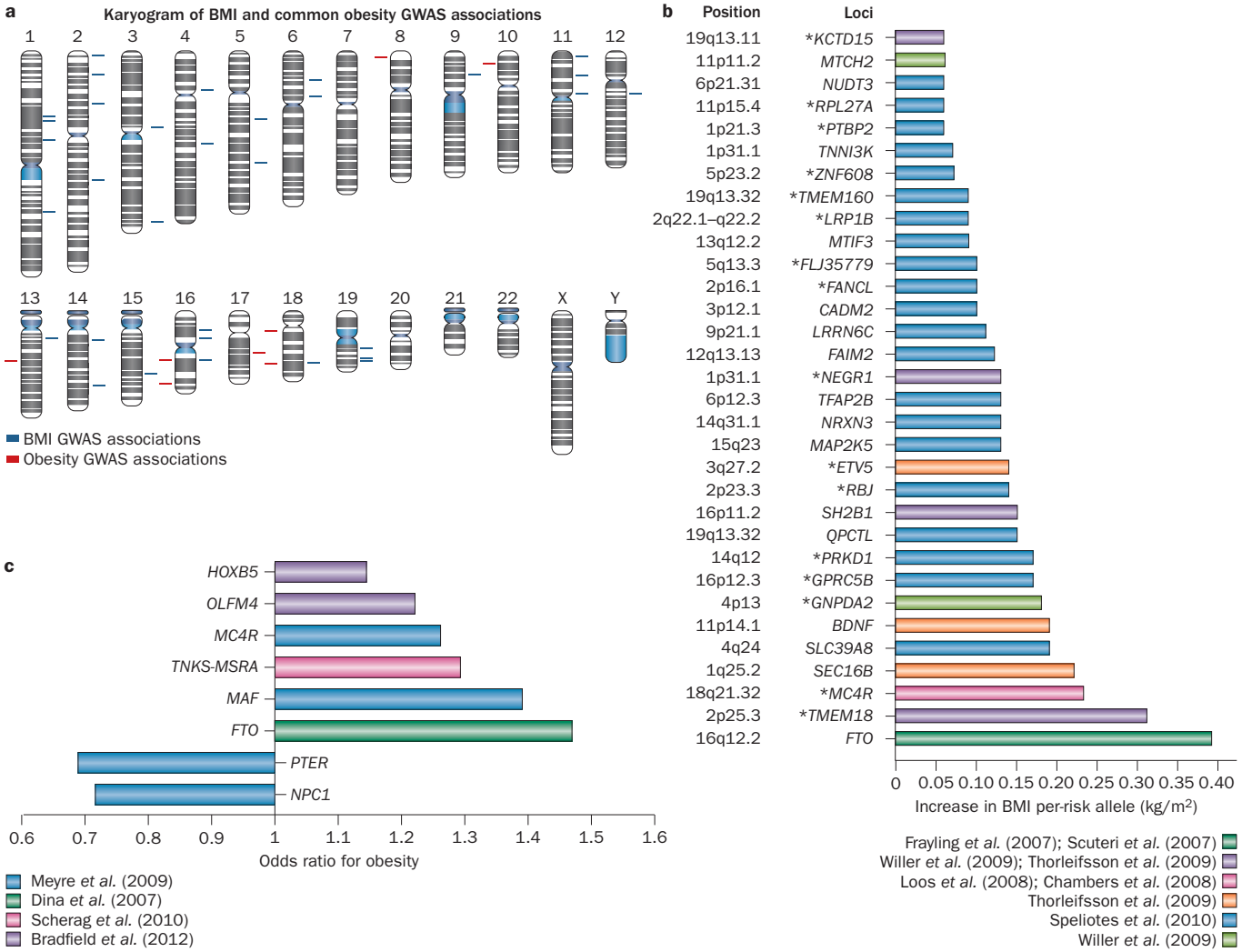

Figure 1 | The genetics of BMI and common obesity. **a** | A karyogram depicting loci that have been associated with BMI (blue bars) and obesity (red bars) through genome-wide association studies. **b** | Reported effect sizes for genetic variants associated with BMI. Listed genes are those in which the association was reported (* indicates gene closest to the reported association). Increase in BMI per risk allele is presented for the SNP marker showing the most significant association with BMI at each locus. **c** | Reported odds ratios for genetic variants associated with obesity in case-control obesity GWAS. Listed genes are those in closest proximity to each reported association. In parts b and c, loci are coloured according to the study in which the association was first reported. Abbreviations: GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

interacting environmental factors can have a synergistic effect, which could potentially contribute to prevention or treatment of obesity.

Genome-wide association studies

Multiple GWAS of BMI and obesity have been carried out to date (Table 2). Figure 1 provides a summary of genetic variants associated with BMI and obesity identified through GWAS. The first important discovery in adiposity GWAS was the identification of strong association at a region on chromosome 16q12, encompassing the *FTO* gene, with BMI and obesity.[117–119] Association of SNPs within the *FTO* gene with BMI and obesity was reported by three groups in rapid succession in 2007,[117–119] and this finding has subsequently been widely replicated in other studies.[120–134] Although bioinformatic studies have shown that FTO shares sequence motifs with Fe(II) dependent and 2-oxoglutarate-dependent oxygenases (which are involved in several cellular processes such as fatty acid metabolism and DNA repair), there is still little known about the function of FTO.[135] In functional studies, FTO has been shown to be localized to cellular nuclei, and to have a role in DNA demethylation which suggests a potential role for FTO in the regulation of gene expression.[135] Analyses of *FTO* expression patterns have revealed that the gene is highly expressed in multiple tissues, with several studies reporting high levels of *FTO* expression in the hypothalamus.[117,135] *FTO* variants have also been associated with brain volume in both adolescent (12–18 years) and elderly (76 ± 5 years) individuals.[136,137]

In order to increase the statistical power in the analysis of gene variants associated with BMI, a multinational collaboration known as the Genetic Investigation of ANthropometric Traits (GIANT) consortium was

Table 2 | Reported loci associated with common obesity through GWAS

Loci associated with obesity	Chromosome position	Effect size*	Risk allele frequency in Europeans (%)	Studies in which association was first reported
FTO	16q12.2	1.47	47	Dina *et al.* (2007)
MAF	16q23.1	1.39	56	Meyre *et al.* (2009)
MC4R	18q21.32	1.26	26	Meyre *et al.* (2009)
NPC1	18q11.2	0.71	47	Meyre *et al.* (2009)
PTER	10p13	0.68	9	Meyre *et al.* (2009)
TNKS-MSRA	8p23.1	1.29	11	Scherag *et al.* (2010)
SDCCAG8	1q43-q44	1.19	87	Scherag *et al.* (2010)
OLFM4	13q21.1	1.22	13	Bradfield *et al.* (2012)
HOXB5	17q21.32	1.14	63	Bradfield *et al.* (2012)

*Effect size is given as an odds ratio for obesity case–control studies.

Box 2 | Association studies of complex traits: study designs

Case–control studies

A case–control study design aims to identify genetic variants associated with a dichotomous disease trait such as obesity. Individuals are categorized into two groups: 'cases' are individuals affected with the disorder of interest, while 'controls' are individuals free of the disease phenotype under study. Obesity case–control studies typically consist of cases with a BMI ≥30 kg/m^2 and normal-weight controls, whose BMI is below 25 kg/m^2.

Quantitative trait studies

Quantitative trait association studies aim to identify genetic factors associated with continuous traits, such as height or BMI. Quantitative trait study designs typically include individuals from the general population unselected for the trait under study, and therefore expected to be representative of the distribution of this trait in the general population. The frequency of alleles or genotypes, either genome-wide or at specific loci in the genome, is then compared between individuals across the spectrum of the phenotype of interest.

established. In the first meta-analysis carried out by this consortium (using a discovery sample of 16,876 individuals), common *MC4R* variants were reported to be associated with BMI (Figure 1).[131] Chambers *et al.*[138] concurrently reported an association of SNPs in *MC4R* with waist circumference and insulin resistance in east-Asian individuals.[138] As discussed above, rare pathogenic variants in *MC4R* were previously associated with monogenic obesity, suggesting that genes harbouring deleterious mutations that result in extreme obesity may also harbour variants associated with common phenotypic variation in BMI. Association of *MC4R* with obesity and BMI has since been reported in multiple studies.[120,122,123,125,127–130]

In a subsequent, larger meta-analysis (using a discovery sample of 32,387 individuals), the GIANT consortium identified variants within or near an additional six genes associated with BMI (Figure 1).These genes are transmembrane protein 18 (*TMEM18*), potassium channel tetramerization domain containing 15 (*KCTD15*), glucosamine-6-phosphate deaminase 2 (*GNPDA2*), SH2B adaptor protein 1 (*SH2B1*), mitochondrial carrier homolog 2 (*MTCH2*) and neuronal growth regulator 1 (*NEGR1*).[133]

Results of a study by a group of investigators from deCODE genetics[132] in a population sample of 31,392 individuals, including those from Icelandic (n = 25,344), Dutch (n = 2,998), European–American (n = 1,890) and African–American (n = 1,160) descent, confirmed the association of four of the above-mentioned loci (*TMEM18*, *NEGR1*, *KCTD15* and *SH2B1*[133]) with BMI and identified SNPs at a further three loci (*SEC16B*, *BDNF* and near *ETV5*) showing significant association with BMI (Figure 1).[132] In a meta-analysis on waist circumference by the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) consortium,[125] an association was reported between neurexin 3 (*NRXN3*) SNPs with waist circumference. This study also reported association of variants at this locus with BMI and obesity at sub-genome-wide levels of significance.[125] This finding was then replicated by a number of other studies.[129,139]

In the largest meta-analysis of GWAS on BMI carried out to date, including over 123,865 individuals in the discovery sample and a further 125,931 individuals in the replication stage, the GIANT consortium[129] confirmed association of a number of previously-identified adiposity loci with obesity and obesity-related traits, and also reported SNPs within a further 18 loci showing association with BMI (Figure 1).[129]

In addition to confirming loci previously shown to be associated with BMI,[126,130,134] case–control studies have also identified a number of variants associated specifically with obesity susceptibility (Table 2). A study by Meyre *et al.*[130] in 2009 confirmed association of *FTO* and *MC4R* with obesity and identified variants within three novel loci, encompassing the *MAF*, *PTER* and *NPC1* genes, that associated with extreme obesity.[130] In a meta-analysis of two child obesity case–control studies (Box 2) from Germany and France, an association was reported between SNPs in the *SDCCAG8*, *TNKS*, and *MSRA* genes and susceptibility to early-onset obesity.[128] In another meta-analysis of child obesity case–control studies carried out by the Early Growth Genetics consortium, variants in nine loci associated with childhood obesity, two of which had not been previously reported (*OLFM4* and *HOXB5*).[120]

Taken together, these data support the involvement of common variants in BMI-associated loci with obesity susceptibility, but also identify a number of loci which appear to contribute to obesity susceptibility, but not normal BMI variation. Notably, variants associated with BMI and obesity identified to date account for only approximately 2–4% of the heritability of BMI,[129] suggesting that much remains to be uncovered in the search for genetic variants influencing BMI and obesity susceptibility.[140,141]

Role of structural variants in obesity

Studies of monogenic and common obesity have focused largely on single nucleotide variants. The precise role of copy number variants (CNVs) in obesity susceptibility, and indeed complex disease, however, remains poorly understood. CNVs are traditionally defined as segments of DNA in the genome that differ in the number of diploid copies carried by 'healthy' individuals.[142–145]

CNVs can be broadly divided into two categories: common variants present at frequencies above 5% in the general population; and rare structural variants often observed in less than 1% of the population. Researchers have reported associations between common CNVs and complex diseases, including obesity. Association of a common CNV on chromosome 10q11.22 that encompasses the pancreatic polypeptide receptor 1 (*PPYR1*) gene with BMI has recently been reported, whereby low copy number was associated with increased BMI.[146] Furthermore, Jarick *et al.*[147] also reported association of a common CNV on chromosome 11q11 that encompasses the olfactory receptor genes *OR4P4*, *OR4S2* and *OR4C6* with early-onset extreme obesity. Additionally, in two large meta-analyses, two common CNVs, one within *NEGR1* and another near the G-protein-coupled receptor family C group 5 member B (*GPRC5B*), have been linked to body weight regulation through association of tagging SNPs with BMI.[129,133]

Interest in the role of rare structural variants of potentially large effect in common disease susceptibility has also increased. Rare CNV analyses can be classified into two main approaches, often undertaken simultaneously. In global CNV burden analyses, the total number of CNVs above a defined size threshold is assessed for enrichment among cases in case–control studies of a disease phenotype of interest. In individual CNV association analyses, one or several large candidate CNVs identified as potentially causative factors for a phenotype are tested for association in either case–control or population studies.

Large CNVs have been linked with susceptibility to obesity. We have shown association of a large deletion encompassing 593 kb of unique sequence on chromosome 16p11.2 (Figure 2) with an increased risk of severe obesity.[148] This variant was simultaneously reported by Bochukova *et al.*[149] and has since been independently replicated by several groups.[150,151] Deletions at this locus resulted in a 43-fold increased risk of morbid obesity, and were identified in 0.7% of individuals with morbid obesity included in our analysis.[148] Notably, this deletion had previously been associated with autism,[152] and duplications at this locus have been associated with both autism and schizophrenia.[152,153] The presence of two segmental duplications with high sequence similarity renders this locus prone to *de novo* structural rearrangements, resulting in the occurrence of both deletions and duplications of the intervening DNA sequence.[148] In another study in 2011, we investigated the impact of the reciprocal duplication at the chromosome 16p11.2 locus on body weight, and found that adults carrying duplications of this 593 kb DNA sequence had an 8.3-fold increased risk of being clinically underweight.[154] The duplication at this locus was also found to show sex-specific differences, with male carriers at increased risk of being underweight compared to female duplication carriers.[154] Individuals carrying the duplication also had a smaller head circumference compared with healthy controls.[154] The reciprocal deletions and duplications at this locus are an interesting example of a mirror effect on phenotype.[154]

In their study, Bochukova *et al.* also reported significant global enrichment for large, rare deletions over 500 kb in individuals with obesity, as well as an association of a second CNV at chromosome 16p11.2 (Figure 2)—a 220 kb deletion that encompasses several genes including *SH2B1*.[149] *SH2B1* knock-out mice have disrupted leptin and insulin signaling,[155] while SNPs within *SH2B1* have been associated with BMI,[129] thus providing support for the involvement of *SH2B1* in body weight regulation. In addition to its association with adiposity, loss-of-function mutations within *SH2B1* have also been associated with social isolation and aggression.[156]

Results of two new studies have also provided insights into the role of rare CNVs in childhood and adult-onset obesity.[150,157] Glessner *et al.*[157] identified 17 rare deletions present exclusively in individuals with obesity, which they suggested might be causal variants for the observed obesity phenotype. The same authors previously assessed the global CNV burden in adults with obesity in a case–control study, and reported a higher incidence of large deletions over 1 Mb in patients with obesity compared with controls, and incidence of deletions over 2 Mb present exclusively in individuals with obesity.[150] Taken together, these results suggest that large CNVs can have an important role in susceptibility to obesity, warranting further investigation of their effect.

In addition to simple deletions and duplications, more complex genomic structural variants can also contribute to obesity susceptibility. We have found evidence of an association with severe obesity at a complex CNV region on chromosome 8p21.2 overlapping the dedicator of cytokinesis 5 (*DOCK5*) gene.[158] The region encompasses two variable number tandem repeats flanking a simple common deletion. All three structural variants in the region were shown to be associated with severe obesity in two case–control samples.[158]

Obesity management and therapy

While substantial advances have been made in the study of genetic factors underlying obesity susceptibility, including the identification of increasing numbers of genetic variants associated with the risk of obesity, translation of these discoveries into preventive and therapeutic measures of direct clinical benefit has proven somewhat challenging. This limited translation of genomic advances into obesity therapy is consistent with what has been observed for other complex diseases, and can largely be attributed to the inverse relationship between the frequency and the effect size of the associated genetic variants identified to date.[159]

Obesity-associated and adiposity-associated variants identified to date have consisted of common variants of small effect size,[129] as well as a number of rare variants of large effect.[28–32,34,39–41,45–48,51–53,148] Analysis of the previously-discussed 32 common BMI-associated SNPs (Figure 1) revealed that these loci have poor predictive value for obesity, with an area under the receiver operating characteristic curve (AUC_{ROC}) of 0.574.[129,160] By contrast, a newly developed childhood obesity risk calculator, which considers a number of clinical parameters

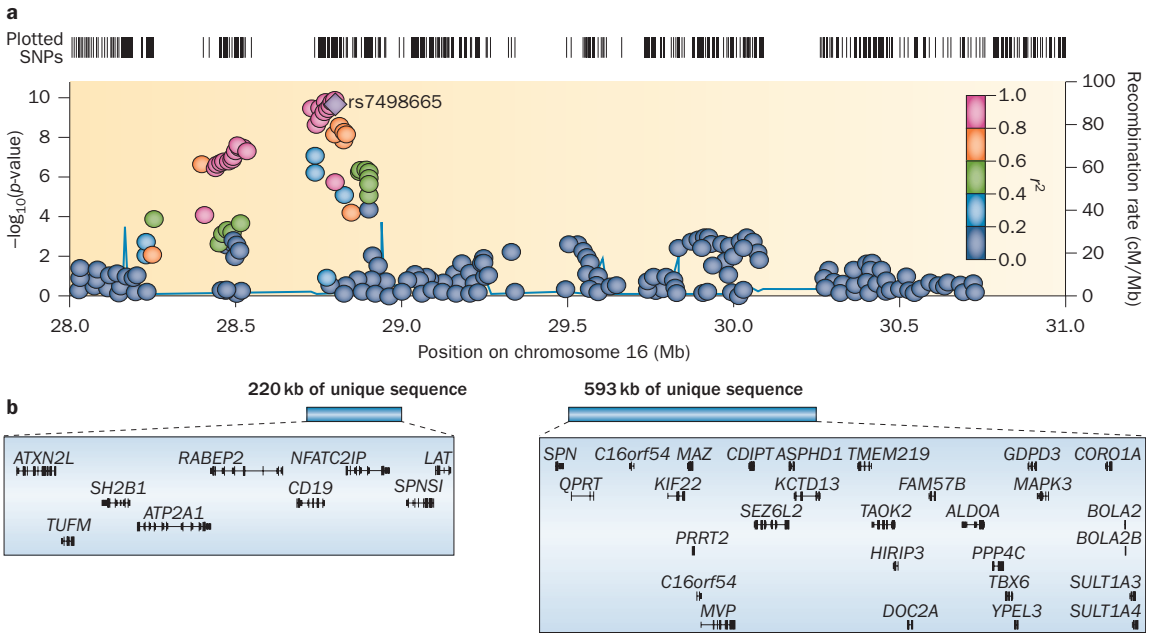

Figure 2 | The chromosome 16p11.2 region. **a** | Association results for SNPs in the 16p11.2 region with BMI in a recent meta-analysis carried out by the GIANT consortium.[129] Chromosome 16 genomic coordinates are plotted on the x-axis, with minus $\log_{10}$(*P*-value) plotted on the y-axis. An association peak can be seen at approximately 28.8 Mb. Plot generated using LocusZoom.[177]. **b** | The positions of two genomic structural variants associated with adiposity levels are depicted. A 220 kb deletion at chr16: 28.73–28.95 Mb and a 593 kb deletion at chr16: 29.51–30.11 Mb have been associated with obesity,[148,149] while a duplication of the latter 593 kb of unique sequence has also been associated with risk of being underweight.[154] The genes falling within each of the two CNVs are also shown. Abbreviations: CNV, copy number variant; GIANT, Genetic Investigation of ANthropometric Traits; SNP, single nucleotide polymorphism.

such as parental BMI, child birth weight, maternal gestational weight gain and smoking status, and several social factors such as number of individuals living in the household and maternal occupation, has been shown to have a stronger predictive capacity, with a maximal AUC_{ROC} for persistent childhood obesity of 0.85.[161] In this study, inclusion of an individual's genetic profile at common obesity-associated SNPs did little to improve predictive capacity of the risk calculator. However, notably, several of the clinical parameters used in this model have important genetic components.[161]

Although common BMI-associated and obesity-associated variants are currently limited in their direct utility in clinical settings, identification of these variants has helped to shed light on some of the pathways and mechanisms by which obesity develops and is maintained. These advances have increased our understanding of, and changed our attitudes (in both social and medical settings) towards, obesity as a disorder. Current evidence derived from studies of genetic factors that contribute to obesity susceptibility has drawn a somewhat unexpected picture of obesity as a disorder driven largely by hyperphagia and dysregulation of satiety signals at the neurological level.[13,16,133] These findings have provided wider recognition of the genetic contributors to obesity. Functional studies are required to further investigate the role of many of these key genomic regulators of adiposity to identify potential therapeutic targets.

The fact that highly penetrant variants associated with monogenic obesity are rare means that they offer little predictive value on a population level. However, the large effect sizes of these variants mean that they are of strong predictive value in individual cases. Genetic screening for known mutations that result in monogenic obesity can be carried out in patients presenting with early, rapid-onset or severe obesity, particularly if the patients present with additional associated clinical features such as severe hyperphagia, developmental delay or growth abnormalities.

Patients with leptin deficiency resulting from loss-of-function mutations in the leptin gene can now be successfully treated by administration of leptin.[33,37] Furthermore, 70% of patients with Prader–Willi syndrome (not discussed in this Review), carry deletions on chromosome 15q.[162] Patients presenting with clinical features suggesting a syndromic form of obesity can be screened using targeted CNV assays or genome-wide copy number analysis techniques such as array comparative genome hybridization. Testing for deletions that are known to result in increased risk of obesity, such as the above-discussed 593 kb deletion at 16p11.2, can also be carried out. Genome-wide screening for genomic structural variants might also be considered, particularly in patients with so-called 'obesity plus' clinical presentations, including clinical features such as mental retardation or dysmorphic features.

Intensive phenotyping of individuals carrying pathogenic mutations known to result in obesity has helped to provide a defined clinical picture of various forms of obesity. Identification of causative mutations in patients

with obesity might thus be beneficial in providing an informed prognosis for the patient and early opportunities for intervention and treatment of any commonly associated pathologies.

In cases in which a monogenic obesity variant is identified in a proband, the patients' families should be offered genetic counselling as they might wish to consider genetic screening of other family members. Early genetic testing could in turn permit the identification of additional at-risk individuals and offer opportunities for early intervention in such patients through the provision of focused education and guidance on healthy eating and lifestyle choices to parents and caregivers.[13,163] Such guidance can be of particular relevance in the case of children and patients with diminished cognitive capacity.

In addition to the identification of at-risk individuals for targeted, preventive, early intervention strategies, one of the ultimate goals of studies in complex disease genetics is the development of personalized therapeutic approaches that are based on an individual's genetic profile. The genetic discoveries in the field of obesity, and the ongoing studies on the effects of genetic variants on the therapeutic outcomes of obesity therapy, are paving the way towards the goal of personalized obesity therapy.

One particularly promising area of research involves the effect of obesity-associated variants on bariatric surgery outcomes. Sarzynski *et al.*[164] studied the role of 11 common BMI-associated variants on weight loss after bariatric surgery. They found a SNP within the *FTO* gene to be significantly associated with postsurgical weight loss.[164] In another study, Still *et al.*[165] divided patients who underwent bariatric surgery into 'low', 'intermediate' and 'high' risk groups based on their genetic profiles at four obesity-associated SNPs.[165] They found significant differences in postoperative weight loss between each of the three groups of patients.[165]

Data from studies in rodents and humans suggest that carriers of *MC4R* mutations resulting in complete MC4R loss-of-function had lower weight loss and poorer outcomes after bariatric surgery compared with noncarriers of these mutations (P. Froguel and colleagues, unpublished work).[166–168] A more complex picture has been reported for heterozygous *MC4R* mutations. In some studies, heterozygous *MC4R* mutations showed no significant effects on bariatric surgery outcomes.[167,169] Our preliminary results, however, indicate that patients with pathogenic mutations in *MC4R* that severely impair appetite can be more resistant to surgical procedures such as gastric banding than patients without the mutations, indicating that procedures such as gastric bypass or pancreatic derivation might be more appropriate to treat such patients (P. Froguel and colleagues, unpublished work). Studies examining the therapeutic outcomes of obesity surgery remain in their infancy. Larger studies, longitudinal analyses, and subsequent meta-analyses are required to definitively establish the role of genetic variants on postsurgical outcomes in individuals with obesity. Such studies will also help in determining whether treatment outcomes can be improved through assignment of patients to personalized intervention strategies on the basis of their genetic profiles.

Future of research in obesity genetics

As is the case with other complex diseases, a substantial portion of the predicted heritability of obesity and inter-individual variability in BMI remains unexplained.[129] This 'missing heritability'[170] raises the important question of whether the heritability of such complex disorders has been overestimated, or might in fact be accounted for by forms of genetic variation currently unexplored by commonly-employed methods for large-scale association analyses.

The advent of cost-effective next-generation sequencing technologies that permit whole-genome or exome sequencing, as well as high-throughput sequencing of targeted genomic regions of interest, is expected to facilitate the investigation of genetic factors that contribute to susceptibility to complex diseases such as obesity. Exome sequencing is increasingly enabling the identification of numerous sequence variants associated with disorders such as neonatal diabetes mellitus,[171] maturity-onset diabetes of the young,[172] severe mental retardation,[173] and autism,[174,175] among others. As the associated costs decrease and resource availability increases, new sequencing technologies are also expected to facilitate higher-throughput routine screening for known pathogenic mutations in cases of severe and/or early-onset obesity in clinical settings.

Advances in the investigation of rare variants, in the form of modifications at the level of single nucleotides as well as larger genomic structural variants, have provided insight into the genetic architecture of obesity susceptibility. However, studies of rare variants are complicated by a need for large numbers of study participants in order to provide sufficient statistical power to definitively confirm their association with disease. Analysis of rare variants is further complicated by incomplete penetrance of some variants, as well as by environmental modifying factors. Therefore, functional studies will have an important role in determining the biological significance of adiposity-associated variants and are necessary to bridge the gap between the discovery of genetic susceptibility loci and the identification of therapeutic applications for these discoveries.

The role of post-genomic functional studies is also particularly important in the case of large, rare CNVs associated with obesity, which encompass multiple genes. Discovery of such variants raises the question of which gene, or genes, falling within each associated CNV are implicated in the observed obesity phenotype. In a recent example of the utility of post-genomic functional studies in such cases, Golzio and colleagues showed gene dosage at *KCTD13*, located within the aforementioned 593 kb CNV in the 16p11.2 region, as the causative factor in the head circumference phenotype associated with copy number variation at this locus.[176]

Furthermore, the complex nature of some genomic structural variants, such as variable number tandem repeats and multi-allelic CNVs, has so far confounded

systematic analysis of their contribution to complex disease susceptibility, which has made it difficult to determine the proportion of disease heritability that these variations might explain. Improved methodology is thus required to investigate these loci in more detail, and comprehensive analysis of such regions can help in identifying additional loci contributing to obesity susceptibility.

Conclusions

Genetics has a considerable role in modulating individual susceptibility to obesity in the face of the modern 'obesogenic' environment. The study of monogenic obesity has provided evidence of the role of appetite regulation and neurological signaling in obesity susceptibility, with the leptin–melanocortin pathway having an integral role in satiety signalling. The identification of carriers of obesity-causing-mutations in some families or identification of these mutations in patients presenting with other associated phenotypes (for instance, Prader–Willi-like features), and the molecular characterization of early-onset severe obesity cases are not only desirable but are increasingly cost-effective thanks to next-generation sequencing technologies.

In GWAS of common SNPs, a large number of genes have been associated with adiposity levels and obesity susceptibility. However, the small effect size of these common variants mean that they currently provide much less predictive value in clinical settings than do clinical and social parameters.[161] Nevertheless, we hope that detailed exploration of these loci using next-generation sequencing technologies and post-genomic functional analyses will provide valuable insights into their role in body weight regulation. Researchers have also begun to explore the relationship between genetic variants and environmental elements such as diet; further studies will be required to shed more light on this subject. Furthermore, with several rare CNVs of large effect size having been associated with obesity, we expect detailed studies of CNVs, particularly of multi-allelic complex variants, to improve our knowledge of the genetics of adiposity levels and obesity. Building on current advances in the field of obesity genetics, accurate and cost-effective molecular characterization of both syndromic and monofactorial forms of obesity is now possible and desirable for evaluation of the outcomes of current obesity therapies and to inform the establishment of new therapeutic approaches.

In a discipline of rapidly evolving technologies and analytical approaches, we hope that the assimilation of multiple data sources will not only enable the identification of an increasingly large number of loci that contribute to obesity susceptibility, but will also increase our understanding of the pathogenetic mechanisms driven by these variants. These advances will ultimately help in promoting a deeper understanding of obesity as a disorder and in permitting personalization of future therapeutic approaches.

Review criteria

PubMed was searched for original articles published between January 1980 and September 2012 using the terms "obesity", "body mass index", "adiposity", "obesity therapy" and "bariatric surgery" with "genetics". Select articles published before January 1980 were also included. Reference lists of retrieved papers were also used to identify additional relevant articles.

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Author contributions
J. S. El-Sayed Moustafa and P. Froguel contributed equally to researching the data for the article, discussion of content, and to writing and editing of the manuscript.

CORRECTION

From obesity genetics to the future of personalized obesity therapy

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In the original published version of this article, the chromosomal positions of the loci in Figure 1b were incorrectly ordered. This error has now been corrected for the HTML and PDF versions of the article.