

# **GENETIC OBESITY SYNDROMES**

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#### ABSTRACT

Genetic factors play a major role in the regulation of body weight and in the susceptibility to obesity in the population. A subset of people with severe obesity carry rare, highly penetrant genetic variants that can result in severe childhood-onset obesity. Current estimates suggest that up to 20% of children with severe obesity may carry pathogenic chromosomal abnormalities or mutations. The diagnosis of a genetic obesity syndrome can provide information that has value for the patient and their family and may help them deal with the social stigma that comes with severe obesity in childhood. In an increasing number of cases, the finding of a genetic cause for a patient's obesity can inform clinical care and the use of targeted therapies.

#### INTRODUCTION

At a population level, obesity is driven by an increase in the intake of easily available, energy-dense, highly palatable foods and a decrease in physical activity at school/work and in leisure time. However, variation in body mass index (BMI: weight in kg/height in meters squared) within the population is influenced by genetic factors (1,2). Studies in twins and families have shown that food intake, satiety responsiveness (fullness after a fixed meal), basal metabolic rate, the amount of energy utilized during a fixed amount of exercise, and body fat distribution are all heritable traits (3).

Genome-wide association studies (GWAS's) in large population-based cohorts have identified thousands of

common variants (minor allele frequency > 5%) that are associated with BMI and/or obesity (4). While individually each variant often has a small effect on BMI, cumulatively, the effect of millions of common and rare variants can now be combined to compute a polygenic risk score which can predict the development of severe obesity (5). Studies are ongoing to test how such scores might be useful in the clinical setting. Most common obesity associated variants lie in noncoding areas of the genome so identifying the mechanism by which they affect body weight can be challenging. It is interesting to note that most obesity- or BMI-associated variants lie in or near genes which are expressed in the brain and some of these variants have been associated with increased food intake (4,6). In contrast, GWAS associations for body fat distribution/waist-to-hip ratio, mostly seem to be linked to genes expressed in adipose tissue (7).

## CLINICAL APPROACH TO DIAGNOSIS OF GENETIC OBESITY SYNDROMES

Rare (less than 1% minor allele frequency), highly penetrant genetic variants in multiple genes have been associated with severe obesity that often presents in childhood. Whilst these disorders are rare, cumulatively up to 20% of children with severe obesity have chromosomal abnormalities or other penetrant rare variants that drive their obesity (8). The assessment of children and adults with severe obesity should be directed at screening for endocrine, neurological, and genetic disorders (9). Important information can be obtained from a detailed family history identify potential consanguineous to

relationships, the presence of other family members with severe obesity and those who have had bariatric surgery, and the ethnic origin of family members (Figure 1). The clinical history and examination can then guide the appropriate use of diagnostic tests. For the purposes of clinical assessment, it remains useful to categorize the genetic obesity syndromes as those with and without associated developmental delay.



Figure 1. Diagnosis of genetic obesity syndromes.

# OBESITY SYNDROMES WITHOUT DEVELOPMENTAL DELAY

The adipocyte-derived hormone leptin acts mainly to defend against starvation (10), with a fall in leptin levels (as seen in weight loss, acute caloric restriction or congenital leptin deficiency) causing an increase in food intake and physiological responses that act to restore energy balance (11). In most people, circulating leptin levels correlate closely with fat mass (12), although there is considerable variation in leptin levels at any given BMI, which is as yet unexplained. Leptin signals through the long isoform of the leptin receptor, which is widely expressed in the hypothalamus and other brain regions involved in energy homeostasis (13). In the arcuate nucleus of the hypothalamus (which has a permeable blood-brain barrier), there are several neuronal populations known to be important in weight regulation expressing the

leptin receptor. In the fed state, leptin stimulates the expression of pro-opiomelanocortin (POMC), which is processed to generate the melanocortin peptides that, in turn, activate the melanocortin 4 receptor (MC4R) on second-order neurons in the paraventricular nucleus. Leptin also inhibits adjacent neurons containing Agouti-related protein (AgRP), a MC4R antagonist. The integration of these two actions leads to reduced food intake (Figure 2). In the fasted state and with weight loss, a drop in leptin levels reduces the activation state of POMC neurons and increases AgRP signaling to cause an increase in food intake. These hypothalamic pathways interact with other brain centers to affect not just eating behaviors but also energy expenditure.

Severe obesity can result from mutations that disrupt key components of the leptin-melanocortin pathway (Figure 2). People with these genetic disorders experience an intense drive to eat (hunger), find food to be highly rewarding, and have impaired fullness (satiety) leading to hyperphagia (increased food intake), resulting in excessive weight gain from early childhood.



### Figure 2. Genes involved in the leptin-melanocortin pathway whose disruption causes obesity.

#### Leptin and Leptin Receptor Deficiency

Congenital leptin (LEP protein; *LEP* gene) and leptin receptor (LEPR protein; *LEPR* gene) deficiency are rare, autosomal recessive disorders associated with severe obesity from a very young age (before 1 year) (14,15). Homozygous frameshift, nonsense, and missense mutations involving *LEP* and *LEPR* have been identified in 1% and 2-3% of patients with severe obesity from consanguineous families, respectively (16-18). Leptin receptor mutations have been found in some non-consanguineous families, where both parents were unrelated but carried rare heterozygous variants.

Serum leptin is a useful test in patients with severe early onset obesity as an undetectable serum leptin suggests a diagnosis of congenital leptin deficiency. Very rare mutations that result in a detectable but bioinactive form of leptin or a form of leptin that antagonizes the leptin receptor, have also been described (19,20). Serum leptin concentrations are appropriate for the degree of obesity in leptin receptor deficiency and as such an elevated serum leptin concentration is not necessarily a predictor of leptin receptor deficiency (17). In some patients, particular *LEPR* mutations that result in abnormal cleavage of the extracellular domain of LEPR (which then acts as a leptin binding protein), are associated with markedly elevated leptin levels (15).

The clinical phenotypes associated with leptin and leptin receptor deficiencies are similar. Patients are born of normal birth weight, experience intense hyperphagia with food seeking behavior and rapid weight gain in the first few months of life resulting in severe obesity (16). While measurable changes in resting metabolic rate or total energy expenditure have not been demonstrated in affected individuals, reduced sympathetic nerve function is associated with impaired fat oxidation and may contribute to obesity (21). Children with leptin deficiency have

abnormalities of T cell number and function (16), consistent with reported high childhood infection rates and childhood mortality from infection, particularly in environments where infectious diseases are prevalent (21).

In keeping with severe obesity, patients with leptin and leptin receptor deficiency are hyperinsulinemic and some adults develop type 2 diabetes in the 3rd to 4th decade. Affected individuals can exhibit hypothalamic (secondary) hypothyroidism characterized by low free thyroxine levels and inappropriately normal (or highnormal) levels of serum thyroid stimulating hormone (TSH) (14,15). Typically, adults with leptin or leptin receptor deficiency have biochemical evidence of hypogonadotropic hypogonadism and do not undergo normal pubertal development (see below). However, there are reports of delayed spontaneous onset of menses in some leptin and leptin receptor deficient adults (17). Linear growth is appropriate in childhood, but in the absence of a pubertal growth spurt, final height is reduced.

Although leptin deficiency is very rare, it is entirely treatable with daily subcutaneous injections of recombinant human leptin (16,22). The major effect of leptin replacement in these patients is on food intake, with normalization of hyperphagia and enhanced satiety. Leptin administration does not enhance energy expenditure. However, weight loss by caloric restriction is associated with decreased total energy expenditure; the absence of this decrease in patients with congenital leptin deficiency, suggests that leptin does affect energy expenditure (23). Leptin replacement permits progression of appropriatelytimed pubertal development, along with expression of secondary sexual characteristics (21). These reproductive system effects are likely mediated through leptin action on hypothalamic neurons containing kisspeptin, which signals via GPR54 to modify the release of gonadotrophin-releasing hormone (24).

Although leptin treatment is not be effective for patients with LEPR deficiency, these patients can now treated with a melanocortin receptor agonist (setmelanotide, Figure 3), which is now licensed in the UK, Europe and USA (25).

Leptin treatment is not clinically effective in people with common obesity (26,27), which may be a manifestation of leptin resistance or defects in downstream neuronal pathways. Studies in heterozygous carriers of LEP mutations who have partial leptin deficiency and an increase in fat mass (28), suggest that people with relatively low leptin levels may benefit from leptin therapy.

### **Pro-opiomelanocortin Deficiency**

Due to impaired production of melanocortin stimulating hormone peptides (a/b MSH) and diminished or absent MC4R signaling (Figure 2), homozygous or compound heterozygous mutations in POMC cause hyperphagia and early-onset obesity (29). People deficient in POMC also have pale skin and red or light colored hair due to the lack of signaling of pigment-inducing melanocortin 1 receptors in the skin (29). In the pituitary gland, POMC is the precursor for adrenocorticotrophin (ACTH). As such, complete POMC deficiency presents in neonatal life with ACTH features of and cortisol deficiency: hypoglycemia and cholestatic jaundice requiring longterm corticosteroid replacement therapy (30). Typically, patients with primary or secondary cortisol deficiency present with hypophagia and weight loss, so adrenal insufficiency with hyperphagia in the absence of a structural hypothalamic abnormality should raise suspicion for a POMC defect. POMC deficiency may also impair the timing of puberty, an effect that appears to be mediated by the melanocortin 3 receptor (MC3R) (31).

Complete POMC deficiency can be treated with a melanocortin receptor agonist (setmelanotide) (32) (Figure 3). Heterozygous missense mutations directly affecting the function of POMC peptides have been

described (Figure 2) (33). These variants significantly increase obesity risk but are not invariably associated with obesity. The potential efficacy of MC4R agonists

in patients with these heterozygous mutations is currently being tested in clinical trials.



~ licensed for adolescents and adults with obesity in several countries. Trials ongoing in children.

Figure 3. Medical treatment of patients with genetic obesity syndromes. POMC: pro-opiomelanocortin. PCSK1: prohormone convertase-1. MC4R: melanocortin 4 receptor. GLP-1: glucagon receptor-1.

#### Prohormone Convertase-1-Deficiency

Prohormone convertase-1 (PCSK1, also known as PC1/3) is an enzyme that acts upon a range of substrates including proinsulin, proglucagon, and POMC. Compound heterozygous or homozygous mutations in *PCSK1* cause neonatal small bowel enteropathy, glucocorticoid deficiency (secondary to ACTH deficiency), hypogonadotropic hypogonadism, and postprandial hypoglycemia due to impaired processing of proinsulin to insulin, as well as severe, early onset obesity (34,35). Elevated plasma levels of proinsulin and 32/33 split proinsulin in the context of low levels of mature insulin are diagnostic for this disorder. Setmelanotide is now licensed for the treatment of this condition (Figure 3).

#### Melanocortin 4 Receptor Deficiency

Heterozygous melanocortin 4 receptor (MC4R) mutations have been reported in people with obesity from various ethnic groups (<u>www.mc4r.org.uk</u>) and occur at a frequency of 1 in 300 people in the population (36), 1% of adults with a BMI > 30 kg/m<sup>2</sup>, and 3-5% of children with severe obesity (37,38). *MC4R* mutations are inherited in a co-dominant

manner, with variable penetrance and expression; homozygous mutations have also been reported. In several studies, MC4R deficiency is the most common genetic form of obesity (37-39).

Given the importance of MC4R for leptin signaling (Figure 2), the clinical features of MC4R deficiency include hyperphagia and rapid weight gain, which often emerges in the first few years of life. Alongside the increase in fat mass, MC4R-deficient subjects also have an increase in lean mass and a marked increase in bone mineral density that exceeds what would be expected for their increased body size and, thus, they often appear "big-boned" (37). They exhibit accelerated linear growth in early childhood, which may be a consequence of disproportionate early hyperinsulinemia and effects on pulsatile growth hormone (GH) secretion, which is retained in MC4Rdeficient adults in contrast to common forms of obesity (40). Despite this early hyperinsulinemia, adult subjects with obesity who are heterozygous for mutations in the MC4R gene have a comparable risk of developing impaired glucose intolerance and type 2 diabetes to controls of similar age and adiposity. Reduced sympathetic nervous system activity in MC4R-deficient patients is likely to explain the lower

prevalence of hypertension and lower systolic and diastolic blood pressures compared to control populations (41). Thus, central melanocortin signaling appears to play an important role in the regulation of blood pressure and its coupling to changes in weight.

At present, there is no specific therapy for MC4R deficiency, but patients with heterozygous MC4R mutations do respond to Glucagon-like peptide- (GLP-1) receptor agonists (42) and to Roux-en-Y-bypass surgery (43) (Figure 3), with a variation in weight loss response that is comparable to people with a normal MC4R gene sequence.

## Albright's Hereditary Osteodystrophy/Pseudohypoparathyroidism

Albright hereditary osteodystrophy (AHO) is an autosomal dominant disorder due to germline mutations in GNAS, an imprinted gene that encodes the G alpha s (Gs) protein, which mediates signaling by multiple G-protein coupled receptors (GPCRs). Classically, heterozygous loss-of-function mutations in GNAS affecting the maternal allele lead to short stature, obesity, skeletal defects, and resistance to several hormones that activate Gs in their target tissues (pseudohypoparathyroidism type IA), while paternal transmission leads only to the AHO phenotype (pseudopseudohypoparathyroidism) (44). GNAS mutations affect coupling to, or signaling by, MC4R, which explains hyperphagia and obesity in affected patients (45). Some patients will carry mutations that affect signaling by other GPCRs including the beta-2 and beta-3 adrenoreceptors which contribute to low basal metabolic rate and other clinical phenotypes (45). These patients may not have classical features such as short stature. As such, this diagnosis should be considered in all patients with severe early-onset obesity (45).

## SRC Homology 2B (SH2B1) 1 Deficiency

Deletion of a 220-kb segment of chromosome 16p11.2 is associated with highly penetrant, severe, earlyonset obesity and insulin resistance (46). This deletion includes a small number of genes, one of which is *SH2B1* (Src homology 2B1) known to be involved in leptin, insulin, and Brain-Derived Neurotrophic Factor (BDNF) signaling. These patients gain weight in the first years of life, with hyperphagia and fasting plasma insulin levels that are disproportionately elevated, with increased risk for type 2 diabetes in early adulthood (47). In some patients loss of function mutations in the SH2B1 gene have also been reported in association with early-onset obesity, severe insulin resistance, and behavioral abnormalities (48).

# OBESITY SYNDROMES WITH DEVELOPMENTAL DELAY

# Prader-Willi Syndrome

Prader-Willi syndrome is an autosomal dominant disorder caused by deletion or disruption of a paternally imprinted region on chromosome 15q11.2q12 (49). The clinical features of Prader-Willi syndrome (PWS) include diminished fetal activity, hypotonia, and feeding difficulties in infancy followed by hyperphagia, obesity, developmental delay, short stature, hypogonadotropic hypogonadism, and small hands and feet (Figure 4). Children with PWS display diminished growth, reduced lean body mass and increased fat mass. These body composition abnormalities can be explained, in part, by growth hormone (GH) deficiency and improved with growth hormone treatment, which should be started in early childhood.



Figure 4. Infancy and childhood clinical features of Prader-Willi Syndrome (PWS).

Contained within the 4.5Mb PWS region in 15g11-g13 are silenced paternally imprinted genes and a family of small nucleolar RNAs (snoRNAs) known as the snoRNAs. Small deletions exclusively HBII-85 encompassing these snoRNAs result in the key features of PWS including obesity (Figure 4) (50,51), suggesting that these snoRNAs play a critical role in the development of this syndrome. Histopathological studies on post-mortem brain samples from PWS patients have demonstrated reduced levels of oxytocin expression in the hypothalamus (52) and trials of intranasal administration in PWS are ongoing (53). Brain-derived neurotrophic factor (BDNF) expression is also reduced in PWS, potentially contributing to both the obesity and neurobehavioral features including stereotyped behaviors (54).

## **Bardet Biedl Syndrome**

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disease caused by mutations in over 25 genes and characterized by obesity, developmental delay, syndactyly, brachydactyly or polydactyly, retinal dystrophy or pigmentary retinopathy, hypogonadism, and structural abnormalities of the kidney or renal impairment (55). The differential diagnosis includes Biemond syndrome II (iris coloboma, hypogenitalism, obesity, polydactyly) and Alstrom syndrome (retinitis pigmentosa, obesity, diabetes mellitus, and deafness). To date, BBS proteins are all involved in basal body and centrosomal function and impact on ciliary development and transport (56). There is some evidence that BBS genes affect leptin signaling and trafficking of MC4Rs in cilia. Clinical trials of setmelanotide have shown some benefit in treating hyperphagia in these patients (57) and this drug is licensed for BBS in some countries (Figure 3).

# Brain-Derived Neurotrophic Factor and Tropomycin-Related Kinase B

Brain-Derived neurotrophic factor (BDNF) activates signaling by the tropomycin-related kinase B (TrkB) to play a key role in the development and maintenance of neurons. Rare chromosomal rearrangements and heterozygous point mutations in BDNF and TrkB are associated with speech and language delay, hyperphagia, and impaired pain sensation (58-60). Disordered behaviors including hyperactivity, fearlessness, anxiety, and aggression are also features of these conditions, which can often present as de-novo genetic abnormalities (61).

## Single Minded 1 Deficiency

Single minded 1 (SIM1) is a transcription factor involved in the development of the paraventricular and supraoptic nuclei of the hypothalamus. Chromosomal rearrangements and heterozygous missense mutations in SIM1 and in a closely related transcription factor OTP (Orthopedia) cause severe obesity (62-64). Clinical features of these patients resemble those seen in MC4R deficiency with, in addition, a variable phenotype of developmental delay with autistic like features noted in some, but not all, patients (63).

### **Other Rare Genetic Mutations**

Rare penetrant variants in multiple genes can be associated with, but do not invariably cause, obesity that is inherited in a classical Mendelian manner (Figure 2). Examples include heterozygous loss of function variants affecting the Semaphorin 3 ligands, receptors and co-receptors that direct the development of POMC projections (65); mutations in Steroid receptor coactivator-1 (SRC-1) (66) and Pleckstrin-homology-domain interacting protein, PHIP, which modulate POMC transcription (67); disruption of Serotonin 2c receptor, HTR2C which regulates the electrical activity of POMC neurons causing obesity, social anxiety and impaired memory

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(68,69) and deletions affecting TRPC5 on the X chromosome, which cause obesity, anxiety, autism (in males), and postnatal depression (in females) (70). Variants in genes that regulate MC4R trafficking (*MRAP2*) (71) and genes whose precise function in the hypothalamus is not as yet clear, such as Kinase Suppressor of Ras-2 (*KSR2*) (72) have also been associated with obesity.

## **FUTURE PERSPECTIVES**

The diagnosis of a genetic obesity syndrome can provide information that has diagnostic value for the family to whom genetic counselling can be provided. A genetic diagnosis can help children and their families deal with the social stigma that comes with severe obesity and, in some instances, has prevented children from being taken into care by social services when obesity is blamed on parental neglect. A genetic diagnosis can inform management (many such patients are relatively refractory to weight loss through changes in diet and exercise) and can inform clinical decision-making. For example, bariatric surgery (particularly Roux-en-Y bypass surgery) is contraindicated in many genetic obesity syndromes as it does not reverse the strong hypothalamic drive to eat and continued overeating can be harmful. Importantly, an increasing number of genetic obesity syndromes are now treatable with mechanism-based pharmacologic therapies.

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