Demiroglu Science University Florence Nightingale Journal of Transplantation2021;6(1-2):17-22
doi: 10.5606/dsufnjt.2021.021

RIPK1 and obesity-induced inflammation

Aslı Melike Ekmekçi[1], Fehmi Balandi[1], Oytun Erbaş[2]

[1]*Institute of Experimental Medicine, Gebze-Kocaeli, Turkey*
[2]*Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey*

ABSTRACT

Obesity is a complex disease that affects women more than men, spreading like an avalanche in industrialized, developing, and underdeveloped countries. It is uncertain if inflammation is a cause or an effect in the pathophysiology of obesity-related increased body mass index. Obesity, inflammation, obesity genes, and genetic pathways that contribute to obesity-related inflammation are discussed in this review. The receptor-interacting serine/threonine-protein kinase 1 (RIPK1) gene was also highlighted in the role of genetics on obesity-related inflammation. In addition, studies on the importance of a genetic approach in obesity and the potential role of RIPK1 in inflammatory outcomes or cell death caused by obesity were included in this review. Although studies on the inflammatory consequences of obesity have gained attention recently, the literature on the links between obesity, inflammation, and RIPK1 is limited. Therefore, we believe that further research is needed to fully comprehend their mode of action.

Keywords: Genetics, inflammation, obesity, RIPK1

For adults, a body mass index (BMI) of 25.0-29.9 kg/m^2 is defined as overweight, and a BMI of 30 kg/m^2 and higher is obese. It is recommended to use sex-and age-appropriate percentile charts for children aged 2 to 18 years.[1] The prevalence of obesity is increasing in both developed and underdeveloped countries. The prevalence of obesity in men is higher in Europe.[2] Obesity is a complex disease caused by genetic makeup, socioeconomic status, biological factors, psychosocial status, and other environmental factors.[3] In the treatment of obesity, the psychological and social components of the disease have been focused on. The best results to date have been obtained by diet management, behavior modification, and bariatric surgery.[4] However, genetic factors appear to be strongly associated with obesity.[5] As a result of study with identical twins, it has been determined that genetic tendency determines who will be obese and that the environment affects the severity of obesity.[6] Unlike the typical immune response to injury or inflammatory disorders, the inflammation found in obesity does not resolve substantially over time.[7] A study in mice fed a high-fat and low-fat diet showed that inflammatory genes are elevated in mice fed a high-fat diet.[8] Excess calories are deposited in adipose tissue, more specifically white adipose tissue (WAT), in the form of triglycerides. Study have shown that in obese people, WAT shows more activity compared to healthy individuals, and cells start to die, and immune cells are activated.[9] However, the particular process that causes this inflammation is unknown.

INFLAMMATION

Various defense mechanisms have been established by living beings against attacks on their cells, the most successful of which has been inflammation. Inflammation is a physiological

Correspondence: Aslı Melike Ekmekçi. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.
e-mail: aslimelike01@gmail.com

Cite this article as:
Ekmekçi AM, Balandi F, Erbaş O. RIPK1 and obesity-induced inflammation. D J Tx Sci 2021;6(1-2):17-22.

response of the organism to impending harmful physical, chemical or biological stimuli.[10] Adipocytes are the main cells of adipose tissue. Hypertrophy and the calorie excess, trigger many inflammatory signals, such as an increase in the release of pro-inflammatory adipocytokines and an increase in endoplasmic reticulum stress.[11] High-fat diets cause the activation of cytokine receptors and toll-like receptors (TLRs). These activate the mitogen-activated protein kinase pathway through chaperone molecules, stimulate the translocation of nuclear factor kappa B (NF-κB), and support the transcription of genes involved in the inflammatory process.[12,13] In obesity, the main trigger of inflammation is excessive food consumption. Inflammation observed in obese and overweight patients has been described as meta-inflammation.[13,14] The role of the inflammasome NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) in obesity has been widely described.[15]

OBESITY GENES

The idea of endogenous obesity was first proposed in 1907.[16] Since then, the genetic mechanism of obesity has been the focal point of the investigations. According to a meta-analysis of twin studies, the heritability of lifelong weight change is estimated to be between 45 and 90%.[17] This study showed the highest heritability to be in early childhood, adolescence, and adulthood. In addition, the effect of genetics on obesity-related behaviors such as eating habits and exercise has also been recognized.[17] Examining the central regulatory pathway of appetite regulation will facilitate the understanding of genetic mutations in obesity. The central nervous system plays an important role in controlling food intake in the brain-gut axis through the hypothalamic leptin-melanocortin pathway, the central regulator of energy balance.[18] The ghrelin-like peptide YY hormones, such as cholecystokinin, glucagon-like peptide, and mechanoreceptors that measure distension through the pancreas and insulin, and signals are received by adipokine hormones such as leptin and adiponectin. The hypothalamus acts by combining these signals for the purpose of maintaining energy balance. The leptin-melanocortin pathway is induced by leptin receptors (LEPRs) and insulin receptors. Proprotein convertase 1 (PC1) and proprotein convertase 2 (PC2) [after conversion with proopiomelanocortin (POMC)], α-, β-, and γ-melanocyte-stimulating hormone (MSH), and various peptides, such as β-endorphins, agouti-related peptide (AGRP), and α-MSH, try to bind to the melanocortin-4 receptor (MC4R).[19] Binding with α-MSH results in anorexigenic signals, while binding with AGRP produces orexigenic signals.[20] The signals from the MC4R manage the food uptake process with the brain-derived neurotrophic factor (BDNF) and the neurotrophic tyrosine kinase receptor type 2 (NTRK2) secondary effector neurons. Mutations in various genes involved in this pathway have been found to cause obesity.[21] The first non-syndromic obesity-associated gene has been determined to be the fat mass and obesity-associated gene (FTO).[22] The FTO has been reported to have an effect on fat mass and encode 2-oxoglutarate-dependent nucleic acid demethylase, which is involved in the regulation of the food intake.[23] Mutations in the LEPR gene, such as mutations in the leptin gene (LEP), have been seen to exhibit a similar phenotype.[24] The deficiency in the POMC protein causes the absence of the cleavage products of adrenocorticotropic hormone, α-MSH, and β-endorphins. Because of the dual role of α-MSH in appetite regulation and pigmentation, the outcome is red hair and severe obesity.[25] Some studies have attracted attention to the presence of heterozygous POMC mutations in people with obesity without adrenal insufficiency and other symptoms.[26,27] The MC4R has been known as a highly expressed receptor in the hypothalamus that directs the brain's appetite regulation.[28] A study demonstrated that binding of the MC4R with a-MSH, the high affinity ligand produced from POMC, inhibits nutrition.[29] Studies conducted on both dominant and recessive forms of the MC4R mutations have shown that these mutations are the most common cause of hereditary early-onset obesity.[30,31] Study on PC1/PC2 mutations have shown that its deficiency can cause severe early-onset obesity, as well as adrenal, gonadotropic, somatotropic, and thyrotropic-like deficiencies.[32] Deficiency of single-minded 1 (SIM1) expressed in the paraventricular nucleus of the hypothalamus, which is important in a transcription factor and is an appetite regulator, has been associated with obesity through food impulsivity.[33] Mutations in NTRK2/BDNF, thought to play a role in food intake and body weight regulation, have been identified to be among obesity genes.[34]

The literature on obesity genes suggests that obesity is a result of mutations in several genes in different pathways such as food intake, digestion, impulsivity, and inflammation.

OBESITY-RELATED INFLAMMATION

Although there are many molecular mechanisms in the pathophysiology of obesity, inflammation is a common factor underlying many obesity-related disorders. Obesity-related inflammation is primarily triggered by nutrients and localized in specialized metabolic tissues such as WAT, which is composed of adipocytes that act as the main energy source. Obesity contributes significantly to fat tissue inflammation by increasing the number and activation of macrophages in adipose tissue. Excessive nutrients lead to the activation of metabolic signaling pathways such as c-Jun N-terminal kinases (JNKs) and NF-γB. Activation of these pathways induces small amounts of inflammatory cytokines, resulting in a low-grade inflammatory response. It is known that obesity in rodents and humans increases adipose tissue expression and release of the inflammatory cytokine, tumor necrosis factor (TNF)-α. Deficiency of perilipin (PLIN) 1, a protein associated with lipid droplets that promote lipid formation and adipocyte lipolysis suppression, has been observed in obese individuals even though adipocytes are larger in these individuals.[35] Adipose tissue expression of many genes encoding inflammatory proteins, including interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1), nitric oxide synthase, matrix metalloproteinases, and lipocalin, is associated with adiposity.[12,13]

Nuclear factor kappa B is a complex transcription factor that includes inflammatory proteins such as TNF-α and MCP-1 in the site of action. Activation of TLRs, reactive oxygen species, ultraviolet radiation and proinflammatory cytokines leads to the inflammatory response and subsequent degradation of the inhibitory composition of NF-γB. Similar to its effects on NF-γB, obesity increased the activation of the JNK family in the liver, muscle, and adipose tissue. The JNKs consist of three structurally related serine/threonine kinases (JNK1, JNK2, JNK3), which are key elements of inflammation. They are known to be activated in response to inflammatory cytokines. Genetic studies have shown that JNK1 contributes to obesity-related phenotypes. Blocking JNK1 in mice has slowed the development of obesity in dietary and genetic obesity models. In addition, JNK1 deficiency has improved insulin resistance.[36-40] Studies suggest that a genetic variation close to insulin receptor substrate 1 (IRS1) may impair the ability of subcutaneous fat storage in humans, and this may cause adverse cardiometabolic consequences such as insulin resistance and dyslipidemia. Expression of growth factor receptor-bound protein 14 near IRS1 has been observed to be increased in genetically obese (ob/ob) mice.[41,42] In another study, researchers have produced a strain of mice lacking the PLIN2 gene, which produces a protein that regulates fat storage and metabolism.[43] The study concluded that the fat cells are 20% smaller than in typical mice and do not show the type of inflammation associated with obesity. Fatty liver disease, common in obese humans and rodents, was not seen in mice without the PLIN2 gene. Mice lacking the PANK2 gene had lower triglyceride levels, less inflammation in fat cells, and were more insulin sensitive. Researchers have shown that overexpression of the inducible 6-phosphofructo-2-kinase enzyme enhances fat accumulation but suppresses inflammatory responses and improves insulin sensitivity in both adipose and living tissues.[44] This result could present a useful genetic approach to future studies for obesity treatment. As a result of genetic studies, it was observed that calorie intake is increased in individuals with the minor/risk allele of the FTO locus that contains the coding region for the α-ketoglutarate-dependent dioxygenase enzyme, which is associated with the risk of obesity.[45,46] Similarly, variants near the MC4R have been associated with early-onset obesity due to defects in the appetite control pathway and satiety signals in the brain. As a result of the study of single nucleotide polymorphisms in the human genome, it was revealed that polymorphisms in inflammatory genes constitute 28% of obesity inheritance.[47-49]

OBESITY INFLAMMATION AND RIPK1 RELATIONSHIP

Interacting with receptors, RIPK1 is known as a regulator of autoinflammatory systems involved in the management of events related to cell death. Receptor-interacting

serine/threonine-protein kinase 1 has been found to act as an important regulator of inflammatory events in both normative and disease settings. It has been observed that RIPK1 has an important role in triggering cell death. In addition, RIPK1 regulates inflammatory signaling as well as supports the survival of the cell.[50] Recent studies suggest that genetic variation in or near the RIPK1 locus is linked to the expression of the encoded protein, and these mechanisms are associated with a risk of obesity in humans. In genetic studies conducted to better understand the mechanism of action on obesity, the strong relationship between the genetic variation on chromosome 16 in FTO and obesity has been partially revealed through its logical relationship with type 2 diabetes. Variants at the RIPK1 locus are associated with high expression of RIPK1 in human adipose tissue. Researchers have identified E4 promoter-binding protein 4 as a new transcriptional regulator of RIPK1. In mice, RIPK1 expression in adipose tissue has been associated with adiposity and glucose intolerance, and accordingly, RIPK1 inhibition has been shown to significantly reduce body weight and adipose tissue accumulation. This shows that a high RIPK1 level is a candidate to be a central factor of obesity. In obese individuals, the expression of RIPK1 is elevated in adipose tissue, and blocking RIPK1 in mice significantly reduced adiposity.[22,51,52] Until now, genome-wide association studies have identified many loci for adiposity-related traits, most of which include genes involved in appetite control (LEP, MCR4).[53] With this approach, several variants in inflammatory pathways were found to be associated with an increased risk of obesity at the genome level. Although this analysis suggests that inflammation is linked to a genetic risk of obesity, inflammatory single gene polymorphisms have less of an effect.[54] Given that inflammation is an unwanted consequence of obesity, it is seen as important whether these loci contribute to obesity directly or indirectly by other mechanisms. The possibility that variants at the RIPK1 locus relate to obesity by different pathways independent of inflammation has been stipulated (for example, the role of RIPK1 as a scaffold protein or in cell death). It is thought that BMI may also support obesity with non-inflammatory mechanisms that play a role in the inheritance.[51,55] There are limited studies showing that RIPK1 hyperactivation contributes to obesity and its related complications. Therefore, although it is too early to say that the inflammation associated with obesity is caused by RIPK1, an inflammation gene, it may be a potential candidate.

In conclusion, obesity is a complex disease that progresses like an epidemic in developed, developing and underdeveloped countries. It is more common in women between the ages of 2 and 18 and adults. Inflammation, which is in the pathophysiology of obesity defined by high BMI, is a factor that should not be ignored. Whether the inflammatory outcome associated with obesity is the cause or consequence of obesity, the genetic factors behind it were discussed in this review. The genetic mechanism associated with obesity and genes that cause obesity as a result of mutations in this mechanism such as LEP, LEPR, FTO, MC4R, POMC, SIM1 were mentioned. Studies on inflammatory markers and genetic mechanisms in obesity were compiled. The RIPK1 gene, one of the inflammation genes, was associated with obesity-related inflammation as it acts as the central node of the inflammatory pathway. Since there are limited studies in the literature on the relationship between RIPK1 and obesity, this relationship should be elucidated with further studies on the inflammatory response and other possible mechanisms such as cell death.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129(25 Suppl 2):S102-38.
2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766-81.

3. Skelton JA, Irby MB, Grzywacz JG, Miller G. Etiologies of obesity in children: Nature and nurture. Pediatr Clin North Am 2011;58:1333-54.
4. Skelton JA, DeMattia L, Miller L, Olivier M. Obesity and its therapy: From genes to community action. Pediatr Clin North Am 2006;53:777-94.
5. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. N Engl J Med 1990;322:1483-7.
6. Price RA, Gottesman II. Body fat in identical twins reared apart: Roles for genes and environment. Behav Genet 1991;21:1-7.
7. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860-7.
8. van der Heijden RA, Sheedfar F, Morrison MC, Hommelberg PP, Kor D, Kloosterhuis NJ, et al. High-fat diet induced obesity primes inflammation in adipose tissue prior to liver in C57BL/6j mice. Aging (Albany NY) 2015;7:256-68.
9. Vishvanath L, Gupta RK. Contribution of adipogenesis to healthy adipose tissue expansion in obesity. J Clin Invest 2019;129:4022-31.
10. Ju L, Han J, Zhang X, Deng Y, Yan H, Wang C, et al. Obesity-associated inflammation triggers an autophagy-lysosomal response in adipocytes and causes degradation of perilipin 1. Cell Death Dis 2019;10:121.
11. García-Barrado MJ, Iglesias-Osma MC, Pérez-García E, Carrero S, Blanco EJ, Carretero-Hernández M, et al. Role of flavonoids in the interactions among obesity, inflammation, and autophagy. Pharmaceuticals (Basel) 2020;13:342.
12. Ferrante AW Jr. Obesity-induced inflammation: A metabolic dialogue in the language of inflammation. J Intern Med 2007;262:408-14.
13. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415-45.
14. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature 2017;542:177-85.
15. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med 2011;17:179-88.
16. Pennington AW. A reorientation on obesity. N Engl J Med 1953;248:959-64.
17. Silventoinen K, Rokholm B, Kaprio J, Sørensen TI. The genetic and environmental influences on childhood obesity: A systematic review of twin and adoption studies. Int J Obes (Lond) 2010;34:29-40.
18. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature 2006;443:289-95.
19. Millington GW, Tung YC, Hewson AK, O'Rahilly S, Dickson SL. Differential effects of alpha-, beta- and gamma(2)-melanocyte-stimulating hormones on hypothalamic neuronal activation and feeding in the fasted rat. Neuroscience 2001;108:437-45.
20. Harrold JA, Williams G. Melanocortin-4 receptors, beta-MSH and leptin: Key elements in the satiety pathway. Peptides 2006;27:365-71.
21. Thaker VV. Genetic and epigenetic causes of obesity. Adolesc Med State Art Rev 2017;28:379-405.
22. 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.
23. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science 2007;318:1469-72.
24. 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.
25. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19:155-7.
26. Lee YS, Challis BG, Thompson DA, Yeo GS, Keogh JM, Madonna ME, et al. A POMC variant implicates beta-melanocyte-stimulating hormone in the control of human energy balance. Cell Metab 2006;3:135-40.
27. Challis BG, Pritchard LE, Creemers JW, Delplanque J, Keogh JM, Luan J, et al. A missense mutation disrupting a dibasic prohormone processing site in pro-opiomelanocortin (POMC) increases susceptibility to early-onset obesity through a novel molecular mechanism. Hum Mol Genet 2002;11:1997-2004.
28. Mountjoy KG, Wong J. Obesity, diabetes and functions for proopiomelanocortin-derived peptides. Mol Cell Endocrinol 1997;128:171-7.
29. Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature 1997;385:165-8.
30. Farooqi IS, Yeo GS, Keogh JM, Aminian S, Jebb SA, Butler G, et al. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest 2000;106:271-9.
31. Hinney A, Schmidt A, Nottebom K, Heibült O, Becker I, Ziegler A, et al. Several mutations in the melanocortin-4 receptor gene including a nonsense and a frameshift mutation associated with dominantly inherited obesity in humans. J Clin Endocrinol Metab 1999;84:1483-6.
32. O'Rahilly S, Gray H, Humphreys PJ, Krook A, Polonsky KS, White A, et al. Brief report: Impaired processing of prohormones associated with abnormalities of glucose homeostasis and adrenal function. N Engl J Med 1995;333:1386-90.
33. Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. Hum Mol Genet 2000;9:101-8.

34. Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, et al. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. Nat Neurosci 2004;7:1187-9.
35. Wang Y, Sullivan S, Trujillo M, Lee MJ, Schneider SH, Brolin RE, et al. Perilipin expression in human adipose tissues: Effects of severe obesity, gender, and depot. Obes Res 2003;11:930-6.
36. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature 1997;388:394-7.
37. Devary Y, Rosette C, DiDonato JA, Karin M. NF-kappa B activation by ultraviolet light not dependent on a nuclear signal. Science 1993;261:1442-5.
38. Israël A, Le Bail O, Hatat D, Piette J, Kieran M, Logeat F, et al. TNF stimulates expression of mouse MHC class I genes by inducing an NF kappa B-like enhancer binding activity which displaces constitutive factors. EMBO J 1989;8:3793-800.
39. Schneider A, Martin-Villalba A, Weih F, Vogel J, Wirth T, Schwaninger M. NF-kappaB is activated and promotes cell death in focal cerebral ischemia. Nat Med 1999;5:554-9.
40. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. Nature 2002;420:333-6.
41. Cariou B, Capitaine N, Le Marcis V, Vega N, Bériziat V, Kergoat M, et al. Increased adipose tissue expression of Grb14 in several models of insulin resistance. FASEB J 2004;18:965-7.
42. Kilpeläinen TO, Zillikens MC, Stančáková 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.
43. McManaman JL, Bales ES, Orlicky DJ, Jackman M, MacLean PS, Cain S, et al. Perilipin-2-null mice are protected against diet-induced obesity, adipose inflammation, and fatty liver disease. J Lipid Res 2013;54:1346-59.
44. Huo Y, Guo X, Li H, Xu H, Halim V, Zhang W, et al. Targeted overexpression of inducible 6-phosphofructo-2-kinase in adipose tissue increases fat deposition but protects against diet-induced insulin resistance and inflammatory responses. J Biol Chem 2012;287:21492-500.
45. Speakman JR, Rance KA, Johnstone AM. Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. Obesity (Silver Spring) 2008;16:1961-5.
46. Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gómez-Marín C, et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature 2014;507:371-5.
47. Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008;40:768-75.
48. Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 2009;41:18-24.
49. Nikpay M, Turner AW, McPherson R. Partitioning the pleiotropy between coronary artery disease and body mass index reveals the importance of low frequency variants and central nervous system-specific functional elements. Circ Genom Precis Med 2018;11:e002050.
50. Mifflin L, Ofengeim D, Yuan J. Receptor-interacting protein kinase 1 (RIPK1) as a therapeutic target. Nat Rev Drug Discov 2020;19:553-71.
51. Karunakaran D, Turner AW, Duchez AC, Soubeyrand S, Rasheed A, Smyth D, et al. RIPK1 gene variants associate with obesity in humans and can be therapeutically silenced to reduce obesity in mice. Nat Metab 2020;2:1113-25.
52. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661-78.
53. van der Klaauw AA, Farooqi IS. The hunger genes: Pathways to obesity. Cell 2015;161:119-32.
54. Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, et al. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. Nat Genet 2017;49:1458-67.
55. Welsh P, Polisecki E, Robertson M, Jahn S, Buckley BM, de Craen AJ, et al. Unraveling the directional link between adiposity and inflammation: A bidirectional Mendelian randomization approach. J Clin Endocrinol Metab 2010;95:93-9.