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Review Article

Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity

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Abstract

In high-, middle- and low-income countries, the rising prevalence of obesity is the underlying cause of numerous health complications and increased mortality. Being a complex and heritable disorder, obesity results from the interplay between genetic susceptibility, epigenetics, metagenomics and the environment. Attempts at understanding the genetic basis of obesity have identified numerous genes associated with syndromic monogenic, non-syndromic monogenic, oligogenic and polygenic obesity. The genetics of leanness are also considered relevant as it mirrors some of obesity's aetiologies. In this report, we summarize ten genetically elucidated obesity syndromes, some of which are involved in ciliary functioning. We comprehensively review 11 monogenic obesity genes identified to date and their role in energy maintenance as part of the leptin–melanocortin pathway. With the emergence of genome-wide association studies over the last decade, 227 genetic variants involved in different biological pathways (central nervous system, food sensing and digestion, adipocyte differentiation, insulin signalling, lipid metabolism, muscle and liver biology, gut microbiota) have been associated with polygenic obesity. Advances in obligatory and facilitated epigenetic variation, and gene–environment interaction studies have partly accounted for the missing heritability of obesity and provided additional insight into its aetiology. The role of gut microbiota in obesity pathophysiology, as well as the 12 genes associated with lipodystrophies is discussed. Furthermore, in an attempt to improve future studies and merge the gap between research and clinical practice, we provide suggestions on how high-throughput '-omic' data can be integrated in order to get closer to the new age of personalized medicine.

Key words: epigenetics, genetics, leanness, metagenomics, obesity and body fat distribution, pathophysiology, personalized medicine.

INTRODUCTION

Obesity is defined as an increase in fat mass that is sufficient to adversely affect health and reduce life expectancy [1]. The presence of obese individuals has been reported across human history, through both art and science [2,3], but the rising prevalence of obesity has become an important health concern only in the last 30 years [4]. Once considered a problem only in high-income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries as well, particularly in urban settings [4]. Co-morbidities associated with obesity include sleep disturbance, respiratory difficulties, joint and mobility issues, psychological distress, type 2 diabetes mellitus (T2D), hypertension, dyslipidaemia, cardiovascular diseases and certain types of cancer [5].

Lifestyle changes remain the foundation of obesity treatment, even though adherence to weight loss and physical activity intervention programmes is poor [6]. Anti-obesity medications and surgery may also be utilized to ameliorate severe cases of obesity in adults [7–9].

The rise of obesity can be attributed to several major societal and environmental changes. The term 'obesogenic'

Abbreviations: AHO, Albright hereditary osteodystrophy; BBS, Bardet–Biedl syndrome; BFL, Börjeson–Forssman–Lehmann; BMI, body mass index; CGL, congenital generalized lipodystrophy; CNS, central nervous system; CNV, copy number variant; CpG, 5′-C-phosphate-G-3′; DIO, diet-induced obesity; EWAS, epigenome-wide association study; FFA, free fatty acid; FPL, familial partial lipodystrophy; GWAS, genome-wide association study; GxE, gene–environment; GxG, gene–gene; HC, hip circumference; HDLc, high-density lipoprotein cholesterol; IR, insulin resistance; KSR2, kinase suppressor of Ras 2; PVN, paraventricular nucleus; PWS, Prader–Willi syndrome; SMS, Smith–Magenis syndrome; SNP, single nucleotide polymorphism; T2D, type 2 diabetes; VAT/SAT, visceral adipose tissue/subcutaneous adipose tissue; VNTR, variable number tandem repeat; WAGR, Wilms tumour, aniridia, genitourinary anomalies and mental retardation; WC, waist circumference; WHR, waist-to-hip ratio; WHRadjBMI, WHR adjusted for BMI.

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encompasses these changes, which include excessive consumption of energy dense foods, sedentary lifestyles, urbanization and socioeconomic-dependent access to a healthy diet [10,11]. However, a huge variability in body mass index (BMI) values, from leanness to obesity, can be observed in the presence of an obesogenic environment [12,13]. More recently, epigenetic-induced alterations in gene expression have emerged as an alternative way in which environmental factors may influence obesity phenotype [14].

For the purposes of overall body fat quantification for genetic and epigenetic studies, underwater weighing and dual-energy X-ray absorption (DXA) have proven reliable, whereas computer tomography and MRI are used for regional measurements of body fat distribution [15]. Despite their technical accuracy, they are too costly and time consuming for routine care or large-scale genetic studies [15]. Alternative measures such as waist-to-hip ratio (WHR) or skin-fold thickness are used in clinical settings, despite their relative inaccuracy in estimating adiposity [16]. BMI is the most common anthropometric measure for estimating obesity [15,17,18]. A BMI cut-off of 30 kg/m^2 is generally used to declare the patient as obese [19]. However, this threshold has been assessed by the risk for morbidity and mortality in populations of European ancestry [20]. Using a single standard cutoff value to define obesity has been questioned, and ethnic-specific BMI cutoffs have been proposed [21–23].

The completion of the human genome sequence, combined with technological and methodological developments has led to the identification of an abundance of genes modulating anthropometric traits. However, considerable effort is still required to identify the remaining genetic and epigenetic contributors to obesity. This paper aims to review the current literature's stand on the molecular basis of adiposity variation and to provide a synthesis of what the genetic, epigenetic and metagenomic studies have contributed to our understanding of the pathophysiology of obesity so far.

OBESITY AS A HERITABLE DISORDER

Heritability is the proportion of total phenotypic variation in a population attributable to genetic variation among individuals in that population. When additive genetic effects are accounted for in the genetic variance, heritability is named narrow-sense heritability or just heritability (h2). When all the genetic variance from additive, dominant and epistatic effects is accounted for, heritability is defined as broad-sense heritability (H2) [24]. The familial aggregation of body size was first reported by Sir Francis Galton in 1894 [25]. Since then, family history of obesity has become a well-established risk factor for childhood obesity. Studies indicate parental BMI or overweight/obesity status is associated with BMI or the risk of overweight/obesity in children, and is an important predictor of obesity in adulthood [26–29]. The ethnic-dependent pattern of obesity prevalence further supports heritability of obesity, which could be explained by specific lifestyles or environmental exposures, but admixture studies have demonstrated an important contribution of genes [18]. Furthermore, twin studies have shown that genetic inheritance contributes towards 40–75% of obesity cases [30]. Monozygotic twins show more similar body fat acquisition in comparison with dizygotic twins, suggesting that an altered energy balance is highly influenced by the genotype [31,32]. Adoption studies further confirm the genetic component of obesity, as the BMI of adopted children correlates more to the BMI of their biological parents than their adopted parents [33].

Based on the hypothesis that a substantial proportion of heritability in the population can be explained by common single nucleotide polymorphism (SNP) [34], recent heritability studies have found that 27–30% of the total BMI variance in children and adults can be attributed to common SNPs [35,36].

Although heritability studies have been influential in our understanding of the genetics of obesity, interpreting these studies requires caution as some heritability estimates may be inflated based on unaccounted shared conditions [37].

MENDELIAN OBESITY

Genetic obesity sometimes follows a Mendelian pattern of inheritance. It results from structural variations or mutations affecting genes that encode proteins most probably involved in appetite regulation and metabolism under autosomal or X-linked patterns of inheritance [38].

Syndromic monogenic obesity

Syndromic monogenic obesity is exceptionally rare and characterized by mental retardation, dysmorphic features and organ-specific abnormalities, in addition to obesity [38]. More than 30 syndromes have been reported in literature, out of which many have not been genetically elucidated [39]. Table 1 lists obesity syndromes, which are at least partially elucidated at the molecular level.

Prader–Willi syndrome (PWS), first reported in 1956 by Andrea Prader, is a highly researched neurodevelopmental obesity syndrome and has an incidence of 1 in 15000–30000 [40]. Common PWS characteristics include hypotonia, feeding difficulties, poor growth and delayed development in the first year of life, followed by hyperphagia, childhood obesity, short stature and cognitive disability [40]. Obesity and its co-morbidities have been identified as the major cause of health complications in PWS patients [41]. PWS is a maternally imprinted disorder, meaning that the maternal copy of genes implicated with PWS are typically silenced, and only the paternal gene copies are expressed [42]. PWS is a result of three types of genetic defects in the paternally inherited chromosome 15q11.2-q13. Paternal deletions are the most common and contribute towards 65–75% of the cases [43]. Maternal uniparental disomy is found in 20–30% of PWS cases [43]. Imprinting defects are the least common types of genetic errors (1–3%), caused by epimutations or incomplete processing of the imprint from the father or from microdeletions in the DNA imprinting centre [43]. The genes implicated with PWS features include makorin ring finger protein 3 (*MKRN3*), MAGE family member L2 (*MAGEL2*), Necdin (*NDN*), nuclear pore associated

Table 1 List of Mendelian loci associated with obesity and body fat distribution traits

Name(s) of the syndrome/gene	Clinical features	Type of inheritance	Genetic cause	References
		Monogenic obesity syndromes		
Albright hereditary osteodystrophy	Brachymetaphalangism, short stature, obesity and mental retardation	Autosomal dominant	*GNAS1*	[62,464]
Alström syndrome	Blindness, hearing impairment, childhood obesity, insulin resistance and type 2 diabetes mellitus	Autosomal recessive	*ALMS1*	[57,59]
Bardet–Biedl syndrome	Retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioural dysfunction and hypogonadism	Autosomal recessive	*BBS1*	[465]
			BBS2	[466]
			BBS3/ARL6	[467]
			BBS4	[468]
			BBS5	[469]
			BBS6/MKKS	[470]
			BBS7	[471]
			BBS8/TTC8	[472]
			BBS9	[473]
			BBS10	[474]
			BBS11/TRIM32	[475]
			BBS12	[476]
			BBS13/MKS1	[477]
			BBS14/CEP290	[477]
			BBS15/WDPCP	[478]
			BBS16/SDCCAG8	[479]
			BBS17/LZTFL	[480]
			BBS18/BBIP1	[481]
			BBS19/IFT27	[482]
Börjeson–Forssman–Lehmann syndrome	Severe intellectual disability with epilepsy, microcephaly, short stature, obesity, hypogonadism and gynecomastia	X-linked	*PHF6*	[68]
Carpenter syndrome / acrocephalopolysyndactyly type II	Acrocephaly, soft tissue syndactyly, brachy- or agenesis mesophalangy of the hands and feet, preaxial polydactyly, congenital heart disease, mental retardation, hypogenitalism, obesity and umbilical hernia	Autosomal recessive	*RAB23*	[72]
Cohen syndrome	Mental retardation, facial dysmorphism, microcephaly, retinal dystrophy, truncal obesity, joint laxity and intermittent neutropenia	Autosomal recessive	*VPS13B/COH1*	[75,76]
Kabuki syndrome	Facial gestalt, intellectual disability, visceral and skeletal malformations and, postnatal short stature with overweight	Autosomal dominant	*KMT2D/ MLL2/ ALR/ KABUK1*	[80]
		X-linked dominant	*KDM6A/ UTX/ KABUK2*	[81]

Table 1 Continued

Name(s) of the syndrome/gene	Clinical features	Type of inheritance	Genetic cause	References
Prader–Willi syndrome	Low muscle tone, short stature, incomplete sexual development, cognitive disabilities, problem behaviours, and a chronic feeling of hunger that can lead to excessive eating and obesity	Variable	*MKRN3*	[45]
			MAGEL2	[46]
			NDN	[47]
			NPAP1/ C15orf2	[48]
			SNURF-SNRPN	[483]
			5 small nucleolar RNA	[484]
			Paternally inherited chromosome 15q11-q13 abnormalities	[485]
Smith–Magenis syndrome	Intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances and behavioural problems	NA	*RAI1*	[84]
WAGR	Aniridia, Wilms tumour, genitourinary abnormalities, and growth and mental retardation	NA	11p13 deletions	[89,486]
	Monogenic non-syndromic obesity			
Leptin	Rapid weight gain, behavioural problems when food is denied, hyperphagia, hypogonadotrophic hypogonadism, defective T-cell mediated immunity, low blood pressure	Autosomal recessive	*LEP*	[91]
Leptin receptor	Rapid weight gain, behavioural problems when food is denied, hyperphagia, hypogonadotrophic hypogonadism, defective T-cell mediated immunity, low blood pressure	Autosomal recessive	*LEPR*	[95]
SH2B adaptor protein 1	Hyperphagia, childhood onset obesity, insulin resistance, reduced height, behavioural abnormalities	NA	*SH2B1*	[109,487]
Proopiomelanocortin	Obesity, hypocortisolism, red hair and skin hypopigmentation, neonatal hypoglycaemia, seizures, cholestasis, voracious appetite	Autosomal recessive	*POMC*	[115,116]
Pro-protein convertase subtilisin / kexin type 1	Early-onset obesity, hyperphagia, postprandial hypoglycaemia, endocrine dysfunction, diarrhoea, diabetes insipidus	Autosomal dominant or recessive	*PCSK1*	[120,122–125,420]
Melanocortin 4 receptor	Hyperphagia, rapid weight gain, hyperinsulinaemia, increased linear growth, increase in bone mass, increase in both fat and lean mass	Autosomal dominant or recessive	*MC4R*	[130–133]

Table 1 Continued

Name(s) of the syndrome/gene	Clinical features	Type of inheritance	Genetic cause	References
Neurotrophic tyrosine kinase receptor type 2 (tyrosine receptor kinase B)	Early-onset obesity, hyperphagia, developmental delay, impairment in short-term memory, impaired nociception	NA	*NTRK2 (TrkB)*	[135,137]
Brain-derived neurotrophic factor	Hyperphagia, severe obesity, cognitive impairment, hyperactivity	NA	*BDNF*	[138]
Single-minded homologue 1	Hyperphagia, obesity, reduction in paraventricular nucleus, excessive growth, Prader–Willi like neurobehavioural features	NA	*SIM1*	[146,149–152]
Kinase suppressor of Ras 2	Hyperphagia, early-onset obesity, low heart rate, reduced basal metabolic rate, severe insulin resistance	NA	*KSR2*	[154]
Tubby bipartite transcription factor	Deteriorating vision, obesity, normal glucose, cholesterol, triacylglycerols levels	Autosomal recessive	*TUB*	[156]
Monogenic lipodystrophy syndromes				
Keppen Lubinsky syndrome	Generalized lipodystrophy, severe developmental delay, microcephaly, facial dysmorphy and aged appearance	Autosomal dominant	*KCNJ6 (GIRK2)*	[183]
Mandibuloacral dysplasia syndrome	Partial lipodystrophy, hypoplasia of the lower mandible and clavicle	Autosomal recessive	*ZMPSTE24*	[184]
Mandibular hypoplasia, deafness, progeroid features and lipodystrophy syndrome	Partial lipodystrophy, male hypogonadism, neurosensory deafness and progeroid features	Autosomal dominant	*POLD1*	[192]
Monogenic non-syndromic lipodystrophy				
Berardinelli–Seip syndrome/ congenital generalized lipodystrophy (types 1, 2, 3, 4)	Generalized lack of fat tissue, hypertriglyceridaemia, low HDLc and severe insulin resistance causing T2D, prominent musculature, acanthosis nigricans and pseudoacromegaly	Autosomal recessive	*AGPAT2*	[178]
		Autosomal recessive	*BSCL2*	[179]
		Autosomal recessive	*CAV1*	[180]
		Autosomal recessive	*PTRF*	[181]
Familial partial lipodystrophy (types 2, 3, 4)	Partial lipodystrophy	Autosomal dominant	*LMNA*	[187]
		Autosomal dominant	*PPARγ*	[188,189]
		Autosomal dominant	*PLIN1*	[191]
Familial partial lipodystrophy (type 5)	Partial lipodystrophy	Autosomal recessive	*CIDEC*	[185]
Familial partial lipodystrophy (type 6)	Late-onset partial lipodystrophy	Autosomal recessive	*LIPE*	[186]
Monogenic obesity with metabolic syndrome				
Abdominal obesity-metabolic syndrome	Central obesity, T2D, hypertension and early-onset coronary artery disease	Autosomal dominant	*DYRK1B*	[207]

protein 1 (*NPAP1*), SNRPN upstream reading frame (*SNURF-SNRPN*) and 5 small nucleolar RNA [44–49].

Bardet–Biedl syndrome (BBS) was the first obesity syndrome reported in 1866 by Laurence and Moon [50]. BBS is a genetically and clinically heterogeneous ciliopathy with an autosomal recessive mode of inheritance. Characteristic clinical features of BBS include retinal degeneration, cognitive disability, polydactyly and genital and renal anomalies [51]. Central and peripheral obesity is also a major feature and presents in 72–92% of BBS patients, appearing mostly in the early years of life due to hyperphagia and sometimes resulting in T2D [52]. To date, 19 BBS genes have been identified through various gene identification strategies [44–46,54]. The BBSome complex comprises BBS proteins, and constitutes a coat complex that sorts membrane proteins to primary cilia [53]. Due to the key role played by primary cilium in the differentiation of adipocytes, the pathogenesis of obesity in BBS is in part attributed to a defect in adipogenesis [54]. Moreover, BBS proteins mediate leptin receptor (LEPR) signalling [55].

Alström syndrome is a recessively inherited ciliopathy [56]. The major clinical features include retinal dystrophy, hearing impairments, early-onset obesity, insulin resistance (IR) and T2D [57]. With only ∼300 known cases so far, the prevalence of Alström syndrome is particularly low [56]. In 1997, Alström syndrome was mapped to chromosome 2p13.1 [58]; a few years later mutations in Alström syndrome protein 1 (*ALMS1*) were found in six unrelated families [59]. In mouse models, the absence of ALMS1 was shown to result in stunted cilia and disable mutant cells from increasing calcium influx in response to mechanical stimuli [60].

Albright hereditary osteodystrophy (AHO), also known as pseudohypoparathyroidism Ia, is associated with hyperphagia, obesity, short stature, round facies, skeletal anomalies and mental disability [61]. AHO is inherited in an autosomal dominant (AD) pattern and is due to mutations in the guanine nucleotide binding protein, alpha-stimulating (*GNAS*) gene [62,63]. *GNAS* encodes the alpha-subunit of the stimulatory G protein (Gsα), which is a signalling protein that generates the second messenger cAMP and mediates the actions of hormones, neurotransmitters and paracrine/autocrine factors [64]. Mutations decrease Gsα expression, resulting in resistance to hormones such as the parathyroid hormone, thyroid stimulating hormone and gonadotropins [65].

Börjeson–Forssman–Lehmann (BFL) syndrome is an X-linked disorder first described in 1962 [66]. It has since been reported in numerous families and characterized by severe mental disability, epilepsy, microcephaly, hypogonadism, obesity and gynecomastia [67]. In 2002, BFL syndrome was linked to the presence of mutations in the PHD finger protein 6 (*PHF6*) gene located on chromosome Xq26.2 [68]. However, not all BFL syndrome patients carry mutations in *PHF6*, indicating the presence of other unknown genetic causes. PHF6 is a key chromatin adaptor protein, playing an important role in the regulation of neurogenesis and haematopoiesis and could also regulate transcription and ribosome biogenesis [69].

Carpenter syndrome, also known as acrocephalopolysyndactyly type II, is an autosomal recessive disorder characterized by acrocephaly, soft tissue syndactyly, brachy- or agenesis mesophalangy of the hands and feet, preaxial polydactyly, congenital heart disease, mental retardation, hypogenitalism, obesity and umbilical hernia [70]. Mutations in the *RAB23* gene are responsible for the Carpenter syndrome [71,72]. The gene product is a negative regulator of the Sonic Hedgehog signalling pathway in dorsal neural cells, and has also been implicated in ciliary trafficking [73].

Cohen syndrome, also known as the obesity-hypotonia syndrome, follows an autosomal recessive pattern of inheritance [74]. Patients suffering from Cohen syndrome exhibit features such as non-progressive psychomotor retardation, motor clumsiness, characteristic facial features, microcephaly, childhood hypotonia, progressive myopia and truncal obesity [75]. Mutations in the Cohen 1 (*COH1*/*VPS13B*) gene on chromosome 8q22 result in the Cohen syndrome [76]. COH1 has been identified as a Golgi-enriched protein that contributes to the structural maintenance and function of the Golgi complex. Depletion of COH1 in primary neurons negatively interferes with neurite outgrowth. The decreased neuritogenesis could probably lead to the reduced brain size in Cohen syndrome patients [77].

Kabuki syndrome was first reported in 1981 [78]. Although symptoms are heterogeneous, it is commonly characterized by mental retardation, facial gestalt, visceral and skeletal malformations, growth deficiency, obesity and endocrinological anomalies [79]. An exome sequencing strategy identified heterozygous mutations in the gene lysine (K)-specific methyltransferase 2D (*KMT2D*/*MLL2*) as the cause of Kabuki syndrome in 56–76% of the cases [80–82]. *KMT2D* encodes an H3K4 histone methyl transferase which acts as an epigenetic transcriptional activator during development. Some cases of the Kabuki syndrome have also been linked to a mutation in the lysine (K)-specific demethylase 6A (*KDM6A*) gene, which is located on the X-chromosome and encodes a histone demethylase, which directly interacts with KMT2D [81].

Smith–Magenis syndrome (SMS) is an autosomal dominant neurobehavioural disorder characterized by sleep disturbance, multiple developmental anomalies and obesity [83], due to heterozygous mutations in retinoic acid induced 1 (*RAI1*) gene, located on chromosome 17p11.2 [84,85]. Mouse models have shown that the correct expression of *Rai1* is essential for development, body weight regulation, activity levels, circadian rhythmicity, learning and memory [86–88].

Wilms tumour, aniridia, genitourinary abnormalities and mental retardation (WAGR) syndrome is caused by 11p13 deletions of varying sizes [89]. Obesity has been observed in approximately 30% of WAGR patients [90]. In some cases, the brain-derived neurotrophic factor (*BDNF*) gene, located at 11p14.1, can be spanned by the deletion. Compared with patients with intact *BDNF*, heterozygous *BDNF* deletions carriers had significantly higher BMI *z*-scores over childhood. The critical region was located within 80 kb of exon 1 of *BDNF*, demonstrating the link between *BDNF* haploinsufficiency and childhood-onset obesity in WAGR syndrome [89].

Non-syndromic monogenic obesity

Non-syndromic monogenic obesity refers to a single gene disorder that leads to a highly penetrant form of the disease.

Studying extreme obesity from single gene mutations has provided valuable information on the role of leptin–melanocortin pathway in energy balance (Figure 1, Table 1).

A frameshift homozygous mutation in the leptin (*LEP*) gene resulting in truncated transcription of leptin was first discovered in 1997 in two severely obese cousins within a highly consanguineous family of Pakistani origin [91]. Other reports have confirmed this initial discovery in additional patients with no detectable leptin, in Pakistan, Turkey and Egypt [92,93]. Two patients with severe early-onset obesity with a homozygous *LEP* mutation exhibited detectable circulating leptin levels, indicating that the mutation affects the protein function rather than the expression, leading to a bioinactive leptin protein [94].

Similarly, congenital *LEPR* deficiencies were found in severely obese siblings in 1998 [95]. Eight other cases with severe early-onset obesity with homozygous or compound heterozygous mutations in *LEPR* have been reported [96]. These patients exhibited high serum levels of leptin, reflecting the loss of sensitivity of the receptor [96]. In consanguineous populations, such as Pakistani, new case reports have revealed novel homozygous mutations in *LEPR* that constitute 3 % of severely obese Pakistani children [97]. Similarly, a novel frameshift mutation in *LEPR* was identified in a French population from Reunion Island, which suggests a founder effect in genetically isolated populations [98].

Clinical manifestations of patients with mutations in *LEP* or *LEPR* include rapid weight gain within the first year of life, severe hyperphagia and intolerant behaviour when presented with food restrictions [99]. Onset of puberty is often delayed due to hypogonadotrophic hypogonadism [96]. One report of spontaneous pregnancy in a woman with homozygous *LEPR* mutation challenged the idea that homozygous *LEP* or *LEPR* mutation carriers present with hypofertility [100]. Leptin deficient children exhibit defective T-cell mediated immunity, explaining the high rates of infection and mortality in developing countries [96]. Furthermore, humans with loss-of-function mutations in *LEP* and *LEPR* have low blood pressure, despite severe obesity, suggesting an effect of leptin signalling on the vegetative system [101]. The clinical features that result from leptin deficiency can be reversed with leptin therapy. Twelve months of leptin treatment in a 9-year-old girl with leptin deficiency resulted in reduction in weight mainly due to loss of body fat, reduced energy intake and increase in gonadotropin concentrations [102]. In another study, leptin-deficient patients in a fed state gave higher ratings to food images, but these ratings were reduced after leptin treatment [103]. Studies with magnetic resonance imaging techniques also confirmed alteration in the functional cortical activity to food cues in key feeding and reward-related areas, suggesting the role of leptin in both homeostatic and hedonic regulation of appetite [104,105].

The SH2B adaptor protein 1 (*SH2B1*) is a key regulator of leptin, as it enhances leptin signalling by both stimulating Janus kinase 2 (JAK2) activity and assembling a JAK2/IRS1/2 signalling complex [106–108]. Loss-of-function mutations in *SH2B1* patients resulted in severe early-onset obesity [109,110]. Clinical features included hyperphagia, childhood-onset obesity, IR, reduced height and behavioural abnormalities [109]. Genomic imbalances and recurrent deletions of the *SH2B1* containing region on the short arm of chromosome 16 have been associated with behavioural disorders, IR and obesity [111,112].

The first recessive form of obesity due to proopiomelanocortin (*POMC*) deficiency was discovered in 1998 [113]. In addition to obesity, patients with *POMC* mutations displayed hypocortisolism, red hair and skin hypopigmentation, neonatal hypoglycaemia, seizures, cholestasis and voracious appetite [113–115]. POMC deficiency may lead to increased fetal mortality and is involved in neonatal adrenal crisis, early-onset obesity, adrenal insufficiency and hypoglycaemic seizures in neonatal period [114,116–118]. Other clinical features such as severe motor mental retardation were reported in a female with a homozygous *POMC* loss-of-function mutation [119].

Three patients with a recessive monogenic form of obesity were found to be deficient in pro-protein convertase subtilisin/kexin type 1 (*PCSK1*) gene [120–122]. Complete deficiency in prohormone convertase 1 (PC1/3), encoded by *PCSK1*, results in early-onset obesity, hyperphagia, postprandial hypoglycaemia and other endocrine dysfunction, due to one of its roles in the cleavage of proinsulin into insulin and POMC into alpha-melanocyte-stimulating hormone (α-MSH) [120–122]. Null mutations causing PC1/3 congenital deficiency also lead to diarrhoea and diabetes insipidus in some instances [120,122–125]. A rare nonsense loss-of-function mutation at the heterozygous state causes a dominant form of Mendelian familial obesity associated with glucose intolerance/diabetes [126]. Therefore, mutations in *PCSK1* are associated with the dominant or recessive form of monogenic obesity, depending on whether the mutation is partial or total loss-of-function [126]. This is further supported by the PC1/3 mutations with dominant negative effects that alter the expression of wild-type proteins, with consequential effects on PC1/3 availability [127].

The first heterozygous mutation in melanocortin 4 receptor (*MC4R*) discovered in obese humans was in 1998 [128,129]. *MC4R* mutations were once considered an autosomal dominant form of obesity, but not all heterozygous carriers of *MC4R* become obese, although homozygous mutants display fully penetrant early-onset obesity. Homozygous *MC4R* mutations are exceptionally rare [130]. Homozygous carriers of this mutation are hyperphagic and show rapid weight gain in the first few months of life [130]. *MC4R* deficient patients display hyperinsulinaemia, increased linear growth, and an increase in bone mass in both children and adults [131–133]. Additionally, patients experience an increase in both fat and lean mass, which is not observed in other forms of monogenic obesity [134].

The neurotrophic tyrosine kinase receptor type 2 (*NTRK2*) was screened in a boy with early-onset obesity, hyperphagia, developmental delay, impairment in short-term memory and impaired nociception, revealing a missense mutation in *NTRK2* [135]. The impaired hypothalamic neurogenesis in patients with *NTRK2* mutations may explain the observed hyperphagia and obesity [136]. Further analysis showed an alteration of the *BDNF* stimulated protein kinase phosphorylation [135]. The developmental and neurological impairments in this case are consistent with the wide spread of tyrosine receptor kinase B (*TrkB* – en-

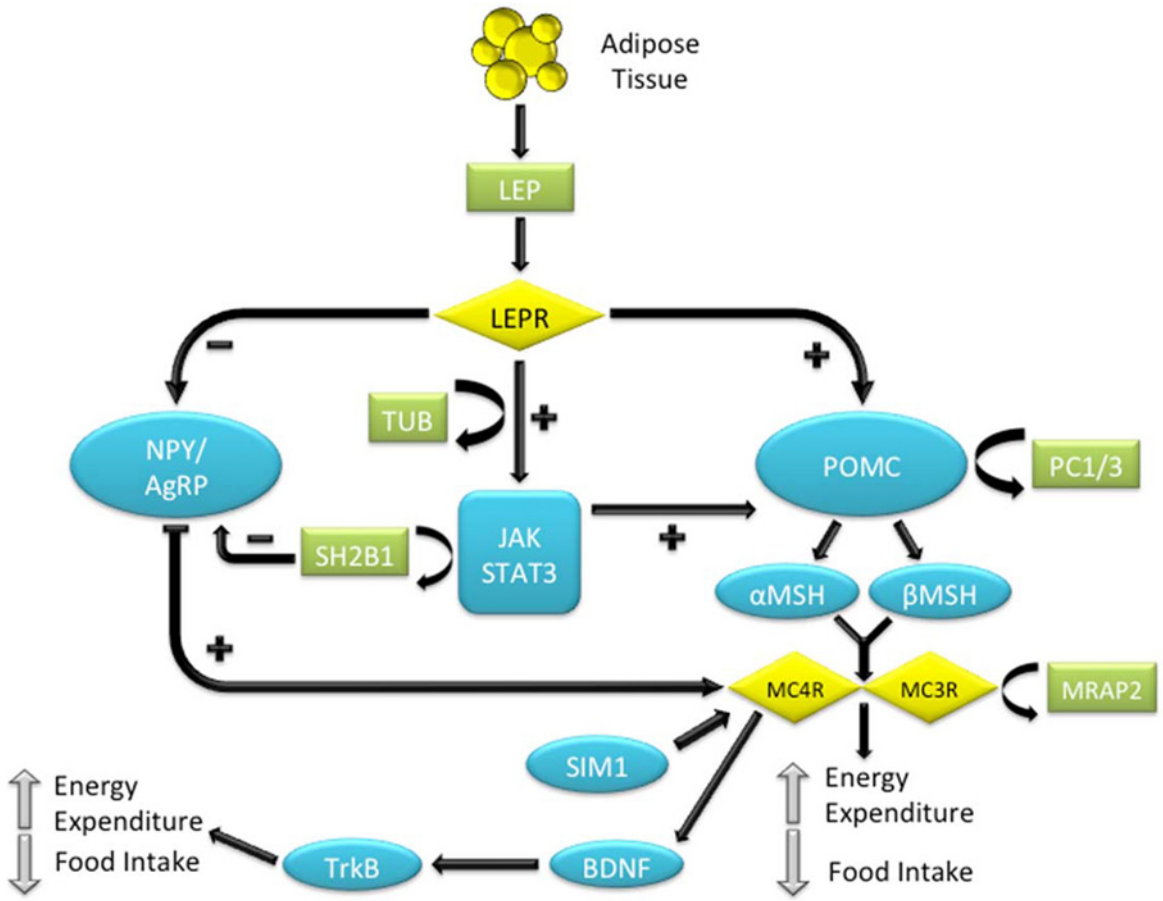

Figure 1 **Genes involved in the leptin–melanocortin pathway that have been associated with monogenic obesity through their influence on food intake and energy expenditure**

Leptin secreted from adipose tissue binds to the leptin receptor in the hypothalamus. Leptin binding inhibits the neuropeptide Y/agouti-related protein (NPY/AgRP) production and stimulates pro-opiomelanocortin (POMC) production, which undergoes post-translational modifications to produce peptides such alpha and beta-melanocyte-stimulating hormone (α- and β-MSH) via the processing of prohormone convertase 1 (PC1/3). Alpha and β-MSH bind to melanocortin 3 and melanocortin 4 receptors (MC3R and MC4R) and induce their activity. Melanocortin 2 receptor accessory protein 2 (MRAP2) can reduce the responsiveness of both MC3R and MC4R to α- and β-MSH and result in obesity. On the other hand, single-minded 1 (SIM1) acts as a facilitator of MC4R activity. Increase in the MC3R and MC4R activities results in a decrease in food intake and increase in energy expenditure. MC4R activity also stimulates release of brain-derived neurotrophic factor (BDNF) which will bind to the neurotrophin receptor (TrkB) and influence food intake and energy expenditure. Aside from activation of the POMC, leptin binding to its receptor also activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling. This pathway, through the help of Src homology 2 B adapter protein 1 (SH2B1), results in activation of signal transducer and activator of transcription 3 (STAT3). STAT3 will then migrate to the nucleus with the help of Tubby bipartite transcription factor (TUB) and activate its target genes related to energy homoeostasis and mediate in the anorexigenic effects of leptin.

coded via *NTRK2*) throughout the central nervous system (CNS), where it is responsible for neuronal survival and differentiation and regulation of synaptic function [137]. In another case, a girl with loss of one functional copy of *BDNF* presented with hyperphagia, severe obesity, cognitive impairment and hyperactivity [138]. As mentioned previously, hyperphagia and obesity observed in a subgroup of patients with WAGR syndrome have been attributed to deletions on chromosome 11p14 that induce haploinsufficiency of *BDNF* [89].

Single-minded homologue 1 (*SIM1*) was considered a highly relevant candidate gene among the 12 genes present in the 6q16 region, a critical region for Prader–Willi like syndrome [139–143]. *SIM1* is expressed in the CNS and plays an essential role in formation of the paraventricular nucleus (PVN) of the hypothalamus [144,145]. Whereas complete *SIM1* deficiency is lethal in mice, *SIM1* haploinsufficiency leads to hyperphagia, obesity and reduction in the PVN [146]. *SIM1* haploinsufficiency has been shown to inhibit the leptin–melanocortin–oxytocin pathway [147,148]. Excessive growth, severe early-onset obesity but no features suggestive of PWS were observed in a girl with a balanced translocation leading to *SIM1* haploinsufficiency [149]. More recently, heterozygous deleterious mutations in *SIM1* were observed in obese children who displayed additional Prader–Willi like/neurobehavioural features [150–152].

Kinase suppressor of Ras 2 (KSR2) is a scaffolding protein involved in multiple signalling pathways through kinase cascades [153,154] that are linked to regulation of food intake, body fat content and glucose homoeostasis [155]. By using a whole-exome sequencing strategy, *KSR2* loss-of-function mutations were identified in humans and were associated with hyperphagia, early-onset obesity, low heart rate, reduced basal metabolic rate and severe IR [154].

Mutations in Tubby bipartite transcription factor (*TUB*) were observed in an 11-year-old boy from a consanguineous Caucasian family. His symptoms included deteriorating vision, obesity and normal glucose/cholesterol/triacylglycerols levels, but other clinical features were not observed to classify the patient as displaying Bardet–Biedl or Alström syndrome [156]. Autozygosity mapping and whole-exome sequencing in another consanguineous UK family identified a homozygous frameshift mutation, which results in a truncated form of TUB. Homozygous loss-of-function *TUB* mutation is extremely rare in humans [156]. Although not formally defined as a syndrome, the clinical features of TUB deficiency in humans may be consistent with a novel ciliopathy.

Oligogenic obesity

Homozygous/compound heterozygous loss-of-function mutations in monogenic obesity genes from the leptin/melanocortin pathway lead to fully penetrant obesity, but are exceptionally rare in humans [157]. A substantially higher proportion of obesity is observed in subjects carrying heterozygous deleterious coding mutations in these genes, resulting in non-fully penetrant obesity [157]. For instance, based on loss-of-function mutation frequency of *MC4R* in the general population of United States (US) (0.07%), 426701 heterozygous *MC4R* carriers compared with 149 homozygous carriers ($N = 305000000$) can be expected. Based on the average penetrance of *MC4R* (60% for heterozygous and 100% for homozygous reported in the literature) [158], partial MC4R deficiency may explain obesity in 256021 individuals, whereas complete MC4R deficiency may be the cause of obesity for only 149 subjects in the US population [159]. *MC4R* heterozygous loss-of-function mutation carriers have milder forms of obesity, and exhibit an interaction with the 'obesogenic' environment [158,160]. A prevalence of 0.2–5.6% of *MC4R* heterozygous, heterozygous compound and homozygous loss-of-function mutation carriers has been reported in obese children and adults from different ethnic backgrounds [130].

Heterozygous loss-of-function mutations in *POMC* result in a non-fully penetrant form of obesity [114,116,161–163]. Biochemical processing of POMC through post-translational modification enzymes results in derivation of α-*MSH* and β-*MSH*. A novel heterozygous mutation in α-*MSH* gene was found in a 12-year-old girl with early-onset obesity, due to a dramatic impairment of α-*MSH* [116]. A loss-of-function missense mutation in β-*MSH* has been associated with childhood obesity. The lack of function of β-*MSH* reduces the amount of MSH peptide in the POMC/MC4R pathway, resulting in obesity [161]. Furthermore, partial deficiency of *LEP* and *LEPR* has been associated with a higher percentage of body fat mass [96,164]. Partial loss-of-function heterozygous mutations in *PCSK1* present a non-fully penetrant form of Mendelian obesity [165]. Heterozygous loss-of-function coding mutations in the melanocortin 3 receptor (*MC3R*) gene could predispose humans to increased risk of obesity, but more evidence is needed to confirm these findings [166–168]. Melanocortin 2 receptor accessory protein 2 (*MRAP2*) is expressed in the brain and adrenal gland [169]. *MRAP2* can interact with all melanocortin receptors, and reduces the responsiveness of melanocortin 1 receptor (*MC1R*), *MC3R*, *MC4R* and melanocortin 5 receptor (*MC5R*) to α-*MSH* [169]. Four rare heterozygous mutations of *MRAP2* have been found to be associated with early-onset severe obesity in humans [170]. A frequent copy number variant (CNV) on the Amylase 1 (*AMY1*) gene, which is involved in expression of AMY1 salivary enzyme that breaks down starch, was associated with an oligogenic form of obesity in European populations [171]. The odds ratio of 1.19 per copy of *AMY1* translates to an 8-fold difference in the risk of obesity between subjects in the top (CNVs$>$9) and bottom (CNVs$<$4) of the top 10% of copy number distribution [171]. The association between the *AMY1* CNV and obesity has been independently replicated in Mexican and Finnish populations [172,173]. In comparison with normal weight children, an increased burden of rare CNVs has been found in severely obese, but further studies are required to confirm that rare CNVs contribute to oligogenic human obesity [174]. For example, the results of a study conducted by Usher et al. [175] contradict the findings that *AMY1* CNVs are associated with obesity. This contradiction, however, may be due to study design differences, as the original findings were reported in a case-control study with severely obese individuals, and Usher's paper included only 500 individuals with BMI $>$ 33 [171,175].

Complete and partial lipodystrophy

Disruption of the body's energy storage mechanism can result in excess or impaired storage of adipocytes, as well as fat distribution abnormalities. Generalized or partial lack of adipose tissue can be inherited or acquired [176]. There are approximately 1000 case reports of patients with inherited forms and their estimated prevalence in the general population is less than one in a million [177]. Generalized lack of fat tissue results in hypertriglyceridaemia, low high-density lipoprotein cholesterol (HDLc) and severe IR, causing refractory T2D. The higher circulating level of insulin contributes to prominent musculature, acanthosis nigricans and pseudoacromegaly. The severity of symptoms is heterogeneous as some patients experience total loss of adipose tissue, and others retain some adipose depots. Congenital generalized lipodystrophy (CGL), also known as Berardinelli–Seip syndrome, is mostly caused by mutations in 1-acylglycerol-3-phosphate *O*-acyltransferase 2 gene (*AGPAT2*) [178] and Berardinelli–Seip congenital lipodystrophy 2 gene (*BSCL2* (*seipin*)) [179], although mutations in other genes, such as caveolin 1 gene (*CAV1*) [180] and polymerase I and transcript release factor gene (*PTRF*) [181], have also been reported. Moreover, homozygous mutations in peroxisome proliferator-activated receptor gamma gene ($PPAR\gamma$) have been identified to cause CGL [182]. Heterozygous mutations in potassium channel inwardly rectifying subfamily J member 6 (*KCNJ6*) cause Keppen–Lubinsky syndrome, characterized not only by severe CGL, but also by a cascade of other features, including severe

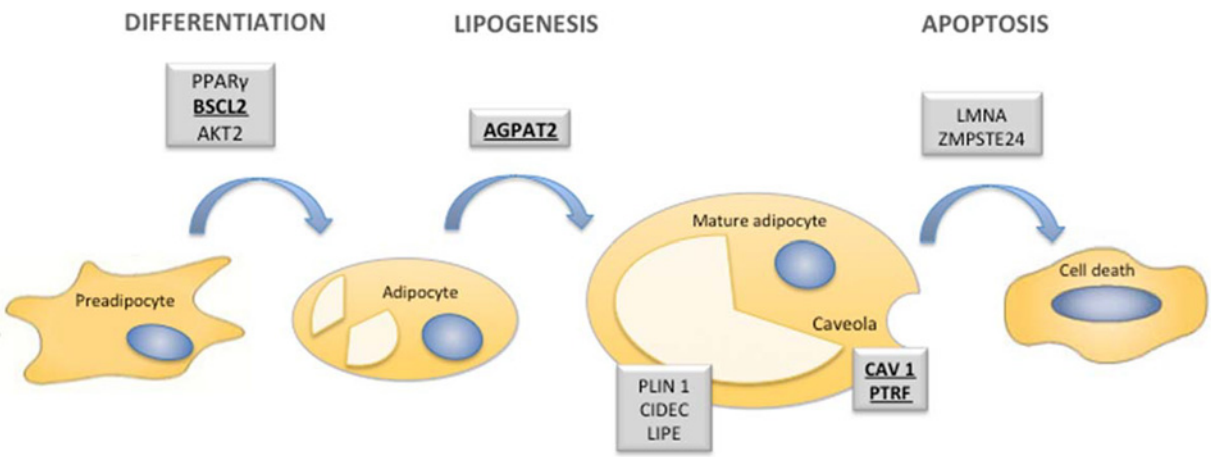

Figure 2 Genes involved in inherited complete (underlined and bold) and partial lipodystrophies
Mutations in genes PPARγ, BSCL2, AKT2 may impair adipose-tissue differentiation; mutations in AGPAT2 may disrupt lipogenesis, mutations in CAV1 and PTRF may disrupt lipid trafficking in the caveolae; mutations in PLIN1, CIDEC are responsible for disruption of lipid droplet, and LIPE of lipolysis; mutations in LMNA and ZMPSTE24 appear to lead to abnormal nuclear architecture and premature cell death.

developmental delay, microcephaly, facial dysmorphy and aged appearance [183]. Familial partial lipodystrophy (FPL) can be due to autosomal recessive or dominant mutations in several genes, resulting in a heterogeneous phenotype of fat loss and metabolic severity. FPL is characterized by the co-occurrence of fat loss limited to the limb, gluteal and trunk regions and spared fat depots, located in the face, neck and intra-abdominal regions [176]. Since the severity of symptoms is proportional to the degree of fat loss, metabolic consequences of FPL are less severe than those seen with CGL. However, FPL still causes severe metabolic complications such as T2D, dyslipidaemia, and coronary heart disease, for which women are more severely affected than men [176]. The autosomal recessive form of FPL is due to mutations in the zinc metalloproteinase STE24 gene (*ZMPSTE24*), and is also a multisystem disease known as mandibuloacral dysplasia, characterized by an underdevelopment (hypoplasia) of the lower mandible and clavicle, and is involved in the maturation of the lamin A protein [184]. Furthermore, a homozygous loss-of-function mutation in cell death-inducing DFFA-like effector c gene (*CIDEC*) has also been reported to cause autosomal recessive FPL [185]. A strong characteristic of this patient was the presence of many multilocular white adipocytes, which are adipocytes divided into many small droplets. Moreover, a homozygous nonsense mutation on the hormone sensitive lipase gene (*LIPE*) has been found in late-onset FPL [186]. On the other hand, mutations in the lamin A/C (*LMNA*) [187], *PPARγ* [188,189], v-akt murine thymoma viral oncogene homologue 2 (*AKT2*) [190], perilipin 1 (*PLIN1*) [191] or polymerase (DNA directed) delta 1 catalytic subunit (*POLD1*) [192] genes result in autosomal dominant FPL. The disorder caused by a mutation in *POLD1* is characterized not only by the metabolic features of FPL, but also by complications such as male hypogonadism, neurosensory deafness and progeroid features (i.e. premature aging) [192].

Mutations in genes *AGPAT2*, *CAV1* and *PTRF* may disrupt adipocyte function [178,180,181] (Figure 2). *AGPAT2* encodes an enzyme responsible for synthesizing the precursors of phospholipids and triacylglycerol, whereas *CAV1* and *PTRF* have both been implicated in lipid trafficking through their roles in the formation of caveolae (i.e. small invagination of the adipocytes plasma membrane) [178,193–195]. Mutations in *PLIN1* are responsible for smaller adipocytes and *in vitro* experiments suggest that disruption of this lipid droplet protein increases basal lipolysis [191]. Mutations in genes *PPARγ* and *BSCL2* may inhibit the expression of adipogenic genes and impair adipose-tissue differentiation [188,196,197]. Mutations in *AKT2* may impair adipose-tissue differentiation and downstream insulin receptor signalling [190]. Mutations in *LMNA* and *ZMPSTE24* appear to lead to abnormal nuclear architecture and premature cell death [184,198,199]. *CIDEC* mutations result in multilocular smaller lipid droplet, contributing to the elevated level of basal lipolysis [185,200]. *LIPE* mutations impair lipolysis free fatty acid (FFA) flux from adipocytes [186]. *KCNJ6* mutations impair the inwardly rectifying K+ channel, for which the biological function remains unexplored [183]. Ectopic fat accumulation (in liver, skeletal muscle, pancreas) in lipodystrophic subjects is strongly and consistently associated with IR and T2D [201,202]. Coronary atherosclerosis could be explained not only by the metabolic risk factors present in these subjects, but also by endothelial cells' dysfunction and senescence as reported in some cases [203]. Epicardial fat is totally absent from CGL [204]. Metabolic features can be improved by recombinant leptin therapy [205,206].

Mendelian form of obesity with metabolic syndrome

Gene identification efforts for the metabolic syndrome have so far been limited, likely due to a lack of consensus on the diagnostic criteria. Only one study has highlighted the role of dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1B gene (*DYRK1B*) in a Mendelian form of metabolic syndrome [207]. The mutation R102C within *DYRK1B* was

identified by linkage analysis and whole-exome sequencing in three large Iranian families with a perfect co-segregation with central obesity, T2D, hypertension and early-onset coronary artery disease. Moreover, screening for *DYRK1B* among 300 morbidly obese white Caucasian subjects with coronary artery disease and metabolic phenotype led to the identification of mutation H90P in five unrelated patients, co-segregating with metabolic syndrome in an autosomal dominant pattern. The mutations alter two important functions of *DYRK1B*: promotion of adipogenic differentiation and induction of the hepatic gluconeogenic enzymes, such as glucose-6-phosphatase [207].

POLYGENIC OBESITY

Polygenic obesity is caused by multiple gene defects with modest effects that interact with the environment [208]. Several approaches, such as linkage/positional cloning, candidate gene and genome-wide association study (GWAS) have been used to discover genes associated with polygenic obesity.

Genetic linkage analysis has been used to detect the chromosomal location of a disease gene [209]. By linkage analysis, a three SNP haplotype in ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) was found to contribute to childhood and adult obesity in a recessive model in European populations [210,211]. Follow-up meta-analyses of the gain-of-function coding variant K121Q confirmed the association with adult obesity in European populations [212]. Mouse models have established that overexpression of *ENPP1* results in adipocyte IR and defective adipocyte maturation [213,214]. The variant R125W in TBC1 domain family member 1 (*TBC1D1*) was identified as a candidate for severe obesity in females through a linkage study in US and French populations [215,216]. Congenic female mice lacking *TBC1D1* presented with a reduction in body weight, suggesting that *TBC1D1* mutations suppress high-fat diet-induced obesity (DIO) by increasing lipid use in skeletal muscle [217,218]. Additionally, *Tbc1d1*$^{-/-}$ mice demonstrated that *TBC1D1* is involved in the regulation of glucose transporter type 4 (GLUT4) levels and in exercise mediated glucose uptake in non-oxidative muscle fibres [219]. The R125W variant, in particular, impairs skeletal muscle glucose transport and results in complete loss of insulin-responsiveness acquisition [220,221]. Following the identification of a linkage region for adult obesity on chromosome 5q14-21 in the French population, *PCSK1* was also defined as a positional candidate gene for polygenic obesity with three coding non-synonymous variants (N221D, Q665E and S690T) consistently associated with severe obesity in both adults and children [222,223]. Recently, a systematic review in more than 330000 individuals demonstrated an association of the same variants with moderate obesity and BMI variation [224]. Impairments in the N221D-mutant PC1/3 protein's catalytic activity were observed [223]. Through transfected rat models, the presence of the triple variants caused a subtle deficit of PC1/3 enzymatic activity in endocrine and neuroendocrine cells, resulting in impairments in converting prohormones and proneuropeptides to their bioactive forms [225].

Candidate gene studies involve the identification and analysis of a gene with a likely role in the pathogenesis of the disease, due to the gene's chromosomal location [226]. Using this approach, the Val66Met polymorphism in *BDNF* was related to BMI in healthy adults [227], and subsequently replicated in two large populations comprising of British women [228]. This variant decreases BDNF secretion and leads to memory impairment and increased susceptibility to neuropsychiatric disorders such as anxiety and depression [229,230]. A deleterious non-synonymous variant p.R270H in the G protein-coupled receptor 120 (*GPR120*/*O3FAR1*) gene, a receptor for unsaturated long-chain FFA, was found to be associated with obesity by decreasing signalling activity [231]. Similar phenotypes were observed in *Gpr120* knockout mice that were fed a high-fat diet [231]. The −13910C>T polymorphism, upstream from the lactase (*LCT*) gene, provides lactase persistence (LP) and is associated with a higher consumption of dairy products [232]. Within the past 5000–10 000 years, a strong selection for this allele was observed in areas with extensive dairy farming as LP conferred an evolutionary advantage [233,234]. A meta-analysis found that European carriers of this LP variant had a higher BMI [235]. These results were replicated in French and Spanish populations [232] and in a multiethnic population comprising of children [236,237], suggesting that lactose digestion is significantly associated with increased BMI [237].

GWAS involve the rapid and dense screening of markers across the genome, and have contributed to identification of genetic variations associated with polygenic obesity [238]. Common variants in the fat mass and obesity-associated (*FTO*) gene that increase susceptibility to obesity in children and adults were the first to be successfully identified through GWAS. The variants were simultaneously discovered in four independent studies. Frayling et al. [239] identified that *FTO* predisposes individuals to T2D through an increase in BMI. Homozygosity for the risk allele was associated with a 3 kg body weight increase and 1.67-fold higher chance of developing obesity [239]. Through a GWAS, Scuteri et al. [240] found that *FTO* was positively associated with BMI, hip circumference (HC), and weight. Hinney et al. [241] conducted a GWAS for early-onset extreme obesity in German children and found *FTO* to be strongly associated with childhood obesity. Concurrently, Dina et al. [242] used a population stratification approach to identify an association between *FTO* and childhood and adult extreme obesity. Although all four of the initial studies were conducted in European populations, positive associations between *FTO* and obesity in other ethnicities, such as East and South Asian, Latino American, African American and Native Indian, have also been found [243–246]. Approximately 1% of BMI variance can be explained by the intron 1 variants [239].

Humans homozygous for a catalytically inactive FTO and *Fto*$^{-/-}$ mice show similarities such as severe growth retardation, however, only humans are reported to show developmental abnormalities in the central nervous or cardiovascular systems [247]. *Fto*$^{-/-}$ mice develop leanness due to an increase in energy expenditure and systemic sympathetic activation [248]. Correspondingly, Church et al. [249] demonstrated that overexpression

of *Fto* in mice results in obesity. *FTO* functions as a transcriptional coactivator and demethylates N6-methyladenosine residue in nuclear RNA [38,247].

Studies have also shown that *FTO* variants, especially in intron 1, can have pleiotropic effects on the expression of *FTO* and other genes involved in energy homoeostasis. Bell et al. [250] demonstrated a linear relationship between homozygous non-risk, heterozygous and homozygous risk alleles and DNA methylation on the risk haplotype. For instance, homozygosity for *FTO* risk allele results in an increase in DNA methylation of its own obesity risk haplotype [250]. *FTO* risk allele rs1421085 leads to a doubling of iroquois homeobox 3 (*IRX3*) [251] and iroquois homeobox 5 (*IRX5*) expression during early adipocyte differentiation, resulting in a shift from energy-dissipating beige adipocytes to energy-storing white adipocytes, and an obesity phenotype [252]. Noncoding sequences within the first intron of *FTO* are functionally connected with *IRX3* through a long-range interaction of enhancers [251]. By sequencing a region encompassing the *FTO*, *RPGRIP1L* and *IRXB* cluster genes in a Danish male population, a novel non-coding region upstream of *IRX5* was found to be associated with BMI in an age dependent manner [253].

RPGRIP1-like (*RPGRIP1L*) is a ciliary gene located near *FTO*. *Rpgrip1l*$^{+/-}$ mice tend to be hyperphagic and fatter and display a lesser suppression of food intake in response to leptin, indicating that *RPGRIP1L* may be partly responsible for the obesity susceptibility signal observed at the *FTO* locus [254]. *FTO* and *RPGRIP1L* are regulated by isoforms P200 and P110 of cut-like homeobox 1 (*CUX1*), a transcription factor [255]. Presence of *FTO* SNP rs8050136 reduces the affinity for P110, resulting in decreased *FTO* and *RPGRIP1L* mRNA levels, decreased LEPR trafficking to the cilium and subsequently, a diminished cellular response to leptin [255]. Studies by Claussnitzer et al. and others have demonstrated that *RPGRIP1L* may not be 'wholly responsible' for this signal as manipulation of AT Rich Interactive Domain 5B (*ARID5B*), rs1421085, *IRX3* and *IRX5* also displayed pro-obesity and anti-obesity effects [252,256]. However, researchers have indicated a lack of confidence in the methods used by Claussnitzer et al. [257–260]. For instance, Claussnitzer et al. did not determine whether there is a relationship between carriers of alleles associated with an increased risk of obesity and reduced energy expenditure [258], and overlooked the regulation of target-gene expression critical to adipocyte browning at an epitranscriptomic level [257,259]. Moreover, their paper did not include the link between FTO deficiency and an induction of beige adipocytes through uncoupling protein 1 (*UCP1*) expression and mitochondrial uncoupling [257]. Additional studies are required to better elucidate the impact of *FTO*'s genetic variants on obesity.

Since the discovery of *FTO*, many other loci that contribute to BMI, adult obesity, childhood obesity and WHR have been identified using GWAS and an up-to-date list of these polymorphisms is presented in Table 2 [174,261–264]. By using different BMI thresholds depending on the ethnicity/age group under investigation, GWAS have identified 135 variants associated with BMI level and/or obesity status so far, including 89 loci associated only with BMI, 21 loci associated only with obesity, and 24 loci associated with both BMI and obesity (Figure 3). SNPs in most Mendelian non-syndromic genes (*BDNF, NTRK2, LEPR, MC4R, PCSK1, POMC, SH2B1, TUB*) and some Mendelian syndromic genes (*SDCCAG8, BBS4*) have been shown to contribute towards polygenic obesity.

To estimate fat distribution, the WHR adjusted for BMI (WHRadjBMI) seems to be the most relevant, as it captures and combines the adverse effects of the deleterious abdominal fat and the beneficial effects of gluteal subcutaneous fat, independent of overall adiposity [265]. Independent GWAS [266–272] and GWAS meta-analysis [273–278] have now identified 97 loci related to all the measures of fat distribution in all ancestries, but most signals have been identified in populations of Europeans. Five of these loci overlap with BMI level and/or obesity status, including one that used BMI non-adjusted waist circumference (WC) to evaluate the fat distribution (Figure 3). Sixty-nine loci were associated with WHRadjBMI [271,272,274,276–278], five with unadjusted WHR [268,269,273,274,277], fifteen with WC [266,267,269,271,273,275,277], nine with HC [277], three with body fat percentage [267,275,276], three with visceral adipose tissue/subcutaneous adipose tissue (VAT/SAT) [270] and three with fat body mass [275,276]; among them eight loci overlap between several fat distribution traits. Interestingly, only PPARγ is involved in the polygenic variation of fat distribution (WHR) and monogenic forms of lipodystrophy.

Recent studies have conducted GWAS on non-European populations and identified novel loci, some of which have been replicated in European ancestry populations. A meta-analysis identified that three novel common variants in or near CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), *PCSK1* and glycoprotein 2 (*GP2*) are associated with BMI in East Asians, but only one of the *CDKAL1* SNPs was replicated in populations of European ancestry [279]. A meta-analysis conducted in an African ancestry population identified a new locus near polypeptide *N*-acetylgalactosaminyltransferase 10 (*GALNT10*) to be associated with BMI [280]. A Metabochip-wide discovery analysis in African Americans found two new BMI-associated loci at brain and reproductive organ-expressed gene (*BRE*) and DEAH (Asp-Glu-Ala-His) box polypeptide 34 (*DHX34*) [281]. In a GWAS conducted in Bangladeshi adults, a significant positive association was observed between nitric oxide synthase 1 (neuronal) adaptor protein gene (*NOS1AP*) and change in BMI in women over a 2-year period [282]. Another GWAS in 62245 East Asians identified two novel loci associated with BMI (*CDKAL1,* Kruppel-like factor 9 (*KLF9*)) [283]. In the process, they also discovered gene–gene (GxG) interactions between *KLF9* and growth differentiation factor 8 (*GDF8*) [283].

Considering the ethnic specificity of body fat distribution, *FTO* and *MC4R*, along with another new locus [cathepsin S (*CTSS*)] were identified by a GWAS for fat mass in a multiethnic population [276]. Furthermore, two new loci for WC [Lim homeobox 2 (LHX2)] and WHRadjBMI [Ras responsive element binding protein 1 (*RREB1*)] are found in populations of African ancestry, as well as six previously identified loci in European ancestries [271]. A new locus associated with WHR [HECT domain containing E3 ubiquitin protein ligase 4 (*HECTD4*)] has also been discovered in the Korean population [268].

Table 2 List of polygenic loci associated with obesity and body fat distribution traits

Gene	SNP	Anthropometric trait	References
ABCA1	rs10991437	WHR, WHRadjBMI	[277]
ADAM23	rs13387838	Childhood BMI	[488]
ADAMTS9	rs6795735, rs2371767	WHRadjBMI	[274,277]
ADCY3	rs7586879, rs6545814, rs11676272	BMI	[261,279,280]
ADCY9	rs2531995	Obesity	[489]
AGBL4	rs657452	BMI	[263]
AKAP6	rs12885467	BMI	[490]
ALDH2/MYL2	rs671, rs12229654	BMI	[279]
ARL15	rs1664789	WC	[277]
ASB4	rs6465468	BMI	[263]
ATP2B1	rs1966714	BMI	[490]
BCL2	rs12454712	WHR, WHRadjBMI	[277]
BDNF	rs6265, rs4923461, rs10767664, rs2030323, rs10767664, rs988712	BMI, obesity, overweight	[279,283,293,491–493]
BMP2	rs979012	WHR, WHRadjBMI	[277]
BRE	rs116612809	BMI	[281]
BTNL2	rs7759742	WHR, WHRadjBMI	[277]
C5	rs7044106	HC	[277]
C9orf93	rs4740619	BMI	[263]
CADM1	rs12286929	BMI	[263]
CADM2	rs13078807	BMI, overweight	[293,489]
CALCR	rs9641123	BMI	[263]
CALCRL	rs1569135	WHR, WHRadjBMI	[277]
CBLN1	rs2080454	BMI	[263]
CBLN4	rs11908421	BMI	[278]
CCDC92	rs4765219	WHR, WHRadjBMI	[277]
CCNJL	rs17472426	WC	[277]
CDH10	rs972303	WHRadjBMI	[278]
CDKAL1	rs2206734, rs9356744	BMI	[279,283]
CEBPA	rs4081724	WHR, WHRadjBMI	[277]
CECR2	rs17809093	WHRadjBMI	[278]
CLIP1	rs11057405	BMI	[263]
CMIP	rs2925979	WHR, WHRadjBMI	[277]
CNTN5	rs1394461	WHR	[277]
COBLL1	rs3769885	BMI	[278]
CPEB4	rs6861681, rs7705502	WHRadjBMI	[274,277]
CREB1/KLF7	rs17203016	BMI	[263]
CTSS	rs2230061	Fat body mass	[494]
DCST2	rs905938	WHR, WHRadjBMI	[277]
DDC	rs4947644	BMI	[278]
DNM3/PIGC	rs1011731, rs714515	WHRadjBMI	[274,277]
EHBP1	rs11688816	BMI	[263]
ELAVL4	rs11583200	BMI	[263]
ELP3	rs13253111	Childhood BMI	[488]
EPB41L4B/C9orf4	rs6477694	BMI	[263]
ERBB4	rs7599312	BMI	[263]
ETS2	rs2836754	BMI	[263]
ETV5	rs7647305, rs9816226	BMI, obesity, overweight	[293,489,491]
EYA2	rs6090583	WHR, WHRadjBMI	[277]

Table 2 Continued

Gene	SNP	Anthropometric trait	References
FAIM2	rs7138803, rs7132908	BMI, obesity, overweight, young-onset extreme overweight	[262,293,458,489,491]
FAM120AOS	rs944990	Childhood BMI	[261]
FAM13A	rs9991328	WHR, WHRadjBMI	[277]
FANCL	rs887912, rs12617233	BMI, obesity, overweight	[293,489,492]
FGFR4	rs6556301	WHR, WHRadjBMI	[277]
FHIT	rs2365389	BMI	[263]
FIGN	rs1460676	BMI	[263]
FLJ35779	rs2112347	BMI, obesity, overweight	[293,489]
FOXO3/HSS00296402	rs9400239	BMI	[263]
FTO	rs1421085, rs9922619, rs1121980, rs9936385, rs9941349, rs3751812, rs1558902, rs8050136, rs62033400, rs17817449, rs9939609, rs9930506, rs1121980, rs12149832, rs9940128	BMI, obesity, childhood obesity, young-onset extreme overweight, subcutaneous adipose tissue, overweight, body fat percentage, WC, fat body mass	[174,239–242,262,264, 267–270,275,279,283, 291,293,458,459,489,491, 494,495]
GALNT10	rs7708584	BMI	[280]
GANAB	rs2956993	WHRadjBMI	[278]
GBE1	rs3849570	BMI	[263]
GDF15/PGPEP1	rs17724992	BMI	[263]
GDF5	rs224333	WHR, WHRadjBMI	[277]
GIPR	rs2287019, rs11671664	BMI	[279,283,293]
GMDS	rs722585	HC	[277]
GNAT2	rs17024258	obesity	[489]
GNPDA2	rs10938397, rs13130484, rs348495	BMI, obesity, overweight	[291,293,489,496]
GNPNAT1	rs4898764	WHRadjBMI	[278]
GORAB	rs10919388	WHR, WHRadjBMI	[277]
GP2	rs12597579	BMI	[279]
GPC6	rs319564	WHR	[277]
GPR120	rs116454156	Obesity	[231]
GPRC5B	rs12444979	BMI, obesity, overweight	[293,489]
GRB14	rs10195252	WHRadjBMI	[274,277]
GRID1	rs7899106	BMI	[263]
GRP	rs7243357	BMI	[263]
HECTD4	rs2074356	WHR	[268]
HHIP	rs11727676	BMI	[263]
HIF1AN	rs17094222	BMI	[263]
HIP1/PMS2L3/PMS2P5/ WBSCR16	rs1167827	BMI	[263]
HMGA1	rs206936, rs1776897	BMI, WHR, WHRadjBMI	[277,293]
HMGXB4	rs2092029, rs1053593	HC, WHRadjBMI	[277,278]
HNF4G	rs4735692	Obesity, overweight	[489]
HOXA11	rs7801581	WHR, WHRadjBMI	[277]
HOXB5	rs9299	Childhood obesity	[262]
HOXC13	rs1443512	WHRadjBMI	[274,277]
HS6ST3	rs7989336	Obesity	[489]
HSD17B12	rs2176598	BMI	[263]
HSD17B4	rs10478424, rs1045241	WHR, WHRadjBMI	[272,277]
IFNGR1/OLIG3	rs13201877	BMI	[263]

Table 2 Continued

Gene	SNP	Anthropometric trait	References
IQGAP2	rs2069664	WHRadjBMI	[278]
IRS1	rs2673140, rs2943650	WHRadjBMI, body fat percentage	[275,278]
ISPD	rs9648211	WHRadjBMI	[278]
ITGB6	rs2124969	WC	[277]
ITIH4	rs2535633	BMI	[279]
ITPR2/SSPN	rs718314, rs10842707	WHRadjBMI	[274,277]
JUND	rs12608504	WHR, WHRadjBMI	[277]
KAT8/ZNF646/VKORC1/ ZNF668/STX1B/FBXL19	rs9925964	BMI	[263]
KCNJ2	rs8066985	WHR, WHRadjBMI	[277]
KCNK3	rs11126666	BMI	[263]
KCNK9	rs2471083	BMI	[497]
KCNMA1	rs2116830	Obesity	[493]
KCNQ1	rs2237892	BMI	[279]
KCTD15	rs11084753, rs29941	BMI	[291,293,491]
KIAA1731	rs1784203	WC	[277]
KLF13	rs8042543	WHR, WHRadjBMI	[277]
KLF14	rs6971365, rs13241538	HC, WHRadjBMI	[277,278]
KLF9	rs11142387	BMI	[283]
KLHL31	rs7739232	HC	[277]
LEKR1	rs17451107	WHR, WHRadjBMI	[277]
LEMD3	rs7307410	WHRadjBMI	[278]
LEPR	rs11208659	Childhood obesity	[174]
LHX2	rs2075064	WC	[271]
LMX1B	rs10733682	BMI	[263]
LOC100287559/BBS4	rs7164727	BMI	[263]
LOC284260/RIT2	rs7239883	BMI	[263]
LOC285762	rs9374842	BMI	[263]
LPIN2	rs643507	Adult obesity in asthmatic subjects	[498]
LRP1B	rs2890652	BMI	[293]
LRRN6C	rs10968576	BMI, obesity	[293,489]
LY86	rs1294421, rs1294410	WHRadjBMI	[274,277]
LYPLAL1	rs4846567, rs2820443, rs11118316, rs2605100	WHR, WHRadjBMI, visceral/subcutaneous adipose tissue ratio	[270,273,274,277]
MACROD1-VEGFB	rs11231693	WHR, WHRadjBMI	[277]
MAF	rs1424233	Extreme obesity	[264]
MAP2K3	rs11652094	BMI	[499]
MAP2K5	rs2241423, rs4776970, rs997295, rs8028313	BMI, obesity, overweight	[279,293,489,492]
MAP3K1	rs11743303, rs9687846	WHR, WHRadjBMI	[272,277]
MAPK3/KCTD13/INO80E/ TAOK2/YPEL3/DOC2A/ FAM57B	rs4787491	BMI	[263]
MC4R	rs17782313, rs571312, rs12970134, rs2331841, rs6567160, rs8089364, rs7234864, rs723486	BMI, extreme obesity, obesity, overweight, fat body mass, WC	[174,261,262,264,266,279, 283,287,293,458,489,491, 492,494–496]
MEIS1	rs1385167	WHR, WHRadjBMI	[277]
MIR148A/NFE2L3	rs10261878	BMI	[280]
MIR548A2	rs1441264	BMI	[263]

Table 2 Continued

Gene	SNP	Anthropometric trait	References
MIR548X2/PCDH9	rs9540493	BMI	[263]
MRPS33P4	rs13041126	obesity	[489]
MSC	rs12679556	WHR, WHRadjBMI	[277]
MSRA	rs7826222	WC	[273]
MTCH2	rs10838738, rs3817334	BMI, obesity, overweight	[291,293,489]
MTIF3	rs4771122	BMI	[293]
MYEOV	rs11607976	HC	[277]
NAV1	rs2820292	BMI	[263]
NCAM2	rs11088859	WC	[269]
NEGR1	rs2815752, rs2568958, rs1993709, rs3101336	BMI, obesity, overweight, childhood obesity	[174,291,293,489,491]
NFE2L3	rs1055144, rs10245353	WHRadjBMI	[274,277]
NISCH/STAB1	rs6784615	WHRadjBMI	[274]
NKX2-6	rs7830933	WHR, WHRadjBMI	[277]
NLRC3	rs758747	BMI	[263]
NMU	rs3805389	WHR, WHRadjBMI	[277]
NPC1	rs1805081	Extreme obesity	[264]
NRXN3	rs10150332, rs11624704, rs10146997	BMI, obesity, WHR, WC	[267,269,293,489]
NT5C2/CYP17A1/SFXN2	rs11191560	BMI	[263,279]
NTRK2	rs1211166	BMI	[492]
NUP54/SCARB2	rs17001654	BMI	[263]
OLFM4	rs12429545, rs9568856, rs9568867	Childhood BMI, childhood obesity, obesity	[261,262,489]
OR2W5-NLRP3	rs10925060	WC	[277]
PACS1	rs564343	Childhood obesity	[174]
PARK2	rs13191362	BMI	[263]
PBRM1	rs2276824	WHR, WHRadjBMI	[277]
PCSK1	rs261967, rs6232, rs6234/rs6235	BMI, obesity	[223,279]
PDXDC1	rs4985155	HC	[277]
PEMT	rs4646404	WHR, WHRadjBMI	[277]
PLCD4/CYP27A1/USP37/ TTLL4/STK36/ZNF142/ RQCD1	rs492400	BMI	[263]
PLXND1	rs10804591	WHR, WHRadjBMI	[277]
PMS2L11	rs2245368	BMI	[263]
POMC	rs713586, rs6545814, rs1561288, rs6752378, rs10182181	BMI, childhood obesity, obesity, overweight	[262,279,293,489,496]
PPARG	rs4684854, rs17819328	WHR, WHRadjBMI	[272,277]
PRKCH	rs1957894	Childhood obesity	[174]
PRKD1	rs11847697, rs12885454	BMI	[263,293]
PTBP2	rs1555543	BMI	[293]
PTPDC1	rs2398893	WHR	[277]
PTPRD	rs7042428	WHRadjBMI	[278]
QPCTL	rs2287019	Obesity, overweight	[489]
RAB27B	rs8092503	Childhood BMI	[488]
RABEP1	rs1000940	BMI	[263]
RALYL	rs2033732	BMI	[263]
RARB	rs6804842	BMI	[263]
RASA2	rs16851483	BMI	[263]

Table 2 Continued

Gene	SNP	Anthropometric trait	References
RFX7	rs8030605	WHR, WHRadjBMI	[277]
RMST	rs11109072	Childhood obesity	[174]
RPL27A	rs11042023	Obesity	[489]
RPS6KA5	rs7492628	WHRadjBMI	[278]
RPTOR	rs7503807	Overweight	[489]
RREB1	rs6931262	WHR, WHRadjBMI	[271]
RSPO3	rs9491696, rs1936805	WHRadjBMI	[274,277]
RXRA	rs10881574	WHRadjBMI	[278]
SBK1/APOBR	rs2650492	BMI	[263]
SCG3/DMXL2	rs3736485	BMI	[263]
SDCCAG8	rs12145833	Childhood obesity	[459]
SEC16B	rs10913469, rs543874, rs574367, rs516636, rs591120	BMI, childhood obesity, obesity, overweight	[262,279,283,293,489,491, 496]
SFXN2	rs7917772	WHR, WHRadjBMI	[277]
SGCZ	rs17470444	WHRadjBMI	[278]
SH2B1	rs7498665, rs4788102, rs7359397, rs4788099	BMI, obesity, overweight	[291,293,489,491,492]
SIM1	rs17185536	WHRadjBMI	[278]
SLC22A3	rs3127574	BMI	[278]
SLC2A10	rs3091869	BMI	[497]
SLC2A3	rs741361	WHRadjBMI	[278]
SLC39A8	rs13107325	BMI	[293]
SMAD6	rs1440372	WHR, WHRadjBMI	[277]
SMG6/N29617	rs9914578	BMI	[263]
SNX10	rs1534696	WHR, WHRadjBMI	[277]
SOX11	rs10929925	HC	[277]
SPATA5-FGF2	rs303084	WHR, WHRadjBMI	[277]
SPRY2	rs534870, rs1144	Body fat percentage, WC	[275,277]
SRPK2	rs1144	WC	[277]
STXBP6	rs10132280	BMI	[263]
TAL1	rs977747	BMI	[263]
TBX15/WARS2	rs984222, rs2645294	WHRadjBMI	[274,277]
TCF7L2	rs7903146	BMI	[263]
TDRG1/LRFN2	rs2033529	BMI	[263]
TFAP2B	rs987237, rs734597, rs2272903	BMI, obesity, overweight, WC	[273,293,458,489,492]
THNSL2	rs1659258	Visceral adipose tissue	[270]
TLR4	rs1928295	BMI	[263]
TMCC1	rs2811337	WHR, WHRadjBMI	[276]
TMEM160	rs3810291	BMI, obesity	[293,489]
TMEM18	rs6548238, rs7561317, rs2867125, rs12463617, rs4854344	BMI, childhood obesity, obesity, overweight	[174,262,291,293,489,491, 492,496]
TNKS	rs17150703	Childhood obesity	[459]
TNNI3K	rs1514175, rs12142020, rs1040070, rs1514174	BMI, obesity, childhood obesity	[262,293,489,496]
TOMM40/APOE/APOC1	rs2075650	BMI	[492]
TTN	rs2042995	WHRadjBMI	[278]
TUB	rs4929949	BMI	[293]
UBE2E3	rs1528435	BMI	[263]
VEGFA	rs6905288, rs1358980	WHRadjBMI	[274,277]

Table 2 Continued

Gene	SNP	Anthropometric trait	References
VPS53	rs2034088	HC	[277]
ZBTB10	rs16907751	BMI	[263]
ZNF423	rs2047937	WC	[277]
ZNF608	rs48361333	BMI	[293]
ZNRF3/KREMEN1	rs4823006, rs2294239	WHRadjBMI	[274,277]
ZZZ3	rs17381664	Obesity	[489]

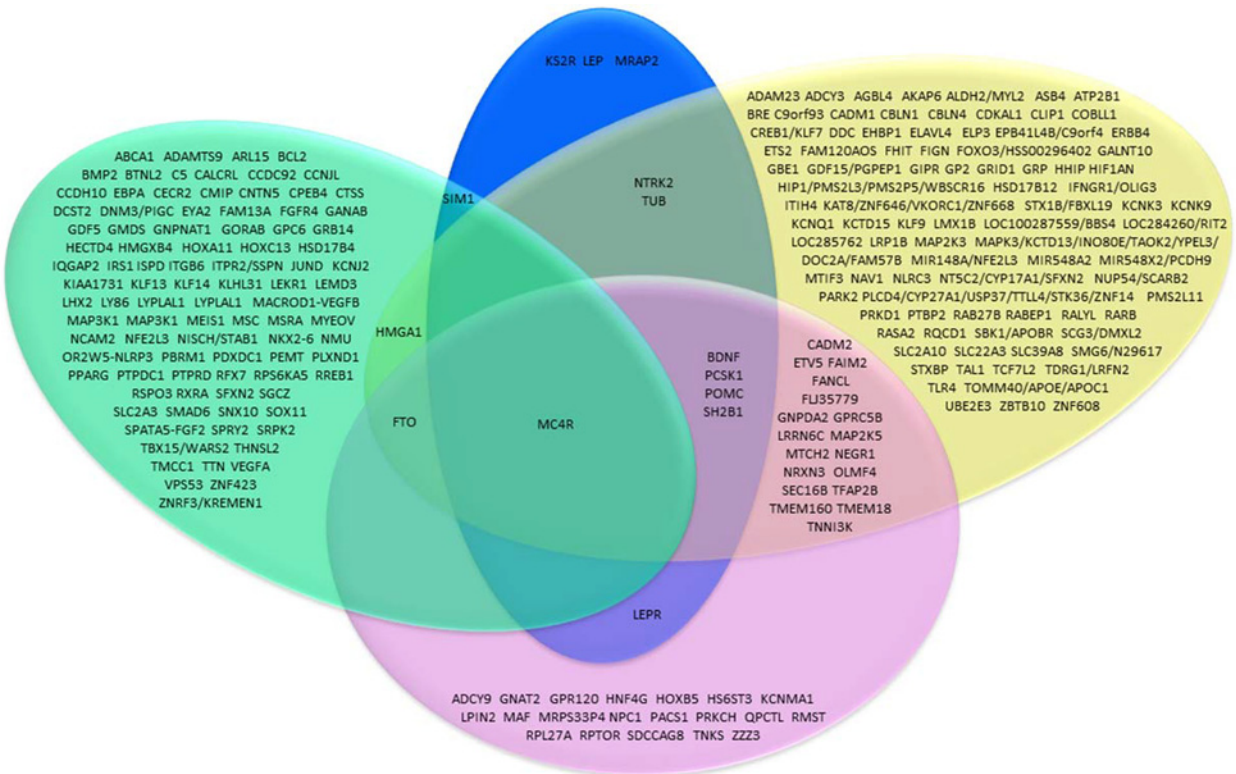

Figure 3 Venn diagram of genes involved in monogenic, oligogenic and polygenic obesity
Monogenic, oligogenic obesity genes are depicted in blue, polygenic BMI-related genes in yellow, overweight or obesity-related genes in purple and fat distribution-related genes in green.

However, some findings call for interpreting GWAS signals with caution. Uncommon or rare variants may create 'synthetic associations' by occurring more often in association with one of the alleles at the common site compared with the other allele, and these synthetic associations account for part of the association signals identified through GWAS [284]. Subsequent studies demonstrated that synthetic associations due to rare variants are unlikely to explain most of the GWAS signals [285,286]. By using GWAS data to study a genomic region encompassing *MC4R* and after analysing synthetic associations, *MC4R* coding variants appeared to have a negligible impact on the association signal [287]. Similarly, a role of rare coding mutations in the association of common variants in *PCSK1* with polygenic obesity was excluded [165].

Altogether SNPs have been estimated to explain 27–30% of BMI variance [35,36]; however, our current knowledge of genome-wide significant obesity SNPs explains only ∼3% of this variance and more variants still remain to be discovered [263].

To identify the 'missing heritability' of obesity, innovative approaches have been employed [288]. Hagg et al. [289] conducted a meta-analysis of genome-wide association studies (GWAS) using the 'VErsatile Gene-based Association Study' (VEGAS) approach, looking for loci that could not be identified in standard single-marker analyses due to allelic heterogeneity, and found six novel loci associated with BMI missed by conventional GWAS.

The HumanExome BeadChip was recently used to identify novel associations between low frequency coding variants and T2D susceptibility [290]. In the near future, similar studies using data from the international Genetic Investigation of ANthropometric Traits (GIANT) consortium will undoubtedly identify additional coding variants predisposing to obesity.

Another source of heritability often missed by GWAS studies is the contribution of CNVs. CNVs are chromosomal segments encompassing large replications or deletions in genes [38]. An 8 kb deletion near the neuronal growth regulator 1 (*NEGR1*) locus is associated with a lower risk of severe obesity [174]. A common CNV at 1p31.1, near *NEGR1*, was found to be associated with BMI through a meta-analysis and was confirmed by other studies [291,292]. A GWAS identified a 21 kb deletion CNV near G protein-coupled receptor, class C, group 5, member B (*GPRC5B*), to be associated with BMI [293]. A GWAS conducted in the Chinese population found a CNV located at 10q11.22, contributing 1.6% to BMI variation [294]. The pancreatic polypeptide receptor 1 (*PPYR1*) gene, a key regulator of energy homoeostasis, is located within this region, providing an insight into the CNV's association with BMI [294]. Located on chromosome 11q11, a common CNV covering the three olfactory genes was found to be associated with obesity [292]. Although some CNV associations with obesity have been replicated and confirmed by independent studies, authors highlighted the difficulties associated with replicating rare CNV associations across populations [295]. Interestingly, CNVs can also have ethnicity-specific impacts. For instance, the *PCSK1* SNP rs6234/rs6235 was found to be associated with obesity in white Caucasian, African and Hispanic ethnic groups, but not in the East Asian populations [224]. Ethnic-specific epistasis was hypothesized to be the cause of the differential associations [224].

Using a novel variable number tandem repeats (VNTRs) association method, significant associations between dedicator of cytokinesis 5 (*DOCK5*) VNTRs and childhood and adult severe obesity have been shown. VNTRs explain approximately 0.8% of BMI variance [296].

Recently, fine-mapping has also been used for the identification of loci, as it refers to the process of searching a region previously identified by GWAS for possible causal alleles that better account for the missing heritability of obesity than proxy SNPs [297]. Gong et al. [281] conducted a Metabochip-wide discovery analysis in African Americans and found two new BMI-associated loci at brain and reproductive organ-expressed gene (*BRE*) (rs116612809) and DEAH (Asp-Glu-Ala-His) box polypeptide 34 (*DHX34*) (rs4802349). Fine-mapping in populations of African descent refined the list of potentially causal variants at the *FTO* locus to 28 SNPs [238,271,289]. This was followed by a multi-ethnic fine-mapping study that further narrowed down the *FTO* causal variants to 25 [298]. Fine-mapping experiments are also useful in identifying secondary independent obesity association signals, as recently shown at the *MC4R*, Long Intergenic Non-Protein Coding RNA 1122 (LINC01122), NLR Family, CARD Domain Containing 3-Adenylate Cyclase 9 (*NLRC3-ADCY9*), *GPRC5B-GP2* and *BDNF* loci by Locke et al. [263]. Another novel approach involves calculating gene scores derived from a regional association to improve trait prediction [299,300]. Functional characterization can also be used to identify causal variants among a restricted list, as shown for *FTO* SNP rs1421085 involved with adipocyte browning [252].

Two recent studies have taken advantage of the strong interplay between genes and environment in the determination of obesity to identify additional susceptibility missed by conventional GWAS. A variance prioritization approach performed in 5892 individuals from the dbGAP consortium identified novel [*LOC100507652*, proteoglycan 2 (*PRG2*), gamma-glutamyltransferase light chain (*GGTLC*) and disabled-1 (*DAB1*)] and confirmed (*NEGR1*) genetic contributors to BMI [301]. A joint GWAS meta-analysis of SNP and SNP by environment regression coefficients performed in up to 320485 individuals of European descent led Winkler et al. to identify 4 novel BMI and 17 novel WHR loci that display age and sex-dependent association patterns [270].

Lastly, studying GxG interactions can contribute to obesity heritability. However, as these studies require greater power to detect significant associations, only a few studies have reported nominal results [283,302].

GENETICS OF LEANNESS

Obesity and underweight could potentially have mirroring aetiologies, possibly through opposing effects on energy balance. A complementary approach based on studies of genes that are associated with a lean phenotype or resistance to weight gain in an obesogenic environment could lead to a better understanding of the molecular basis of bodyweight regulation and identify new pharmacological obesity targets [303,304].

Leanness is present in the clinical synopsis of a dozen syndromes (http://omim.org). Most of them are neurodegenerative in nature, cause poor swallowing and result in low food intake, such as the Niemann–Pick disease [305]. We focused on the subset of leanness syndromes due to metabolic alterations. The region 16p11.2 is particularly interesting because large deletions have been associated with severe hyperphagic obesity [112] and duplications with underweight phenotype accompanied by an unusually high frequency of selective and restrictive eating behaviours [306]. The deletion spanned 28 genes [112], including *SH2B1*, that enhances leptin and insulin signalling [111]. One-hundred and thirty eight duplication carriers were identified from over 95,000 individuals with intellectual disabilities, psychiatric disorders, or from European population-based cohorts, for whom the phenotypes correlated with changes in transcription levels for genes mapping within the duplication [306]. Anthropometric measures have also been correlated with CNVs of genes in the 17p11.2 region. As described previously, Smith–Magenis obesity syndrome is caused by a haploinsufficiency of RAI1 [307]. The reciprocal duplication in 17p11.2 causes Potocki–Lupski syndrome [308,309], an opposite phenotype of SMS, characterized by leanness, hyperactivity and resistance to DIO [308] due to an overexpression of *RAI1* [87]. Another relevant syndrome is the LEOPARD syndrome, also known as the Noonan syndrome with multiple lentigines. It is a rare autosomal dominant disorder associated with various developmental defects, cardiopathies, dysmorphism, short stature and lower-than-average BMI [310]. It is caused by mutations in protein tyrosine phosphatase, non-receptor type 11 gene (*PTPN11*), which inactivates the tyrosine

phosphatase Src-homology 2 domain-containing phosphatase 2 (*SHP2*), a component of LEPR signalling [310]. LEOPARD syndrome in mice reveals strong reduction in adiposity, resistance to DIO and better overall metabolic profiles, resulting from impaired adipogenesis, increased energy expenditure and enhanced insulin signalling [310].

Polygenic determinants of leanness are not as researched as the ones for obesity, even though genetic factors have been shown to influence BMI across the entire range, from extreme leanness to extreme obesity [311]. Negative associations of *MC4R* V103I and I251L variants with obesity were initially found in two studies conducted in Europeans [312,313]. The associations were later confirmed by GWAS [293]. The gain-of-function obesity-protective mutations I251L and V103I in *MC4R* are also in opposition to the loss-of-function mutations in the same gene associated with hyperphagic obesity [134,314].

Additional reports showed that individuals homozygous for the 67Thr allele of agouti related neuropeptide (*AGRP*) had a BMI slightly below the ideal range for their age [315]. A rare variant in the visfatin gene (*NAMPT/PBEF1*) was associated with protection against obesity [316], and a common variant in neuropeptide FF receptor 2 gene (*NPFFR2/GPR74*) was associated with leanness and increased lipolysis [317]. However, these results have not been replicated and require further confirmation.

Although anorexia nervosa-induced underweight is thought to have a distinct aetiology from inherited leanness because of its strong psychological component, an inverse genetic correlation between BMI, childhood obesity and anorexia has recently been demonstrated using a cross-trait LD score regression analysis from GWAS summary statistics [318]. However, no anorexia predisposing genes have been identified by GWAS so far [319].

GENE–ENVIRONMENT INTERACTIONS IN OBESITY

The genotype can interact with biological factors such as age and sex, as well as obesogenic environment and lifestyle factors (Figure 4).

Studies have shown that the overall contribution of genes towards the BMI increases from childhood to early adulthood. As the puberty stage advances, the influence of the genetic component towards BMI increases, and that of environmental factors decreases [320]. In a meta-analysis, *PCSK1* variants had a stronger effect in children/adolescents than in older adult Europeans [224]. Longitudinal and cross-sectional studies have shown that an *FTO* variant increases BMI from birth up to the age of 20–30 years [321]. A longitudinal study in children from birth to age 11 showed that some obesity risk alleles had a larger impact on increased weight gain during early infancy than on subsequent childhood weight gain [322]. An olfactomedin 4 (*OLFM4*) variant was also found to be associated with increased BMI at 8 years and increased BMI change through childhood [261]. Shared genetic effects were found between BMI and BMI change, with a weakening from adolescence to adulthood [323]. Household effects, or unmeasured non-genetic factors, were mostly noticed

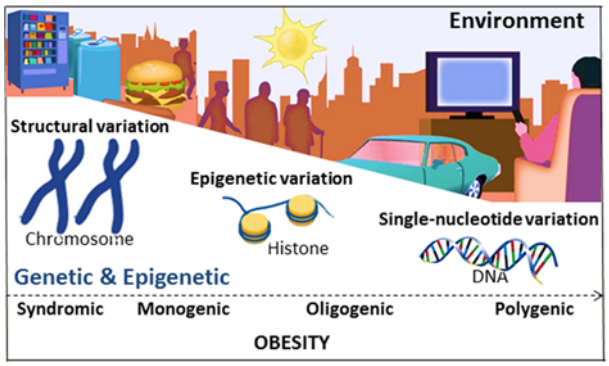

Figure 4 The contribution of genetic, epigenetic and environmental stimuli to obesity

In monogenic and syndromic obesity, a single gene mutation could result in severe obesity, irrespective of environmental stimuli. However, in case of oligogenic and polygenic obesity, environmental factors can exacerbate the progression of obesity if the individuals have a genetic predisposition to weight gain. Adapted from [463]: van der Klaauw, A.A. and Farooqi, I.S. (2015) The hunger genes: pathways to obesity. Cell **161**, 119–132.

during young adulthood, and not adolescence [323]. Similarly, Winkler et al. showed that, compared with younger adults, 11 loci associated with BMI in an age-dependent manner had a 1.5–3.5 times smaller effect in older adults [278].

A sexual dimorphism was present for half of the loci associated with WHRadjBMI, showing higher effect sizes in women compared with men [277]. The cumulative effect of the WHRadjBMI-related alleles was estimated at 1.36% (0.82% in men and 2.40% in women) of the phenotypic variance [277].

Despite the increase in an obesogenic environment, studies have shown that the genetic influence on BMI and adiposity is significantly high. Children born since the onset of the paediatric obesity epidemic have demonstrated an increase in the additive genetic variance of BMI [30]. Between 1951 and 1983, the BMI heritability increased from 75% to 78.8%, suggesting that the obesogenic environment enhanced the influence of adiposity related genes [324]. Similarly, another study confirmed the high heritability for BMI and WC (77% for both) in twins aged 8–11 years born after the onset of the paediatric obesity epidemic [30]. *MC4R* heterozygous loss-of-function mutation carriers exhibit an interaction with the obesogenic environment, with an increased penetrance for MC4R deficiency across three generations [158,160]. Mutation carriers consume three times more food than their unaffected siblings during an *ad libitum* meal [134], and have a preference for consumption of foods with a high-fat content [325]. Interestingly, the low penetrance of *MC4R* loss-of-function mutation in a Greek population suggests a beneficial interaction with the Mediterranean diet [326], which consists of different fatty acids, oleic acid or omega 3 compared with saturated acid. The reduction in food intake and body weight is through modulation of the POMC and MC4R signalling [327]. A variation in the effect of the *FTO* risk allele on BMI was found in the longitudinal Framingham Heart Study. This variation was dependent on the birth cohort, possibly due to global environmental changes that influence allelic penetrance [328].

Through a meta-analysis of GWAS, Yang et al. found the *FTO* SNP rs7202116 to be associated with phenotypic variability, in addition to obesity [329]. A difference of approximately 7%, or 0.5 kg, in the BMI variance of individuals with opposite homozygous genotypes at the *FTO* locus was observed [329]. Several studies have shown that pre-existent obesity can further amplify the effect of certain genes and their genetic variants, and lead to an exaggerated increase in body weight [330]. For instance, obesity risk alleles of *FTO*, *MC4R*, *TMEM18*, *BDNF*, TNNI3 interacting kinase (*TNNI3K*), neurexin 3 (*NRXN3*), *SEC16B* and glucosamine-6-phosphate deaminase 2 (*GNPDA2*) were found to be more strongly associated with increases in BMI z-scores in children with higher BMI [331]. Compared with children with the protective *FTO* genotype, those heterozygous or homozygous for the *FTO* risk allele were less protected from the effects of an obesity-promoting socioeconomic status [332]. Physical activity can substantially reduce the influence of genetic factors on BMI in both young and older adults [333–335]. Sleep duration is associated with increased BMI and increased genetic influences on BMI in heritability studies, suggesting that shorter sleep duration increases expression of genetic risks for high body weight [336].

EPIGENETICS OF OBESITY

Epigenetics is defined as changes in gene transcription and expression that occur without altering the DNA sequence and result in long-term changes in cellular and biological functions.

David Barker was the first to hypothesize that nutritional and other environmental exposures in early life can 'reprogram' the fetus and lead to changes in predisposition to cardio-metabolic disorders in the long term [337]. His hypothesis was supported by epidemiological data from the 1944 Dutch famine cohort [338]. Higher levels of obesity, coronary heart disease, lipids and altered clotting were observed if offspring were exposed to the famine during early gestation, illustrating the effect of maternal nutrition on the offspring's health in later life [339].

Epigenetic variation is classically categorized according to the extent of dependence on genetic changes. Obligatory and facilitated epigenetic variations reflect a complete dependence on genetic changes (such as transposon insertion) and a semi-independence (such as retrotransposon insertion) respectively; and pure epigenetic variation is without genetic changes [340]. The epigenetic states can be transferred through (i) mitotic inheritance to maintain epigenetic changes across cell cycles; and/or (ii) meiotic inheritance carried by sperm cell and oocyte to transmit epigenetic changes across generations [341]. Epigenetic change is considered acquired when the epigenome is affected *de novo* by an environmental event. In this way, the effect can be (i) intra-generational, occurring within the exposed individual's lifespan and resulting in later life changes; (ii) inter-generational, occurring within the gamete of fetal stage of life, but without transmission to the future generations [342]. The true trans-generational transmission of inherited epigenetic change means that the F1 gametes are exposed *in utero* to maternal experiences (F0), which subsequently affects the F2 offspring. The epigenetic traits are then passed through unexposed F2 gametes to the F3 offspring [342]. The mechanisms that underlie the epigenetic marks mainly consist of (i) DNA methylation; (ii) histone post-translational modifications and chromatin remodelling; (iii) inheritance of specific mRNAs, such as long non-coding RNAs and siRNAs/miRNAs, that regulate gene expression and other epigenetic mechanisms, such as DNA methylation [341].

DNA methylation consists of the introduction of methyl groups in the 5-carbon position of cytosine bases by DNA methyltransferases, usually at 5′-C-phosphate-G-3′ (CpG) sites. These sites are unequally distributed across the genome, giving rise to vast low-density CpG regions with interspersed clusters located mainly on CpG islands, to regulate gene expression [341]. Histones can be modified by different enzymes at external N- and C-terminal tails as well as at internal histone-fold domains. These post-translational modifications mainly consist of acetylation, methylation, phosphorylation and carbonylation. These modifications on histone tails have the potential to modify the structure of chromatin, resulting in the activation or silencing of genes [341]. All core histone proteins have diverse variants establishing different regulated regions that can be activated or repressed for transcription. Histone variants may confer a level of gene expression regulation, they may be tissue or cell-specific, or may be related to a specific cellular event [341].

Analysis of DNA methylation and histone acetylation patterns in monozygotic twin pairs showed that even if twins were epigenetically similar during the early years of life, they differed considerably later in life, which illustrates the impact of acquired epigenetic changes [343]. On the other hand, the percentage of phenotypic variance that can be explained by non-pure inherited epigenetic trans-generational variation still remains unclear and new methodologies are currently being developed to fill this gap [344].

As DNA methylation remains a key mechanism to assess epigenetic patterns, various approaches have been developed to study the associations between gene methylation levels and obesity, including the candidate gene approaches and epigenome-wide association studies (EWASs).

Periconceptional exposure to the Dutch famine was associated with a lower methylation of the insulin like growth factor 2 (*IGF2*) differentially-methylated region. However, exposure later in the gestation period was not associated with *IGF2* methylation demonstrating that the early development period is crucial for establishing and maintaining epigenetic marks [345].

DNA of 479 individuals of European origin and two replication cohorts for a total of 2128 participants was used to analyse whole blood DNA CpG-sites in relation to BMI [346]. Increased BMI in adults was found to be associated with increased methylation at the hypoxia-inducible factor 3 alpha (*HIF-3α*) locus in blood cells and adipose tissue [346]. The association between HIF-3α methylation levels in blood and adiposity has been replicated in independent populations [347,348]. Another EWAS for BMI and WC was performed in leucocyte DNA obtained from 2097 African Americans. The more promising associations were replicated using whole-blood DNA from 2377

White adults, CD4+ T-cell DNA from 991 White individuals and adipose tissue DNA from 648 White women. The methylation level at 18 CpG sites located in/near the Carnitine Palmitoyltransferase 1A (*CPT1A*), ATP-Binding Cassette, Sub-Family G Member 1 (*ABCG1*), *LYS6GE*, Lysine (K)-Specific Demethylase 2B (*KDM2B*), *RALB*, *PRRL5*, Lectin, Galactoside-Binding, Soluble, 3 Binding Protein (*LGALS3BP*), Chromosome 7 Open Reading Frame 50 (*C7orf50*), Pre-B-Cell Leukaemia Homeobox 1 (*PBX1*), erythrocyte membrane protein band 4.9 (*EPB49*) and *BBS2* genes were associated with BMI in blood and adipose tissue cells [347]. By analysing whole-genome DNA methylation and expression data in human adipose tissue from 96 males and 94 females of European ancestry, a correlation between BMI and DNA methylation and expression was identified in 2825 genes [349].

Compared with children born before maternal weight loss, those born after maternal weight loss by bariatric surgery have been shown to have a lower risk for obesity [350]. This indicates the presence of a strong epigenetic influence early in life on the development of obesity later in life.

Another study analysing DNA methylation patterns in adipose tissue of obese women showed hypermethylation for all gene regions in subcutaneous and omental adipose tissue, before weight loss through gastric bypass [351]. Moreover, relative to promoter regions, this higher methylation was observed in the 3′ untranslated region, especially in genes associated with obesity, epigenetic regulation and development, such as, forkhead box P2 (*FOXP2*), DNA (cytosine-5-)-methyltransferase 3 beta (*DNMT3B*) and the *HOX* clusters [351]. However, interpreting this study requires some caution due to the global measures of methylation across all regions without sub-setting in functional loci. Another study on methylation patterns in individuals who went from being obese to normal weight concluded that peripheral blood mononuclear cell methylation is associated with BMI [352].

Studies have also suggested associations between genetic and epigenetic factors. The obesity risk allele of *FTO* has been implicated with higher methylation of sites within intron 1 of the *FTO* gene and methylation of other genes [250]. Out of 52 known obesity-associated SNPs, 28 are associated with DNA methylation levels at 107 proximal CpG sites, which implies that they may affect multiple genes [353]. Interestingly, several obesity-associated SNPs were associated with CpGs that were in the promoters of genes known to participate in the pathogenesis of obesity, such as *POMC, BDNF* and *SH2B1*; or were located in regions that interact with such genes. Associated CpGs were also enriched in enhancers, which highlights their potential in gene regulation [353].

However, when leading EWAS, some biological, technical and methodological issues should be taken into consideration when designing a study and interpreting the results, such as specific localization of DNA methylation rather than whole methylation, differences between cells and tissue, limited sample size and lack of analytical methodology [354].

A majority of epigenetics and obesity studies have used DNA from peripheral blood leucocytes to analyse global methylation patterns [355]. Despite the ease of access in obtaining blood samples, this can be problematic as different blood cells have varying methylation profiles [356]. The potential negative consequences of this cellular heterogeneity can be prevented by correcting the data based on the number of each cell type in the sample [355], and by utilizing emerging single-cell epigenomic applications [357]. Another method resembles regression calibration, considering DNA methylation signature as a high dimensional multivariate surrogate for the distribution of white blood cells, for predicting or modelling diseases such as obesity [358].

Unlike early life, environmentally induced epigenetic modifications later in life may be more tissue-specific and not accurately represented in blood cells [355]. Thus, despite the fact that blood can mirror epigenetic signatures in target tissues for metabolic diseases such as adipose tissue, caution should be applied when using blood cells to analyse epigenetic patterns in the context of obesity [349].

GUT MICROBIOTA AND OBESITY

The human gut microbiota is composed of up to 100 trillion microbes and encompasses more than 5 million genes (microbiome) [359]. The dominant phyla in the gut are Firmicutes (60–65%), Bacteroidetes (20–25%), Proteobacteria (5–10%) and Actinobacteria (3%), which together constitute over 97% of the gut microbe population [359]. This composition not only presents variability among individuals, but also longitudinal variability within individuals. In examining the heritability of the gut microbiome, the largest twin cohort found that the bacterial family Christensenellaceae has the highest heritability ($h^2 = 0.39$) [360]. Other studies have focused on heritability of the microbiome composition in the entire body, and have found it to be associated with the host's genetic makeup [361]. The abundance and composition of microbial populations are also largely influenced by diet, medication, weight and metabolic state of the host [362]. Most [363,364] but not all [365] studies report on the diversity of the microbiota, particularly the decrease in fractional proportion of Bacteroidetes species relative to Firmicutes in obese compared with lean individuals [363–366]. Weight loss was shown to increase the relative proportion of Bacteroidetes species and microbial diversity [367,368]. Similarly, diversity of the genes is diminished in obese compared with lean individuals [364] and is increased by dietary weight loss [369,370]. A key question is whether the increase in Firmicutes and decrease in Bacteroidetes due to body weight changes represents a direct effect of changes in energy balance or of changes in energy stores. The predominance of the environment in determining the composition of the gut microbiome is also evident [371]. By examining the effects of both underfeeding and overfeeding, differences between caloric intake and weight maintenance calories were positively correlated with the relative abundance of Firmicutes species and negatively correlated with the relative depletion of Bacteroidetes species in lean and obese subjects [369]. Moreover, the population of Firmicutes was found to be negatively correlated with resting energy expenditure, but not in multiple regression analysis including fat mass as a covariate [366]. Specific alterations of the gut microbi-

ota might constitute a potential therapeutic intervention to prevent obesity and/or to promote and sustain weight loss in humans. Further studies are necessary to test the efficacy and safety of using manipulations involving prebiotics, probiotics and diet composition before they are implemented in clinical routine. Preliminary rodent studies showed that administration of probiotics, such as Lactobacillus species, reduces weight and body fat in DIO mice without changing energy intake [372]. Administration of prebiotics such as dietary inulin-type fructo-oligosaccharides, stimulates the growth of health-promoting Bifidobacterium, Lactobacillus, Roseburia and Faecalibacterium species in humans [373]. Manipulation of the microbiota by transplantation, diet or prebiotics in different metabolic states (obese, formerly-obese and never-obese) could be used to isolate the possible roles of microbiota in the regulation of energy homoeostasis. As there is a large inter-individual variation in human responses to diet, exercise, pharmacological or other weight loss interventions, there are likely to be differences between individuals in the salience of the roles of microbiota in energy homoeostasis as well.

INHERITED OBESITY AND UNDERLYING BIOLOGICAL MECHANISMS

The vast majority of variants associated with obesity do not possess a clear biological function [293]. Aside from gene targeting experiments in animal models, other techniques such as functional genomics, crystallography, endophenotype studies and molecular biology experiments, have contributed to improve our knowledge of obesity mechanisms [374–379]. For example, the development of BBS knockout mice supported the role of cilium function in the central regulation of energy balance, as abrogating cilia in POMC neurons is sufficient to increase food intake and cause obesity in mice [380].

Defects in non-syndromic monogenic candidate genes point to the leptin–melanocortin pathway (Figure 1) in controlling food intake and energy balance, as patients harbouring these defects display hyperphagia and obesity [381]. Aside from their role in the leptin pathway, *SIM1, BDNF* and *NTRK2* are also essential in development and differentiation of the PVN [144,147], which is an important integrator of sensory information influencing the coordination of visceromotor and neuroendocrine responses [382]. The hypothalamic role in energy balance suggests that traits related to appetite and satiety represent an underlying behavioural mechanism in one's genetic susceptibility to obesity. In line with this hypothesis, the behavioural susceptibility model was developed, which emphasizes that genetic predisposition to obesity may act through appetitive traits reflecting lack of control over eating or eating in response to negative emotions [383,384].

With progress in the methodology of genetic studies, the roles of other regions of the brain in energy homoeostasis have also been discovered. For example, the role of the hippocampus and limbic system, that have previously been associated with learning, cognition, memory and emotion, has been discovered in the regulation of BMI [263]. Furthermore, genes that are associated with BMI are also involved in pathways such as in neural transmission and development [263]. In polygenic obesity, satiety responsiveness also mediated the association between predisposition to obesity and adiposity, in parallel to what has been observed in monogenic obesity studies [385]. The GPR120 is an unsaturated long chain fatty acids receptor and plays a role in preference for fat as well as adipogenesis, and is a genetic contributor to human obesity [231,386]. Further analysis on polygenic obesity SNPs has shown an association with snacking behaviour, preference for macronutrient-specific foods and higher energy intake [387–390].

Looking at genes involved in digestion of food, CNVs on the *AMY1* gene, which is involved in expression of AMY1 salivary enzyme that breaks down starch, impact obesity [171–173]. This finding suggests that a reduction in *AMY1* CNVs is associated with higher BMI, most likely due to a reduction in proper carbohydrate metabolism [171]. Furthermore, adult individuals who are able to digest lactose (carriers of variants on the lactose gene *LCT*) show higher BMI levels [235]. After intestinal absorption, dietary nutrients travel through the hepatic portal vein to the liver. The liver uptakes a part of glucose and fatty acids, removing it from circulation, and converting it to glycogen for storage, or to lipids respectively, which are in part stored and in part re-secreted as VLDL particles, going then to adipocytes [391]. Hence the liver plays a crucial role in conversion and transport of nutrients to different organs. Evidence of its causal role in obesity has been made from monogenic obesity with metabolic syndrome (with the effect of *DYRK1B* mutations on hepatic gluconeogenesis), and from polygenic obesity with the involvement of several variants in the hepatic lipid and cholesterol metabolism (such as *NPC1* [392], *CYP27A1* [393]), lipoprotein transport (such as *APOC1*, *APOE* [394]) or glycogen storage (such as *GBE1* [395]). Furthermore, gut microbiota, as mentioned previously, are sensitive to energy balance, and overfeeding or underfeeding can affect BMI levels through disrupting the gut microbiota equilibrium [355].

Impaired glucose metabolism in obesity implies that genes in the insulin pathway are also involved in obesity pathophysiology [263]. Some T2D risk variants, such as gastric inhibitory polypeptide receptor (*GIPR*), *CDKAL1,* potassium channel-voltage gated KQT-like subfamily Q, member 1 (*KCNQ1*), and transcription factor 7-like 2 (*TCF7L2*), play a protective role against increased BMI [293,396]. This could be due to deficient insulin secretion, as insulin regulates fat storage in adipocytes [396]. Moreover, a Mendelian randomization study identified a causal association between fetuin-A and BMI [397]. Fetuin-A is a multifunctional protein of hepatic origin and inhibits insulin receptor autophosphorylation and tyrosine kinase activity [398]. This study concluded that for every 1 mg/l increase in fetuin-A expression, BMI increases by 0.83 kg/m^2, most likely due to IR [397].

Genes involved in fat differentiation and metabolism have also been highlighted in association with obesity and body fat distribution. Despite the heterogeneity in phenotypes in different types of lipodystrophies, most patients suffer from the same metabolic complications that obese patients suffer from, such as IR, T2D, hepatic steatosis and dyslipidaemia [399]. This raises the possibility of a 'final common pathway' that may result in

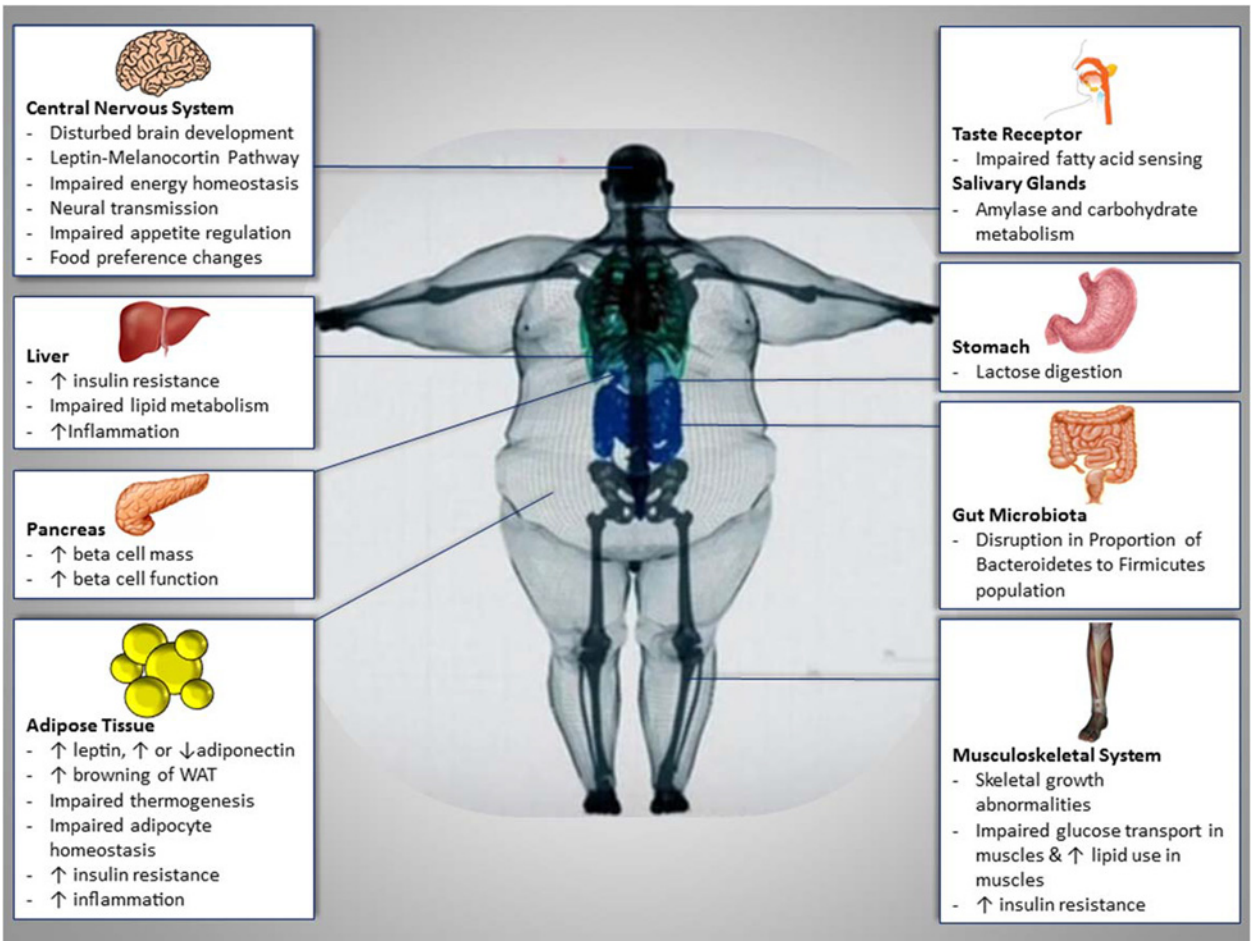

Figure 5 **Pathophysiology of obesity**

Several organs are affected by genes associated with predisposition to obesity. The CNS is the main regulator of energy expenditure and feeding behaviour, and mutations in genes in this region result in increase in bodyweight. In the digestive tract, mutations in taste receptor genes and digestive enzymes in the mouth correlate to higher BMI as well. Furthermore, mutations in genes involved in digestion of lactose in the stomach, disruption of gut microbiota equilibrium, lipid and glucose metabolism could result in obesity. The genes involved in the musculoskeletal system's growth and glucose transport are associated with obesity. Genes involved in fat distribution and adipogenesis can result in obesity through a cascade of events that affect the body's energy homoeostasis. WAT, white adipose tissue.

defective adipocyte differentiation, development and function. Levels of adiponectin, a hormone produced predominantly by adipocytes that are involved in glucose regulation and fatty acid oxidation, have been associated with increased BMI through a Mendelian randomization study [400]. Polygenic loci associated with body fat distribution are shown to be enriched for genes expressed in adipose tissue and for putative regulatory elements in adipocytes. For example, *PPARγ*, CCAAT/enhancer binding protein alpha (*CEBPA*) and R-spondin 3 homologue (*RSPO3*) are candidate genes for adipogenesis, but also play an important role in white adipose tissue differentiation [401] and may influence expansion or loss of adipose tissue [255,266]. Induction of *HIF-3α*, can accelerate adipogenesis through the activation of adipocytes-related genes [402,403]. Studies on the *FTO* and adrenoceptor beta 3 (*ADRβ3*) genes have highlighted biological pathways that relate to the browning of white adipocytes, lipid storage gene expression, repression of basal mitochondrial respiration, decrease in thermogenesis in response to stimulus, and an increase in adipocyte size [252, 399]. In lipodystrophy, the fat accumulation in skeletal muscles is associated with IR and T2D [201,202]. Furthermore, *TBC1D1* polymorphisms have been associated with impaired glucose transport in muscles [218]. Normally, the adipose tissue sequesters FFAs and other lipids in the form of inert triacylglycerols. In conditions such as metabolic syndrome, the neutral lipid storage of the adipose tissue is exceeded after the saturation of normal depots [404]. In lipodystrophy, impairments in triacylglycerol synthesis, adipocyte differentiation or adipocyte apoptosis could also lead to excess FFAs (Figure 2). In both cases, the excess FFAs can result in ectopic triacylglycerol depositions in the muscle, liver or pancreas that could consequentially lead to IR and dyslipidaemia [399].

Thus, polygenic obesity encompasses a diverse number of biological pathways and portrays a complicated framework of under-

lying mechanisms in obesity aetiology (Figure 5). It is important to note that although thermogenesis or alterations in adipocytes or impaired insulin signalling could contribute to increase in weight gain, what separates monogenic obesity from polygenic obesity is the hyperphagic clinical feature. Mechanisms involved in polygenic obesity could have an additive effect, contribute to excessive weight gain and result in increased BMI levels, but genetically driven hyperphagic behaviour is a necessary and sufficient mechanism in monogenic obesity. These suggest that excessive food intake is the main culprit in severe obesity and controlling energy intake is the first line of defense against obesity.

FROM GENOMICS TO CLINICAL PRACTICE

There is a growing enthusiasm for personalized medicine, an approach allowing a proactive maintenance of wellness specific to the individual, that is predictive, preventive, personalized and participatory (P4) [405–407]. This trend is partially due to the development of high-throughput next generation sequencing and whole-genome or customized microarrays with decreasing costs [406]. In addition, *in silico* pipelines consisting of fast bioinformatics analysis, can predict the pathogenicity of variants (http://www.ngrl.org.uk/Manchester/page/missense-prediction-tool-catalogue). Going beyond genomics, development of other omics, such as transcriptomics, proteomics, epigenomics, metagenomics, metabolomics and nutriomics, is expected to increase the phenotypic prediction [408], and aid in better categorizing of individuals based on risk profiles for BMI and development of comorbidities [409]. Whereas combining genetic and epigenetic information have greater utility for complex-trait prediction [408], technologies could soon lead to the creation of epigenetic test panels for obesity [410]. In the same way, integrating metagenomic information on a systems biology-wide approach would allow a better understanding of the interplay between gut microbiome and host metabolism, and provide novel therapeutic approaches [411]. All of this information could be integrated using machine learning computational methods to select the more pertinent information in disease prediction [412–414].

Traditional boundaries, however, continue to separate clinical care and research. Currently, patients presenting syndromic obesity can be screened depending on the diagnosis hypothesis, with conventional cytogenetic, molecular tests, fluorescence *in situ* hybridization, chromosomal microarray analysis technique capable of detecting CNVs [415] or next generation sequencing panels (example: the BBS genes) [416]. Identification of causative chromosomal structural variation or mutations in patients might be beneficial in providing an informed prognosis, early opportunities for intervention and adapting treatment of any commonly associated pathologies, such as, specific behavioural management and hormone therapy for PWS patients [49].

Genetic screening for mutations in monogenic obesity could be performed in patients presenting with early, rapid-onset or severe obesity, severe hyperphagia, hypopigmentation of hair and skin, hypogonadism, intestinal dysfunction, postprandial hypoglycaemia, diabetes insipidus, abnormal leptin level and coexistence of lean and obese siblings in the family. This is especially important since patients with leptin deficiency resulting from loss-of-function mutations in *LEP* can be successfully treated by administration of leptin [99]. Acknowledging the importance of permanent lifestyle modifications at a young age is essential in monogenic obesity mutation carriers, as children with *MC4R* functional mutations were able to lose weight in a lifestyle intervention but had greater difficulties maintaining this weight loss [417]. A similar observation was reported in children carrying a rare mutation in *POMC* [418]. Furthermore, at the Obesity Week 2015 conference, Rhythm Pharmaceuticals presented preliminary results from a phase 1b clinical trial assessing the safety and efficacy of setmelanotide (RM-493), an MC4R agonist, in obese patients with a heterozygous genetic defect in *MC4R*. After four weeks of continuous subcutaneous infusion of setmelanotide, patients lost weight and the treatment was well tolerated, with no serious adverse events or discontinuations. The company is now extending the clinical trial to patients with monogenic obesity mutations in *POMC*. The US Supreme Court considers gene patenting as illegal [304]. However, some patents are still active, so identifying mutations must be done within a legal framework, using expensive patented genetic tests instead of whole genome/exome sequencing experiments [419,420].

On the other hand, screening for polygenic obesity has had less clinical application so far [421]. For instance, adding 32 common BMI-associated SNPs to a combination of classical clinical risk factors did not lead to a clinically meaningful increase in prediction for childhood obesity in three longitudinal cohorts [422]. Moreover, a simulation study that took GxG and gene–environment (GxE) interactions into account demonstrated that the inclusion of such effects in risk-prediction models is not likely to significantly improve appropriate diagnosis [423]. As common SNPs may explain up to 30% of BMI variance [35,36], there is no doubt that the use of Bayesian inference and learning machine methods will contribute to generalizing the use of SNP genetic information in obesity prevention programmes [412–414].

Some studies showed that obesity-related variants (alone or integrated in a genetic risk score) could be associated with weight loss and its maintenance, during energy restriction diet or lifestyle intervention [424–430]. In children, no evidence was found for effects of 12 GWAS-based obesity marker alleles on weight regain [431], and only the *FTO* common variants [432] were associated with weight regain. However, these findings await further confirmation and highlight the challenges of replicating gene–diet interactions in randomized clinical trials [425].

Using GWAS derived gene scores is questionable in terms of benefits for the patient. This may result in a change in patients' health-related behaviours based on low evidence to guide intervention [319]. Secondly, the motivation to change behaviours may be affected by the genetic risk information [433]. Most of studies on patient compliance, after genetic risk assessment, showed a high compliance in patients receiving information of a high-risk estimate compared with patients not receiving information [434–437]. However, behavioural modification is a complex pro-

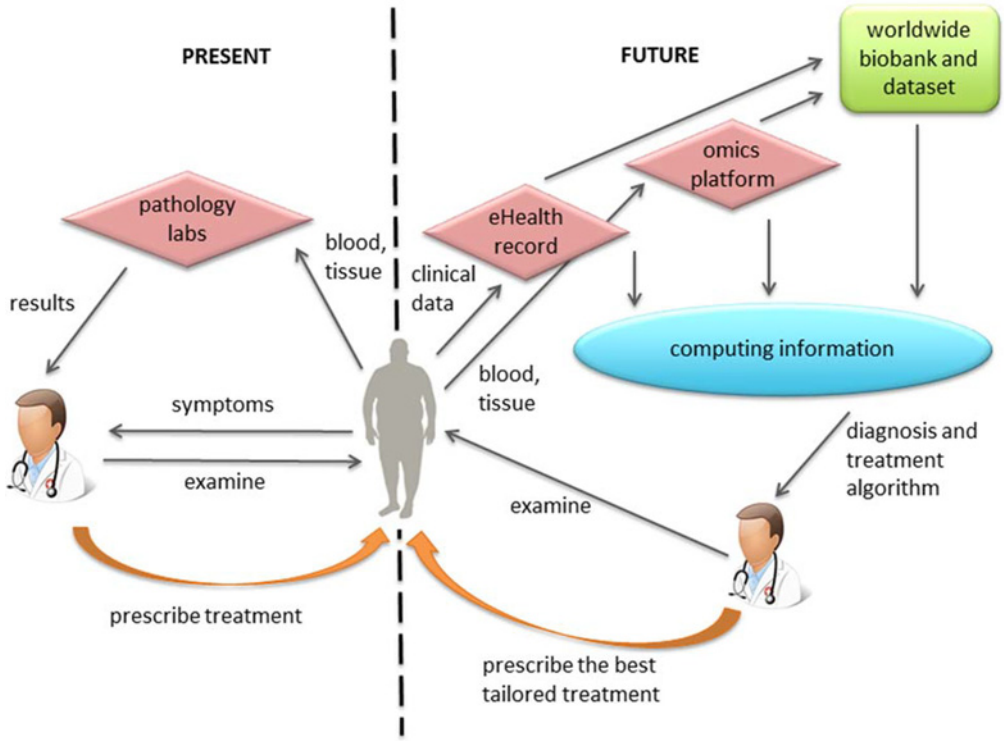

Figure 6 Translation from current medicine to personalized medicine
For personalized medicine to become part of routine care, we will have to develop longitudinal studies of large patient populations, participating in exhaustive phenotyping and biobank program (monitoring of clinical data by e-health record, collecting blood or tissue samples to analyse data from omics), and new clinical diagnosis support to compute all these individual data and give guidance algorithms for diagnosis and treatment to the physician.

cess and is influenced by a variety of factors [438]. In contrast, without adequate counselling and guidance, patients may interpret risk estimates with anxiety, resulting in a counter-productive reaction [439,440].

Studying response to therapy in order to tailor nutritional strategies is particularly interesting in bariatric surgery [441]. Even though the heritability of weight loss following bariatric surgery has been demonstrated [442], current interpretation of these studies varies based on the duration of follow-up and the type of surgery. Case reports on carriers of homozygous *LEPR* and *MC4R* mutations showed lower weight loss and poorer outcomes after bariatric surgery [443,444]. A more complex relationship has been reported for heterozygous *MC4R* mutations, showing no significant effects on bariatric surgery outcomes [444,445]. In a study matching carriers of functional *MC4R* mutations or *MC4R* variants and two randomly paired controls without mutations, no difference in weight loss was observed [446], however, the design of functional characterization of mutations and variants was questionable [447]. Carriers of rare variants of *MC4R* matched with the *MC4R* reference allele carriers also demonstrated comparable weight loss [448]. In the Swedish Obesity Study, *FTO* was associated with maximum weight loss in gastric banding surgery subjects but not in gastric bypass subjects [449]. GWAS of gastric bypass subjects found that the 15q26.1 locus was significantly associated with weight loss [450]. However, larger studies, longitudinal analyses, and subsequent meta-analyses comprising of not only the genome, but also the epigenome and metagenome, are required to definitively establish whether treatment outcomes can be improved through assignment of patients to personalized surgical techniques.

The multifactorial origin of obesity gives rise to a variable response to anti-obesity medication, suggesting that efficacy of all new centrally active anti-obesity drugs [451] should be carefully assessed by using genomic information to ensure proper prescription and dispensing, in order to avoid unnecessary and potentially life-threatening side effects [452]. Identifying biomarkers for the development of diagnostics to guide prescriptions carries the potential of reducing adverse drug reactions and improving outcomes, while saving the healthcare system and patients from ineffective prescriptions.

For personalized medicine to become routine care, we also need to develop innovative and integrative polices in order to rebuild a new healthcare system, based on a more preventive and patient-participatory approach [406,453–455] (Figure 6). The only way to map the natural history of diseases is through longitudinal studies of large patient populations, with exhaustive phenotyping methods (self-monitoring of physical activity, diet, sleep patterns by new connected devices, collecting blood or tissue samples to analyse data from genome, proteins, epigenome, metagenome, etc.). New electronic health records and clinical diagnosis support should be developed to compute all these individual data and give guidance algorithms for dia-

gnosis and treatment to the physician. This new generation of physicians will emerge from innovative and integrated medicine courses (with new translational specialties) that are not focused on organ diseases, but on a holistic approach towards the patient, during, before and after the disease. Economical evaluation will be required to evaluate the short and long-term cost-effectiveness of this novel approach. Personalized medicine can potentially dramatically improve health and decrease health costs. These evaluations should convince governments and health insurance companies to develop new benefits plans and a new heath care system for individuals, while respecting personal information.

CONCLUSION AND PERSPECTIVES

Great progress in genetics, epigenetics and metagenomics has made significant strides to unveil the pathophysiological architecture of obesity, even though most of the genes for syndromic, monogenic, oligogenic and polygenic obesity remain to be discovered. Technological and methodological advancements may lead to an exhaustive gene harvest, but understanding their relevance is a long and complex process. The genetic heterogeneity in different ethnic groups invites collaborations between scientists in order to initiate multiethnic international recruitment and come up with novel methodologies to exhaustively study genetic associations. High-throughput hypothesis-driven approaches have created an inflection point in the progression of genomic discovery, but methodological developments such as hypothesis driven GWAS relaxing Bonferroni [456], case control case design studies [456], Bayesian approaches [457] and deep phenotype-based cohorts [241,264,292,306,458,459] are needed to cope with the power issues. Although significant efforts have been made to identify genes and classify syndromic and monogenic obesity, the real effect of genes and their interplay with environmental risk factors is not completely understood yet. GxE interactions is an emerging discipline with exciting recent developments to estimate the impact of environmental factors on genetic effects. Taking advantage of GxE interactions to increase the harvest of genes have led to original experimental designs, such as genome-wide environmental interaction studies [460], variance prioritization [461] and studying weight gain in specific obesity-prone contexts (university transition, use of anti-depressive drug, smoking cessation). Apart from the knowledge gained from congenic mouse models, which has been instrumental in our understanding of epistatic effects on BMI, GxG interactions have not yet produced convincing results [462]. Beyond classical genetics, disciplines such as epigenetics and metagenomics have recently emerged. They may improve the understanding of the complex aetiology of obesity, and moving forward, aid us in better understanding complex diseases. Finally, genomic medicine has triggered great enthusiasm, but clinical applications remain limited. In order to overcome such limitations, we not only require more scientific knowledge, but also a shift in our education, health expenses, agro-industrial lobbying, medical practice and individual responsibility to take care of our own metabolic health.

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