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Obesity and the role of genetic polymorphism: A review of genes as the risk of obesity

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ABSTRACT

Obesity can be caused by environmental factors, which are higher energy input or lower energy expenditure. Environmental factors supported by genetic factors cause a person to have a different risk for developing obesity from to another. Genetics factors cause obesity through several pathways, which are impaired regulation in the hypothalamus and the regulation of energy expenditure. Obesity may be caused by one gene as monogenic-associated obesity, however, commonly caused by several genes together with environmental factors as the main multi-factorial risk of obesity. Obesity causes inflammation which leads to metabolic diseases. Many efforts are performed to prevent or treat obesity through the intervention to environmental and or genetic factors. Many attempts to reduce the prevalence of obesity were performed by influencing the environmental risk factors or the genetic risk factors. The genetic risks of obesity may be different from one to another country or between ethnic groups. In this review, we identified the main genes which influence obesity. Therefore, a better treatment approach should consider the differences role of genes in obesity rather than only changes in lifestyle. Nutrigenetic approach by considering the difference role of genes in responding to nutrients or drugs is recommended in individualized treatment plans.

ABSTRAK

Obesitas dapat disebabkan faktor lingkungan, yaitu masukan energi yang tinggi atau pengeluaran energi yang rendah. Faktor lingkungan yang didukung faktor genetik menyebabkan seseorang memiliki risiko obesitas yang berbeda antara satu orang dengan orang lain. Gena mempengaruhi terjadinya obesitas melalui beberapa jalur, yaitu terganggunya regulasi dalam hipotalamus dan pengaturan pengeluaran energi. Obesitas mungkin disebabkan oleh gena tunggal, tetapi umumnya beberapa gena bersama faktor lingkungan sebagai penyebab obesitas. Obesitas menyebabkan peradangan yang dikaitkan dengan timbulnya penyakit metabolik. Berbagai usaha dilakukan untuk mencegah atau mengobati obesitas dengan mempengaruhi faktor lingkungan atau genetik. Banyak upaya untuk menurunkan prevalensi obesitas dilakukan dengan mempengaruhi risiko faktor lingkungan dan genetik. Risiko genetik obesitas mungkin berbeda di satu antar negara atau antar kelompok etnik. Oleh karena itu, pendekatan pengobatan yang lebih baik harus mempertimbangkan perbedaan peran gena dalam obisetas daripada hanya perubahan gaya hidup. Pendekatan nutrigenomik dengan mempertimbangkan perbedaan peran gena dalam merespon nutrien atau obat disarankan dalam perencanaan pengobatan secara individu.

Keywords:
energy expenditure;
genetic;
nutrigenetic;
obesity;
polymorphism

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INTRODUCTION

Obesity is defined as abnormal or excessive fat accumulation that may impair health. The main cause of obesity is excess energy intake with long-term and low-calorie use. Obesity increases the risk of metabolic diseases such as type 2 diabetes mellitus, dyslipidemia, hypertension, musculoskeletal disease, and various types of cancer. Since 1975, the prevalence of obesity is increasing worldwide. A rapid increase in obesity is recorded in South East Asia, including in Indonesia.[1]

Obesity is caused by the environment and genetic factors. Some individuals are more susceptible to becoming obese than others even in the same environments. When the population is in the same condition as an obesogenic environment, there are obese and normal-weight persons. This means that some individuals are more susceptible to becoming obese than others. These differences are influenced by the genetic variation in individuals. Over the past two decades and with the development of molecular technology, some studies have proven that several genes are associated with obesity. More than a hundred loci related to the polygenic of obesity in these genes have been identified.[2]

Based on genetic criteria, the causes of obesity are classified into monogenic, syndromic, and polygenic. Monogenic obesity is caused by a single gene mutation that affects increased input of food and reduces energy use.[3] This is related to polymorphism or variation in genes associated with the hypothalamic system in the control of energy balance, which includes the leptin-melanocortin system. The result of this mutation leads to changes in the activity of hormones, enzymes, and receptors, which causes hyperphagia with the onset of obesity. Sometimes, these mutations are also correlated with endocrine abnormalities. Some mutation genes correlated with monogenic obesity are *LEP* (leptin), *LEPR* (leptin receptor), *POMC* (pro-opiomelanocortin), *MC4R* (melanocortin-4-receptor), and *PCSK1* (preprotein convertase subtilisin/kexin type 1).[4]

Obesity as a syndrome is caused by a group of genes. Usually, this condition happens in obese patients with cognitive delays, hyperphagia, hypothalamic dysfunction, and organ abnormalities. Obesity is associated with intellectual disorders, dysmorphic disorders, organ-specific abnormalities, and hypothalamic disorders. Some examples of related syndromes are Prader-Willi, Bardet-Biedl, Cohen, Alstrom, and X-fragile syndrome.[5]

Polygenic obesity is found in 95% of cases of obesity and many related genes cause this type of obesity while they are also influenced by environmental factors such as the obesogenic environment. Certain individuals can be susceptible to variations in obesity-causing genes through various pathways: i) appetite control (NPY, POMC, MC4R, etc.), ii) energy expenditure (uncoupling protein/UCP), or iii) inflammatory (adiponectin/ADIPOQ, tumor necrosis factor-α/TNFα, interleukon-6/IL6, Resistin/RETN, etc.).[5]

This review outlines some of the genetic factors that play a role in the occurrence of obesity through appetite control by the hypothalamic system, energy expenditure, and inflammation compared with other studies.

DISCUSSION

Genes associated with energy and appetite regulation in the hypothalamus

Obesity occurs due to a disorder in the regulation of energy metabolism. The central nervous system (CNS) plays an important key in controlling energy homeostasis, and the hypothalamus has a role in integrating and regulating

the entire balance of the body. The hypothalamus is the part of the brain involved in the main controls of the intake of food and energy expenditure. In particular, the arcuate nucleus (ARC) located near the median eminence (ME) in the hypothalamus is essential in regulating metabolism. This ME organ facilitates the transport of peripheral hormones and nutritional signals by the ARC nerve. Thus, the ARC integrates hormonal metabolic signals and nutrients from peripheral circulation.[6]

There are two different types of functional antagonist neurons in ARC, which are orexigenic (appetite-stimulating) neuropeptide Y (NPY) and agouti-related protein-neuropeptide Y (AgRP/NPY) and the anorexigenic pro-opiomelanocortin (POMC). Neuropeptide Y is an appetite stimulator that directly sends signals to the PVN (paraventricular nucleus) to increase appetite and adiposity in humans. AgRP (agouti-related protein) is an appetite-stimulating neurotransmitter that involves the antagonists MC3R (melanocortin-3-receptor) and MC4R (melanocortin-4-receptor) in the hypothalamus. Pro-opiomelanocortin is an appetite-inhibiting molecule that produces α, β, γ-MSH (melanocyte-stimulating hormone) and plays a role through MC4R and MC3R.[7]

When nutrients are enough, POMC undergoes hydrolysis into α-MSH to activate MC3R and MC4R and provide satiety. A disorder in MC4R causes the failure to give an appropriate response to the full condition which causes obesity due to hyperphagia.[6]

Pro-opiomelanocortin

The melanocortin system of the central nerve is an important point to control nutritional conditions, controlling appetite, and metabolic response. Some research shows the molecular pathways of melanocortin as central control of energy homeostasis and appetite to maintain body weight. Melanocortin is highly expressed in the pituitary and ARC in the hypothalamus and released into the blood circulation through the sympathetic nervous system. Melanocortin signal pathways are regulated in two ways i.e. leptin related signals and G protein-couple receptor-related signals.

Leptin-related signals

In this signaling pathway, leptin is produced by white adipose tissue (WAT) and after passing through the blood-brain barrier it will be bound to specific leptin receptors in the hypothalamus. Leptin, through two groups of neurons POMC/CART (Cocaine and amphetamine-regulated transcripts) and NPY/AgRP, increases POMC/CART and produces α, β, γ-MSH in post-translation, which inhibits NPY/AgRP.

G protein-coupled receptor (GPCR)-related signals

At this signal, POMC peptides are activated by cAMP when it is bound to the G-proteins in MCR. In cell membranes, MCR is activated by ligand bonds resulting in changes in the conformation and translating of extracellular signals into biological responses. The MCR joins the Gs family of G-proteins and stimulates the cAMP/ERK1/2 path. The Gs family forwards the signal from the MCR to adenylate cyclase converts ATP into cAMP to activate PKA which will involve the phosphorylated CREB family. This phosphorylated CREB will induce or inhibit the expression of genes containing CRE sequences (cAMP-responsive elements) in the promoter. The Gs subunit complex will modulate the ERK 1/2 path. This modulation facilitates the different biological functions of MCR[7]. Energy homeostasis involves chemical and neuronal signals

in the human body to maintain the amount of energy expenses and regulate the input of energy through the sensation of hunger. MC3R and MC4R peptides and molecular signals of the central melanocortin pathway regulate energy balance and homeostasis by activating or inhibiting leptin and its receptors by MC3R and MC4R in the hypothalamus.

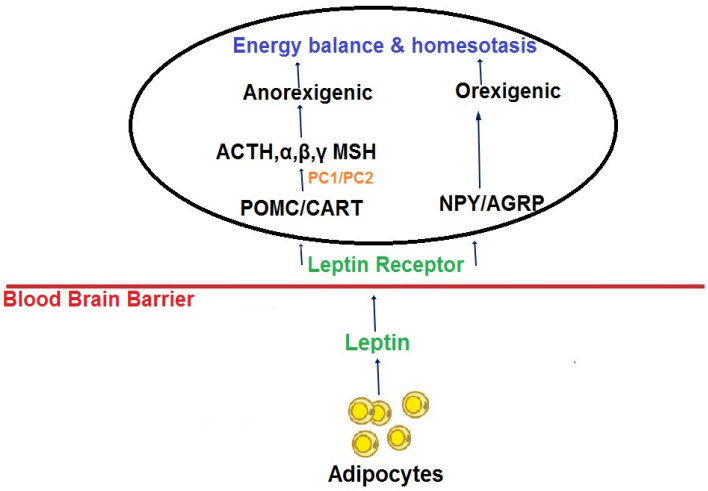

FIGURE 1. Energy balance and homeostasis are regulated by POMC/CART and NPY/AGRP influenced by leptin via leptin receptor (Modified from Singh *et al.*[7]).

Adipocytes secrete leptin polypeptides which pass through the blood vessels of the brain and are bound to specific receptors on two parts of neurons in the hypothalamus ARC. The first part of the neuron is NPY/AgRP with an appetite-enhancing effect as orexigenic, which can be inhibited by leptin receptors. The second is an appetite-lowering POMC/CART neuron as anorexigenic, which can be enhanced by leptin receptors. In this mechanism, POMC/CART by the influence of prohormone convertase 1 and 2 (PC 1 and PC2), is converted into ACTH, and subsequently converted into α-, β-, and γ-MSH. These results can activate the signal to the MCR 1-5 family, which plays an important role in the regulation of energy balance and its homeostasis (FIGURE 1).[7]

POMC is an appetite-suppressing gene, which produces α-, β-, γ-MSH, and ACTH through MC3R and MC4R. As a result of acute POMC and ACTH deficiency in the adrenal cortex, the deficit causes childhood obesity from birth. Research in children with POMC gene mutations led to the occurrence of ACTH disorders with characteristics such as growth delay, mild hypothyroidism, reddish hair, and pale skin as a sign of α-MSH deficiency. In Pakistan, it was found Arg236Gly mutations in the POMC gene affected heterozygous obese subjects by 0.4%.[8] Research in children carrying the Tyr221Cys variant that encodes β-MSH causes impaired MC4R activation thus leading to hyperphagia and obesity conditions.[9] Polymorphism of POMC (C8246T) genes correlated with leptin levels in obese people of the Javanese population in Indonesia, carriers of CC and TC genotypes had higher leptin levels.[10] This result is in accordance with other studies [11-14] but in Caucasian females, this polymorphism is not significantly different[15].

MC3R genetic mutation

This gene has one exon located on

chromosome 20 (20q.13.2-q13.3). MC3R also plays a role as an anti-inflammatory response. There are 15 missense mutations out of 18 mutations reported in the MC3R gene. Mutations in the MC3R gene are associated with obesity in humans. Research in Singapore found 183I/N, 69S/C, 70A/T, 87I/T, 134M/I, 249L/V, 260A/V, 280T/S, 275M/T and 297L/V polymorphisms. There are also reports of 33I/S variants being identified in obese subjects in the USA, Italy, and Poland. Other studies have also shown Thr280Ser mutations that can decrease gene expression resulting in ligand bond failure and intracellular cAMP signal failure.[7,16]

MC4R genetic polymorphism

MC4R is the major MCR in melanocortin pathways. It is also a family of G-protein coupled receptors(GPCR) with seven transmembrane domains expressed in the hypothalamus, brain, muscles, adipocytes, and astrocytes. Single nucleotide polymorphisms (SNP) mutations that occur near the MC4R genes are associated with obesity. The SNP rs1778231 and rs129070134 are reportedly linked to obesity in Europe and India. MC4R mutations are more common in northern Europe compared to Asia. The polymorphism of Val103Ile is associated with abdominal obesity with a minor allele frequency (MAF) of 2-4% in heterozygous (103Val/Ile) compared with homozygous (103Val/Val).[11] There are 376 single-nucleotide variants (SNVs) in the MC4R gene area. These mutations cause failure in ligand bonds and affect the gene expression.[12]

Pro-convertase/ectonucleotide pyrophosphatase pyrodiesterase (PC1/ ENPP1)

PC1/ENPP1 enzyme is an endoprotease serine enzyme that depends on calcium (calcium-dependent serine) which causes the maturation of several nucleotides. In mammals, this PC family consists of several members: PC1/3 (PCSK1)-PCSK9. PC1, and PC3 are widely expressed in neuroendocrine cells, and this enzyme breaks down prohormone and proneuropeptides in secretory granules. It is found with 14 exons and 13 introns in the PCSK1 gene located on chromosome 5 in humans.[17]

PC1/ENPP1 is an enzyme encoded by the PCSK 1 gene that breaks down POMC. Mutations in the PCSK 1 are correlated with obesity, impaired glucose tolerance, low plasma cortisol levels, and hypogonadotropic hypogonadism. This mutation also increased concentrations of proinsulin and POMC in plasma, but plasma insulin concentrations remained at very low levels.[18] Other studies have suggested that there is a positive correlation between PCSK1 deficiency and obesity. In European populations, the prevalence of PCSK1 deficiency as a heterozygous carrier was 0.83% of the population. Other studies have also mentioned that the heterozygous variant PCSK1 is associated with obesity and impaired glucose metabolism in children.[19] Polymorphism of PC-1 K121Q (G > T) (rs10444981) gene had higher leptin levels in GG genotype of the obese group compared to the control group in the Javanese population of Indonesia.[10] This variation of genotype is a risk factor for T2DM in Indonesia[20] and this result is in line with other studies[21-23], but some research found this gene variation was not a significant risk factor for obesity and T2DM[15,24-26].

Leptin

Leptin is an adipokine with the function as a regulator of appetite through its action in the hypothalamus through POMC, AgRP, and MC4R. A homozygous leptin mutation causes leptin deficiency causes hunger and rapid weight gain. Patients with heterozygous

leptin mutations showed low leptin levels and increased weight gain. Mutations in the leptin receptor gene (LEPR) can also cause monogenic obesity which can be treated with the administration of MC4R agonist drugs[26]. Leptin is produced mainly by white adipose tissue (WAT) cells. Biosynthesis and secretion of leptin depend on the amount of WAT and the status of energy storage. Leptin is also known as a hormone that provides satiety. Leptin as an active protein secreted into circulation will be transported to the brain through its receptors in the hypothalamus causing decreasing expression of genes encoded NPY, POMC, and corticoliberin (CRH) with decreased appetite and reduced consumption of food that decrease body weight and increase energy use. Leptin is a factor that protects against hunger and obesity. Leptin may also increase insulin sensitivity in peripheral tissues and increase glucose uptake and oxidation in skeletal muscles. Leptin also has thermogenesis action through the regulation of mitochondrial proteins in brown adipose tissue (BAT).[27]

Leptin and leptin receptors can regulate fat catabolism and energy intake. In the ARC in the hypothalamus, leptin is bound to its receptors and inhibits the NPY/AgRP pathway increasing appetite (orexigenic) and activating the POMC/CART pathway, which decreases appetite (anorexigenic). Leptin deficiency in humans can occur due to frame-shift mutations in the homozygous gene (deletion G133) and result in shorter protein molecules with impaired function.[7] A study showed that two leptin receptor gene polymorphisms in rs1137100 (109K/R) and rs1137101 (223Q/R) were found higher in body weight, waist circumference, and leptin levels in the obesity group than in the control. The frequency of 103R/R homozygous in the obesity group was higher than in the control, while 223Q/R polymorphism was associated with obesity and leptin levels[28] in the Western and Eastern of Indonesia.[29] Additionally, this polymorphism was correlated with metabolic syndrome in the Chinese population[30] and hypertension,[31-32] but this polymorphism was not found to be a risk factor for metabolic syndrome and obesity,[33] in Turkish children nor hypertension in Chinese populations.[34] A summary of mutations of genes that cause obesity through regulation in the hypothalamus is presented in TABLE 1.

TABLE 1. Effect of mutation genes causes obesity in energy balance through the hypothalamus

Genes	Effect of mutation	Some mutations found	References
NPY	Changes in the signal sequence, affect the signal of energy balance, and inhibit lipolysis	rs17149106 (G>T), rs16147 (C>T), rs16139 (T>C), rs5574 (C>T	11,12,13
POMC	Impaired MC4R activation and loss of melanocortin signaling in melanocortin receptor and leptin-melanocortin pathway	Arg236Gly Tyr221Cys C8246T	8,10, 14, 15
MC3/3R	Decreased expression, failure in ligand bond, intracellular cAMP signal failure	183I/N, 69S/C, 70A/T, 87I/T, 134M/I, 249L/V, 260A/V, 280T/S, 275M/T and 297L/V, 33I/S, Thr280Ser	7, 16, 17
MC4/MC4RR	Failure in ligand bonds and affect the expression	rs1778231, rs129070134 Val103Ile	9
Leptin/receptor leptin	Disturbance of the leptin signal causes increases food intake, positive energy balance, and the accumulation of fat.	Lys109Arg, Gln223Arg G133 del	28-34
PC1	Failure in the processing of POMC to some peptides	K121Q (G > T) (rs10444981)	10, 15, 20-26

Genes related to energy expenditure

There are two types of adipose tissue in mammals i.e. white adipose tissue (WAT) and brown adipose tissue (BAT). WAT plays a role in energy homeostasis in the body by storing excess energy as triglycerides and releasing free fatty acids (FFAs) when the energy is needed. BAT specifically regulates energy consumption to give heat production in response to maintaining body temperature. BAT plays an important role in regulating energy balance.[35] Obesity-related genes in maintaining energy expenditure include uncoupling proteins (UCP1, UCP 2, and UCP 3) and adrenoceptor-β (ADRB1, ADRB 2, and ADRB 3).

Uncoupling protein (UCP)

Uncoupling proteins (UCPs) are a group of mitochondrial proteins contained in mitochondrial membranes that serve to transport protons to the mitochondrial matrix. Mitochondrial respiration releases the extrusion of protons (H^+) out of the mitochondria into the intermembrane of mitochondrial, producing potential redox and encouraging ATP synthase. UCP pumps protons from the intermembrane to the mitochondrial matrix and removes proton gradients while reducing ATP production and superoxide production.[36]

UCP1 has been extensively studied and is mostly found in brown adipocyte mitochondria. A total of 8% of UCP1 are found in mitochondrial proteins. UCP1 is characterized as an important transporter for mitochondrial membranes. A Cold environment, increased thyroid hormones, norepinephrine, and stimulation of adrenergic and cAMP may increase UCP1 gene expression. UCP1 plays a role in the regulation of energy consumption, thermogenesis, and reactive oxygen species (ROS). The mechanism is associated with the pathogenesis of type 2 diabetes mellitus and obesity. UCP2 and UCP3 are homologous of UCP1. UCP2 is found in mitochondria of adipose tissue, skeletal muscle, kidneys, liver, lungs, and macrophages. Meanwhile, UCP3 is found in many skeletal muscles. UCP 4 and UCP5 are found commonly in the nerves of the central nervous system (CNS).[36]

Mutations in the UCP genes cause decreased energy consumption and increased risk of weight gain and are associated with metabolic diseases. The UCP1 gene is present on chromosome 4 in q31.1, which consists of 6 exons with 9-kb length. Some studies found SNPs in the noncoding region of the UCP1 gene, such as A3826G (rs1800592), A1766G(rs3811791), and A112C (rs10011540), and coding region Ala64Thr (rs45539933) and Met229Leu (rs2270565). SNP A>G's position at -3826 bp (rs1800592) of 5' noncoding gene is found in Canada with G allele and is associated with increased body weight, and increased risk of diseases correlated with obesity. In another study in Australia, allele G was associated with an increase in body weight and high blood glucose concentrations in women. Another study on women in India found that the GG genotype is linked to obesity and increased blood pressure. Research in Italy found that the G allele is associated with decreased insulin sensitivity in the obese group.

Another mutation is substitution A in G in the -1766 (rs3811791) nucleotide of the *UCP1* gene. The allele variant -1766G is associated with severe obesity with waist-hip ratio, body fat percentage, and increased amount of abdominal fat parameters. Studies in Korea found that the carriers of the haplotype polymorphisms A3826G and A1766G have a high percentage of body fat. Another polymorphism at A112C in the UCP1 gene involving the allele C showed decreases in the promoter activity of the UCP1 gene, which were correlated

with insulin response and associated with insulin resistance in patients with T2DM.[37]

UCP2 is highly expressed in skeletal muscle and adipose tissue, involved in energy regulation in the metabolism of lipids. DNA sequencing found there is a substitution of alanine by valine in exon 4 and insertion/deletion 45 bp 3'UTR in exon 8 of UCP2 gene. This polymorphism contributes to the variation in metabolic rate and adiposity in adipose tissue. There is a correlation between UCP2 mRNA in adipose tissue and body weight in humans, in which the UCP2 overexpression is correlated with obesity.[7] Polymorphism of 55A/V occurs in exon 4 UCP2 where substitution C by T nucleotide causes alanine substitution for valine at position 55 amino acid sequence of the UCP2. Some studies found carriers of V/V genotype have a higher risk of type 2 diabetes mellitus and obesity compared with carriers of A/V and A/A genotype. Insertion/deletion of 45 bp at 3'UTR of exon 8 of UCP2 and downstream polymorphism of 158 bp of stop codon increases the risk of obesity. In Indonesia, polymorphism of 55A/V UCP2 genotype in the male group showed that V/V genotype and V allele significantly lower the risk of obesity. Insertion/deletion of 45 bp UCP2 gene in the male group showed that insertion/insertion genotype and insertion allele significantly increase the risk of obesity whereas for females it showed that the insertion/deletion genotype and insertion allele lowered the risk of obesity.[38] The increase of UCP2 expression involves decrease of ATP synthesis lead to decrease of insulin secretion and increase risk of T2DM. G allele polymorphism of G866A is associated with decreased mRNA expression, increased body weight, body fat mass, and risk of height/ body weight. Allele -866A is associated with obesity and high insulin level in the Indian people. In Indonesia, variations of UCP2 (Ala55Val and I/D45 bp) are risk factors for obesity with different stratification of gender.[39] In some populations, this polymorphism is considered as a risk factor for obesity,[40-43] risk of diabetes,[44,45] and chronic kidney disease.[46] However, in Italian[47] and French populations[48] this polymorphism is not found to be a risk factor for obesity.

UCP3 gene polymorphism, i.e. substitution of nucleotide C/T at position 55 occurs in the promoter and near the TATA box. The SNP's in this location has an effect on the transcription of the UCP3 gene and influences the expression of UCP3 mRNA in skeletal muscles which is correlated with metabolic function. One study found that body weight increased in someone carrying 55T allele in Scandinavia.[37]

β2-adrenergic receptors

β-adrenergic receptors are a family of GPCR and catecholamine targets, specifically epinephrine through the sympathetic nervous system (SNS). β-adrenergic receptors play an important role in the risk of excess body weight and are associated with the regulation of inflammatory cytokines. These receptors consist of three classes: β1, β2, and β3-adrenergic receptors (ADRB1, ADRB2, ADRB 3). Molecular signals that occur in the body can trigger activation of β-adrenergic receptors such as β-adrenergic receptors following the PKA/c-AMP pathway through activation in the SNS. Epinephrine stimulates ADRB and then activates the Gs family, especially Gα. Furthermore, Gα binds adenylate cyclase enzyme to catalyze the conversion of ATP into cAMP. After that, cAMP will activate cAMP-dependent kinase which will stop the epinephrine action. This pathway will eventually regulate energy expenditure and lipolysis.[3]

There is evidence that ADRB receptors participate in human weight regulation and some gene polymorphisms in ADRB

receptors affect metabolic complications and increase weight. The ADRB2 gene is located on chromosome 5q31-32 and consists of 2 kb DNA length. ADRB2 gene encodes proteins with a length of 413 amino acids. ADRB2 is found in fat cells, blood vessels, heart, and respiratory tract. These receptors are responsible for stimulating lipolysis activity in adipose tissue and controlling the smooth muscles. The ADRB2 gene includes some polymorphisms in the population. Around 80 polymorphisms have been identified, and some are in SNPs that occur in the 5'-untranslated region (UTR) associated with obesity. The SNPs of 34V/M, 16R/G 27Q/E, and 16T/I. Of the two SNPs, 16R/G and 27Q/E have a minor allele frequency (MAF) of 40-50%, 16T/I with MAF of 1-3%, and the 34V/M with MAF of less than 1%.[49]

Variation in the ADRB2 gene is identified as cause increased body weight and lipid metabolism disorders in females in codon 27 (27Q/E). 27E alleles are associated with increased body weight, subcutaneous fat, and increased levels of leptin and triglycerides in males, while women are associated with increased body weight, body fat mass, and waist-hip ratio.[7] 16R/G polymorphism (rs1042713) and 27Q/E (rs1042714) in the ADRB2 gene are associated with the risk of weight gain, high blood pressure, metabolic syndrome, and asthma. Polymorphism is also often associated with changes in the activity of the SNS and results in lipolysis, metabolic and cardiovascular regulation. There is some correlation between asthma in 16R alleles and 27E alleles in obese individuals in Javanese populations.[50] Polymorphisms of 16R/G shows that carriers of R/G genotype had decreased risk of obesity compared to the R/R genotype. Q/E genotype of 27Q/E increases the risk of obesity. Q/Q and Q/E genotypes had significant differences for plasma insulin in the obese group. The combination of 16R/G and 27Q/E genotypes decreased the risk of obesity compared to 16R/R + 27E/E.[51] This result is in accordance with studies in white[52] and Korean population.[53] However, Kawamura *et al.*[52] reported that polymorphism of ADRB 2 is not a risk factor for obesity in the Japanese-American population. A detailed summary of polymorphisms of the UCP1, 2, 3 and ADRB genes is presented in TABLE 2

TABLE 2. Effect of mutation genes that cause obesity to influence energy expenditure

Genes	Effect of mutation	Some mutation found	Reference
UCP1/3	Decrease UCP protein expression and lower energy expenditure	A3826G, A-1766G, A112C, Ala64Thr, Met229Leu, C55T	37
UCP2	Decrease UCP protein expression and lower energy expenditure	Ala55Val, I/D 45 bp	39-48
β-adrenergic/ receptor	Regulate energy by stimulating lipolysis and thermogenesis through activation of catecholamine induction from adenylate cyclase through the G protein overexpression of adiponectin adipocytes it caused an increase in adipogenesis and lipid storage	34V/M, 16R/G 27Q/E, 16T/I +276G > T	51-54

Genes association of obesity and inflammation

Inflammation is the body's defense mechanism. Obesity is a chronic low-level inflammatory condition. This inflammation is different from general inflammation because there are no signs of inflammation, but it has similarities because this disorder is caused by inflammatory signaling pathways. Obesity that is associated with inflammation is caused by increased adipose tissue, increased production of adipocytokines, and causes inflammation associated with certain pathophysiological processes.

The inflammatory process happens if blood cells (neutrophils, eosinophils, monocytes, and lymphocytes) enter adipose tissue. An increase in the number of adipocyte cells that occurs in obesity leads to an increase in the number of pro-inflammatory molecules such as adipokine/chemokine. Increases of these molecules have an effect on the endothelium to increase the production of intercellular adhesion molecule (ICAM) and vascular adhesion molecules (VCAM**),** polymorphonuclear and mononuclear phagocytes out into the extravascular compartment. Adipocytokines include leptin, which activates endothelial cells and causes the accumulation of macrophages in adipose tissue, will releasing pro-inflammatory molecules. Other adipocytokines, such as resistin induce the expression of adhesion molecules (VCAM-1 and ICAM-1) in endothelial cells and increase the synthesis and secretion of inflammatory cytokines such as TNF-α, and IL-6. and IL-12. In the inflammatory process, macrophages in adipose tissue will release chemoattractants for macrophages, resulting in chronic inflammation. The accumulation of macrophages in adipose tissue plays an important role in the increase of inflammatory mediators (IL-8, IL-6, IL-1, and TNF-α) causes oxidative stress, hypoxia, and lipolysis in the adipose continuing in increasing the production of adipositokin.[55] Some of the genes associated with inflammation and obesity are shown in FIGURE 2.

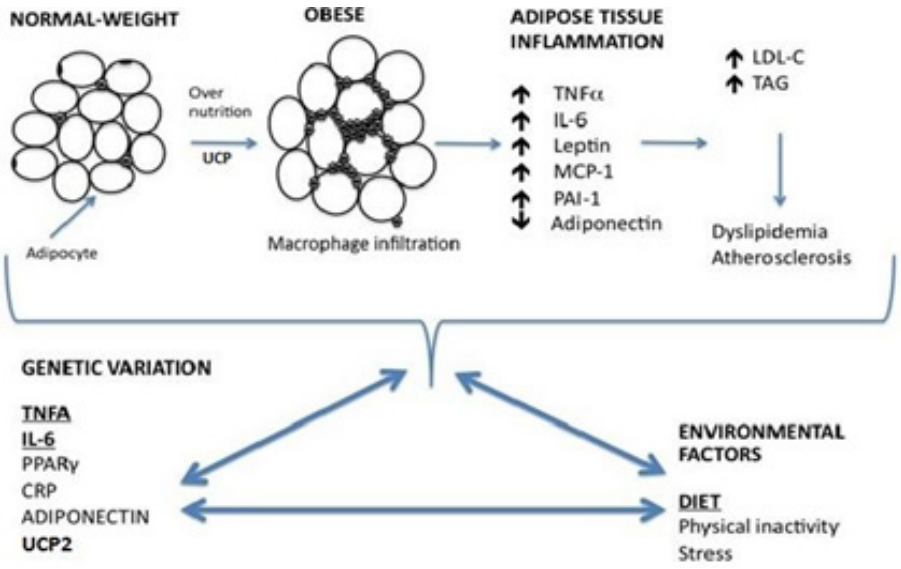

FIGURE 2. Obesity causes an increase in inflammation and is influenced by variations of genes and environment factors.

Adiponectin

Adiponectin is a 28 KDa protein consisting of 244 amino acids with a role as an anti-inflammatory cytokine.[56] Adiponectin is secreted by various types of cells including adipocyte and endothelial cells. The anti-inflammatory effects of adiponectin are mediated by two adiponectin receptors (AdipoR1 and AdipoR2). The binding of adiponectin to its receptors will activate several signals such as IRS-1/2, AMPK, and MAPK p38. Activation of IRS-1/2 by adiponectin signals is involved in the sensitization of insulin. In the liver, adiponectin activates glucose transporters and inhibits gluconeogenesis through AMPK, stimulating catabolism of lipids and lowering inflammation through the PPARα pathway. Adiponectin is also found to modulate eating behavior and energy expenditure during fasting through central effects. Adiponectin levels are inversely proportional to obesity, insulin sensitivity, type 2 DM, and metabolic syndrome.[57]

Adiponectin levels in the blood are lower in obese individuals compared to normal weight. There is a gene that encodes adiponectin located on the third chromosome (3q27) close to the locus responsible for the presence of type 2 DM and obesity. Some research on obese subjects found SNP in the adiponectin gene. There is a genetic variation of about 30-70% that affects plasma adiponectin levels. One of the SNP's adiponectin genes is +45T>G (rs2241766) on exon 2 which does not change amino acid sequences.[58] Polymorphism of +276G>T of adiponectin gene in Indonesia is not considered a risk factor for obesity nor DM. Polymorphism of ADRB is a risk factor for obesity with diabetes in the Indian population,[59] adult women,[60] and a risk factor for coronary artery disease,[61] metabolic syndrome,[62] and hypertension.[63]

Resistin

Resistin is produced and released from WAT tissue. It is produced at low levels in preadipocyte, endothelial cells, and vascular skeletal muscle cells, but resistin is mostly found in peripheral mononuclear and spinal cells. Resistin has 11 cysteine residues at the end of the C-terminal. Peptide resistin is rich in cysteine 12.5 kDa and consists of 108 amino acids in humans. The human resistin gene (Retn) is found on chromosome 19. Resistin has a role in activating TNF-α and IL-12 in macrophages and monocytes.[64]

The release of human resistin is mediated by inflammatory factors such as stimulation of lipopolysaccharide or cytokines, IL-1, IL-6, and TNF-α. *In vivo,* resistin can increase cell adhesion molecules in endothelial cells so that there is an increase of ICAM-1, VCAM-1, and Monocyte chemoattractant protein-1 (MCP-1) as opposed to the effect of the adipokine, adiponectin. This increase in resistin levels is correlated with an increase in pro-inflammatory cytokines, especially in patients with metabolic syndrome. Some studies found that increased resistin levels are correlated with increased levels of C-reactive protein and TNF-α. These data stated that the increased level of resistin is associated with increased inflammation.[64]

The relationship between serum resistin, BMI, and body fat was reported that the expression of resistin mRNA and protein levels are detected in subcutaneous and visceral abdominal adipocyte, and serum resistin levels are higher in obesity. Resistin is also a marker in fat distribution because it is specifically associated with abdominal fat deposits. The relationship between resistin and obesity is stronger in the female subjects compared to men. Diet and physical exercise can lower resistin

levels, which is followed by a decrease in BMI and fat mass.[65]

Some SNPs are identified in the Retn gene but only a minor allele frequency of 5% is associated with disease risk. There are several SNP in Retn (-537 and -420) and +299 (IVS2 +181G→A) associated with an increase in BMI. Increased serum resistin is reported in type 2 DM subjects carrying -420G/G genotype. Obesity research in Japan reported SNP −638G>A, −420C>G, and −358G>A although associated with serum resistin, but no significant difference was found in obese subjects and controls and was not correlated with insulin resistance[66]. In research on obese people in Indonesia, polymorphism of +299G > A is associated with insulin resistance and resistin level, negatively correlated with insulin level but -420 C/G and +62G>A polymorphism was not correlated with DM risk[67-69] while resistin is correlated with a marker of inflammation.[70]

TNF-α

TNF-α is a pro-inflammatory cytokine that can provide an immunological response. Activation of the immunologic system during infection or injury causes metabolic changes.[71] TNF-α is expressed on the surface of transmembrane protein cells and is involved in the pathogenesis of various inflammatory diseases. The TNF-α gene is located on chromosome 6.p21.1—21.3. TNF-α is involved in the metabolism of fat and causes a higher level of triglycerides in the blood as a result of decreased activity of lipoprotein lipase and increased synthesis of hepatic fatty acids in the body. Subjects with obesity are associated with high TNF-α expression and correlated with higher insulin levels. In addition, TNF-α is known to regulate the expression and secretion of leptin[72]. In WAT obese individuals, pro-inflammatory M1 macrophages form crown-like structures and surround dead adipocyte cells. Increased macrophages M1 in WAT obesity is a major source of TNF-α and IL-6.[73]

Substitution of guanine by adenine in the promoter (-308G/A TNF-α gene) has been identified to be associated with higher blood pressure, leptin levels, and higher cholesterol level leading to the development of the metabolic syndrome. Research into Caucasian and Chinese populations found a correlation between -308G TNF-α alleles and obesity risk. Other studies have also found that AA and GA genotypes are more common in male obese individuals, whereas in female individuals AG genotype is associated with a higher risk of obesity.[71] In another study in Brazil, -308G/A polymorphism in TNF-α promoters, A allele, GA, and AA genotypes contribute to increased insulin resistance and excess body weight in adult.[73] In the Javanese population, this gene polymorphism showed that GA genotype patients have lipid and TNF-α levels higher than the GG genotype, and variation of -308 G/A TNF-α gene plays a role in a higher risk of obesity,[74,75] risk of breast cancer,[76] hypertension,[77] and inflammatory bowel disease.[78]

Interleukin-6

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that influences the activity of the brain, metabolic regulation, and the development of various cancers. IL-6 cytokines are bound to IL-6R membrane receptors and the complex IL-6 and IL-6R are associated with glycoprotein 130 kDa in which dimerization will initiate signals via Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and phosphoinositide-3 kinase pathways.

IL-6 plays an important role in inflammatory signaling pathways and is associated with obesity as well as visceral adipose tissue. Genetic variants of IL-6 in the promoter of genes affect the function and expression. Polymorphism in functional promoter IL-6-174G/C affects

IL-6 transcription. The human IL-6 gene is located on the 7p21 chromosome, and -174G/C polymorphism is thought to be associated with obesity risk.[79] In the obese group of western Indonesia, carriers of the CC genotype had higher CRP and lower IL-6 levels than the GC and GG genotypes. The frequency of CC genotype in the obese group is 47.2% compared with 28.1% in controls and these genotypes and the allele are considered a risk factor for obesity.[80-84] Effects of gene mutation correlated with obesity and inflammation are summarized in TABLE 3.

TABLE 3. Effects of mutation genes that cause obesity and inflammation

Genes	Effect of mutation	Some mutation found	Reference
Adiponectin	Anti-inflammatory cytokine	+45T>G (rs2241766), +276G>T	20, 57, 58-63
Resistin	Binding of a transcription factor on RETN promoter, activating TNF-α, IL-11, IL-6, IL-12	+62G>A, -420C>G, +299G>A, −638G>A, −358G>A	66-70
TNF-alpha	Modification of the binding sites in certain transcription factors, and affect the regulation of transcription and secretion. TNF-α binds to the receptor will increase the cellular and pro-inflammatory NF-kB and activation of mitogen-activated protein (MAP) kinase	-308 G/A	74-79
Interleukin-6	Affect a transcriptional system, release truncated protein, initiates signals via Janus kinase and phosphoinositide-3 kinase pathways	-174G/C	80-84
Endothelin-1	Affect the synthesis of endothelin-1 and increase levels of endothelin concentration.	T-1370G, 198K/N, G2288T, T-1370G, +138/ins/del	85-87

Endothelin-1

A recent study found there is a positive correlation between higher body weight and endothelin-1 (ET-1) levels. ET-1 is a vasoactive peptide primarily produced and released by endothelial cells. Most ET-1 circulation is derived from vascular endothelial cells and is synthesized by adipocyte tissue. There are ET-2 and ET-3, but ET-1 is the most dominant molecule and has an effect. Active ET-1 is a hormone with 21 amino acids the result of the translation process as preproendothelin with 200 amino acids and hydrolyzed and modified by endothelin converting enzymes (ECEs), resulting in mature and secreted ET-1. Its receptors occur in various tissues such as endothelium, vascular skeletal muscle cells, adipocytes, and hepatocytes. The secretion of ET-1 helps the metabolic function in healthy individuals. When ET-1 levels increase in plasma it can lead to a variety of health problems.

Obese patients have an increase in plasma ET-1 levels when compared to normal-weight individuals. This increase in ET-1 production is mainly in adipose tissues. Adipose in obese patients can release ET-1, which can be 2 to 3 times higher than in normal-weight subjects. The increase in ET-1 contributes to lipid regulation and is a risk factor for insulin resistance in some patients with obesity due to their interactions with ETA and ETB subtype receptors. Stimulation of ET-1 is associated with increased expression of TNF-α by macrophages and increased transcription rate of IL-6, NFκβ, and monocyte chemotactic protein-1.[85] In the Javanese population, variation of 198K/N ET-1 gene, 198N/N genotype is a risk factor of obesity compared to

198K/K genotype. Levels of ET-1 plasma are higher in obese subjects than that of control subjects, and N/N genotype has the highest ET-1 plasma level.[86]

ET-1 or EDN-1 is a polypeptide that has vasoconstriction activity and mitogenic effects, in the heart has positive inotropic and chronotropic characters, stimulates sympathetic and renin-angiotensin-aldosterone systems, as well as homeostasis modification. The human *ET-1* gene consists of 6836 nucleotides located on the 6p23-p24 chromosome, capable of producing pre-pro-ET-1 that can be hydrolyzed into large ET-1s. There are several variants of the *ET-1* gene, including transversion, transition, insertion, and repeated nucleotide polymorphisms, which affect the genetic risk of cardiovascular and other related diseases. Ten polymorphisms including transversions have been found: -1370 (T-1370G), +5665 (198K/N), G2288T polymorphisms (rs2070699), and -974 C>A (rs3087459). Transitional polymorphisms are +3660 (106E/E), G8002A (rs2071942), rs1476046, rs2071943, and rs9296345 polymorphisms. In addition, the polymorphism of insertion/deletion is +138 (+138/ex1ins/delA) (rs1800997). Some are associated with significantly different diseases (phenotypes), especially cardiovascular system-related diseases such as high blood pressure, ischemia, angina, and coroner's syndrome. Some other related diseases are asthma, lung edema, hearing loss, obesity, and sleep apnea.[87]

The differences in results and the limitation of the genetic study in the various populations are due to differences in the gene pool for each population which has different genetic variations, genes associated with obesity are numerous, environmental factors and eating habits in each population/ethnic are different. The pathogenesis of obesity is complex, where one variation of a gene can affect the genes located nearby that influence these diseases. Additionally, the studies of genes and obesity are not able to control all of the confounding factors and differences in criteria or design variables used in the research protocols.

CONCLUSION

There are some genetic factors that contribute to the causes of obesity by acting through control mechanisms in the hypothalamus or changes in energy expenditure. Some genetic variations can influence obesity and may have different risks within some ethnic groups in the world. These results can be used for consideration if treatment will be conducted in different populations, and there may be nutrigenetic or pharmacogenetic variations which could give different results.

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