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Genetics and Obesity

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1. Introduction

Obesity, in both children and adults, has reached epidemic proportions in multiple countries worldwide, with serious health problems and imposing a substantial economic burden on societies [1–4]. The increase in obesity prevalence among children is particularly alarming because obesity-related complications, including obesity-associated sleep apnea,[5] non-alcoholic fatty liver disease [6], and type 2 diabetes,[7] are increasingly diagnosed in pediatric patients. Excess weight in children may increase the likelihood of heart disease in adulthood as a result of the early establishment of risk factors [8]. Pediatric obesity has been shown to have a tremendous impact on later health [8], even independent of adult weight [9]. Additionally, childhood obesity is linked with important psychosocial consequences and poor general quality of life [10].

In order to create the best management programs and determine novel therapeutic targets, it becomes essential to understand the factors causing today's rising epidemic of childhood obesity.

Obesity develops as a result of dietary and lifestyle factors, but studies also suggest a genetic influence on obesity [11]. Obesity is highly influenced by genetics; available data suggest that 40% to 77% of the observed variance in human body weight can be accounted for, by inherited factors [12–14]. Obesity, also just as clearly has environmental causes; our genetic endowments have changed minimally during the last 40 years, yet the prevalence of childhood obesity has tripled in US [15] and significantly increased worldwide [16], an observation that can only be explained by changes in external factors affecting children's energetic balance.

This chapter provides an overview of the current knowledge on genetic factors implicated in the obesity epidemic.

Methodology

This review chapter has been developed using an evidence-based approach. Data from clinical and observational studies, review articles and twin studies were all considered when shaping this review. Literature searches for topics relating to genetic obesity were carried out in PubMed and EMBASE between 10 June and 10 August 2012, using Medical Subject Heading Terms and relevant keywords. To ensure relevance to the modern day clinical setting, literature searches were limited to articles published since 1 January 2000. Older, historically significant, articles identified by the authors were also included. Only articles from the peer-reviewed literature were included in the literature search. Articles in a non-English language were not included. Abstracts from industry-sponsored meetings were not included.

2. Hypothesis for etiology of the obesity epidemic

Currently, there are quite a few theories that intend to explain the etiology of human obesity: the thrifty gene hypothesis, the fetal programming hypothesis, the predation release hypothesis, the sedentary lifestyle hypothesis, the ethnic shift hypothesis, the increased reproductive fitness hypothesis, the assortative mating hypothesis, and the complex hypothesis [17]. However, an acceptable consensus in the field is still lacking, probably due to the fact that the development of obesity comes from highly complex interactions. The vast majority of genetic factors are presumed to affect body weight enough to cause obesity, only when specific environmental conditions pertain.

The thrifty gene hypothesis was proposed by Neel in 1962 [18] and suggests we evolved genes for efficient food collection and fat deposition, in order to survive periods of famine. Now, that food is continuously available, these genes are disadvantageous because they make us obese in preparation for a famine that never comes. In respect to this hypothesis, natural selection favored individuals carrying thrifty alleles that promote the storage of fat and energy. Polynesians likely experienced long periods of cold stress and starvation during their settlement of the Pacific and today have high rates of obesity and type 2 diabetes, possibly due to past positive selection for thrifty alleles [19].

A growing body of empirical evidence suggests the concept of *fetal programming* of health and disease risk. The origins of obesity and metabolic dysfunction can be traced back to the intrauterine period of life, at which time the developing fetus is influenced by suboptimal conditions during critical periods of cellular proliferation, differentiation, and maturation by producing structural and functional changes in cells, tissues and organ systems. These changes, in turn, may have long-term consequences to increase the individual's risk for developing obesity and metabolic dysfunction [20–23]. The major nutrition-related pathways discussed in the current literature relate to the effects of maternal nutritional insults on maternal-placental-fetal glucose/insulin physiology and their downstream effects on the developing brain and peripheral systems in the fetal compartment. Also, the potential role of intrauterine stress and stress biology is brought up for discussion in developmental programming of health and disease susceptibility [23]. In the early 1990s, Hales and Barker et

al. [24], published a paper in Diabetologia postulating that not only type 2 diabetes, but also the key components of the metabolic syndrome, seemed to have at least parts of their origin in early life. Authors proved, in an unselected population sample (407 men) from Hertford-shire, UK, a direct link between low weight at birth and increased risks of developing type 2 diabetes, hypertension, elevated triglycerides and insulin resistance later in life. Thus, showing the role of fetal programming in itself and equally as important, the notion that fetal programming could represent a significant player in the origin of type 2 diabetes, the metabolic syndrome and cardiovascular disease. However, the extent to which the global diabetes epidemic may be driven by a mismatch between being born with a low birth weight and the fast propagation of overnutrition and physical inactivity, seen over recent years in developing countries, needs to be further determined [25].

The *predation release hypothesis*, also called the "drifty gene" hypothesis, is opposing the thrifty gene hypothesis, because famines are relatively infrequent modern phenomena that involve insufficient mortality for thrifty genes to propagate. Speakman suggests that early hominids would have been subjected to stabilizing selection for body fatness, with obesity selected against the risk of predation. Around two million years ago predation was removed as a significant factor by the development of social behavior, weapons, and fire. The absence of predation led to a change in the population distribution of body fatness due to random mutations and drift. This novel hypothesis involves random drift, rather than directed selection, thus, explaining why, even in Western society, most people are not obese [26,27].

The *sedentary lifestyle* together with excessive energy intake is the most popular etiologic hypothesis for the worldwide increasing prevalence of overweight and obesity [28–30].

The *ethnic shift hypothesis*, claims the mounting obesity rates are due to disproportionate prevalence in the fastest growing ethnicities (namely Hispanic Americans) [31,32].

The *increased reproductive fitness hypothesis* is also debated as a possible cause for obesity epidemic. Reproductive fitness can be defined as the capacity to pass on one's DNA. It is postulated that body mass index-associated reproductive fitness (natural selection) increases obesity prevalence, due to the fact that BMI has a genetic component and because individuals genetically predisposed toward higher BMIs, reproduce at a higher rate, than do individuals genetically predisposed toward lower BMIs [33–35].

The *assortative mating hypothesis* proposed by Hebebrand et al. [36] emphasizes the fact that the current obesity epidemic has a genetic component mediated by increased rates of assortative mating for body fatness. Theoretically, the genetic consequences of assortative mating for complex traits, such as obesity, are expected to become more significant as the correlation between genotype and phenotype (penetrance) increases, even if rates of assortative mating remain constant across generations [37,38]. Spouse concordance for obesity was associated with a 20-fold higher obesity risk for biologic offspring compared with children of concordantly non-obese parents [37].

The *complex hypothesis* focuses on the shared nature of common alleles in related common disorders, including obesity. This model, the common variants/multiple disease hypothesis, emphasizes that many disease genes may not be disease specific. Common deleterious al-

leles, found at a relatively high frequency in the population may play a cumulative role in related clinical phenotypes in the context of different genetic backgrounds and under different environmental conditions [39].

Genes can favor fat accumulation in a given environment by increased desire to overeat; the tendency to be sedentary; a diminished ability to utilize dietary fats as fuel; an enlarged, easily stimulated capacity to store body fat. The variation in how people respond to the same environmental conditions is an additional indication that genes play an important role in the development of obesity [40]. This is also consistent with the notion that obesity results from genetic variation interacting with shifting environmental conditions. The influence of genes ranges from polygenic genetic predisposition with impact on appetite, metabolism, and the deposition of fat, to rare monogenic disorders where obesity is the primary feature. Arduous efforts have been made by the scientific society to better understand the physiological basis of obesity. Crucial to this research is the inquiry of how does our body control ingestion, digestion, absorption, and metabolism and how nutrients are distributed among various tissues, organs, and systems [41]. Simultaneously, there is a growing interest regarding the role of genetics in further explaining feeding regulatory systems [14].

3. Genetic research methods used for identification of obesity susceptibility genes

The genetic contribution to common obesity has been established initially through family, twin, and adoption studies. Twin studies have shown a relatively high heritability ranging from 40%-77% [12–14]. However, the search for obesity susceptibility genes has been an arduous task. Gene identification for the last 15 years has been based on two broad genetic epidemiological approaches (candidate gene and genome-wide linkage methods). Recently, genome-wide association studies have brought great information on obesity related genes.

Candidate gene methods

The candidacy of a gene for obesity is based on the following resources: animal models using gene knockout and transgenic approaches; cellular model systems showing their role in metabolic pathways involved in glucose metabolism; linkage and positional cloning studies using extreme cases. This approach emphasizes on an association between a variant or mutation within or near the candidate gene and a trait of interest (such as obesity). Candidate gene approach needs to be on a large scale and well powered, in order to detect the expected small effects of genetic variants involved in common traits and disease [42].

The latest update of the Human Obesity Gene Map reported 127 candidate genes for obesity-related traits. Results of large-scale studies suggest that obesity is strongly associated with genetic variants in the melanocortin-4 receptor (MC4R) gene, leptin gene, adrenergic β3 receptor (ADRB3) gene, prohormone convertase 1 (PCSK1) gene, brain-derived neurotrophic factor (BDNF) gene, and endocannabinoid receptor 1 (CNR1) gene [43,44].

Genome-wide linkage studies

Genome-wide linkage studies, through surveying the whole genome, aim to identify new, unanticipated genetic variants associated with a disease or trait of interest. Genome-wide linkage studies rely on the relatedness of study participants and test whether certain chromosomal regions cosegregate with a disease or trait across generations [42]. The latest Human Obesity Gene Map update reported 253 loci from 61 genome-wide linkage scans, of which 15 loci have been replicated in at least three studies [45]. Yet, none of these replicated loci could be narrowed down sufficiently to pinpoint the genes or variants that underline the linkage signal.

Genome-wide association studies

Genome-wide association studies are used in genetics research to look for associations between many (typically hundreds of thousands) of specific genetic variations (most commonly, single nucleotide polymorphisms -SNP) and particular diseases or traits. Similar to genome-wide linkage, the genome-wide association approach sweeps the entire genome, unrestricted by prior assumptions. Genome-wide association studies screen the whole genome at higher resolution levels than genome-wide linkage studies and are capable to narrow down the associated locus more accurately. The genome-wide association approach has effectively replaced genome-wide linkage approach for common disease [42].

Recent success of genome-wide association studies has drawn a lot of attention. High-density multistage genome-wide association analyses have so far discovered ~30 loci consistently associated with BMI and obesity-related traits. The strongest signal remains the association with variants within FTO (the fat-mass and obesity-related gene). Other signals near BDNF, SH2B1, and NEGR1 (all implicated in aspects of neuronal function),further support the idea that obesity is a disorder of hypothalamic function [42].

4. The influential role of genes in obesity

The strongest risk factor for childhood and adolescent obesity is parental obesity [46]. The risk becomes especially elevated if both parents are obese [47]. However, obesity inheritance does not usually follow classic Mendelian patterns. A combination of gene mutations, deletions and single nucleotide polymorphisms are all known to contribute to obesity. Most cases are polygenic, the result of multiple genes interacting with a shifting environment. Each "obesity gene" only makes a small contribution to phenotype, but collectively, inherited genetic variations play a major role in determining body mass and how the body maintains a balance between physical activity and nutrition. While obesity is most commonly associated with polygenic inheritance, there are other instances in which the cause is monogenic or syndromic. Monogenic obesity typically is caused by a single gene mutation with severe obesity as the main symptom. Syndromic obesity, on the other hand, has many characteristics, of which obesity is one symptom [48].

A. Monogenic obesity, that is the obesity associated with a single gene mutation. In these cases single gene variants are sufficient by themselves to cause obesity in food abundant so-

cieties. Patients with monogenic obesity usually show extremely severe phenotypes characterized by early childhood obesity onset, often associated with additional behavioral, developmental or endocrine disorders, like hyperphagia and hypogonadism. Significant developmental delays, however, are not commonly seen.

B. Syndromic obesity includes some disorders with Mendelian inheritance, in which patients are clinically obese and are additionally characterized by mental retardation, dysmorfic features, and organ-specific developmental abnormalities.

C. Polygenic obesity, the very common kind of obesity, which concerns the great majority of obese children, arises when an individual's genetic make-up is susceptible to an environment that promotes energy consumption over energy expenditure [49].

A. Monogenic obesity

A "monogene" is by textbook definition, a gene with a strong effect on the phenotype (Mendelian traits or Mendelian - single gene conditions), giving rise to a one-on-one relationship between genotype and phenotype. A "major gene" is defined as a gene harboring, a variant which is associated with a high lifetime risk for a disease. Modifier genes and environmental factors additionally play a role in the etiology of the respective diseases [50].

The genetic causes of monogenic obesity tend to be related to the leptin-melanocortin pathway. This pathway is critical for energy balance and food intake; a disruption in this pathway will lead to severe obesity. Energy homeostasis involves the integration of afferent signals from fat (leptin) and pancreatic beta cells (insulin) and meal-related afferent signals from the gut. These inputs are integrated within the brain and regulate food intake, energy expenditure, energy partitioning and neuroendocrine status. Table 1. summarizes the peptides proposed to affect appetite regulation (adapted from Burrage and McCandless 2007) [51].

Leptin is an adipocyte-derived hormone that is secreted proportionally to body fat content, it crosses the blood–brain barrier, and stimulates a subset of neurons in the hypothalamus to produce peptides that reduce feeding and promote increased energy expenditure (leptin–melanocortin pathway). Additionally, leptin inhibits hypothalamic neurons that produce peptides promoting feeding and decreased energy expenditure.

Attention has focused on identifying the molecular events that lie downstream of the leptin receptor in hypothalamic target neurons. In particular, neurons within the hypothalamus act as primary sensors of alterations in energy stores to control appetite and energy homeostasis. Pro-opiomelanocortin (POMC) neurons produce the *anorectic* peptide a-MSH (a-melanocyte stimulating hormone) together with CART (cocaine and amphetamine-related transcript), whilst a separate group expresses the *orexigens:* neuropeptide Y (NPY) and agouti-related protein (AGRP). AGRP is a hypothalamic neuropeptide that is a potent melanocortin-3 receptor (MC3R) and melanocortin-4 receptor (MC4R) antagonist. Activation of the NPY/AGRP neurons increases food intake and decreases energy expenditure, whereas activation of the POMC neurons decreases food intake and increases energy expenditure [52].

Compounds Mainly Acting to Increase Energy Intake (Orexic)	
Central Nervous System	*Peripheral*
Neuropeptide Y	Ghrelin
Melanin-concentrating hormone (MCH)	
Orexins/hypocretins	
Agouti-related peptide (AGRP)	
Galanin	
Endogenous opioids	
Endocannabinoids	
Compounds Mainly Acting to Reduce Energy Intake (Anorexic)	
Central Nervous System	*Peripheral*
Cocaine- and amphetamine- related transcript (CART)	Leptin
Melanocortins (POMC)	Peptide YY
Corticotropin-releasing factor (CRF)	Cholecystokinin (CCK)
Insulin	Insulin
Serotonin	Amylin
Glucagon-like peptides	Glucagon-like peptides
Neurotensin	Bombesin

Table 1. Peptides proposed to affect appetite regulation. adapted from Burrage and McCandless, 2007

The cumulative prevalence of monogenic obesity among children with severe obesity is about 5% [44]. Several monogenic disorders resulting from disruption of the leptin–melano-cortin pathway have been identified. In these disorders, severe obesity of early onset is itself the predominant presenting feature, although often accompanied by characteristic patterns of neuroendocrine dysfunction. Mutations in the melanocortin-4 receptor gene (*MC4R*) and the leptin receptor gene (*LEPR*) have been reported in about 2.5 % and 1.5 % of children with severe obesity. An additional 0.5 % of cases can be attributed to a chromosome 16p11.2 deletion where a gene known as *SH2B1* is deleted [48].

Congenital leptin deficiency

In 1997 two severely obese cousins were reported from a highly consanguineous family of Pakistani origin [53]. Despite their severe obesity, both children had undetectable levels of serum leptin and a mutation in the gene encoding leptin. Leptin deficiency is associated with hyperphagia and increased energy intake. Other phenotypic features include hypogo-nadotropic hypogonadism, elevated plasma insulin, T-cell abnormalities, and advanced bone age [54].

The role of leptin in some monogenic forms of obesity was further supported by the striking effect of leptin replacement in an extremely obese child with congenital leptin deficiency. In a 9-year-old boy with congenital leptin deficiency, daily subcutaneous injection of recombi-nant human leptin for a year, led to a complete reversal of obesity, with sustained fat-mass loss. Moreover, partial leptin deficiency in 13 Pakistani subjects, due to a heterozygous

frame shift mutation in the leptin gene, was found to be associated with increased body fat [55,56]. However, only a handful of families with extreme forms of obesity in early infancy have mutations in these genes [57].

Mutation in the leptin receptor

Shortly after leptin deficiency was discovered, a similar phenotype, but with elevated plasma leptin levels, was identified [58]. The cause was a homozygous mutation in the leptin receptor. A later study suggested that approximately 3% of severe morbid obesity in a population including both non-consanguineous and consanguineous families could be explained by mutations in the leptin receptor [59].

Melanocortin-4 receptor deficiency (MC4R)

Mutations in another component of the leptin–melanocortin pathway melanocortin-4 receptor have also been associated with obesity. MC4R deficiency represents the most common monogenic obesity disorder that has been identified so far. It is present in about 5-6% of obese individuals from different ethnic groups, with a higher prevalence in cases with increased severity and earlier age of onset [60,61]. Affected subjects exhibit hyperphagia, but this is not as severe as that seen in leptin deficiency, although it often starts in the first year of life. Alongside the increase in fat mass, MC4R-deficient subjects also have an increase in lean mass, that is not seen in leptin deficiency and a marked increase in bone mineral density. The accelerated linear growth is apparently not related to a dysfunction of the GH axis and may be a consequence of the disproportionate early hyperinsulinaemia. Interestingly, both heterozygous and homozygous mutations in MC4R have been implicated in obesity, but extreme obesity is incompletely penetrant in heterozygous patients. In other words, some individuals with a single copy of the mutation are obese, whereas others are not obese [51].

Currently, there is no specific therapy for MC4R deficiency, however, it is highly likely that these subjects would respond well to pharmacotherapy that overcame the reduction in the hypothalamic melanocortinergic tone that exists in these patients [12].

Pro-opiomelanocortin (POMC) deficiency

Small numbers of patients have been described with mutations in the gene encoding pro-opiomelanocortin, which is involved in the leptin-melanocortin pathway [62,63]. In neonatal life, these patients present with adrenal crisis due to ACTH deficiency (POMC is a precursor of ACTH in the pituitary), also, the children have pale skin and red hair due to the lack of MSH action at melanocortin-1 receptors in the skin and hair follicles. POMC deficiency results in hyperphagia and early-onset obesity due to loss of melanocortin signaling at the melanocortin-4 receptor (MC4R) [12].

Prohormone convertase-1 (PC1) deficiency

Jackson et al described a woman with severe early-onset obesity, hypogonadotropic hypogonadism, postprandial hypoglycaemia, hypocortisolemia, and evidence of impaired processing of POMC and proinsulin who was a compound heterozygote for prohormone convertase-1 mutations [63].

Although great hope was invested in the studies of patients with early-onset severe obesity, they have revealed the identity of very few genes associated with obesity. Interestingly, the few gene mutations associated with morbid obesity appear to influence body weight primarily by altering appetite. Some of the molecules may also impact activity, but this has not yet been shown to be a significant contributor to obesity. A significant limitation of the strategy of focusing on morbid obesity is that mutations or genetic variants in these genes may not be associated with more common forms of the condition [51].

B. Syndromic obesity

Syndromic obesity is represented by at least 20 rare syndromes (shown in Table 2), that are caused by discrete genetic defects or chromosomal abnormalities, both autosomal and X-linked, that are characterized by obesity. Most of these obesity syndromes associate mental retardation.

It was expected that the syndromic forms of obesity could help unravel novel genes relevant for idiopathic obesity. However, although the genes for several of the syndromic forms have been detected, the relevance of these genes for general obesity is still unclear [45,57].

1	Achondroplasia
2	Alström Syndrome
3	Bannayan-Riley-Ruvalcaba Syndrome
4	Beckwith-Wiedemann Syndrome
5	Biedl Bardet Syndrome
6	Borjeson-Forssman-Lehmann Syndrome
7	Carpenter syndrome
8	CDG 1a
9	Cohen Syndrome
10	Fragile X Syndrome
11	Mehmo Syndrome
12	Meningomyelocoele
13	Prader Willi Syndrome
14	Psdeuohypoparathyroidism 1a
15	Simpson-Golabi-Behmel Syndrome
16	Smith-Magenis Syndrome
17	Sotos Syndrome
18	Wilson-Turner Syndrome
19	Ulnar-Mammary Schinzel Syndrome
20	Weaver Syndrome

Table 2. Syndromes characterized by obesity.

Prader–Willi syndrome

Prader–Willi syndrome (PWS) is the most frequent of these syndromes (1 in 25,000 births). It is an autosomal-dominant disorder, characterized by obesity, hyperphagia, muscular hypotonia, mental retardation, short stature and hypogonadotropic hypogonadism. It is usually caused by a paternally inherited deletion at the chromosomal region 15q11.2–q12, and less frequently by maternal uniparental disomy (Orphanet). The cause of hyperphagia in PWS is not proven, although PWS phenotypes are consistent with a combined hypothalamic impairment, causing several endocrine abnormalities. Also, it was suggested that the elevated production of the stomach secreted peptide ghrelin seen in PWS might increase appetite by interacting with the POMC/CART and NPY hypothalamic neurons [57].

Single Minded Homologue 1 (SIM-1)

The loss of the single minded homologue 1 (SIM1) gene has also been associated with hyperphagia in syndromic obesity. This gene encodes a transcription factor that has a pivotal role in neurogenesis. In humans, deletion or disruption of the SIM1 region results in either a "Prader–Willi-like" phenotype or a form of early-onset obesity, associated with excessive food intake [64].

WAGR Syndrome

The WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies and mental retardation syndrome and obesity) is caused by heterozygous contiguous gene deletions that involve at least two genes, *WT1* and *PAX6*, which are present in the 11p13 region. Although persons with the WAGR syndrome typically have low-normal birth weight, marked obesity subsequently develops in a substantial subgroup [65].

Pseudohypoparathyroidism type 1A (PHP1A)

PHP1A syndrome is due to a maternally transmitted mutation in GNAS1, which encodes the α-subunit of the Gs protein. Food-intake abnormalities in patients with this syndrome might be due to the expression of the resulting variant Gs protein in the hypothalamic circuitry that controls energy balance, which involves many G-protein coupled receptors [66].

Bardet–Biedl syndrome (BBS)

Bardet–Biedl syndrome is characterized by six main features: Rod-Cone Dystrophy (the most frequent phenotype), polydactyly, learning disabilities, hypogonadism in males, renal abnormalities and obesity. In BBS patients, obesity has early onset, usually arising within the first few years of life. However, one study of post-pubertal BBS patients found that only 52% were clinically obese; therefore, this syndrome can present with a heterogeneous phenotype [67].

Albright's hereditary osteodystrophy

Albright's hereditary osteodystrophy describes a constellation of physical features, including short adult stature, obesity, brachydactyly, and ectopic ossifications. It is an autosomal dominant disorder due to germline mutations in GNAS1, which encodes for a-subunit of the stimulatory G protein (Gsa) [68].

Fragile X syndrome

Fragile X syndrome is characterized by moderate to severe mental retardation, macroorchidism, large ears, macrocephaly, prominent jaw (mandibular prognathism), high-pitched jocular speech and obesity. Fragile X syndrome is an X-linked, single gene disorder caused by dysfunction in the transcription of the *FMR1* gene that codes for fragile X mental retardation protein (FMRP) [69].

Borjeson–Forssman–Lehmann syndrome

Borjeson, Forssman and Lehmann described a syndrome characterized by moderate to severe mental retardation, epilepsy, hypogonadism, and obesity with marked gynecomastia [70]. Mutations in a novel, widely expressed zinc-finger gene plant homeodomain (PHD)-like finger (PHF6) have been identified in affected families, although the functional properties of this protein remain unclear [71].

Alstrom syndrome

Alstrom syndrome is a homogeneous autosomal recessive disorder that is characterized by childhood obesity associated with hyperinsulinaemia, chronic hyperglycemia and neurosensory deficits. Subsets of affected individuals present with additional features such as dilated cardiomyopathy, hepatic dysfunction, hypothyroidism, male hypogonadism, short stature and mild to moderate developmental delay. Symptoms first appear in infancy and progressive development of multi-organ pathology leads to a reduced life expectancy. Variability in age of onset and severity of clinical symptoms, even within families, is likely due to genetic background. Mutations in a single gene, ALMS1, have been found to be responsible for all cases of Alstrom syndrome [72].

C. Complex polygenic obesity

Complex polygenic obesity represents the end result of behavioral, environmental, and genetic factors that may influence individual responses to diet and physical activity. Changes in our environment over the last decades, in particular the unlimited supply of cheap, highly palatable, energy-dense foods; plus a sedentary lifestyle, the so called "obesogenic" environment together with a genetic susceptibility are the culprits for today's obesity epidemic [73].

Compared with obesity syndromes or single-gene obesity, the recent rapid increase in prevalence of childhood obesity suggests that environmental factors most likely have a larger impact on body weight in common obesity patients, although individual responses to these environmental factors are influenced by genetic factors -"susceptibility genes".

Some traits can be due to simultaneous presence of DNA variation in multiple genes. Any of a group of alleles, at distinct gene loci that collectively control the inheritance of a quantitative phenotype or modify the expression of a qualitative character, are termed "polygenic" variants. It is generally assumed that for quantitative traits, each allele has a small effect, but the allelic effects can be additive or non-additive. Potentially, many such polygenic variants play a role in body weight regulation. It is estimated that the total number of genes with a small effect most likely exceeds 100 [50].

SNP	Chr	Position	Nearest gene	Sample size in original publication	Frequency of the risk allele	Effect on BMI in the original publication
rs2815752	1	72,524,461	NEGR1	32,387	62% (A)	+0.10 kg/m2 per A allele[b]
rs2568958	1	72,537,704	NEGR1	25,344	58% (A)	+0.43 kg/m2 for AA genotype[c]
rs10913469	1	176,180,142	SEC16B,RASAL2	25,344	20% (C)	+0.50 kg/m2 for CC genotype[c]
rs6548238	2	624,905	TMEM18	32,387	84% (C)	+0.26 kg/m2 per C allele[b]
rs7561317	2	634,953	TMEM18	25,344	84% (G)	+0.70 kg/m2 for GG genotype[c]
rs7566605	2	118,552,495	INSIG2	9,881	37% (C)	+1.00 kg/m2 for CC genotype
rs7647305	3	187,316,984	SFRS10, ETV5, DGKG	25,344	77% (C)	+0.54 kg/m2 for CC genotype[c]
rs10938397	4	45,023,455	GNPDA2	32,387	48% (G)	+0.19 kg/m2 per G allele[b]
rs4712652	6	22,186,593	PRL	2,796	41% (A)	+0.031 kg/m2 per A allele in children[d]
rs10508503	10	16,339,956	PTER	2,796	8.5% (C)	+0.144 kg/m2 per C allele in children[d]
rs6265 (V66M)	11	27,636,492	BDNF	25,344	85% (G)	+0.67 kg/m2 for GG genotype[c]
rs10838738	11	47,619,625	MTCH2	32,387	34% (G)	+0.07 kg/m2 per G allele[b]
rs7138803	12	48,533,735	BCDIN3D, FAIM2	25,344	37% (A)	+0.54 kg/m2 for AA genotype[c]
rs7498665	16	28,790,742	SH2B1	32,387	41% (G)	+0.15 kg/m2 per G allele[b]
rs7498665	16	28,790,742	SH2B1, ATP2A1	25,344	44% (G)	+0.45 kg/m2 for GG genotype[c]
rs8050136	16	52,373,776	FTO	25,344	41% (A)	+1.07 kg/m2 for AA genotype[c]
rs9939609	16	52,378,028	FTO	38,759	40% (A)	+0.40 kg/m2 per A allele
rs9939609	16	52,378,028	FTO	32,387	41% (A)	+0.33 kg/m2 per A allele[b]
rs1421085	16	52,358,455	FTO	2,796	40% (C)	+0.112 kg/m2 per C allele[d]
rs1424233	16	78,240,251	MAF	2,796	43% (A)	+0.091 kg/m2 per A allele in children[d]
rs1805081	18	19,394,429	NPC1	2,796	44% (A)	-0.087 kg/m2 per A allele in children[d]
rs17782313	18	56,002,077	MC4R	16,876	24% (C)	+0.22 kg/m2 per C allele
rs17782313	18	56,002,077	MC4R	32,387	22% (C)	+0.22 kg/m2 per C allele[b]
rs17782313	18	56,002,077	MC4R	2,796	17,5% (C)	+0.097 kg/m2 per C allele[d]
rs12970134	18	56,035,730	MC4R	25,344	30% (A)	+0.36 kg/m2 for AA genotype[c]
rs52820871 (I251L)	18	56,189,806	MC4R	16,797	0.75% (251L)	-0.35 SD of their BMI Z-score/ 251L allele
rs2229616 (V103I)	18	56,190,256	MC4R	7,713	2% (103I)	-0.48 kg/m2 per 103I allele
rs29941	19	39,001,372	CHST8,KCTD15	25,344	70% (C)	+0.46 kg/m2 for CC genotype[c]
rs11084753	19	39,013,977	KCTD15	32,387	67% (G)	+0.06 kg/m2 per G allele[b]

Table 3. [a] Either in the GWAS or the initial sample [b] Reported in the population-based cohorts EPIC, FINRISK97, BPPP and METSIM (N = 18,812) [c] Reported for the Islandic sample (N = 25,344) [d] Reported for children from the Northern Finland Birth Cohort (N = 5,291)NEGR1: neuronal growth factor regulator 1; SEC16B; cerevisiae, homolog of, B; RASAL2: RAS protein activator like 2; TMEM18: transmembrane protein 18, INSIG2: insulin induced gene 2, SFRS10: splicing factor, arginine/serine-rich, 10; ETV5:etsvariant 5; DGKG diacylglycerol kinase, gamma, 90kD, GNPDA2: glucosamine-6-phosphate deaminase 2; PRL: prolactin; PTER: phosphotriesterase related; BDNF: brain derived neurotrophic factor; MTCH2: mitochondrial carrier homolog 2 (C. elegans); BCDIN3D: BCDIN3 domain containing; FAIM2: Fas apoptotic inhibitory molecule 2; SH2B1: SH2B adaptor protein 1; ATP2A1: ATPase, Ca++ transporting, cardiac muscle, fast twitch 1; FTO: fat mass and obesity associated; MAF: v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian); NPC1: Niemann-Pick disease, type C1; MC4R: melanocortin 4 receptor; CHST8: carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8; KCTD15: potassium channel tetramerisation domain containing 15Genetic variants with a polygenic effect on body weight in humans [50]

A large number of candidate gene association studies, of variable power, have been searched in obesity and related phenotypes. By far the most strongly replicated candidate gene from these analyses is melanocortin 4 receptor, but other replicated associations include those with adipokine and adipokine receptor genes. Further confirming the central role of behavioral stimuli in obesity, alleles of genes encoding dopamine, serotonin, and cannabinoid receptors (DRD2, HTR2C, and CBI) [74–76] are also reported to be associated with feeding behavior and related traits.

Genome-wide association studies have led to the identification of new candidate genes in obesity, most notably the "fat mass and obesity associated" gene (FTO). Rodent studies indicate that FTO mRNA is highly expressed in brain areas important for regulation of energy- and reward driven consumption. Food deprivation alters FTO expression in the hypothalamus in rats and mice. The contribution of the FTO variant is fairly modest, with adult homozygotes for the risk allele having only a 2- to 3-kg increase in weight [77], but the obesity high-risk allele is common in Caucasian populations and its effects begin early in life. Higher fat mass is observable from the age of 2 weeks, and carriage of the allele is associated with higher BMI and reduced satiety in children [11,50].

Other loci detected in genome wide association studies were identified in large study groups and via meta-analyses. Genome wide association studies (GWAS) reported novel obesity genes with small effects on human body weight. A total of more than 150,000 individuals was analyzed. Hinney et al. made a comprehensive review of these new loci in their paper published in 2010 in European Child Adolescent Psychiatry, see Table 3-adapted from Hinney et al [50].

Alternatively, the missing heritability may be accounted for by other genetic factors like genomic copy number variation and epigenetic modifications.

5. Epigenetics

Some people have a different response of to environmental conditions and this may be the result of genetic variation alone, but there is increasing recognition that genetic expression related to disease risk may be modified by the environment during development. The "epigenetic changes" include methylation and alterations to histone proteins that alter the likelihood that specific genes are transcribed. Epigenetic changes usually occur during prenatal development or the early postnatal period. Maternal nutrition is a major factor leading to epigenetic changes. Thus, the levels of vitamins consumed in pregnancy, such as folate, methionine, and vitamin B12, which affect methylation become very important [78]. Undernutrition during prenatal development has been suggested to lead to postnatal consumption of a fatty diet. On the other hand, overnutrition of the mother is just as influential. The most convincingly shown factor is glycemic status during pregnancy. Hyperglycemia clearly affects infants' birth weight but, beyond its effects on body weight, may increase the risk for subsequent development of insulin resistance and obesity. Nutritional signals reaching the developing hypothalamus during pregnancy may influence the sensitivity of these neurons

to respond to similar signals postnatally. Infant nutrition in the neonatal period may also potentially affect future risk for obesity and its complications [79].

6. Assessment of the obese child

In order to establish the diagnosis of overweight or obese in a child, the clinician must evaluate the BMI and compare it to the standardized reference chart, appropriate for the age and sex of the child. According to World Health Organization the definition of overweight and obesity in children is established at the following cut-offs [80]:

Overweight: >+1Standard Deviations (equivalent to BMI 25 kg/m^2 at 19 years)

Obesity: >+2 Standard Deviations (equivalent to BMI 30 kg/m^2 at 19 years).

The cumulative prevalence of monogenic obesity among children with severe obesity is about 5%. There are a lot of genes implicated in obesity and too many obese patients in the world to perform molecular study for everyone. Most genetic and hormonal causes of obesity are rare. The decision to test for these abnormalities should depend upon the presence of particular phenotypes and clinical features suggesting the possibility of a diagnosable disorder [table 4]. The presence of severe obesity in a young child (<5 yr old) associated to extreme hyperphagia, severe insulin resistance disproportionate for the degree of obesity and a positive family history of early-onset obesity may support a genetic analysis.

History	Suggested Diagnosis
Early onset (!!! 5 years of age)	genetic disorders
Visual impairment and deafness	genetic disorders
Primary hypogonadotropic hypogonadism or hypogenitalism	genetic disorders
Family history: consanguineous relationships, other children affected	genetic disorders
Hyperphagia-often denied, ask specific questions such as waking at night to eat, demanding food very soon after a meal	if severe, suggests a genetic cause for obesity
Mood disturbance and central obesity	Cushing's syndrome
Frequent infections and fatigue	ACTH deficiency due to POMC mutations
Dry skin, constipation, intolerance to cold, or fatigue	hypothyroidism
Developmental delay	behavioral disorders
Short duration of obesity	endocrine or central cause
Onset and tempo of pubertal development	endocrine disorders
Damage to the CNS (e.g. infection, trauma, hemorrhage, radiation therapy, seizures)	hypothalamic obesity, pituitary GH deficiency or pituitary hypothyroidism

History	Suggested Diagnosis
Morning headaches, vomiting, visual disturbances, excessive urination or drinking	tumor or mass in the hypothalamus
Treatment with certain drugs or medications known to promote weight gain	obesity related to drugs

Examination	Suggested Diagnosis
Dysmorphic features or skeletal dysplasia	genetic disorders
Red hair (if not familial)	mutations in POMC in white Caucasians
Tall stature (on the upper centiles)	common obesity, but also MC4R deficiency
Selective fat deposition (60%)	leptin and leptin receptor deficiency
Short stature or a reduced rate of linear growth	GH deficiency, hypothyroidism, cortisol excess, pseudohypoparathyroidism, or a genetic syndrome such as Prader–Willi
Central body fat distribution with purple striae	Cushing's syndrome
Diminished growth rate and pubertal development	growth hormone deficiency, hypothyroidism, cortisol excess, and genetic syndromes
Accelerated growth rate and pubertal development	precocious puberty and some girls with PCOS
Acanthosis nigricans	insulin resistance

Investigations when clinically indicated

- Fasting and 2-hour glucose and insulin levels

- Proinsulin if PC-1 deficiency considered

- Fasting lipid panel

- Thyroid function tests

- Serum leptin - Karyotype, DNA for molecular diagnosis

- Bone age, Growth hormone (GH) secretion and function tests, when indicated

- Assessment of reproductive hormones, when indicated

- Serum calcium, phosphorus, and parathyroid hormone levels to evaluate for suspected pseudohypoparathyroidism

- MRI scan of the brain with focus on the hypothalamus and pituitary

- ACTH, adrenocorticotropic hormone;

- POMC, pro-opiomelanocortin; MAOI, monoamine oxidase inhibitor; MC4R, melanocortin-4 receptor; PC-1, prohormone convertase-1.

Table 4. Assessment of the obese child.

7. Conclusions

Obesity is caused by complex interactions between environment, behavior and genetic pre-disposition. The increased heath risk that obesity brings is well established by now. There is growing evidence that genetic predisposition presents a cornerstone role in the development of obesity. Nevertheless, despite the enormous success of genetic studies, there are still

important gaps in knowledge. Obesity-specific gene expression pattern may help in understanding the pathogenic mechanisms of obesity and its associated metabolic diseases. Recent advances in identifying genetic risk factors for obesity have contributed to understanding disease pathology, which, in term, may lead to development of new therapeutic strategies, including personalized medicine. In the everyday practice of a clinician, when facing a patient with obesity, it is important to identify particular phenotypes and clinical features that can help to recognize the children who need genetic screening.

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