



The genetics of obesity

A narrative review

Young Bae Sohn

Department of Medical Genetics, Ajou University Hospital, Ajou University School of Medicine, Suwon, Korea

Received: December 12, 2022

Revised: December 23, 2022

Accepted: December 27, 2022

Corresponding author:

Young Bae Sohn
Department of Medical
Genetics, Ajou University
Hospital, Ajou University School
of Medicine, 164 World cup-ro,
Yeongtong-gu, Suwon 16499,
Korea
Tel: +82-31-219-4522
E-mail: ybsohn@ajou.ac.kr

ABSTRACT

Monogenic obesity is a rare, early-onset, and severe form of obesity that has a Mendelian inheritance pattern, high penetrance, and large genetic effect. In contrast, common polygenic obesity is more prevalent and has pattern of heritability derived from many variants in several genes with low penetrance. This influences phenotype interaction with environmental factors. However, the influence of genetics on obesity is a continuous spectrum rather than the distinct classification. Genetic studies have found that leptin-melanocortin pathway is a key circuit in regulating appetite, satiety, and body weight, and most cases of monogenic obesity result from defects in this pathway. Genetic variations associated with common polygenic obesity have been found by population-based association studies, such as genome-wide association studies (GWAS). GWAS have discovered many obesity-associated loci, the majority of which harbor genes identified in monogenic obesity involving the leptin-melanocortin pathway. Genetic insights have enabled in not only understanding the molecular mechanisms and biology of obesity, but also in the development of novel therapeutic drugs for several types of monogenic obesity in the context of precision medicine. Moreover, therapeutic approaches could work in common polygenic obesity given that the genetic variations identified in the leptin-melanocortin circuit also plays a role in common polygenic obesity.

Keywords: Genome-wide association study; Leptin; Melanocortins; Obesity

INTRODUCTION

Obesity is an important public health issue that is prevalent worldwide and is associated with early death and complications such as type 2 diabetes, dyslipidemia, hypertension, and cardiovascular diseases and certain cancers [1,2]. According to the genetic contribution, obesity can be classified into three categories. The majority cases of obesity are classified as “common polygenic obesity,” which result from the interaction of genetic susceptibilities and environmental factors [3]. “Syndromic obesity” is characterized by obesity combined with developmental delay or dysmorphism. Bardet-Biedle, Prader-Willi, and Alstrom syndromes are well known examples of syndromic obesity. “Monogenic obesity” is resulted from pathogenic variants in single genes, which are generally involved in the hypothalamic leptin-melanocortin pathway asso-

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>).

ciated with regulation of hunger and satiety [3]. Monogenic obesity has a Mendelian inheritance pattern, low prevalence, and early-onset severe clinical manifestations, whereas common polygenic obesity has heritability similar to other multifactorial diseases and high prevalence [4]. Genetic variants in single genes lead to large effects and high penetrance in monogenic obesity. In contrast, various of variants in several genes interacting with environmental factors are responsible for polygenic obesity. However, the influence of genetics on obesity is on a continuous spectrum rather than the distinct phenotypic classification [4]. Although the majority cases of obesity are common polygenic obesity, many insights regarding the biology and molecular mechanisms have been discovered from monogenic obesity.

This review covers the genetics of monogenic and common polygenic obesity, including the difference in genetic approaches, known monogenic obesity disorders, therapeutic implications, and perspectives of genetic studies in obesity.

GENETIC APPROACHES FOR MONOGENIC OBESITY

Early studies for identification of causative genes in monogenic obesity were designed in a case-controlled format. Thus, patients with severe early-onset obesity and their affected or unaffected family members were investigated for identification of causative genes by Sanger sequencing analysis [4]. However, the advances in next-generation sequencing (NGS) technology led to expansion of candidate gene panel sequencing and whole exome or whole genome sequencing. NGS-based genetic investigations in groups of patients with severe early-onset obesity have identified causative genetic variations in monogenic obesity.

MONOGENIC OBESITY

Genetic studies have found that the leptin-melanocortin pathway plays a crucial role in regulation of appetite, hunger, satiety, and body mass index (BMI), and many cases of monogenic obesity result from defects in this pathway [5]. Leptin, a hormone secreted from adipose tissue, works through the leptin receptor located in the arcuate nucleus in the hypothalamus. It stimulates the production of proopiomelanocortin (POMC) in the POMC neurons. Then, proprotein convertase subtilisin/kexin type 1 (PCSK1) mediates the process of converting POMC to melanocyte-stimulating hormone (MSH) [5]. MSH interact with the melanocortin receptors, including the

melanocortin 4 receptor (MC4R) in the brain. Activation of MC4R results in reduction of food intake and concomitant increase of energy consumption [5]. In addition, leptin-mediated synaptic plasticity of neurons is modulated by brain-derived neurotrophic factor (BDNF) in the brain [3].

Clinical manifestations of individuals with monogenic obesity are distinct from those of common polygenic obesity. Patients with monogenic obesity gains body weight rapidly starting early infancy, and the velocity of increasing BMI reach to peak during childhood [3]. Therefore, clinicians should suspect monogenic obesity when patients have extreme obesity (BMI $\geq 120\%$ of the 95th percentile or ≥ 35 kg/m²) during childhood, fast weight gain in the first several years after birth, with hyperphagia [6]. Patients with monogenic obesity can have additional clinical manifestations, such as short stature, red hair, susceptibility to infection, recurrent diarrhea, or endocrine defects, including pituitary insufficiencies, diabetes insipidus, adrenal insufficiency, hypothyroidism, or hypogonadism [3,6]. The clinical and genetic implications of monogenic obesity disorders are shown in Table 1.

MC4R deficiency

MC4R deficiency is the most common monogenic obesity disorder [3,7]. Pathogenic variants in the *MC4R* gene cause approximately 2% to 5% of the cases of extreme early-onset obesity [5,8]. Clinical manifestations of *MC4R* deficiency include hyperphagia, severe early-onset obesity, hyperinsulinemia accompanied with lean body mass increase, and rapid linear growth [9]. In contrast, individuals who have gain-of-function mutations in *MC4R* gene have decreased food intake, high energy expenditure, and low BMI [10]. The variants in *MC4R* gene can be inherited either in an autosomal dominant or recessive pattern. Clinical symptoms in patients carrying homozygous or compound heterozygous variants are more severe than those in patients with heterozygous variants.

Leptin deficiency

Leptin deficiency is an extremely rare monogenic obesity disorder and under 100 cases have been published to date [4,11]. Leptin deficiency is caused by the pathogenic variants in the *LEP* gene. The clinical symptoms include severe hyperphagia and early-onset obesity. If patients have biallelic variants in *LEP*, they can have additional clinical manifestation, including frequent infections and endocrine defects, such as hypogonadotropic hypogonadism and hypothyroidism [12]. Patients with leptin deficiency have nondetectable serum leptin levels [13].

Table 1. Genetic and clinical implications of monogenic obesity disorders

Gene	Protein	Mode of inheritance	Clinical manifestations	Treatment option(s)
<i>LEP</i>	Leptin	AR	Obesity, hyperphagia, hypogonadism, frequent infection, neuroendocrine dysfunction	Metreleptin, Setmelanotide
<i>LEPR</i>	Leptin receptor	AR	Obesity, hyperphagia, hypogonadism, neuroendocrine dysfunction	Setmelanotide
<i>MC4R</i>	Melanocortin 4 receptor	AD	Obesity, hyperphagia, accelerated growth	Setmelanotide
<i>POMC</i>	Proopiomelanocortin	AR	Obesity, red hair, pale skin, ACTH deficiency	Setmelanotide
<i>PCSK1</i>	Proprotein convertase subtilisin/kexin	AR	Obesity, defects of prohormones, postprandial hypoglycemia, enteropathy	Setmelanotide
<i>SH2B1</i>	SH2B adaptor protein 1	AR	Obesity	Setmelanotide
<i>SIM1</i>	Single-minded homologue 1	AR	Obesity, developmental delay	Setmelanotide
<i>ADCY3</i>	Adenylate cyclase type 3	AR	Obesity	NA
<i>BDNF</i>	Brain-derived neurotrophic factor	AR	Obesity, hyperphagia, impaired memory, impaired pain sensation, hyperactivity, developmental delay	NA
<i>SEMA3A-G</i>	Semaphorin 3A-G	AR	Obesity, hypogonadotropic hypogonadism with or without anosmia	NA

AR, autosomal recessive; AD, autosomal dominant; ACTH, adrenocorticotropic hormone; NA, not available.

Leptin receptor deficiency

Leptin receptor deficiency is a rare autosomal recessive disease caused by biallelic pathogenic variants in the *LEPR* gene [14]. The phenotype is similar to leptin deficiency except increase of serum leptin levels [14]. Individuals having leptin receptor deficiency show rapid weight gain and severe childhood obesity resulted from prominent food-seeking behaviors from childhood, hyperphagia, and insufficient satiety [15]. Accompanied endocrine defects are comparable to the those of leptin deficiency, but recurrent infections are nearly observed [14,15].

POMC deficiency

POMC deficiency is an autosomal recessive monogenic obesity disorder. Clinical symptoms include hyperphagia resulting in severe early-onset obesity, pigmentary abnormalities including red hair or pale skin color, and adrenal insufficiency. A pituitary preproprotein encoded by *POMC* is a precursor of several neuroendocrine peptides. α -MSH, one of the neuroendocrine peptides derived from POMC by the action of PCSK1, works for suppression of appetite and eating through the interaction with MC4R [16].

PCSK1 deficiency

Patients with PCSK1 deficiency presents with early-onset severe obesity accompanied by diarrhea in the infancy and

postprandial hypoglycemia [17,18]. Additional clinical manifestations include neuroendocrine defects, such as diabetes insipidus, hypogonadotropic hypogonadism, adrenal insufficiency, and hypothyroidism [17,18]. Biallelic pathogenic variants in the *PCSK1* gene cause impairment in converting prohormones to active hormones, gastric peptides, and proinsulin [3,17,18].

GENETIC APPROACHES FOR POLYGENIC OBESITY

Genetic variations attribute to common polygenic obesity have been identified through population-based large association studies [4]. Over the past 2 decades, the advances in genome-wide association studies (GWAS) accompanied by high-throughput genome-wide genotyping technics have enabled the identification of genetic variants throughout the whole genome [4]. In 2007, the GWAS for obesity phenotype demonstrated that several common variants in the intron of *FTO* was associated with BMI in the large populations [19,20]. Numerous following GWAS identified more than 1,000 loci associated with the obesity trait to date [4,21]. Following that, GWAS for refined traits of obesity have been conducted, such as percentage of body fat, lean body mass, imaging-derived adipose tissue, serum leptin and leptin receptor levels, and persistent healthy thinness [4,22-29]. These detailed pheno-

types represent more accurate aspect of appetite and body weight regulation, and the identified loci are associated with more relevant biological pathways underlying obesity [4].

Although GWAS have concerned with common sequence variants with >5% minor allele frequency, there are studies demonstrating the impact of copy number variations (CNVs) in common polygenic obesity. For example, the deletion of 1p31.1 near *NEGR1* [30], 16p12.3 deletion upstream of *GPRC5B* [31], 10q11.2 CNV in *PPTR1* [32], and 1p21.1 multi-allele CNV encompassing *AMY1A* [33] are reported as CNVs associated with obesity traits.

Similar to the discovery of genetic variations for other multifactorial diseases, the genetics of common obesity also have a substantial bias in study population [4]. As the majority of GWAS have been conducted in population from European ancestry, the result is not always generalizable to people of Asian, African, Hispanic, or other ancestries. Because obesity is a multifactorial disorder, some GWAS have considered environmental factors, including sex, age, physical activity, diet, or smoking into genetic analyses [34–37]. However, this approach is still challenging given that only 12 loci have been identified to date [4]. The impacts of environmental factors on obesity could attenuate or exacerbate the impacts of genetic variations. Nevertheless, the *FTO* locus and a healthy lifestyle have been replicated and reproduced firmly. A healthy diet or increased physical activity could attenuate the effect of the *FTO* locus on obesity risk by 30% to 40% [38,39]. As large-size population cohorts and biobanks, including UK biobank, All of Us, and Biobank Japan, are ongoing, more comprehensive meta-analysis could expand the insight regarding genetic-environmental interactions.

NEW PHARMACOLOGICAL THERAPEUTIC APPROACHES

Genetic insights have enabled development of new therapeutic drugs for several types of monogenic obesity in the context of precision medicine. The precise genetic diagnosis can allow the prescription of personalized treatment. Although standard genetic panel testing is not available so far, genetic testing in special patient groups who have early-onset extreme obesity are recommended for early diagnosis of “treatable” monogenic obesity and timely intervention [5]. The development of pharmacological agents for monogenic obesity is meaningful given that a therapeutic agent developed for one disorder could also benefit for other types of monogenic obesities because these diseases are caused by impairment

of common leptin-melanocortin pathway [40]. Furthermore, these therapeutic approaches could be also effective in common polygenic obesity given that the genetic trait have an important role in common polygenic obesity, too.

Metreleptin

Subcutaneous injection of human recombinant leptin (metreleptin) is remarkably beneficial for patients with leptin deficiency resulting in rapid improvement in food-seeking behavior, a decrease of food intake, reduction of fat mass and consequential body weight loss [41]. It also lead to amelioration of metabolic and endocrine abnormalities, such as hyperinsulinemia, hyperlipidemia, fatty liver, and hypogonadotropic hypogonadism [3,41]. Reported side effects of metreleptin include the production of neutralizing antibodies and an increased risk of lymphomas [3,42].

Setmelanotide

Setmelanotide is a selective MC4R agonist mimicking the POMC derivative α -MSH [43]. Daily subcutaneous injection of setmelanotide resulted in significant loss of body weight and reduction of hunger [43,44]. In 2020, the Food and Drug Administration (FDA) approved the use of setmelanotide for treatment of monogenic obesity due to POMC, PCSK1, or leptin receptor deficiency in adults and children aged 6 years and older [45]. The adverse events of setmelanotide were mild and included hyperpigmentation, nausea, vomiting, and injection site reactions [4]. The phase II or phase III clinical trials are ongoing to evaluate the efficacy of setmelanotide as a therapeutic option for other genetic disorders involving the MC4R pathway [3]. Efficacy of setmelanotide is also being investigated in patients with syndromic obesity, such as Bardet-Biedle syndrome and Alstrom syndrome as well as in the chromosomal rearrangement of the 16p11.2 [3,46,47].

CONCLUSION

It is being remarkably known that monogenic and polygenic obesities are not distinct categories, but are on a continuous spectrum and share biological pathways. As GWAS have discovered more obesity-associated loci, the majority of the loci identified in monogenic obesity involve the leptin-melanocortin pathway. Although the translation from variants discovered through GWAS to function is still challenging, in advent with high-throughput techniques, omics data, and advanced analytic tools could provide more opportunities to understand the genetics of obesity which could contribute to

development of novel therapeutic approaches in context of precision medicine.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Young Bae Sohn <https://orcid.org/0000-0002-4664-1941>

AUTHOR CONTRIBUTIONS

Conception or design: YBS.

Acquisition, analysis, or interpretation of data: YBS.

Drafting the work or revising: YBS.

Final approval of the manuscript: YBS.

REFERENCES

1. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;377:13-27.
2. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA* 1999;282:1523-9.
3. Hinney A, Korner A, Fischer-Posovszky P. The promise of new anti-obesity therapies arising from knowledge of genetic obesity traits. *Nat Rev Endocrinol* 2022;18:623-37.
4. Loos RJ, Yeo GS. The genetics of obesity: from discovery to biology. *Nat Rev Genet* 2022;23:120-33.
5. Dayton K, Miller J. Finding treatable genetic obesity: strategies for success. *Curr Opin Pediatr* 2018;30:526-31.
6. Sohn YB. Genetic obesity: an update with emerging therapeutic approaches. *Ann Pediatr Endocrinol Metab* 2022;27:169-75.
7. Farooqi IS. Monogenic human obesity syndromes. *Handb Clin Neurol* 2021;181:301-10.
8. Lubrano-Berthelie C, Dubern B, Lacorte JM, Picard F, Shapiro A, Zhang S, et al. Melanocortin 4 receptor mutations in a large cohort of severely obese adults: prevalence, functional classification, genotype-phenotype relationship, and lack of association with binge eating. *J Clin Endocrinol Metab* 2006;91:1811-8.
9. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, et al. Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2017;102:709-57.
10. Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* 2008;4:569-77.
11. Yaswen L, Diehl N, Brennan MB, Hochgeschwender U. Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. *Nat Med* 1999;5:1066-70.
12. Wasim M, Awan FR, Najam SS, Khan AR, Khan HN. Role of leptin deficiency, inefficiency, and leptin receptors in obesity. *Biochem Genet* 2016;54:565-72.
13. Funcke JB, von Schnurbein J, Lennerz B, Lahr G, Debatin KM, Fischer-Posovszky P, et al. Monogenic forms of childhood obesity due to mutations in the leptin gene. *Mol Cell Pediatr* 2014;1:3.
14. Kleinendorst L, Abawi O, van der Kamp HJ, Alders M, Meijers-Heijboer HE, van Rossum EF, et al. Leptin receptor deficiency: a systematic literature review and prevalence estimation based on population genetics. *Eur J Endocrinol* 2020;182:47-56.
15. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med* 2007;356:237-47.
16. Yeo GS, Chao DH, Siegert AM, Koerperich ZM, Ericson MD, Simonds SE, et al. The melanocortin pathway and energy homeostasis: from discovery to obesity therapy. *Mol Metab* 2021;48:101206.
17. Farooqi IS, Volders K, Stanhope R, Heuschkel R, White A, Lank E, et al. Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3. *J Clin Endocrinol Metab* 2007;92:3369-73.
18. Jackson RS, Creemers JW, Ohagi S, Raffin-Sanson ML, Sanders L, Montague CT, et al. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet* 1997;16:303-6.
19. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007;316:889-94.
20. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet* 2007;3:e115.

21. Buniello A, MacArthur JA, Cerezo M, Harris LW, Hayhurst J, Malangone C, et al. The NHGRI-EBI GWAS catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res* 2019;47:D1005-12.
22. Sun Q, Cornelis MC, Kraft P, Qi L, van Dam RM, Girman CJ, et al. Genome-wide association study identifies polymorphisms in LEPR as determinants of plasma soluble leptin receptor levels. *Hum Mol Genet* 2010;19:1846-55.
23. Kilpelainen TO, Zillikens MC, Stancakova A, Finucane FM, Ried JS, Langenberg C, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nat Genet* 2011;43:753-60.
24. Javed A, Jumean M, Murad MH, Okorodudu D, Kumar S, Somers VK, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity in children and adolescents: a systematic review and meta-analysis. *Pediatr Obes* 2015;10:234-44.
25. Kilpelainen TO, Carli JF, Skowronski AA, Sun Q, Kriebel J, Feitosa MF, et al. Genome-wide meta-analysis uncovers novel loci influencing circulating leptin levels. *Nat Commun* 2016;7:10494.
26. Chu AY, Deng X, Fisher VA, Drong A, Zhang Y, Feitosa MF, et al. Multiethnic genome-wide meta-analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. *Nat Genet* 2017;49:125-30.
27. Zillikens MC, Demissie S, Hsu YH, Yerges-Armstrong LM, Chou WC, Stolk L, et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun* 2017;8:80.
28. Riveros-McKay F, Mistry V, Bounds R, Hendricks A, Keogh JM, Thomas H, et al. Genetic architecture of human thinness compared to severe obesity. *PLoS Genet* 2019;15:e1007603.
29. Orthofer M, Valsesia A, Magi R, Wang QP, Kaczanowska J, Kozieradzki I, et al. Identification of ALK in thinness. *Cell* 2020;181:1246-62.e22.
30. Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009;41:25-34.
31. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010;42:937-48.
32. Jarick I, Vogel CI, Scherag S, Schafer H, Hebebrand J, Hinney A, et al. Novel common copy number variation for early onset extreme obesity on chromosome 11q11 identified by a genome-wide analysis. *Hum Mol Genet* 2011;20:840-52.
33. Falchi M, El-Sayed Moustafa JS, Takousis P, Pesce F, Bonfond A, Andersson-Assarsson JC, et al. Low copy number of the salivary amylase gene predisposes to obesity. *Nat Genet* 2014;46:492-7.
34. Graff M, Scott RA, Justice AE, Young KL, Feitosa MF, Barata L, et al. Genome-wide physical activity interactions in adiposity: a meta-analysis of 200,452 adults. *PLoS Genet* 2017;13:e1006528.
35. Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, Chu S, et al. The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. *PLoS Genet* 2015;11:e1005378.
36. Qi Q, Chu AY, Kang JH, Huang J, Rose LM, Jensen MK, et al. Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. *BMJ* 2014;348:g1610.
37. Kilpelainen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med* 2011;8:e1001116.
38. Smith CE, Follis JL, Dashti HS, Tanaka T, Graff M, Fretts AM, et al. Genome-wide interactions with dairy intake for body mass index in adults of European descent. *Mol Nutr Food Res* 2018;62:1700347.
39. Justice AE, Winkler TW, Feitosa MF, Graff M, Fisher VA, Young K, et al. Genome-wide meta-analysis of 241,258 adults accounting for smoking behaviour identifies novel loci for obesity traits. *Nat Commun* 2017;8:14977.
40. Poitou C, Mosbah H, Clement K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. *Eur J Endocrinol* 2020;183:R149-66.
41. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med* 1999;341:879-84.
42. de Candia P, Prattichizzo F, Garavelli S, Alviggi C, La Cava A, Matarese G. The pleiotropic roles of leptin in metabolism, immunity, and cancer. *J Exp Med* 2021;218:e20191593.
43. Kuhnen P, Clement K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, et al. Proopiomelanocortin deficiency treated with a Melanocortin-4 receptor agonist. *N Engl J Med* 2016;375:240-6.
44. Clement K, van den Akker E, Argente J, Bahm A, Chung WK, Connors H, et al. Efficacy and safety of setmel-

- notide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol* 2020;8:960-70.
45. Markham A. Setmelanotide: first approval. *Drugs* 2021;81:397-403.
46. Haws R, Brady S, Davis E, Fletty K, Yuan G, Gordon G, et al. Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. *Diabetes Obes Metab* 2020;22:2133-40.
47. Haws RM, Gordon G, Han JC, Yanovski JA, Yuan G, Stewart MW. The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alström syndrome: phase 3 trial design. *Contemp Clin Trials Commun* 2021;22:100780.