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REVIEW

Updates on Monogenic Obesity in a Multifactorial Disease

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Abstract

Obesity is a worldwide epidemic with rates nearly doubling over the last 30 years. Despite increasing prevalence, the multifactorial pathogenesis of obesity continues to be widely misunderstood. Investigating genetic drivers in the development of obesity is an important area of focus, as genetics move to the forefront of medicine and personalized treatment evolves. Thus, this narrative review focused on four genes which have genome-wide association study–documented links to obesity and obesity syndromes. We explored their involvement in the predisposition, progression, and prognosis of obesity. Leptin, leptin receptor, pro-opiomelanocortin, and melanocortin 4 receptor are our four genes of interest, and herein we elaborated on the current literature, pathogenesis, and available treatments for patients with these specific genetic mutations.

Keywords Monogenic obesity · Genetics · Obesity · Gene mutations

Introduction

Obesity is a worldwide epidemic with rates nearly doubling over the last 30 years. As obesity continues to trend upward, the study of risk factors for its development and further exploration into attenuation of its progression is invaluable [1]. Recent World Health Organization (WHO) data from 2016 estimates over 1.9 billion adults are overweight or obese [1]. In addition, more than 41 million children under the age of five were overweight or obese [1]. Obesity is a major risk factor for many metabolic disturbances and other comorbid conditions such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [2]. The progression of the obesity and its comorbidities greatly increases healthcare costs around the world [1, 3]. Kent et al. have shown worldwide estimates for increased annual healthcare costs as high as 24% and 54% for overweight and obese populations, respectively, compared with healthy control populations [3].

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Although an imbalance between food intake and energy expenditure is traditionally thought to contribute to the development of obesity and its comorbidities, there is growing research suggesting a genetic component that has not been fully elucidated [4, 5]. Although genetics represent only a small percentage of obesity, this group represents a disproportionate amount of increased morbidity and healthcare costs [5]. This genetic contribution has been validated thoroughly through studies of families, twins, and adopted children [5]. Some estimates put the heritability of both monogenic and polygenic causes of obesity to be as high as 70% [5].

In this review, we will focus on four genes which have genome-wide association study (GWAS)–documented links to obesity and obesity syndromes in multiple age and ethnicity groups (Table 1). We will explore their involvement in the predisposition, progression, and prognosis of obesity: leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), and melanocortin 4 receptor (MC4R), and we will discuss how each of these unique gene variants impacts treatment going forward (Tables 1 and 2) [2, 4, 5].

Overview of Nutrition Physiology

Our total caloric intake is achieved by the ingestion of food containing the macronutrients of fats, carbohydrates, and proteins [6]. All three of these macronutrients are digested in different ways on a molecular level and, thus, have varying speeds of digestion [6]. The rate of digestion affects the

Table 1 Specific genes associated with obesity

Gene	Clinical phenotype
Leptin (LEP)*	• Severe, early-onset obesity • Undetectable serum leptin levels • Abnormal puberty
Leptin receptor (LEPR)*	• Severe, early-onset obesity • Undetectable serum leptin levels • Abnormal puberty
Pro-opiomelanocortin (POMC)*	• Severe, early-onset obesity • Pale skin • Red hair
Melanocortin 4 receptor gene (MC4R)*	• Most common form of monogenic obesity • Severe, early-onset obesity • Severity of obesity declines as carriers age
Fat mass and obesity-associated gene (FTO)	• Homozygous genotype associated with higher BMI
PPAR-gamma	• Associated with higher BMI • Associated with type 2 diabetes

BMI body mass index

*Signifies monogenic form of obesity

feelings of hunger and satiety, and endocrine functions [6]. Insulin and leptin are two major hormones that are in dysregulation in obesity, and they affect all three of these macronutrients [6].

Insulin is produced by beta, or islet, cells of the human pancreas in response primarily to recent carbohydrate intake [6]. Insulin functions as a storage hormone that signals carbohydrates that have just been ingested to be stored if there is an excess of energy (calories) beyond our body's metabolic needs for immediate survival [6]. Insulin has many effects in circulation, however, most importantly are its storage effects on adipocytes and its central effects on the hypothalamus [6, 7]. Changes in adipocyte cellular machinery and processing in response to insulin binding to its receptors on the extracellular surface of adipocytes allow the storage of excess caloric intake primarily as triglycerides within the adipocytes [6]. This results in an increase in fat mass and when this increase exceeds a normal limit, as defined traditionally by BMI, a patient will progress from healthy to overweight and obese [6]. Insulin also acts centrally on the hypothalamus to regulate hunger and satiety together with leptin [6, 7].

Leptin is produced by adipocytes and its levels in the blood are directly proportional to fat mass, and thus, it effectively signals our brains about just how much energy, in the form of adipose tissue, that we have on board and available for fuel [6]. Leptin, from the Greek word for *thin*, is released in response to satiety and has anorexigenic effects. This effect is due to leptin binding to its receptor at the hypothalamus and is an important regulatory step in calorie balance. However, if high levels of fat mass result in high levels of leptin, a hunger-suppressing hormone, why is it common for overweight and obese patients to maintain, or even increase, their level of body fat? Today, calorically dense foods are readily available. This accessibility is a hypothesized contributor to the major prevalence of obesity among developed countries and complicates the physiologic role of leptin in regulation of hunger. Furthermore, there is an inversely proportional relationship between leptin sensitivity and BMI, as the BMI increases, leptin sensitivity decreases [6]. This results in barrier to leptin sensitivity among obese populations, resulting in inadequate hunger-suppressant effects [6].

Leptin and Leptin Receptor

Complete leptin (LEP) and leptin receptor (LEPR) deficiencies have similar clinical presentations and, thus, will be discussed concurrently. Patients with complete LEP or LEPR deficiencies have often normal birth weight. These patients gain weight rapidly in the first few months of life resulting in severe early-onset obesity [5]. Symptoms of LEP and LEPR include hyperinsulinemia and intense hyperphagia coupled with aggressiveness if food is denied [5]. These patients have undetectable serum leptin levels, as well as other endocrine abnormalities such as hypogonadotropic hypogonadism and hypothalamic hypothyroidism [5]. These endocrine findings are due to intertwined leptin-hypothalamic signaling cascades involving sex and thyroid hormone production [5]. These patients will not experience the sexual development nor surge in growth hormone associated with puberty and, subsequently, their final adult height is shorter than normal [5]. Administering human recombinant leptin to leptin-deficient patients results in consistent weight and fat mass loss, even when restoring levels to as low as 10% of normal expected serum levels [5]. Restoring leptin activity results in proper satiety signaling and can accomplish a reduction of *ad libitum* food intake by as much as 84% [5]. Conversely, leptin administration to obese patients without leptin deficiencies is not effective at reducing adiposity due to the leptin resistance present in obese patients [5].

Due to the rarity of complete congenital LEP and LEPR deficiency, the prevalence is challenging to quantify. In a 2016 paper, Hannema et al. stated there have only been 25 published cases of the phenotype consistent with complete congenital LEP and LEPR deficiency [8]. Other studies have suggested severe LEP and LEPR mutated allele prevalence in severely obese patients to be between 2.2 and 3%; however, this data is extremely limited in terms of ethnicities studied [9]. A small French island has an estimated 20% frequency of LEP deficiency; however, researchers suspect a distant common ancestor of the geographically related patient group, thus a founder effect having a large impact on the perceived frequency [9].

Table 2 Selected literature on monogenic obesity response to surgery

Gene	Title	Authors	Year	Population/intervention	Findings
Leptin receptor (LEPR)	"Functional and phenotypic characteristics of human leptin receptor mutations"	Nunziata A, Funcke JB, Borck G, von Schnurbein J, Brandt S, Lennerz B, Moepps B, Gierschik P, Fischer-Posovszky P, Wabitsch M	2018	*N* = 6 Adolescents Varied bariatric surgical procedures	Mixed results for surgical outcomes Bariatric surgery may be less effective in women in this population than men
Pro-opiomelanocortin (POMC)	"Gene variants and binge eating as predictors of comorbidity and outcome of treatment in severe obesity"	Potoczna N, Branson R, Kral JG, Piec G, Steffen R, Ricklin T, Hoehe MR, Lentes K-, Horber FF	2004	*N* = 85 Laparoscopic gastric banding Various bariatric surgeries	Potential short- and long-term success after bariatric surgery
Melanocortin 4 receptor (MC4R)	"Melanocortin-4 receptor signaling is not required for short-term weight loss after sleeve gastrectomy in pediatric patients"	Jelin EB, Daggag H, Speer AL, Hameed N, Lessan N, Barakat M, Nadler EP	2016	*N* = 4 Adolescents Laparoscopic sleeve gastrectomy	Successful short-term weight loss One patient had significant weight re-gain

In regard to LEPR mutations that do not result in a complete loss of function, one study of 469 unrelated severely obese Caucasian patients presented 186 total patients with mutations at the leptin-binding domain of LEPR [10]. A 38% prevalence in the obese patients (n = 178) and a 32% prevalence in the control group (n = 8) were found. Nearly 98% of these mutations were all the same, seemingly non-pathogenic, mutation (T88641C, Ser343Ser) which had similar frequencies in the obese ($n = 175, f = 0.214$) and control ($n = 7, f = 0.14$) groups. Thus, this T88641C/Ser343Ser mutation did not significantly correlated with obesity ($p = 0.41$) [10].

Branson et al. showed that there was no evidence of any large-scale pathological effects of any of the studied LEPR mutations [10]. The lack of phenotypic expression was supported by no significant difference in serum leptin levels, timing of onset of obesity, rates of family history of obesity, binge eating disorder (BED) prevalence, amount of body fat, resting energy expenditure, or thermic effect of food between carriers and non-carriers of the studied LEPR mutations. However, only obese patients were found to have the homozygous T88641C/Ser343Ser allele mutation [8]. This homozygous T88641C/Ser343Ser genotype was found in 26 of the 175 obese patients (~ 15%) and 0 of the 7 control patients indicating that obesity and holding two copies of the T88641C/Ser343Ser allele mutation are correlated, but not necessarily causative [8].

When evaluating 300 patients who elected to undergo laparoscopic adjustable gastric banding surgery, Potoczna et al. found an 82.3% prevalence of LEPR mutations at the LEP-binding site [11]. However, they stated that none of these mutations was of a severe pathological type which causes the aforementioned loss of leptin activity and subsequent endocrine manifestations. They did not comment on the genotypes being homozygous or heterozygous for the mutation, so further stratification cannot be made. It is reasonable to consider that some of these mutations will have a larger effect than others and may predispose patients to varying degrees of obesity. Similar mean BMI measurements were found in the study samples of the Branson and Potoczna studies, 44.1 and 43.5, respectively; one could argue that perhaps the patients undergoing gastric banding could have had obesity that was more difficult to manage through lifestyle and pharmaceutical management leading them to a surgical treatment, although this aspect was unexplored in the paper [10, 11].

POMC

POMC is a protein precursor to many other hormones and neuropeptides [11]. It is released by hypothalamic neurons in response to insulin and leptin [7]. The protein is cleaved into several smaller peptides vital to normal function such as adrenocorticotropic hormone (ACTH), α-MSH, and β-endorphin, among others [11]. Alpha-MSH binds to melanocortin receptors in the

hypothalamus, including MC4R, resulting in satiety, making POMC a vital part to normal energy balance [7].

Patients with pathogenic mutations in POMC, specifically affecting the α-MSH region, present with severe early-onset obesity due to chronic hyperphagia as well as pale skin and red hair due to a lack of α-MSH effects at peripheral melanocortin receptors that regulate pigment production in the skin and hair follicles [7]. Heterozygotes, or patients carrying just one copy of a mutated allele, for POMC mutations are less obese than their homozygous counterparts who carry two copies of mutated alleles [5]. Santoro et al. also noted that POMC mutations can have a drastic effect on glucose metabolism in the Italian child and adolescent population, manifesting in hyperinsulinemia and increased insulin resistance [12]. This is likely due to glucocorticoid dysregulation due to a lack of proper ACTH production. Adrenal insufficiency presents with hypocortisolemia secondary to a lack of ACTH, hypoglycemia, and hyperinsulinemia, among other clinical phenotypes [5]. Due to the severity of these symptoms, adrenal insufficiency can lead to neonatal or infant death resulting in much lower patient numbers.

Potoczna et al. evaluated 300 gastric band surgical candidates and found 48% carried thirteen POMC variants; however, these mutations were largely non-pathogenic as they were not associated with a severe phenotype, early-onset obesity, an increase in BMI, frequency of metabolic syndrome (MetS), T2DM, BED, nor any of the other 17 other health parameters that the authors analyzed when compared with noncarrier patients [11]. These mutations also did not impact overall weight loss, surgical complications, reoperation, and conversion rates.

Genome-wide searches have elucidated links between the region of DNA containing the POMC locus, serum leptin, and fat mass in Mexican-Americans, African-Americans, and French Caucasians [13]. In genotyping nearly 400 obese North Indians and 300 non-obese North Indian controls, Srivastava et al. found that patients heterozygous or homozygous for a specific allele variant (rs1042571) were significantly more likely to be obese (BMI ≥ 30 kg/m^2, $p < 0.05$) compared with controls [14]. Their study found that the heterozygous variant CT and homozygous variant TT genotypes had odds ratios (OR) indicating an, on average, 1.7 (OR 1.1–2.6, $p = 0.005$) times and 4.0 (OR 1.1–14.1, $p = 0.03$) times increased likelihood, respectively, of obesity when compared with the homozygous non-rs1042571 variant CC genotype [14]. These two genotypes, CT and TT, had frequencies of 29.0% and 3.8%, respectively, in the almost 400 obese subjects in their study.

MC4R

While there are many forms of genetic obesity, MC4R mutations are reportedly the most common monogenic cause of dominantly inherited severe early-onset obesity in humans [4]. MC4R mutations were first recorded in obese human populations of varying ethnicities starting in 1998 [15].

Carriers of pathogenic MC4R mutations present with severe early-onset obesity, hyperinsulinemia with euglycemia, a higher prevalence of MetS (as high as 68%), increased use of antihypertensive medications, and oftentimes BED, among other clinical phenotypes [11, 12, 15]. It has been well documented that pathogenic mutations that retain even minimal receptor function result in improved clinical phenotypes compared with patients with a complete loss of MC4R function [15]. Interestingly, the severity of these phenotypes seems to partially decline as subjects age, meaning children with MC4R mutations have a more severe phenotype, expressed as more intense hunger, less satiety, and more severe hyperinsulinemia, than they will have as adults [5]. Studies have presented rare cases of constitutively active mutations in which subjects are of healthy BMI or even anorexic [16].

There is significant variance in the frequency of the hundreds of documented pathogenic mutations and single nucleotide polymorphisms (SNPs) at or near the MC4R gene in obese populations. The prevalence ranges from 0.5 to 6% in obese children and adults; however, this has not been confirmed in all populations [5, 13]. Mildly pathogenic mutations exert only a small effect on body composition and are more common than the severely pathogenic counterparts. Most frequently encountered in our review of the literature examined were the near-MC4R SNPs rs17782313 and rs12970134 which lie 188 kB and 154 kB downstream of the MC4R gene, respectively [4]. Both SNPs are associated with obesity and obesity-related traits in GWAS of Asian and European adults and children [4, 17].

While the rs17782313 SNP has not been shown to correlate with obesity and obesity-related traits in all ethnic backgrounds and age groups, many studies have shown strongly significant correlations at the population level [4, 17, 18]. A meta-analysis, published in *Nature Genetics*, covering over 28 European studies, showed a correlation of 0.13 BMI *Z*-score unit increase per copy of the mutation in almost 6000 children ages 7–11 [18]. In the same meta-analysis, results for over 77,000 adults showed that rs17782313 had a significant ~ 12% per-allele increase in the odds of being obese (BMI ≥ 30 kg/m^2, $p < 0.001$) and roughly 8% per-allele increase in being overweight (BMI ≥ 25 kg/m^2, $p < 0.001$). Even more severe was the significant increase in odds of being morbidly obese (OR = 1.31, $p < 0.001$) in a study of over 2700 French adults showing a 31% per-allele increase.

In regard to obesity-related traits, a meta-analysis of over 123,000 Europeans, East Asians, and South Asians, conducted by Xi et al., found that the rs17782313 SNP was significantly associated with T2DM risk even after adjusting for BMIs [17]. The exact mechanism of the link between the rs17782313 SNP and T2DM is unknown; however, they

proposed that it involves the irregular energy metabolism balance since MC4R has been indicated in both food intake and energy expenditure dysregulation in other studies.

A meta-analysis, by Xi et al., published in *PLOS ONE*, found that all five common SNPs, when examined in stratified subgroups by ethnicity, were associated with a significantly increased risk for obesity in European and East Asian adults, but not in African adults; however, only one study included subjects of African descent [19]. Their study included over 48,000 cases of rs17782313 mutations compared with over 134,000 controls and over 19,000 cases of rs12970134 mutations compared with over 31,000 controls. Their results proposed that the five near-MC4R SNPs (rs17782313, rs12970134, rs571312, rs17700144, rs4450508) showed significant odds ratios of 1.06–1.25 comparing obese to lean controls and showed similar per allele effect size on obesity risk among Europeans and East Asians [19]. The authors also described that, among over 17,000 children evaluated with common MC4R SNPs, the risk of obesity was significantly higher than the risk found in adults with the same SNPs. Although adolescent bariatric surgery has not shown much promise in this area, there is promise in adult patients who respond well to specific types of bariatric surgery. One loss-of-function MC4R adolescent patient treated with laparoscopic adjustable gastric banding and vagotomy was unable to maintain long-term weight loss, despite initial weight loss immediately after surgery [20]. Adults from a larger study were screened for MC4R mutations following Roux-en-Y gastric bypass surgery. Those who screened positive for MC4R mutations were found to have a similar amount of excess weight loss at 1-year follow-up to those without the mutation [21]. Conversely, a study in mice which underwent Roux-en-Y gastric bypass found that those mice without MC4R lost significantly less weight than their MC4R-positive counterparts [22]. This suggests that, in mice, MC4R function is required for weight loss following bariatric surgery in mice; however, a pediatric population that was homozygous for loss-of-function MCR4 mutation showed successful and significant weight loss and improvement in, or resolution of, their comorbidities in the short term after laparoscopic sleeve gastrectomy [23]. Clearly, more information must be collected on the response to bariatric surgery treatment in this population. When to intervene, as well as the type of surgery, may play an important role in treatment moving forward.

Discussion

Despite the aforementioned gene mutations being involved in the development of obesity due to their involvement in normal hunger, eating, weight gain, and other metabolic processes, there are some notable differences in clinical phenotype, physical exam, and laboratory data among patients with similar mutations. These factors can help delineate who is more likely to have one mutation over another, regardless of commonly shared comorbidities, such as hyperinsulinemia.

Complete LEP and LEPR deficiencies are extremely rare and result in a lack of normal sexual development and growth in puberty, hypothalamic hypothyroidism, and hypogonadotropic hypogonadism [5, 8]. Patients with this mutation can be identified with unique laboratory abnormalities, such as undetectable serum leptin levels, undetectable or severely low serum thyroid-releasing hormone (TRH) levels, and low gonadotropin-releasing hormone (GnRH) with low levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). POMC mutations that occur near or at the α-MSH coding region can present with pale skin and red hair due to a lack of melanocyte stimulation and pigment production in the skin and hair follicles [7]. Lastly, MC4R is touted as the most common cause of monogenic obesity with a similarly disturbed mechanism in hypothalamic satiety signaling and energy balance [15]. Unlike the three previously mentioned mutations, partially and completely inactivating MC4R mutations are frequently associated with an increase in BED and MetS and seem to exhibit a decreasing severity of the phenotypes as the patients age [5, 11, 12, 15].

In clinical practice, these different genetic abnormalities can certainly require different ways to approach their respective treatments. In LEP-deficient patients, but not LEPR-deficient patients, administration of human recombinant leptin has been shown to have as high as an 84% reduction in ad libitum feeding, making leptin replacement therapy highly effective in these patients [5]. LEPR mutations specifically may result in obesity that is more difficult to manage through lifestyle and pharmaceutical management, thus, possibly necessitating surgical treatment; however, this was formally unexplored in reviewed articles and should be formally assessed [10, 11]. Some studies have shown that patients with LEP and LEPR mutations who undergo bariatric surgery have an appropriate response postoperatively, with adequate weight loss trends even with early-onset obesity. However, recent literature has shown the possibility that women with certain LEPR mutations may have a decreased response to bariatric surgery compared to males with similar mutations [24]. This difference in outcome has yet to be shown in LEP mutations. Still, this population reaches lower rates of weight loss when compared with patients affected by other monogenic causes of obesity [25, 26].

Full elucidation of the clinical outcomes of complete loss of POMC will be difficult to fully assess as it can often lead to neonatal or infant death secondary to adrenal insufficiency [5]. In cases of partial loss or mutations to POMC, results are mixed as to if carriers have different outcomes in weight loss. Some studies suggest that POMC mutations may not impact

weight loss; however, aspects of the patients' pre- and post-operative metabolic profiles are often not different in carriers vs. non-carriers suggesting that mutations seen may be largely non-pathogenic if they are not in the α-MSH coding region [11]. However, other studies looking at the role of α-MSH in long-term weight loss suggest an anorexigenic role of α-MSH, thus suggesting patients with pathogenic POMC mutations or partial losses that include changes to the α-MSH coding region may result in deceased short- and long-term success after bariatric surgery [27].

Similar to the previously mentioned genes and their integral role in overall metabolism and weight homeostasis, complete loss of MC4R significantly impairs the body's ability to have successful long-term weight loss, even after bariatric surgery [20]. In the absence of complete loss, the metabolic derangements precluding clinical weight loss can be overcome with bariatric surgery and other appropriate clinical intervention, resulting in weight loss similar to non-carriers [20–22]. However, MC4R variant carriers have been shown to have higher post-operative complication rates including higher likelihood of conversion to gastric bypass for various reasons and a propensity to lose as much as 8.6% less weight when undergoing gastric banding compared with non-carriers [11]. Interestingly, however, if MC4R variant carriers underwent conversion to gastric bypass, weight loss was similar between carriers and noncarriers [11]. It is also possible that MC4R variant carriers have a greater response to bariatric surgery that involves changes in the neurohormonal processes rather than by decreasing gastric volume alone [15].

Currently, there are numerous clinical trials looking into treatment of genetic obesity which are largely focused on the medication Setmelanotide (RM-493), a selective agonist of the MC4 receptor being researched by Rhythm Pharmaceuticals, Inc. [28]. POMC and LEPR deficiencies are among the many obesity-related genetic mutations currently being studied. Additionally, there has been a rise in the theory that obesity may not be largely monogenic in nature.

Conclusion

The pathophysiology of obesity has yet to be fully elucidated, with literature suggesting a sizeable influence of genetics on the development and progression of obesity and obesity-related diseases. LEP, LEPR, POMC, and MC4R gene mutations each show promise, serving as a platform on which more genetic and interrelated surgical knowledge can be built. Genetic variance will be paramount in understanding processes related to obesity, and how gene mutations interact with normal and abnormal physiology. As technology evolves to allow for detailed characterization of genetic mutations, large, well-controlled studies of genetic mutations from multi-ethnic populations, and their subsequent outcomes on surgical and non-surgical weight loss, must be undertaken. Further research must be done in order to fully understand the implications and prognostic predictors, as well as appropriate management of these diseases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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