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THE GENETICS OF OBESITY IN HUMANS

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ABSTRACT

Over the past twenty years a growing number of genes have been described in which loss of function mutations are consistently associated with the development of severe obesity beginning in early childhood. Whilst individually these disorders are rare, cumulatively at least 10% of children with severe obesity have rare chromosomal abnormalities, nonsense mutations, or missense mutations that strongly drive the carrier's risk of becoming obese. 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 some cases, the finding of a genetic cause for a patient's obesity can lead to specific therapeutic interventions.

INTRODUCTION

The rising prevalence of obesity is driven by an increase in the intake of easily available, energy-dense highly palatable foods and a decrease in energy expenditure at school/work and in leisure time. However, there is considerable variation in body weight and fat mass between individuals within a population. Estimates of the heritability (the proportion of the phenotypic variance of a trait that is attributable to genetic variation) of body mass index (BMI: weight in kg/height in meters squared) range between 40% and 70%, suggesting that this variation in BMI is largely influenced by genetic factors (1, 2). The findings from twin, family, and adoption studies are supported by recent studies in twins born after the recent increase in the prevalence of obesity, which have estimated the heritability of BMI at 77% (3). Whilst the influence on body weight of the shared environment cannot be distinguished from the genetic contribution in most studies, comparable estimates of heritability have been derived from studies of adopted children, whose weights correlate better with that of their biological parents than with that of their adoptive parents (4). Genetic factors may modulate the response to changes in energy intake as evidenced by classical overfeeding studies in monozygotic twins, which showed that the amount of weight gained was similar between members of a twin pair but differed across sets of identical twins (5).

COMMON OBESITY ASSOCIATED VARIANTS IDENTIFIED BY GENOME WIDE ASSOCIATION STUDIES

Different approaches have been used to identify genetic factors that contribute to the heritability of increased BMI and obesity. One such approach involves Genome-wide association studies (GWAS's), which examine thousands of common genetic variants spanning the genome, often in large population-based cohorts in whom BMI data is available (6). Altogether, GWAS analyses of BMI levels as a continuous quantitative trait or of obesity as a categorical variable have led to the discovery of over 200 associated loci (7, 8). These common variants uncovered in GWAS's are characterized by modest effect sizes (per-allele odds ratios between 1.1. and 1.5), and the proportion of total variability explained by GWAS-identified loci to date remains relatively modest. Many of the genes within these loci are expressed in the brain and some have been shown to modulate body weight in experimental studies in animals (9). Importantly, gene burden scores for obesity risk alleles are significantly associated with validated childhood eating behaviour scores for satiety and food responsiveness, which themselves predict obesity, reinforcing the conclusion that most of these genes are exerting their obesogenic effects through the brain and the control of food intake (10).

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 at least 10% of children with severe obesity have chromosomal abnormalities or other penetrant rare variants that drive their obesity (11). The assessment of severely obese children and adults should be directed at screening for endocrine, neurological, and genetic disorders (12). Useful information can be obtained from a detailed family history to identify potential consanguineous relationships, the presence of other family members with severe obesity or who have had bariatric surgery, and the ethnic origin of family members. 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.

OBESITY SYNDROMES WITHOUT DEVELOPMENTAL DELAY

Some genetic obesity syndromes are associated with learning difficulties and clinical disorders which mean that children come to medical attention at a young age. However, there is a large and increasing group of genetic disorders where severe obesity itself is the presenting feature. Severe obesity can result from a multiplicity of defects involving the leptin-melanocortin pathway.

Briefly, leptin is an adipocyte-derived hormone whose circulating levels correlate closely with fat mass (13). Its clearest role is to defend against starvation (14). A fall in leptin levels (as seen in weight loss, acute caloric restriction or congenital leptin deficiency) leads to a set of physiological responses that act to restore energy homeostasis by driving an increase in energy intake and a reduction in daily energy expenditure (15).

Many of the physiological effects of leptin are mediated through the long isoform of the leptin receptor, which is widely expressed in the hypothalamus and other brain regions involved in energy homeostasis (16). Leptin stimulates the expression of pro-opiomelanocortin (POMC) in primary neurons located in the arcuate nucleus of the hypothalamus. POMC is extensively post-translationally modified to generate the melanocortin peptides, which activate the melanocortin receptors to modulate diverse functions in the central nervous system, adrenal glands, and skin. In the hypothalamus, activation of the melanocortin receptors suppresses food intake. In addition, leptin inhibits orexigenic pathways mediated by neurons expressing the melanocortin antagonist, Agouti-related protein, and neuropeptide Y (NPY); in turn, NPY has been shown to suppress the expression of POMC. These two sets of primary leptin-responsive neurons project to second-order neurons expressing the melanocortin 4 receptor (MC4R). Targeted genetic disruption of MC4R in mice leads to not only increased food intake and adiposity, but also increased lean mass and linear growth (17). These hypothalamic pathways interact with other brain centres to coordinate appetite control with modulation of efferent signals in peripheral organs regulating intermediary metabolism and energy expenditure.

Leptin and Leptin Receptor Deficiency

Congenital leptin (LEP) and leptin receptor (LEPR) deficiency are rare, autosomal recessive disorders associated with severe obesity from a very young age (before 2 years) (18, 19). Homozygous frameshift, nonsense, and missense mutations involving *LEP* and *LEPR* have been identified in 1% and 2-3% of severely obese patients from consanguineous families, respectively (20-22). 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 is highly suggestive of a diagnosis of congenital leptin deficiency. Very rare mutations that result in a detectable but bio-inactive form of leptin have also been described (23). Serum leptin concentrations are appropriate for the degree of obesity in leptin receptor deficient patients and as such an elevated serum leptin concentration is not necessarily a predictor of leptin receptor deficiency (21). 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 (18).

The clinical phenotypes associated with congenital leptin and leptin receptor deficiencies are similar. Patients are born of normal birth weight but exhibit rapid weight gain in the first few months of life resulting in severe obesity. Affected subjects are characterized by intense hyperphagia with food seeking behaviour and aggression when food is denied (20). While measurable changes in resting metabolic rate or total energy expenditure have not been demonstrated, abnormalities of sympathetic nerve function suggest that defects in substrate utilisation may contribute to the phenotype observed (24). Children with leptin deficiency have profound abnormalities of T cell number and function (20), consistent with high rates of childhood infection and a high reported rate of childhood mortality from infection (24).

Patients are hyperinsulinemic consistent with the severity of obesity and some adults develop type 2 diabetes in the 3rd to 4th decade. Leptin and leptin receptor deficiency are associated with hypothalamic (secondary) hypothyroidism characterized by low free thyroxine levels and inappropriately normal or high-normal levels of serum thyroid stimulating hormone (TSH) (18, 19). Typically, normal pubertal development does not occur in adults with leptin or leptin receptor deficiency, with biochemical evidence of hypogonadotropic hypogonadism. However, there is some evidence for the delayed but spontaneous onset of menses in a small number of leptin and leptin receptor deficient adults (18-20). 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 that result in beneficial effects on hyperphagia, fat mass and hyperinsulinemia, reversal of the immune defects, and permissive effects on the development of puberty (20, 25). Such treatment is currently available to patients on a compassionate-use or individual patient basis.

The major effect of leptin administration is on food intake, with normalization of hyperphagia and enhanced satiety. Leptin is also involved in mediating food reward. In the leptin-deficient state, images of food (compared to non-food images) were associated with a marked increase in neuronal activation in the ventral striatum an area associated with pleasure and reward, visualised using functional MRI (26). This response was normalized after seven days of leptin treatment. On the other hand, leptin administration does not result in a change in energy expenditure. However, given that weight loss by caloric restriction is associated with an adaptive decrease in basal and daily energy expenditure, the absence of this adaptive thermogenic response is notable as demonstrated in obese volunteers in whom the fall in energy expenditure seen after 10% weight loss is blunted by the administration of leptin (27).

Leptin administration also permits progression of appropriately-timed pubertal development, suggesting that leptin is a permissive factor for the development of puberty in humans (20). In adults with leptin deficiency, leptin induced the development of secondary sexual characteristics and pulsatile gonadotrophin secretion (24). Leptin may exert these effects on the reproductive system through a number of molecules including kisspeptin, which signals through GPR54, to modify the release of gonadotrophin-releasing hormone.

Pro-opiomelanocortin Deficiency

Leptin suppresses food intake in part by acting on hypothalamic neurons expressing POMC. People who are homozygous or compound heterozygous for loss of function mutations in the pro-opiomelanocortin gene, *POMC,* are hyperphagic and develop early-onset obesity due to loss of melanocortin signalling at the MC4R in the hypothalamus (28). The clinical features are comparable to those reported in patients with mutations in the receptor for POMC-derived ligands, MC4R (see below). In the pituitary, POMC is the precursor for adrenocorticotrophin (ACTH). As such, POMC deficiency presents in neonatal life with findings of secondary adrenal insufficiency: hypoglycaemia, cholestatic jaundice, or other features of adrenal crisis requiring long-term corticosteroid replacement therapy (29). Such children have pale skin, and white Caucasians have red hair, due to the lack of melanocortin

function at melanocortin 1 receptors in the skin (28). POMC deficiency may also impair the central control of reproduction through mechanisms that are as yet unclear. Children from different ethnic backgrounds may have a less obvious phenotype such as dark hair with red roots. A number of heterozygous point mutations affecting POMC peptides and POMC processing have been described (30). These variants significantly increase obesity risk but are not invariably associated with obesity.

The marked weight loss seen in adults with POMC deficiency studied in a recent trial of a selective melanocortin receptor agonist (setmelanotide) holds considerable promise for the treatment of this group of patients in the future (31).

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 hypoglycaemia due to impaired processing of proinsulin to insulin as well as severe, early onset obesity (32, 33). Elevated plasma levels of proinsulin and 32/33 split proinsulin in the context of low levels of mature insulin provide the basis for a diagnostic test for this disorder.

Melanocortin 4 Receptor Deficiency

Heterozygous melanocortin 4 receptor (MC4R) mutations have been reported in people with obesity from various ethnic groups (www.mc4r.org.uk). The prevalence of pathogenic MC4R mutations varies from 0.5 -2.5% of people with a BMI > 30 kg/m^2 in UK and European populations to 5% in patients with severe childhood obesity (34, 35). As MC4R deficiency is the most common genetic form of obesity (35, 36), assessment of the sequence of the MC4R is increasingly seen as a necessary part of the clinical evaluation of the severely obese child.

Given the large number of potential influences on body weight, it is perhaps not surprising that both genetic and environmental modifiers have important effects on the severity of obesity associated with MC4R mutations in some pedigrees. Taking account of all of these observations, co-dominance, with modulation of expressivity and penetrance of the phenotype, is the most appropriate descriptor for the mode of inheritance.

The clinical features of MC4R deficiency include hyperphagia, which often starts 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, thus they often appear “big-boned” (35). 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 MC4R-deficient adults in contrast to common forms of obesity (37). Despite this early hyperinsulinemia, obese adult subjects who are heterozygous for mutations in the MC4R gene have a comparable risk of developing impaired glucose intolerance and type 2 diabetes compared to controls of similar age and adiposity.

Further studies have established that MC4R plays a role in fat oxidation and nutrient partitioning. These effects are also seen in rodents and appear to be mainly mediated by the sympathetic nervous system. 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 (38). Thus, central melanocortin signalling 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 Roux-en-Y-bypass surgery, which can be considered in adults (39). As most patients are heterozygotes with one functional allele intact, it is possible that small molecule MC4R agonists (36) or pharmacological chaperones which improve receptor trafficking to the cell surface, might become appropriate treatments for this disorder.

Albright's Hereditary Osteodystrophy

Albright hereditary osteodystrophy (AHO) is an autosomal dominant disorder due to germline mutations in GNAS1, an imprinted gene that encodes the G alpha s protein that mediates signalling by multiple G-protein coupled receptors (GPCRs). Classically, heterozygous loss-of-function mutations in GNAS lead to AHO, a disorder characterized by short stature, obesity, skeletal defects, and impaired olfaction. Maternal transmission of GNAS1 mutations leads to AHO plus resistance to several hormones (e.g., parathyroid hormone) that activate Gs in their target tissues (pseudohypoparathyroidism type IA), while paternal transmission leads only to the AHO phenotype (pseudopseudohypoparathyroidism) (40). Studies in both mice and humans demonstrate that GNAS1 is imprinted in a tissue-specific manner, being expressed primarily from the maternal allele in some tissues and biallelically expressed in most other tissues. Thus, multi-hormone resistance occurs only when Gs (alpha) mutations are inherited maternally. Recent studies have suggested that rare variants in GNAS may lead to obesity without short stature and some of the other clinical features associated with AHO (11), suggesting that this diagnosis should be considered in a broader group of patients with severe early-onset obesity.

SRC Homology 2B (SH2B1) 1 Deficiency

Deletion of a 220-kb segment of 16p11.2 is associated with highly penetrant familial severe early-onset obesity and severe insulin resistance (41). 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) signalling. These patients gain weight in the first years of life, with hyperphagia and fasting plasma insulin levels that are disproportionately elevated compared to age- and obesity-matched controls. Loss of function mutations in the SH2B1 gene have also been reported in association with early-onset obesity, severe insulin resistance, and behavioural abnormalities in some patients (42).

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 15q11.2-q12. The clinical features of Prader-Willi syndrome (PWS) include diminished fetal activity, hypotonia in infancy, obesity, mental retardation, short stature, hypogonadotropic hypogonadism, and small hands and feet. Diagnostic criteria arrived at by a consensus group refer to five major criteria, such as feeding problems and failure to thrive in infancy and seven minor criteria, such as hypopigmentation, which can be added together to give a score used to make a clinical diagnosis of PWS.

Chromosomal abnormalities are principally responsible for PWS either through deletion of an imprinted region on the paternal chromosome 15q11.2-q12 or through loss of the entire paternal chromosome 15 with presence of 2 maternal homologues (uniparental maternal disomy). Maternal deletion of the same imprinted region (or paternal uniparental disomy), causes another characteristic phenotype known as Angelman syndrome. Within the 4.5Mb PWS region in 15q11-q13, where there is a lack of expression of paternally imprinted genes, several candidate genes have been studied and their expression shown to be absent in the brains of PWS patients. These transcripts include SNURF-SNRPN and multiple small nucleolar RNAs (snoRNAs), in particular the HBII-85 snoRNAs. Small deletions encompassing only this family of snoRNAs have been reported in association with the cardinal features of PWS including obesity (43, 44), suggesting that these noncoding sequences may play a critical role in the development of this syndrome.

Some features of PWS distinguish this diagnosis from other genetic obesity syndromes. There is mild prenatal growth retardation with a mean birth weight of about 6 lbs (2.8 kg) at term, hyporeflexia and poor feeding in neonatal life due to diminished swallowing and sucking reflexes; infants often require assisted feeding for about 3 to 4 months. Feeding difficulties generally improve by the age of 6 months. From 12 to 18 months onward, uncontrollable hyperphagia becomes a dominant feature resulting in severe obesity (45). One suggested mediator of the obesity phenotype in PWS patients is the stomach-derived hormone ghrelin, which is implicated in the regulation of meal-time hunger in rodents and humans and is a potent stimulator of growth hormone secretion. Fasting total plasma ghrelin levels are 4.5-fold higher in PWS patients than in equally obese patients without PWS and patients with other genetic obesity syndromes (46). However suppression of ghrelin with octreotide appears to have no impact on the hyperphagia seen in adults with Prader Willi syndrome (47). As such, the clinical relevance of this finding has not as yet been established. Additionally, histopathological studies on post-mortem brain samples from PWS patients have demonstrated reduced levels of oxytocin expression in the hypothalamus (48) and trials of intranasal administration in PWS are ongoing (49).

Children with Prader-Willi syndrome (PWS) display diminished growth, reduced lean body mass and increased fat mass, body composition abnormalities which can be explained in part by growth hormone (GH) deficiency. Growth hormone treatment in these children decreases body fat and increases linear growth, lean mass, fat oxidation, and energy expenditure. These improvements are most dramatic during the first year of GH therapy, although prolonged treatment does not completely normalize these parameters.

Bardet Biedl Syndrome

Bardet-Biedl syndrome (BBS) is a rare (prevalence <1/100,000), autosomal recessive disease characterized by obesity, mental retardation, dysphormic extremities (syndactyly, brachydactyly or polydactyly), retinal dystrophy or pigmentary retinopathy, hypogonadism, and structural abnormalities of the kidney or functional renal impairment (50). The differential diagnosis includes Biemond syndrome II (iris coloboma, hypogenitalism, obesity, polydactyly, and mental retardation) and Alstrom syndrome (retinitis pigmentosa, obesity, diabetes mellitus and deafness).

Bardet-Biedl syndrome is a genetically heterogeneous disorder with multiple genes identified to date. Although BBS is usually transmitted as a recessive disorder, some families have exhibited tri-allelic inheritance where clinical manifestation of the syndrome requires two mutations in one BBS gene plus an additional mutation in a second, unlinked BBS gene. To date, BBS proteins are all involved in basal body and centrosomal function and impact on ciliary development and transport (51).

Brain-Derived Neurotrophic Factor and Tyrosine Kinase Receptor Tropomycin-Related Kinase B

Brain-derived neurotrophic factor (BDNF) is one of several nerve growth factors which activate signalling by the tyrosine kinase receptor tropomycin-related kinase B (TrkB), which may lie distal to MC4R signalling. Rare chromosomal rearrangements and heterozygous point mutations in BDNF and TrkB are associated with speech and language delay, hyperphagia and impaired pain sensation (52-54). Disordered behaviours including hyperactivity, fearlessness, anxiety, and aggression are also features of these disorders, which can often present as de-novo genetic abnormalities.

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 cause severe obesity (55-57). Clinical features of these patients resemble those seen in MC4R deficiency with, in addition, a variable phenotype of developmental delay with some autistic like features noted in some, but not all, patients.

Carboxypeptidase E

Later steps of prohormone processing (see above under PCSK1 deficiency) are undertaken by a range of carboxy and amino peptidases, one of which, carboxypeptidase E (CPE), has long been known to cause obesity when disrupted in mice. The first human homozygous nonsense mutation in CPE was recently reported. In addition to obesity and hypogonadism, the affected proband showed severe developmental delay suggesting a broader role for CPE in CNS development and function (58).

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, where the persistence of severe obesity despite medical advice has been considered a reason to invoke parental neglect, the making of a genetic diagnosis has prevented children from being taken into care by social services. 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 regarding the use of bariatric surgery (feasible in some, high risk in others). Importantly, some genetic obesity syndromes are treatable.

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