Abstract  A number of genetic obesity syndromes have been identified by sequencing candidate genes in patients with severe obesity. Many of the initial findings emerged from studying families who displayed a classical Mendelian pattern of inheritance; however, with more comprehensive genome wide approaches, increasingly more complex models of inheritance are likely to emerge. The functional and physiological characterization of the human obesity syndromes has provided information that has diagnostic value (Fig. 2.1), has led to specific treatments in some patients and continues to provide insights into the mechanisms involved in the regulation of body weight in humans.

Introduction

Traditionally, patients affected by genetic forms of obesity were identified as a result of their association with developmental delay, dysmorphic features and/or other developmental abnormalities, i.e. a pattern of clinical features which represented a recognizable syndrome. However, the identification of genetic disorders that disrupt the hypothalamic leptin–melanocortin signalling pathway has led to the recognition that obesity is the predominant presenting feature in a significant subset of individuals. Based on case series of patients with genetic obesity syndromes, childhood onset of obesity is a consistent feature. For the purposes of clinical assessment, it remains useful to categorize the genetic obesity syndromes as those with dysmorphism and/or developmental delay and those without these features; however, in some cases the spectrum of clinical features can be quite variable (Fig. 2.1).
To date, there are at least 30 disorders where obesity is a consistent clinical feature but often associated with mental retardation, dysmorphic features and organ-specific developmental abnormalities. High-throughput next-generation sequencing technologies, and in particular copy number variant detection, are likely to result in the identification and recognition of multiple new syndromes where obesity and developmental delay are closely associated.

**Prader–Willi Syndrome**

The Prader–Willi syndrome is the most common obesity syndrome (estimated prevalence of about 1 in 25,000). Key clinical features include hypotonia and failure to thrive in infancy, mental retardation, short stature, hyperphagic obesity and hypogonadotropic hypogonadism [1]. Children with Prader–Willi syndrome (PWS) have reduced lean body mass and increased fat mass, abnormalities which resemble those seen in growth hormone (GH) deficiency; GH treatment decreases body fat and increases linear growth, muscle mass, fat oxidation and energy expenditure [2]. Children and adults with PWS have fasting plasma ghrelin levels that are several-fold higher than equally obese controls and patients with other genetic obesity

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**Fig. 2.1** A diagnostic approach to obesity syndromes
syndromes [3]. The significance of this finding and its possible role in the pathogenesis of hyperphagia in these patients is unknown.

PWS is caused by deletion of a critical segment on the paternally inherited copy of chromosome 15q11.2-q12, or loss of the entire paternal chromosome 15 with presence of two maternal copies (uniparental maternal disomy). Most chromosomal abnormalities in PWS occur sporadically. Deletions account for 70–80% of cases; the majority are interstitial deletions, many of which can be visualized by karyotype analysis. There are distinct differences in DNA methylation of the parental alleles, and DNA methylation can be used as a reliable postnatal diagnostic tool in PWS. Small deletions encompassing only the HBII-85 family of snoRNAs have been reported in association with the cardinal features of PWS including obesity [4, 5], suggesting that these noncoding sequences and the genes they regulate may be important.

Albright Hereditary Osteodystrophy

Mutations in GNAS1 that decrease expression or function of G alpha s protein result in Albright hereditary osteodystrophy (AHO), which is an autosomal dominant disorder. Maternal transmission of GNAS1 mutations leads to classical AHO (characterized by short stature, obesity, skeletal defects and impaired olfaction) 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 AHO (pseudopseudohypoparathyroidism). 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 in other tissues; thus multi-hormone resistance occurs only when Gs (alpha) mutations are inherited maternally [6].

Bardet–Biedl Syndrome

Bardet–Biedl syndrome (BBS) is a rare (prevalence <1/100,000), autosomal recessive disease characterized by obesity, mental retardation, dysmorphic extremities (syndactyly, brachydactyly or polydactyly), retinal dystrophy or pigmentary retinopathy, hypogonadism and structural abnormalities of the kidney or functional renal impairment. BBS is a genetically heterogeneous disorder that is now known to map to at least 16 loci, with mutations in more than one locus sometimes required for complete expression of the phenotype. Many BBS genes appear to affect proteins localized to the basal body, a key element of the monocilium thought to be important for intercellular sensing in mammalian cells including neurons [7]. Other disorders of ciliary function (e.g. Alström syndrome and Carpenter syndrome) are also associated with obesity. Recent studies in mice have suggested a connection between ciliary function and leptin signalling [8].
BDNF and TRKB Deficiency

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 melanocortin 4 receptor (MC4R) signalling. We reported a child with severe obesity, impaired short-term memory and developmental delay who had a de novo missense mutation impairing the function of TrkB [9]. We also identified a patient with a de novo chromosomal inversion, which encompasses the BDNF locus and disrupts BDNF expression [10]. Yanovski and colleagues showed that in patients with WAGR syndrome, a subset of deletions on chromosome 11p.12 which encompass the BDNF locus, were associated with early-onset obesity [11].

SIM1 Deficiency

Single-minded 1 (SIM1) is a basic helix–loop–helix transcription factor involved in the development and function of the paraventricular nucleus of the hypothalamus. Obesity has been reported in a patient with a balanced translocation disrupting SIM1 [12] and multiple heterozygous missense mutations have been identified in severely obese patients. SIM1 variants with reduced activity co-segregate with obesity in extended family studies with variable penetrance. The phenotypic similarities between patients with SIM1 deficiency and MC4R deficiency suggests that some of the effects of SIM1 deficiency are mediated by altered melanocortin signalling. In some cases, SIM1 variant carriers have been reported to exhibit a spectrum of neurobehavioural features including autistic type behaviours. These features are not recognized features of MC4R deficiency but show some overlap with the behavioural phenotypes seen in Prader–Willi Syndrome. As the hyperphagia of sim1 haplo-insufficient mice is partly ameliorated by the central administration of oxytocin [13], a neurotransmitter involved in the modulation of emotion and social interaction, impaired oxytocinergic signalling is one possible mechanism implicated in the obesity and behavioural phenotype seen in SIM1 variant carriers.

Obesity Without Developmental Delay

Severe obesity can result from a multiplicity of defects involving the leptin–melanocortin pathway. Leptin is an adipocyte-derived hormone whose circulating levels correlate closely with fat mass. 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. 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, the adrenal gland and the skin. The melanocortins are agonists at melanocortin receptors and suppress food intake. In addition, leptin inhibits orexigenic pathways, mediated by neurons expressing the melanocortin antagonist Agouti-related protein and neuropeptide Y (NPY); NPY can suppress the expression of POMC. These two sets of primary leptin-responsive neurons project to second-order neurons expressing MC4R. Targeted genetic disruption of MC4R in mice leads to increased food intake and increased lean mass and linear growth [14].

## Leptin and Leptin Receptor Deficiency

Amongst patients with hyperphagic obesity of early onset from consanguineous families, the prevalence of leptin mutations is approximately 1 % and of leptin receptor mutations, 2–3 %. Leptin receptor mutations have been found in some non-consanguineous families, where both parents are unrelated but happen to carry rare alleles in heterozygous form. 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 due to homozygous loss of function mutations in the gene encoding leptin. 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 [15].

The clinical phenotypes associated with congenital leptin and leptin receptor deficiencies are similar. Leptin and leptin receptor deficient subjects are born of normal birth weight but exhibit rapid weight gain in the first few months of life resulting in severe obesity [16]. Affected subjects are characterized by intense hyperphagia with food seeking behaviour and aggressive behaviour when food is denied, and energy intake at an ad libitum meal is markedly elevated. While measurable changes in resting metabolic rate or total energy expenditure have not been demonstrated, abnormalities of sympathetic nerve function in leptin deficient adults suggest that autonomic dysfunction may contribute to the obesity phenotype observed. Leptin and leptin receptor deficiency are associated with hypothalamic hypothyroidism; 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 some leptin and leptin receptor deficient adults. Leptin and leptin receptor deficient children have normal linear growth in childhood and normal IGF1 levels. However, because of the absence of a pubertal growth spurt the final height of adult subjects is reduced. Children with leptin deficiency have impaired T cell number and function, consistent with high rates of childhood infection and a high reported rate of childhood mortality from infection.
Although leptin deficiency appears to be rare, it is entirely treatable with daily subcutaneous injections of recombinant human leptin with beneficial effects on the degree of hyperphagia, reversal of the immune defects and infection risk and permissive effects on the development of puberty [16]. Such treatment is currently available to patients on a named patient basis. The major effect of leptin administration is on food intake, with normalization of hyperphagia and enhanced satiety [16, 17]. Leptin is also involved in mediating food reward [18, 19]. Leptin administration does not result in a change in energy expenditure; however, as weight loss by other means is associated with a decrease in basal metabolic rate, the absence of an effect is notable.

Disorders Affecting Pro-opiomelanocortin (POMC) and POMC Processing

Children who are homozygous or compound heterozygous for mutations in the POMC gene present in neonatal life with adrenal crisis due to ACTH deficiency, as POMC is a precursor of ACTH in the pituitary, and they require long-term corticosteroid replacement [20]. Such children have pale skin and white Caucasians have red hair due to the lack of MSH function at melanocortin 1 receptors in the skin. Although red hair may be an important diagnostic clue in patients of Caucasian origin, its absence in patients originating from other ethnic groups should not result in this diagnostic consideration being excluded as children from different ethnic backgrounds may have a less obvious phenotype such as dark hair with red roots. POMC deficiency results in hyperphagia and early-onset obesity due to loss of melanocortin signalling at the MC4R. The clinical features are comparable to those reported in patients with mutations in the receptor for POMC derived ligands, MC4R (see below).

Heterozygous point mutations in POMC have been described which significantly increase obesity risk but are not invariably associated with obesity. R236G disrupts a di-basic cleavage site between β-MSH and β-endorphin, resulting in a β-MSH/β-endorphin fusion protein that binds to MC4R but has reduced ability to activate the receptor [21]. A rare missense mutation in the region encoding β-MSH, Tyr221Cys has impaired the ability to bind to and activate signalling from the MC4R, and obese children carrying the Tyr221Cys variant are hyperphagic and showed increased linear growth, features of MC4R deficiency [22]. These observations support a role for β-MSH in the control of human energy homeostasis. Selective MC4R agonists of melanocortin analogues may be feasible therapies for such patients in the future.

PCSK1 Deficiency

Proprotein convertases (PCs) are a family of serine endoproteases that cleave inactive pro-peptides into biologically active peptides [23]. Two family members, Proprotein Convertase Subtilisin/Kexin type 1 and 2 (PCSK1 and PCSK2) are selectively
expressed in neuroendocrine tissues where they cleave prohormones including pro-opiomelanocortin (POMC), prothyrotrophin releasing hormone (TRH), proinsulin, proglucagon and progonadotrophin releasing hormone (GnRH) to release biologically active peptides. Compound heterozygous or homozygous mutations in the \textit{PCSK1} gene, which encodes PC1/3, cause small bowel enteropathy and complex neuroendocrine effects (including diabetes insipidus) due to a failure to process a number of prohormones as well as severe, early onset obesity [24, 25].

\textbf{MC4R Deficiency}

Heterozygous \textit{MC4R} mutations have been reported in obese people from various ethnic groups. The prevalence of pathogenic \textit{MC4R} mutations has varied from 0.5 to 2.5 \% of people with a BMI > 30 kg/m$^2$ in UK and European populations to 5 \% in patients with severe childhood obesity [26, 27]. As \textit{MC4R} deficiency is the most common genetic form of obesity, assessment of the sequence of the \textit{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 will have important effects on the severity of obesity associated with \textit{MC4R} mutations in some pedigrees. 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 \textit{MC4R} deficiency include hyperphagia in early childhood. Alongside the increase in fat mass, \textit{MC4R}-deficient subjects also have an increase in lean mass and a marked increase in bone mineral density, thus they often appear “big-boned” [27]. They exhibit accelerated linear growth, 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 [28]. Despite this early hyperinsulinemia, obese adult subjects who are heterozygous for mutations in the \textit{MC4R} gene are not at increased risk of developing glucose intolerance and type 2 diabetes compared to controls of similar age and adiposity [27]. The proportion of visceral to subcutaneous fat is not altered in MC4R deficiency. 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 [29]. 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 \textit{MC4R} deficiency, but patients with heterozygous \textit{MC4R} mutations do respond to Roux-en-Y-bypass surgery [30], which can be considered in adults. As most patients are heterozygotes with one functional allele intact, it is possible that small molecule MC4R agonists or pharmacological chaperones which improve receptor trafficking to the cell surface might be appropriate treatments for this disorder.
SH2B1 Deficiency

Severe obesity without developmental delay is associated with a significantly increased burden of rare, typically singleton copy number variants (CNVs) [31]. Deletion of a 220-kb segment of 16p11.2 is associated with highly penetrant familial severe early-onset obesity and severe insulin resistance [32]. This deletion includes a small number of genes, one of which is SH2B1, known to be involved in leptin and insulin 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. Several mutations in the SH2B1 gene have also been reported in association with early onset obesity, severe insulin resistance and behavioural abnormalities in some patients [33].

Clinical History, Examination and Investigation

The assessment of severely obese children and adults should be directed at screening for potentially treatable endocrine and neurological conditions and identifying genetic conditions so that appropriate genetic counselling and in some cases treatment can be instituted. Much of the information needed can be obtained from a careful medical history and physical examination, which should also address the potential complications of severe obesity such as sleep apnoea [34]. In addition to a general medical history, a specific weight history should be taken carefully establishing the age of onset and the presence of hyperphagia. A careful family history to identify potential consanguineous relationships, the presence of other family members with severe early onset obesity and the ethnic and geographical origin of family members should be taken. The history and examination can then guide the appropriate use of diagnostic tests.

Conclusions

Given the rapid application of next-generation sequencing technologies such as whole exome sequencing, it is very likely that new genes and mechanisms will emerge to explain a variety of previously unrecognized obesity syndromes. As more is learned about these genes and more syndromes are described, it is likely that the need to perform a comprehensive evaluation of severely obese patients will be recognized. Knowledge of the specific molecular mechanisms affected by these genetic disorders may lead to better mechanism-directed, stratified pharmacotherapy in the future.
References

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