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GENETIC AND EPIGENETIC CAUSES OF OBESITY

Vidhu V. Thaker, MD[1,2,3]

[1]Division of Molecular Genetics, Department of Pediatrics, Columbia University Medical Center, New York, NY

[2]Harvard Medical School, Boston, MA

[3]Division of Endocrinology, Boston Children's Hospital, Boston, MA

Abstract

Obesity is a complex, heritable trait influenced by the interplay of genetics, epigenetics, metagenomics and the environment. With the increasing access to high precision diagnostic tools for genetic investigations, numerous genes influencing the phenotype have been identified, especially in early onset severe obesity. This review summarizes the current knowledge on the known genetic causes of obesity and the available therapeutic options. Furthermore, we discuss the role and potential mechanism of epigenetic changes that may be involved as mediators of the environmental influences and that may provide future opportunities for intervention.

Keywords

Genetics; Severe early onset obesity; Monogenic obesity; Syndromic obesity; Epigenetics; Personalized medicine

INTRODUCTION

The idea of innate biologic ("endogenous") cause of obesity was first proposed by Von Noorden in 1907[1]. This concept of genetic cause for obesity has been investigated time and again since then[2]. The landmark studies of body fatness in 540 adopted Danish twins by Stunkard and colleagues showed that the weight of the adults was closer to their biological parents despite being reared in an adopted family.[3] Further, they examined the body mass index (BMI) of twins reared together and apart to conclude the heritability of about 70%.[4] Experimental studies of overfeeding in identical twins by Bouchard et al showed a remarkable correlation of weight gain within twin pairs, much higher than that between pairs.[5] The longitudinal follow-up of these subjects showed a similar correlation of initial weight loss and eventual rebound.[6] In a systematic review of twin studies, Silventoinen et al noted variable heritability of weight across lifetime with an overall effect between 45–90%. This meta-analysis of twin studies showed highest heritability in the early childhood,

Address correspondence to: Vidhu Thaker, MD, Division of Molecular Genetics, Department of Pediatrics, Columbia University Medical Center, 1150 St. Nicholas Avenue, New York, NY 10032, vvt2114@cumc.columbia.edu, 212-305-9237.

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adolescence and adulthood. Additionally, they recognized the influence of genetics on obesity related behavior such as eating patterns and exercise.[7]

Secular trends in obesity in children, adolescents[8] and adults[9] have shown an increase in obesity with urbanization, clearly indicating the role of the environment. But in any given environment, there is considerable individual variation in body weight and fat mass, suggesting that adiposity is influenced by complex interactions between genetic, developmental, behavioral, and environmental influences.

Modern genetic technology with precise definition of single nucleotide changes has advanced our understanding of the molecular mechanisms of weight regulation. Specifically, high throughput sequencing with whole exome, genome and targeted sequencing in individual subjects and cohorts of children with severe obesity has identified little known genetic aberrations. Besides providing insight into the pathophysiology of weight regulation, some of these etiologies hold the potential for treatment in selected individuals. Furthermore, studies in model organisms have elucidated epigenetic modifications that may play a role in weight gain. This review will address the identified genetic causes of obesity, and summarize the current literature on the epigenetic changes.

Genetic causes of obesity can be broadly classified into:

1. Monogenic causes: those caused by a single gene mutation, primarily located in the leptin- melanocortin pathway.
2. Syndromic obesity: severe obesity associated with other phenotypes such as neurodevelopmental abnormalities, and other organ/system malformations.
3. Polygenic obesity: caused by cumulative contribution of a large number of genes whose effect is amplified in a ‘weight gain promoting’ environment.

We will focus here on the first 2 categories.

CENTRAL REGULATORY PATHWAY

A basic overview of the central regulatory pathway of appetite regulation will facilitate the understanding of genetic mutations (Figure 1). The central nervous system plays a vital role in regulating food intake through the brain-gut axis, with the hypothalamic leptin-melanocortin pathway as the key regulator of energy balance.[10] Signals are received from several tissues and organs, such as the gut: hormones like ghrelin, peptide YY (PYY), cholecystokinin (CCK), glucagon-like peptide (GLP-1) and mechanoreceptors measuring distention; by pancreas through insulin; and by adipokine hormones such as leptin and adiponectin. The hypothalamus integrates these signals and acts via downstream pathways to maintain energy balance. The leptin/melanocortin pathway is activated via the leptin (LEPR) and insulin receptors (INSR) located on the surface of the neurons of the arcuate nucleus. These signals are in-turn regulated by 2 sets of neurons in a feedback loop. The pro-opiomelanocortin and cocaine and amphetamine related transcript neurons (POMC/CART) regulate production of anorexogenic peptide POMC, while a separate set of neurons regulate production of orexogenic agouti-related peptide (AGRP) and neuropeptide-Y (NPY).[11] After

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post-translational processing with proconvertase 1 (PC1) and proconvertase 2 (PC2), POMC results in the production of a variety of peptides, such as α- β- and γ-melanocyte stimulating hormone (MSH) and β-endorphins.[12] AGRP and α-MSH compete for binding with the melanocortin-4 receptor (MC4R), which is highly expressed in the paraventricular nucleus (PVN) of the hypothalamus. Binding with α-MSH results in anorexigenic signals, while that with AGRP in orexogenic signals.[13] Signals from MC4R govern food intake via secondary effector neurons that lead to higher cortical centers, a process that involves brain-derived neurotrophic factor (BDNF) and neurotrophic tyrosine kinase receptor type 2 (NTRK2 coding for the receptor called tropomyosin-related kinase B, TrkB). Other regulators such as SIM1, have been found to modulate the effect of this pathway. Mutations in the various genes involved in this pathway have been identified to be causal for obesity.

MONOGENIC OBESITY

Many of the genes identified for monogenic obesity disrupt the regulatory system of appetite and weight described above. Most mutations require 2 dysfunctional copies of the gene in homozygous or compound heterozygous form to manifest the phenotype. A summary of the individual causes of monogenic obesity can be found in Table 1.

Leptin (*LEP*) mutations

Leptin is a type I cytokine mainly secreted by the adipocytes to signal the energy state of the body and exerts its function as a satiety signal in the hypothalamus.[14,15] Encoded by the *LEP* gene located on chromosome 7q31.3, it is synthesized as an immature 167-amino acid protein that forms a 146-amino acid mature protein after cleavage of the 21-amino-acid N-terminal peptide.[14]

Congenital leptin deficiency follows a recessive mode of inheritance, and was first identified in two extremely obese first-degree cousins from a Pakistani family caused by a frameshift mutation (c.398*del*G).[16] Since then ten other mutations in the leptin gene have been described.[17–27] The cardinal phenotypic manifestations are rapid weight gain after normal birth weight resulting in severe early onset obesity caused by intense hyperphagia.[28] In addition, some of these children have severe and possibly lethal bacterial infections due to defective T-cell immunity[29] and hypogonadotropic hypogonadism.[16] The children often have secondary adverse effects of severe obesity such as hyperinsulinemia, severe liver steatosis and dyslipidemia. The protein change can vary from early termination of the protein resulting in low to undetectable levels of the leptin hormone to the loss of biological activity with normal levels.[27]

Although relatively rare, and mostly seen in consanguineous families, congenital leptin deficiency presents a unique opportunity for treatment with recombinant leptin that improves the adiposity, and restores gonadal and immune function.[27,30] The Food and Drug Administration has approved the use of Myalept (metreleptin) for the treatment of congenital leptin deficiency and generalized lipodystrophy. [31]

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Leptin Receptor (*LEPR*) mutations

Mutations in *LEPR* can cause phenotype similar to that of leptin deficiency, without low serum levels. [32] The use of next generation sequencing has facilitated the identification of *LEPR* mutations, with estimates of 2–3% in certain populations.[33–36] Co-existing growth hormone and thyroid function deficiency has also been described.[37,38] Unlike leptin deficiency, individuals with homozygous *LEPR* mutations are not amenable to treatment with recombinant leptin.

Pro-opio melanocortin (*POMC*) mutations

Deficiency in the POMC protein results in the absence of cleavage products of ACTH, α-MSH and β-endorphins.[39] Due to the dual role of α-MSH in appetite regulation and pigmentation, the classic presentation is that of red hair and severe obesity. Adrenal insufficiency results from deficiency of ACTH. Early recognition of adrenal insufficiency and rapid glucocorticoid replacement therapy is important for treatment. Fewer than 10 patients have been described around the world. A few studies have also noted the presence of heterozygous POMC mutations in individuals with obesity, without adrenal insufficiency and other classic manifestations.[40,41] A new melanocortin-4 receptor agonist, Setmelanotide, has been shown to have therapeutic potential for *POMC* deficiency.[42]

MC4R deficiency

The melanocortin receptor (MC4R) is a G-protein coupled, seven transmembrane receptor which is highly expressed in the hypothalamus, the region of the brain involved in appetite regulation.[43] Rodent studies indicate that the binding of MC4R with α-MSH, its high affinity ligand produced from POMC, inhibits feeding.[44] Subsequently, mutations in *MC4R*, both in dominant and recessive form, have been demonstrated as the most common cause of inherited early-onset obesity with prevalence between 0.5–6% in different populations. [45–49] Affected children demonstrate hyperphagia with food-seeking behavior in early childhood, are taller than their peers, may have higher blood pressure and advanced bone age, but are otherwise not dysmorphic.[45] Therapeutic perturbation of the MC4R to improve the satiety circuits is an active area of investigation, but not available for clinical use yet.[50–52]

Proconvertase (*PC1/2*) deficiency

Proprotein convertase-1/2 are neuroendocrine convertase endoproteases that process large precursor proteins into mature bioactive products. [53] Absence of activity of PC1/PC2 results in adrenal, gonadotropic, somatotropic, and thyrotropic insufficiency, along with postprandial hypoglycemic malaise caused by lack of insulin processing, severe malabsorptive neonatal diarrhea and central diabetes insipidus, in addition to severe early onset obesity.[54–58] These enzymes are an attractive target for molecular intervention, although no therapies are available at the moment.

SIM1 deficiency

Single-minded homologue of drosophila (*SIM1*) is a transcription factor located on chromosome 6q16 and is strongly expressed in the paraventricular nucleus of the hypothalamus, a critical regulator of appetite. [59] Deletions or heterozygous mutations in

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SIM1 have been associated with hyperphagia, food impulsivity, and neurobehavioral features such as impaired concentration, memory deficit, emotional lability or autism spectrum disorder.[60,61]

NTRK2/BDNF mutations

These neurotrophins are a family of growth factors known to be involved in the development, maintenance and function of peripheral and central neurons. The neurotrophin receptor TrkB and its natural ligand, brain derived neurotrophic factor (BDNF), have been implicated in the regulation of food intake and body weight in animal studies. Heterozygous loss of function mutation in *NTRK2*, that codes for TrkB was demonstrated in a Caucasian male with severe early onset obesity with no other syndromic features.[62] Individuals with deletions in *BDNF* gene as part of the WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies and mental retardatio) have early onset obesity[63].

SH2B1 mutations

Src homology 2 B adapter protein (*SH2B1*) is a positive regulator of leptin sensitivity.[64] Following the identification of its role in animal models, mutations in *SH2B1* were noted in 5 children of mixed European descent with severe early onset obesity inherited from their overweight/obese parents.[65] The mutation carriers were noted to be hyperphagic, had reduced final adult height, hyperinsulinemia without diabetes, delayed speech and language, and aggressive behavior. Subsequent studies of additional variants in the gene have shown milder phenotypes indicating a variability in the presentation.[66]

Other monogenic forms of obesity

With the increasing use of whole exome and genome testing, additional single gene defects causing obesity have been identified. Mutations in kinase suppressor of Ras 2 (*KSR2)*, an intracellular scaffolding protein involved in multiple pathways causes hyperphagia in childhood, low heart rate, reduced metabolic rate and severe insulin resistance.[67] This mutation is of great interest, as metformin may be useful in decreasing the body weight and improving insulin sensitivity in these individuals. A homozygous frameshift mutation in the *TUB* (tubby-like protein) gene was identified in a proband who presented with obesity, decreased visual acuity and night blindness, and electrophysiological features of rod-cone dystrophy.[68] In another case, a severely obese female from a consanguineous Sudanese family with intellectual disability, type 2 diabetes, and hypogonadotrophic hypogonadism was found to have a homozygous truncating mutation in carboxypeptidase (*CPE*) gene. *CPE* is an enzyme involved in the processing of a number of neuropeptide and peptide hormones (akin to proconvertase).[69] Our group has demonstrated a novel truncating mutation in retinoic acid induced gene (*RAI1*) in an individual with hypoventilation, hypothalamic dysfunction, developmental disability, autonomic dysfunction and severe obesity.[70] Mutations in *RAI1* gene interfere with the BDNF expression in the hypothalamus in animals, thus interfering with the leptin-melanocortin signaling[71].

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SYNDROMIC OBESITY

The syndromic forms of obesity are often associated with phenotypes in addition to the early-onset severe obesity. This may be caused by change in a single gene or a larger chromosomal region encompassing several genes. Obesity is a feature of almost 100 syndromes; a little over half are not yet named, and 13.9% have more than one name.[72] The co-presenting phenotypes often include intellectual disability, dysmorphic facies, or organ-system specific abnormalities. The most frequent forms of syndromic obesity are Bardet Biedl and Prader Willi syndrome.

Bardet-Biedel Syndrome (BBS)

BBS is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties and hypogonadism.[73] The prevalence of BBS varies markedly between populations; from 1:160 000 in northern European populations to 1:13500 and 1:17 5000, respectively, in isolated communities in Kuwait and Newfoundland, where a higher level of consanguinity prevails. The phenotype evolves slowly through the first decade of life, and often the only manifestation seen at birth may be post-axial polydactyly, with or without other limb abnormalities.[74] Gradual onset of night blindness, along with photophobia and the loss of central and/or color vision is the next definitive finding, often leading to the diagnosis. Obesity is present in the vast majority (72–86%) of the individuals, although the birth weight may be normal. There is a high prevalence of Type 2 diabetes, hypogonadism, cognitive deficit, labile behavior, speech deficit, renal and cardiac anomalies.[75] The biological defect for the syndrome is an abnormality in immotile cilia that primarily function as the sensory organelle regulating signal transduction pathways. The functional unit of the immotile cilia, or the BBSome, comprises of the cilium, the basal body, the chaperonin complex and other membrane proteins that maintain the function of the cilium. At the time of this writing, mutations in 16 different genes that alter the function of the BBSome at various levels have been identified (BBS1–BBS16). A comprehensive review of BBS can be found at GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1363/).

Prader Willi Syndrome (PWS)

PWS is the commonest cause of syndromic obesity around the world (1 in 15,000–25,000 births).[76] It is characterized by severe neonatal hypotonia, eating disorders evolving in several phases (from anorexia and failure to thrive in the early infancy to severe hypephagia with food compulsivity by about 4–8 years of age). [77] Additional features include dysmorphic facies, global cognitive impairment, behavioral abnormalities, hypotonia, delayed motor development and hormonal deficiencies such as growth hormone, hypothyroidism, hypogonadism and ghrelin abnormalities.[76] The genetic defect in PWS is the inactivation of the Prader-Willi critical region (PWCR) located on the 15q11-13 region of the paternal chromosome. The PWCR on the maternal chromosome is imprinted, and therefore epigenetically silenced through methylation, leading to mono-allelic expression of the paternal genes.[78] Majority of cases of PWS are caused by interstitial deletions of the paternal region of the PWCR (65–70%), while others by maternal uniparental disomy (20–30%) and mutations within the imprinting center (2–5%). At least 5 genes, located in the

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PWCR and expressed in hypothalamus, have been implicated without clarity of their roles: *MKRN3* (makorin 3), *MAGEL2* (MAGE-like 2), *NDN* (necdin), *NPAP1* (nuclear pore associated protein 1), *SNURF-SNRPN* (SNRPN upstream reading frame – small nuclear ribosomal protein 1). [79] A recent study of pluripotent stem cells derived neurons from individuals with microdeletion in the PWCR indicates a lower expression of proconvertase 1 (PC1), previously implicated in monogenic obesity, potentially offering a unifying explanation for the phenotype.[80]

16p11.2 microdeletion syndrome

This heterozygous deletion of ~593-kb region on chromosome 16 is characterized by developmental delay, intellectual disability, and/or autism spectrum disorder along with severe obesity. Walter et al noted the presence of severe obesity in children with the deletion and performed a large scale analysis using population and disease based cohorts to find an enrichment of the deletion in children and their parents with obesity.[81] Further studies by Bochukova and colleagues indicate that the obesity seen in the children and adults with the 16p11.2 deletion may be mediated via *SH2B1*, located in the region.[82]

In addition to PWS, and 16p11.2 deletion syndrome, several other obesity-related syndromes with chromosomal defects have been identified. Obesity is often manifested in many, but not all individuals suggesting variable penetrance, or a specific gene that may be differentially involved in different individuals. Examples include deletion of 1p36 (monosomy 1p36 syndrome), 2q37 (brachydactyly mental retardation syndrome; BDMR), 6q16 (PWS-like syndrome), 9q34 (Kleefstra syndrome), 11p13 (WAGR syndrome), and 17p11.2 (Smith Magenis syndrome; SMS).[83] These syndromes may hold the clue to the single genes in the region that could further explain the biology of the disease, e.g. presence of deletion in the *BDNF* gene in individuals with WAGR syndrome who also presented with obesity.[63]

Table 2 provides a list of syndromes known to be associated with obesity, overgrowth syndromes (sometimes confused with obesity) and syndromes where a genetic etiology is not yet elucidated. Many of these syndromes encompass neurodevelopmental abnormalities of varying spectrum. Large-scale studies, such as genome-wide association studies have shown a widespread expression of the loci associated with BMI in the brain. It is plausible that there is heretofore-unidentified shared basis of the obesity and the neurodevelopmental defect(s). However, due to the high prevalence of obesity in the society and the influence of the neuropsychological medications on weight, and the use of food as a behavior modulator, the presence of obesity may be a mere confounder. Nevertheless, neurodevelopmental defects continue to serve as important marker to consider genetic investigation in children with severe, early onset obesity. The interested reader is referred to a recent systematic review by Kaur et al.[72]

DIAGNOSTIC APPROACH

With the high prevalence of obesity in the modern society, it is imperative that the astute clinician is educated about the indications for genetic testing. For children with severe early onset obesity (BMI > 120% of 95th percentile of CDC 2000 for age), it is useful to enquire for history suggestive of hyperphagia, endocrinological co-morbidities, and a detailed

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pedigree including history of consanguinity. Assortative mating can confound family history, and identification of patterns indicative of autosomal dominant, or *de novo* inheritance is helpful. Individuals with neurodevelopmental and cognitive difficulties may lead to a consideration of tests such as high-resolution karyotype, methylation studies of chromosome 15, or comparative genomic hybridization (CGH) array for chromosomal defects. Based on presence of other features suggestive of syndromic obesity (see Table 2), or other characteristic findings such as prolonged diarrhea (*PCSK1*), or hypoglycemia and orange hair (*POMC*) single gene or panels such as the BBS panel may be considered. Candidate gene panels for genetic obesity (*LEP, LEPR, POMC, PCSK1*) are available in some laboratories and may be considered on a case-by-case basis (see: Genetic Testing Registry. Available at https://www.ncbi.nlm.nih.gov/gtr/).

Assessment of leptin level is useful if there is a consideration of *LEP* deficiency. As leptin levels are generally elevated with adiposity, it is more difficult to ascertain *LEPR* deficiency by measurement of leptin levels. If an autosomal dominant mode of inheritance is established for children with severe early onset obesity, *MC4R* sequencing (1 exon) is widely available. A number of research efforts for rare genetic variants for children with severe early onset obesity are ongoing (www.clinicaltrials.gov). It is important to provide basic counseling prior to genetic testing. Should this be a barrier, a referral to a skilled specialist is suggested.

THERAPEUTIC CONSIDERATION

The characterization of the etiology of a monogenic or syndromic cause of obesity often ends a diagnostic odyssey for the etiology of the clinical condition. Additionally, the promise of targeted treatment in the rapidly progressive field of personalized medicine provides hope for the families struggling with management of obesity and associated comorbidities in children.

For most of the genetic causes of obesity, management of nutrition and physical activity remains the first line of therapy. Children with genetic causes of obesity, such as *MC4R* and *LEPR* mutations have been maintained at lower levels of adiposity with long-term restriction of caloric intake (Lennerz B, Personal Communication). In children with PWS, the nutritional guidelines change with the phases of eating patterns over time. In the hyperphagia phase, weight maintenance has been documented with intakes of 7 kcal/cm of height/day, and sample calorie guidelines have been published by Prader Willi Syndrome Association.[84] There are no systematic prospective studies on the use of these guidelines, and treatment needs to be individualized for each child. Although studies have proposed use of ketogenic and other limited diets[85], the current guidelines continue to recommend a balanced calorie reduction with maintenance of the usual macronutrient proportions (60% carbohydrate, 15% protein and 25% fat), with emphasis on low glycemic index and slow-release carbohydrates.[84]

Medications such as injectable recombinant leptin for treatment of leptin deficiency[29], or biologically inactive leptin[27] present a rare, but valuable opportunity for treatment. A promising new therapy for *POMC* deficiency is Setmelanotide, an eight-amino-acid cyclic

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peptide (RM-493) melanocortin-4 –receptor agonist without the side-effects of hypertension and increased erectile dysfunction[42]. Kuhnen et al report the short-term use of setmelanotide in 2 adult females with POMC deficiency, 21- and 24-years old with baseline BMI of 49.8 kg/m2 (SDS 4.52) and 54.1 kg/m2 (SDS 4.78). Both the patients received treatment for 12 weeks with decrease in weight from 20–26 kg (decrease of 13.4–16.6%), and a marked improvement in satiety and quality of life (clinicaltrials.gov, NCT02896192, http://geneticobesity.com/).[42] This therapy also appears to offer promise in animal models for PWS.[86] Another drug, Beloranib, a Methionine Peptidase 2 (MetAP2) inhibitor, that influences fat metabolism, synthesis and storage, was found to reduce hunger and restored balance to the production/utilization of fat is in early clinical trials.[87] Nasal oxytocin has been tried for therapy in PWS based on the finding of decreased oxytocin neurons in an attempt to improve behavioral and adiposity phenotype.[88–90] A number of other *MC4R* receptor agonists are in preclinical and early clinical trials.[50] Pharmacological chaperones that increase the expression of the cell surface expression of MC4R is a promising approach.[91,92] An important consideration for neuropeptides used in the treatment of genetic forms of obesity is an acceptable route of administration that will provide sufficient central nervous system penetrance for its action on the centers for weight regulation.

Bariatric surgery is increasingly being used as the effective treatment of severe obesity with or without concomitant co-morbidities in adolescents[93] and adults[94]. Soper et al reported the use of bariatric surgery as a treatment of morbid obesity in 7 adolescents with PWS and 18 genetically normal young adults. The individuals with PWS reached a plateau of weight loss faster, and 3 individuals required revision surgeries to improve weight loss.[95] Forty years later, the debate on the use of bariatric surgery for the treatment of genetic and syndromic forms of obesity continues. In a retrospective review of 60 subjects with PWS undergoing bariatric surgery, Scheiman et al reported a myriad of serious complications such as wound infection, deep vein thrombosis, pulmonary embolism, splenectomy with the surgery, weight rebound and poor response to surgery with some requiring revision and death in 2 subjects.[96] The surgical techniques used in this report from 2008 have evolved over time. Two recent reports, one from Saudi Arabia (n = 24)[97] and another from China (n = 3)[98] have reported successful use of laparoscopic sleeve gastrectomy in individuals with PWS. Alqahtani et al performed a case-control (1:3) study of 24 subjects with PWS (mean age 10.9 years, mean BMI 46.2 kg/m2; 66.7% with ≥ 3 comorbidities). They reported a 22.2 (±14.6) % reduction in BMI in cases with PWS compared with 37.9 (±12.1)% in controls (p = 0.05). There was no statistical difference in % excess weight loss in the cases as compared to non-genetic obese controls till 3 years of follow-up with some rebound noted in the cases at 5-years of follow-up. The families reported an improvement in hyperphagia and food-seeking behavior that has largely been attributed to a reduction in the levels of ghrelin after the surgery as noted in the report from China.[98] The same group has previously published favorable reports in subjects with PWS, BBS and ALMS1 syndrome[99] with mixed response from surgeons in the US[100] and France.[101] Regardless of the debate, the need for multi-disciplinary pre- and post-operative care of individuals with syndromic obesity or intellectual disability with careful follow-up is advocated[102], and the need for large scale systematic studies for long-term outcomes remains.

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EPIGENETIC MODIFICATIONS IN OBESITY

While genetic perturbations play an important role in determining individual susceptibility to obesity, the role of environment, and gene-environment interactions remains; leading to a growing interest in the role of epigenetics in the development of obesity and obesity-related comorbidities. This offers a logical explanation for the growing epidemic of obesity over the past few decades without a radical change in the genome. In multicellular organisms like humans, the genetic code is homogenous throughout the body, but the expression of the code can vary in the different cell types. Epigenetics is the study of heritable regulatory changes in the genetic expression without alterations in the nucleotide sequence.[103] Epigenetic modifications can be considered as the differential packaging of the DNA that either allows or silences the expression of the certain genes across tissues. Environmental and dietary factors or gut microbiota, can influence the epigenetic programming of parental gametes, fetus and early postnatal development, or through the various periods of life to influence epigenetic programming.[104]

Epigenetic mechanisms

The currently known epigenetic mechanisms include DNA methylation, histone modifications, and microRNA-mediated regulation, which can be passed on mitotically (through cell division) or meiotically (transgenerational inheritance).

DNA methylation

In DNA methylation, a methyl group can be added to a cytosine with a guanine as the next nucleotide (CpG site) by DNA methyltransferases (DNMTs). These CpG sites are frequently found in the promoter regions of the genes, and a methyl group addition acts as a steric obstacle for the joining of the transcription factors and the expression of the gene: usually hypermethylation is associated with transcriptional repression, and hypomethylation with activation.[103] Candidate gene methylation changes have been implicated in obesity, appetite control and metabolism, insulin signaling, immunity, inflammation, growth, and circadian clock regulation.[104] In a genome wide study of the CpG methylation sites of 479 adults of European origin, an increased methylation at the *HIF3A* (hypoxia-inducible factor 3a) locus was reported in the blood and adipose tissue.[105] Similar associations were also seen in early life where higher methylation at the same sites were associated with greater infant weight and adiposity.[106] As hypoxia response has been reported during obesity, this finding provides direct evidence that perturbation of the HIF signaling plays an important role in the obesity, metabolism and downstream adverse responses to obesity.[105] Similarly, both the *LEP* and *POMC* genes, prominent in the weight regulation pathway have CpG islands, where methylation can affect their expression. In a study of methylation at the *LEP* gene in the maternal, placental and cord blood samples, Lesseur et al found increased maternal blood methylation with pre-pregnancy obesity, cord blood methylation with SGA infants and pre-pregnancy smoking and a good correlation of maternal blood *LEP* DNA methylation with infant blood methylation.[107] Similarly, increased *LEP* methylation was observed in men born after prenatal exposure to wartime (Dutch) famine in 1944–45 compared to their unexposed same-sex siblings.[108] Some other genes investigated in the context of obesity and metabolism include *ADIPOQ* (adiponectin), *PGC1α* (peroxisome proliferator-activated

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receptor coactivator 1 α), *IGF-2* (insulin-like growth factor 2), *IRS-1* (insulin receptor substrate 1), and *LY86* (lymphocyte antigen 86).[104] Epigenetic markers have also been used as predictor(s) for long-term weight loss (or regain). In a study of 18 men who underwent ≥ 5% weight loss after an 8-week nutritional intervention, Crujeiras et al report higher pre-intervention methylation levels of *POMC*, and lower *NPY* methylation in the individuals who maintained weight loss.[109] *POMC* methylation is also being investigated as an early predictor of metabolic syndrome.[110] DNA methylation studies remain an active area of investigation in both animals and humans that will continue to guide our understanding on the effects of genes, environment and their interaction.

Histone modification

Histones are proteins responsible for DNA packaging, made up of a globular domain and an N-terminal tail domain. The highly basic N-terminal tails protrude from the nucleosome and are exposed to covalent reactions such as methylation, acetylation, ubiquitination and phosphorylation. Depending on the combination of these covalent reactions, the DNA will be accessible for translation, repair, replication and recombination.[111] Histone modifications are involved in the epigenetic regulation of adipogenesis and can play an important role in obesity development. Modulation of five key regulatory genes of adipogenesis, pre-adipocyte factor-1 (Pref-1), CCAAT-enhancer-binding protein β (C/EBP β), C/EBPα, PPARγ, and adipocyte protein 2 (aP2), is regulated by histone modifications during adipocyte differentiation.[112] The histone deacetylase (HDAC) family of proteins plays an important role in the regulation of gene transcription in response to stress and energy metabolism. A study of the chromatin expression profile of the liver cells in animals fed high fat diet compared to those fed control diet showed chromatin remodeling by HDAC resulting in changes in expression profile of hepatic transcription factors HNFα, CCAAT/enhancer binding protein α (CEBP/α), and FOXA1.[113] They also demonstrated that these changes are irreversible, when the animals revert to the normal diet in one species, while being transient in another emphasizing the variable expressivity of modifications in a framework of different genetic background.[114] A differential expression of the HDAC proteins in also seen in the hypothalamus in the fasting/fed states and high-fat diet-induced obesity.[115]

miRNA

Micro-RNAs (miRNA) are short noncoding RNA sequences 18 to 25 nucleotides long capable of regulating gene expressions by gene silencing and post-transcriptional changes.[116] miRNA play an important role in various biological processes, including proliferation and differentiation of adipocytes, and have been shown to be associated with insulin resistance and low-grade inflammation seen in obese individuals.[117] A significant association with increased levels of certain miRNA (miR-486-5p, miR-486-3p, miR-142-3p, miR-130 b, and miR-423-5p) was seen with BMI in children with obesity, with a significant change in the profile of 10 miRNAs with weight change.[118] Zhao et al identified miRNA as a signature for weight gain and showed that the individuals with a high-risk score for 8 of these miRNAs had over 3-fold higher odds of weight gain.[119] Changes in adipocyte-derived exosomal miRNAs is also seen following weight loss and decrease in insulin resistance after gastric bypass.[120] All the emerging evidence lends support to the important role of miRNA

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in obesity and the associated metabolic changes that can serve as biomarkers, or potentially therapeutic targets for intervention.

Epigenetic changes caused by the intrauterine and early development environment

The intrauterine environment plays a crucial role in the development of the fetus and has been shown to play a role in the long-term epigenetic programming that may be transmitted to the progeny. Epidemiological studies of two large cohorts exposed in utero to serious nutritional deficits during the Second World War, who later lived in contrasting conditions, returning to normal nutrition in the case of the Dutch cohort exposed to the "Dutch Famine"[121], and conversely, persisting conditions of poor nutrition in case of children who survived the dramatic siege of Leningrad[122,123], have provided clues to the role of epigenetics. The Dutch cohort exposed to enriched nutritional conditions showed less DNA methylation of the imprinted *IGF2* gene compared to their same sex siblings. They also had a higher incidence of chronic metabolic disease compared to the Russian cohort that continued to live in deprived condition supporting the theory of *fetal programming*. Animal studies have provided further evidence to support this theory. Mice born to undernourished mothers and postnatally exposed to high fat diet have shown adverse cardiometabolic profile.[124] Besides undernutrition, presence of maternal obesity or metabolic dysfunction also predisposes infants to obesity. There is also evidence that this programming may be transgenerational that continues even after the environmental influence is eliminated, thus propagating the cycle of obesity and metabolic syndrome.[125]

Endocrine disrupting chemicals ("Obesogens")

In the context of epigenetic changes, it is important to review the role of endocrine disrupting chemicals (EDCs termed "obesogens") on the effects on adipose tissue biology, the hormonal milieu and the influence on the homeostatic mechanisms of weight regulation. Epidemiological studies have provided evidence for the presence of obesity and metabolic changes in offspring of mothers exposed to EDCs likely mediated by epigenetic changes. Offspring of pregnant animals exposed to polycyclic aromatic hydrocarbons during gestation have increased weight, fata mass, as well as higher gene expression of PPARγ, C/EBP α, Cox2, FAS and adiponectin and lower DNA methylation of PPAR γ that extended through the grand-offspring mice.[126] Genomewide epigenetic study in the adult mice born following perinatal exposure to bisphenol A at human physiologically relevant disease, showed an enrichment of significant differentially methylated regions in metabolic pathways among females. DNA methylation as a mediator for the metabolic phenotype was identified in Janus kinase-2 (*Jak-2*), retinoid X receptor (*Rxr*), regulatory factor x-associated protein (*Rfxap*), and transmembrane protein 238 (*Tmem 238*).[127] A comprehensive review of the effects of EDCs is outside the scope of this review, but suffice to say that there is convincing evidence from human and animal studies of epigenetic mechanisms in the effects of EDCs on childhood obesity and metabolic dysfunction.

CONCLUSION

Genetic factors and the environmental factors that influence the expression of these genes play a large role in the development of obesity in children, adolescents and young adults.

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Thoughtful consideration of genetic causes and an understanding of the growing evidence of the epigenetic changes that influence the burgeoning epidemic of obesity provide valuable tools for the clinician in the management of obesity.

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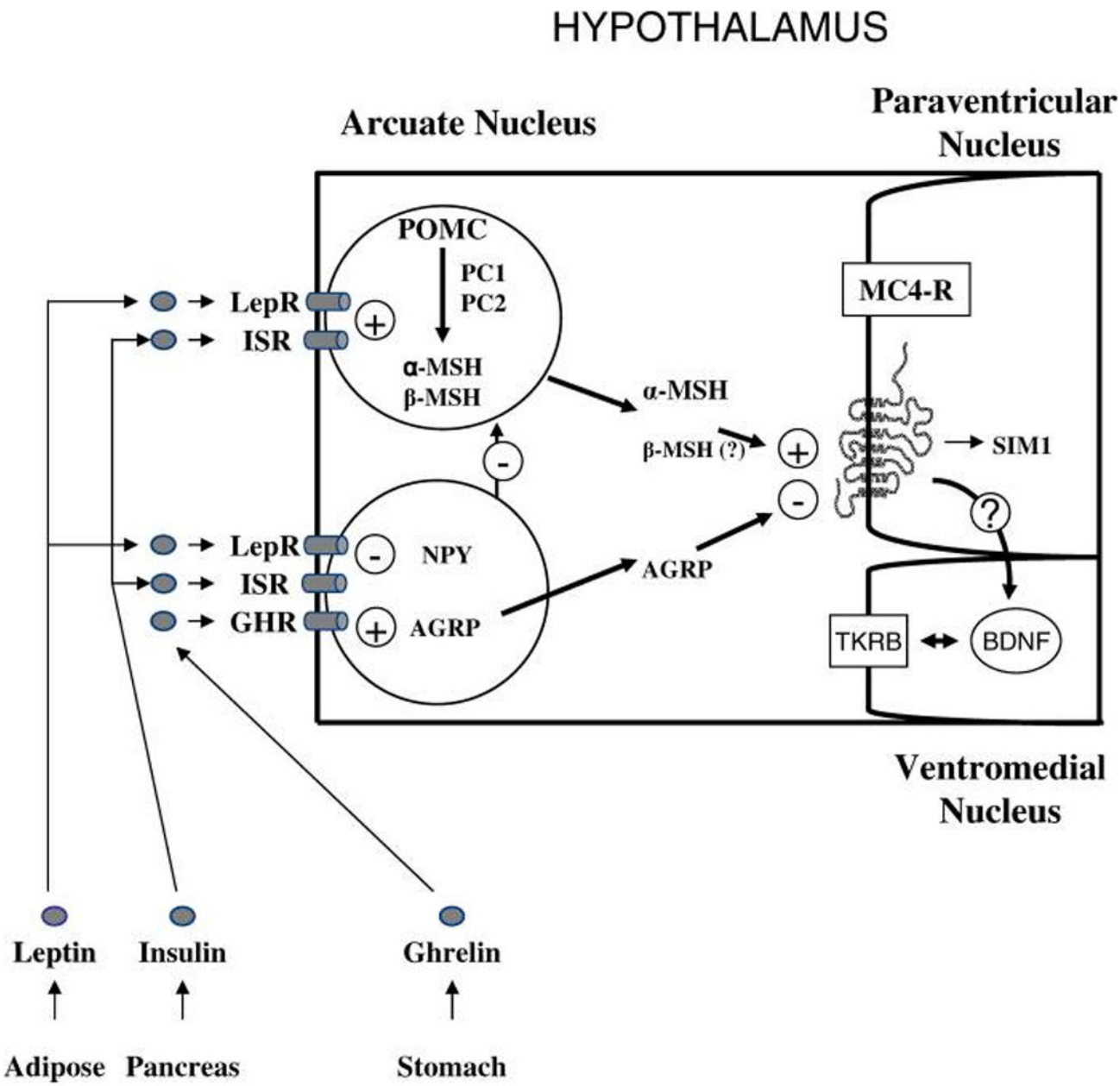

Figure 1. Leptin melanocortin pathway

The integration of the various peripheral and central signals in the hypothalamus is critical to the weight regulation. Hormonal (ghrelin, leptin, insulin) and mechano- and baroreceptor signals are sensed by the receptors located in the arcuate nucleus of the hypothalamus. These result in the production of pro-opiomelanocortin (POMC, anorexogenic) or Agouti-related peptide (AgRP) or PYY (orexogenic), sensed by the melanocortin-4 receptor (MC4R) located predominantly in the paraventricular nucleus. Proconvertase-1 (PC1) and 2 (PC2) are required for processing of the prohormones into α-melanocyte stimulating hormone (α-MSH), and β-MSH, ligands for the MC4R. The downstream expression of MC4R is influenced by Single-minded homologue 1 (SIM1), Brain-derived neurotrophic factor

(BDNF), possibly retinoic induced acid (RAI1, not shown), and mediated via Tyrosine kinase receptor (TrkB). Disruptions in the genes involved in this pathway have been shown to cause monogenic obesity in humans.

Image from: Mutch DM, Clément K. Unraveling the Genetics of Human Obesity. *PLoS Genetics* 2006, 2:12, e188 under Creative Commons License.

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TABLE 1

SINGLE GENES KNOWN TO BE INVOLVED WITH OBESITY

NAME	GENE	MIM	MODE of INHERITANCE	CHROMOSOMAL POSITION
Leptin	*LEP*	164160	AR	7q32.1
Leptin receptor	*LEPR*	601007	AR	1p31.2
Proopiomelanocortin	*POMC*	176830	AR	2p23.2
Melanocortin 4 receptor	*MC4R*	155541	AD/AR	18q21.32
Single-minded Drosophila Homologue-1	*SIM1*	603128	AD	6q16.3
Nurotrophic Tyrosine Kinase Receptor Type 2	*NTRK2*	600456	AD	9q21.33
Kinase suppressor of Ras2	*KSR2*	610737	AD	12q24.22-q24.23
Carboxypeptidase	*CPE*	114855	AD	4q32.3
Proconvertase 1	*PCSK1*	162150	AR	5q15
Brain Derived Neurotropic factor	*BDNF*	113505	AD	11p14.1
SH2B adaptor protein	*SH2B1*	608937	AD	16p11.2
Tubby, Homogue of Mouse	*TUB*	601197	AR	11p15.4

AD= Autosomal dominant, AR = Autosomal recessive.

For detailed information and references, refer to Online Mendelian Inheritance in Man using the MIM number: https://www.omim.org

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TABLE 2

SYNDROMIC OBESITY

A] SYNDROMES WITH OBESITY AS A FEATURE

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
5p13 microduplication syndrome	*NIPBL*	613174		Developmental delay, autistic behaviour, obesity, lymphedema, hypertension, and macrocephaly	AD	5p13	Microduplication
16p11.2 deletion	*?SH2B1*	611913		Autism, severe early onset obesity, intellectual disability, congenital anomalies	-	16p11.2	del
Albright hereditary osteodystrophy/PHP Type 1 a	*GNAS*	103580	139320	Brachymetaphlangism, short stature, obesity, and mental retardation	AD	20q13.32	MS, FS, NS, SS, indel
Alstrom syndrome	*ALMS1*	203800	606844	Blindness, hearing impairment, childhood obesity, insulin resistance, and T2D	AR	2p13.1	FS, NS, MS
Bardet Biedel syndrome (BBS)				Retinitis pigmentosa, obesity, kidney dysfunction, polydactyly, behavioral dysfunction, and hypogonadism			
BBS 1	*BBS1*	209900	209901		AR, DR	11q13.2	MS, NS, SS, FS
BBS 2	*BBS2*	615981	606151		AR	16q13	MS, NS, FS, SS, Duplication
BBS 3	*ARL6*	209900	608845		AR	3q11.2	NS, del
BBS 4	*BBS4*	615982	600374		AR	15q24.1	MS, NS, SS, del
BBS 5	*BBS5*	615983	603650		AR	2q31.1	MS, FS, SS, del
BBS 6	*MKKS*	605231	604896		AR	20p12.2	MS, FS
BBS 7	*BBS7*	615984	607590		AR	4q27	FS, MS, NS, del
BBS 8	*TTC8*	615985	608132		AR	14q31.3	MS, SS, indel
BBS 9	*PTHB1*	615986	607986		AR	7p14.3	FS, SS, del
BBS 10	*BBS10*	615987	610148		AR	12q21.2	MS, NS, FS, SS, del
BBS 11	*TRIM32*	615988	602290		AR	9q33.1	MS, FS
BBS 12	*BBS 12*	615989	610683		AR	4q27	MS, NS, FS, del
BBS 13	*MKS1*	615990	609883		AR	17q22	MS
BBS 14	*CEP290*	615991	610142		AR	12q21.32	NS
BBS 15	*WDPCP*	615992	613580		AR	2p15	NS, SS
BBS 16	*SDCCAG8*	615993	613524		AR	1q43-44	NS, SS
BBS 17	*LZTFL1*	615994	606568		AR	3p21.31	MS, NS
BBS 18	*BBIP1*	615995	613605		AR	10q25.2	NS
BBS 19	*IFT27*	615996	615870		AR	22q12.3	SS

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A] SYNDROMES WITH OBESITY AS A FEATURE

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
BBS 20	*IFT172*	617119	608040		AR	2p23.3	SS
BBS 21	*C8ORF37*	617406	614477		AR	8q22.1	MS
Borjeson-Forssman-Lehmann Syndrome	*PHF6*	301900	300414	Severe intellectual disability, epilepsy, microcephaly, short stature, obesity, hypogonadism and gynecomastia	XLR	Xq26.2	NS, MS, truncating
Carpenter syndrome	*RAB23*	201000	606144	Acrocephaly with variable synostosis, brain malformations, dysmorphic facies, limb abnormalities, heart defects, mental retardation, growth retardation, hypogenitalism and obesity	AR	6p12.1-p11.2	MS, FS, SS, del
CHOPS syndrome*	*AFF4*	616368	604417	Congnitive impairment, coarse facies, heart defects, obesity, pulmonary involvement, short stature, and skeletal dysplasia	AD	5q31.1	MS, SS, del, dup, LOF
Chudley-Lowry syndrome	*ATRX*	309580	300032	mental retardation, short stature, mild obesity, hypogonadism and dysmorphism	XLR	Xq21.1	LOF
Cohen syndrome	*VPS13B/COH1*	216550		Developmental delay, facial dysmorphism, microcephaly, retinal dystrophy, truncal obesity, joint laxity and intermittent neutropenia	AR	8q22.2	MS, NS, del, dup, CNV
Kabuki syndrome/Niikawa-Kuroki syndrome	*KMT2D/MLL2/ALR/KABUK1*	147920	602113	Facial gestalt, intellectual disability, visceral and skeletal malformations and postnatal short stature with overweight	AD	12q13.12	NS, FS, del
Kleefstra syndrome	*EHMT1*	610253	607001	Mental retardation, obesity, hypotonia, brachycephaly, characteristic facial features, cardiac anomalies	AD	9q34.3	NS, FS, del
MORM syndrome	*INPP5E*	610156	613037	Moderate mental retardation, truncal obesity, congenital non-progressive retinal dystrophy, and micropenis	AR	9q34.3	NS
Prader-Willi Syndrome	*MKRN3/ZNF127/MAGEL2/SNRPN*	176270		Failure to thrive & feeding difficulties in infancy, obesity & hyperphagia beginning in childhood, hypotonia, short stature, developmental delay, small hands and feet, genital hypoplasia		15q11.2	del, uniparental disomy
Rubinstein-Taybi syndrome	*CREBBP*	180849	600140	Short stature, obesity, dysmorphic facies, visual difficulties, eating problems, spine curvature	AD	16p13.3	NS, MS, FS, SS, del
Shashi-X-linked mental retardation	*RBMX*			Coarse facies, mental retardation, prominent lower lip, large testis and obesity	XLR		NS, SS, MS
Smith Magenis Syndrome	*RAI1*	182290	607642	Intellectual disability, delayed speech and language, sleep disturbances, behavioral problems and obesity	AD	17p11.2	microdel, MS, FS, NS
WAGRO syndrome	*BDNF*	612469	612469	Wilms tumor, aniridia, genitourinary anomalies, mental retardation and obesity	?AD	11p13-p12	microdel, chrom inversion
OBHD	*NTRK2*	613886	600456	Obesity, hyperphagia and developmental delay, memory impairment and learning disability	?AD	9q21.33	MS
Ulnary Mammary syndrome	*TBX3*	181450	601621	Posterior limb deficiency, apocrine/mammary gland hypoplasia, delayed puberty, genital anomalies and obesity	AD	12q24.21	MS, NS, del
Unnamed syndrome1	*CUL4B*	300354	300304	Delayed puberty, hypogonadism, macrocephaly, short stature, central obesity, behavioral problems, pes cavus, abnormal toes	XLR	Xp24	MS, SS, del

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A] SYNDROMES WITH OBESITY AS A FEATURE

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
Unnamed syndrome2	*UBE2A*	300860	312180	Dysmorphic facies, large head, synophyrs, low hairline, small genitalia, seizures, mental retardation, overweight and obesity	XLR	Xp24	MS, NS, del

B] OVERGROWTH SYNDROMES

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
Bannayan-Riley-Ruvalcaba syndrome	*PTEN*	153480	601728	Macrocephaly, pseudopapilledema, multiple hemangioma, lipomats	AD	10q23.31	MS, NS, SS, del
Beckwith-Weidemann syndrome	*ICR1/H19/KCNQ1OT1/CDKN1*	130650	various	Macrosomia, macroglossia, cleft palate, visceromegaly, earlobe creases, neonatal hypoglycemia, embryonal tumors, hemihypertorphy	AD	11p15.5	del, MS
Klippel-Trenaunay-Weber syndrome	-	14900	-	Large cutanoeus hemangioma with hypertrophy of the related bones and soft tissues	-	8q22.3	
Parkes Weber syndrome	*RASA1*	608355	139150	multiple arteriovenous malformations under the skin, skeletal hypertorhphy	-	5q13.3	MS, FS, NS, del
Proteus syndrome	*AKT1*	176920	164730	asymmetric and disproprotionate overgrowth of one or more body regions, vascular malformations, nevi and abnormal adipose tissue	mosaicism	14q23.31	
Silver-Russell syndrome	-	180860	-	Triangular face with broad forehead and pointed, small chin with a wide mouth, growth retardation (short stature, IUGR), hemihyperplasia	-	7p11.2	
Simpson-Golabi-Behmel syndrome	*GPC3*	312870	300037	Pre- and post-natal overgrowth, coarse facies, heart defects, other congenital anomalies	XLR	Xq26.2	MS, SS, NS
Sotos syndrome	*NSD1*	117550	606681	macrocephaly, overgrowth, developmental delay, advanced bone age, hypotonia, hyperreflexia, motor delay, large hands and feet, may be associated with tumors	AD	5q35	NS, FS, del
Weaver syndrome	*EZH2*	277590	601573	macrocephaly, mild hypertonia, advanced bone age, frontal bossing, broad thumb, contractures of elbows, learning difficulty, limb anomalies	AD	7q36.1	NS, MS, del

C] GENETICALLY NON-ELUCIDATED SYNDROMES

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
Camera-Marugo-Cohen Syndrome	-	604257	-	Obesity, short stature, mental deficiency, hypogonadism, micropenis, contractures of the fingers, cleft lip-palate	-	-	-
Clark-Baraitser Syndrome	-	300602		Macrocephaly, mental retardation, ‘square’ forehead, prominent features, tall stature, large ears, obesity and macroorchidism	-	-	-
MEHMO syndrome	-	300148	-	Mental retardation, epileptic seizures, hypogonadism, microcephaly and obesity	?Mitochondrial	Xp22.13-p21.1	-

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C] GENETICALLY NON-ELUCIDATED SYNDROMES

NAME	GENE	Phenotype MIM	Gene/Locus MIM	CLINICAL FEATURES	MODE of INHERITANCE	CHROMOSOMAL POSITION	GENETIC DEFECT
MOMES syndrome	-	606772	-	Mental retardation, obesity, blepharophimosis, astigmatism, maxillary hypoplasia, mandibular prognathism	?AR	-	-
MOMO syndrome	-	157980		Macrosomia, Obesity, Macrocephaly, Ocular abnormalities	-	-	-
Morgagni-Stewart-Morel Syndrome	-	144800	-	Hyperostosis frontalis interna, Galactorrhea, Hyperprolactinemia, diabetes mellitus, hyperphosphatasia, obesity, hypertrichosis	?AD	-	-
1p36 deletion syndrome	-	607872	-	Hypotonia, developmental delay, growth abnormalities, obesity and craniofacial dysmorphism	-	1p36	del
2p25.3 deletion syndrome	*MYTL1*	616521	-	Intellectual disability, Obesity, Behavioral problems, Sleep disturbances	AD	2p25.3	del

AD = Autosomal dominant, AR= Autosomal recessive, XLR= X-linked recessive, MS = missense mutation, NS = nonsense, SS = splice site, LOF= loss of function, del = deletion, dup = duplication.

For complete description and references, refer to Online Mendelian Inheritance in Man: omim.org using the MIM numbers. Additional info at Gene Reviews: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/

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