Genetic Factors That Act As An Effect Modifier for Environmental Risk Factors of Obesity

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ABSTRACT

Obesity is caused by a failure of complex interrelated homeostasis mechanisms that firmly control body weight and is triggered by multiple, overlapping and complex feeding mechanisms. Pathogenesis of obesity depends on a mutual complex interplay mainly between genetic variants and exposure to environmental risk factors. A minimum of 127 candidates for multiple polymorphic genes for obesity have been identified and characterized. Yet, conclusive and reliable evidence consistently linking gene-environment interactions and energy homeostasis remains inadequately investigated. This critical review therefore provides an up to date summary on current understanding of most common single-nucleotide polymorphisms at the most prominent obesity candidate genes that act as an effect modifier for environmental risk factors; namely leptin, ghrelin, β3-adrenergic receptor, and proopiomelanocortin genes.

Keywords: Obesity, Genes, Sedentary, Lifestyle, Environment.

INTRODUCTION

Obesity is one of the most common global health challenges resulting in augmented risk of both morbidity and mortality. Obesity continues to affect various age and socioeconomic groups in nearly all countries regardless of geographical location (Ramachandrappa and Farooqi, 2011; WHO, 2009). Excess body weight is the fifth main cause of global deaths, and the sixth primary risk factor for worldwide disease burden (Ezzati et al., 2002). Obesity is associated with early development of chronic health conditions (Christian et al; 2011); particularly type 2 diabetes mellitus (Wannamethee et al., 1999), and cardiovascular diseases (Poirier and Eckel, 2002) as well as certain types of cancer (Ceschi et al., 2007), cerebral diseases (Poirier and Eckel, 2002), and hypertension (Christian et al; 2011). Moreover, obesity does not merely reduce the individual’s quality of life, but also shortens life expectancy and entails heavy-associated healthcare costs (Suastika, 2006; Poirier et al., 2006).

Obesity is a disease caused by a persistent imbalance between energy input and energy output. Various complex homeostatic mechanisms firmly regulate body weight (Suzuki et al., 2011). More than thirty gastrointestinal tract hormones and a hundred active peptides are identified and, thus, human gut could be considered as the leading endocrine organ (Rehfeld, 2004).

The rampant increase in the occurrence of obesity in nearly all populations over the past several decades can be restrictively explained by an array of multifactorial, interrelated, overlapping and complex feeding mechanisms that represent the imperative temperament of feeding activities for survival (Suzuki et al., 2011; Must et al., 1999). Although imbalance in feeding mechanisms could possibly be regarded as a failure in the adaptation mechanisms in persons with obesity on caloric-dense diets and sedentary lifestyle (Suzuki et al., 2011), the underlying mechanisms that lead to imbalance in energy intake and energy expenditure that cause obesity have yet been elucidated (WHO, 2009).

Defects in various multifaceted feedback systems implicated in the regulation of adiposity could cause changes in body weight. The process of energy homeostasis is influenced by the ability of the central nervous system to detect and react to changes in body weight. It maintains both body weight and fat mass at relatively desired levels for extended periods regardless of daily variations in energy input intake and energy expenditure (Kaelin et al., 2004).

Obesity is a complex heterogeneous group of disorders, which develops predominantly from a polygenic
multifactorial trait. Obesity develops from a failure of the body-weight control mechanisms due to a complex interplay between both genetic and environmental risk factors mainly diet, and physical activity, which act by means of mediators of energy input and energy output (Agurs-Collins and Bouchard, 2008; Knecht et al., 2008). Mechanisms involved in the heritability of body weight-related phenotypes remain unknown. However, accumulating evidence has indicated that 6-85% of the variations in obesity-related phenotype is heritable and could be determined by genetic factors (Yang et al., 2007; Mutch and Clement, 2006), whereas 30% of this variation could be ascribed to the exposure to different environmental risk factors (Martinez, 2000). Thus, investigating mechanisms and functional pathways involved in the heritability of body weight-related phenotypes remains vital for a better understanding of the pathways that maintain the dynamic energy homeostasis (Kaelin et al., 2004).

Common single-nucleotide polymorphisms at candidate genes for obesity have been identified, which act as an effect modifier for environmental risk factors. Studying obese individuals with genetic variants has provided deepened our knowledge of the metabolic mechanisms that regulate energy balance. This require further studies could provide grounds to understand the framework for the development of a more rational method for the prevention or at least ameliorate the occurrence of obesity in genetically at-risk individuals. Progress in genomics and proteomics research might provide further evidence indicating that additional alleles in adipose-tissue-expressed genes, which regulate the function of the adipocytes, may constitute risk factors for changes in body weight. This is pivotal for the prevention or at least ameliorating the occurrence of obesity as well as the innovation of new therapeutic targets (Dahlman and Arner, 2010).

Consequences of early-onset of obesity are substantial on public health. Importantly, limitations of the available alternatives for either the prevention or treatment of overweight or obesity have necessitate novel insights into the culpable risk factors implicated in the initiation of adiposity. This review, therefore provides an up to date summary on current understanding of the most common single-nucleotide polymorphisms at the most prominent obesity candidate genes that act as an effect modifier for environmental risk factors; namely, leptin (LEP), ghrelin (GHRL), β3-adrenergic receptor (ADRB3), and proopiomelanocortin (POMC). The cytogenetic locations, main functions and their relation to obesity of the aforementioned genes are summarized in Table 1.

**Obesity and the role of anticipated prominent genes**

The importance of chromosomal regions linked to obesity and body composition remains controversial, nonetheless advances in genomics, particularly expression profiling based on microarray have presented a range of new candidate genes that obesity regulates its expression in the adipose tissue. Discovering new liable obesogenic genes requires the integration of the gene expression profiles with genome-wide linkage and/or association analysis (Dahlman and Arner, 2010). It is unlikely that genetic variations involved in a diverse range of the pathogenesis of human obesity are due to single-gene mutations (Liu et al., 2011, Miraglia del Giudice et al., 2004). The sensation of hunger and satiety is a cascading function of signaling proteins activated by food restriction or consumption (Ahima and Osei, 2004), provided that a number of genes play a primary function in uncovering the inter-individual dissimilarity in susceptibility or resistance to the environmental obesogenic risk factors (Ramachandrapa and Farooqi, 2011).

Advanced molecular approaches have provided the necessary means to identify certain forms of human monogenic obesity syndrome. Several single genetic defects that disrupt the molecules in the leptin-melanocortin pathway and, consequently, lead to obesity in humans have recently been identified (Farooqi, 2008). For instance, it has been demonstrated that juvenile-onset morbid obesity is associated with mutations in human genes coding for: LEP, LEPR, POMC, and MC4R (Clément et al., 1998; Krude et al., 1998; Vaisse et al., 1998; Montague et al., 1997). It has been demonstrated that single-gene mutations in eleven independent genes have caused 176 obesity cases in human, in addition fifty loci related to Mendelian syndromes relevant to obesity have been recorded to a specific genomic region; causal or robust candidate genes have been determined for the majority of these Mendelian syndromes (Rankinen et al., 2006 a, b).

Except for the Y chromosomal region, genome-wide linkage studies were linked to human body mass index (Stone et al., 2002). Since the release of the latest version of the Human Obesity Gene Map database (HuGENet, 2011, CDC, 2011), the progress in identifying the genes associated body weight has been speeding up. This
database has verified that in spite of intensive studies, the mechanisms by which genetic polymorphisms are related to energy expenditure or food intake and thus changes in body weight are not fully understood yet (CDC, 2011). Nonetheless, a diverse array of genes implicated in the regulation of appetite and integrated in different metabolic pathways are involved in the initiation of obesity (Ochoa et al., 2004).

Studies using genome-wide scans have verified that of the 61 genome-wide human linkage studies, 253 quantitative trait loci phenotypes related to obesity have been mapped (Yang et al. 2007 and Ochoa et al. 2004); about one-fifth of them were reported by two or more studies (Rankinen et al., 2006 a; Ochoa et al., 2004), moreover 11 single mutations were potentially implicated in more than 176 positive cases of individuals with obesity throughout the world. Diverse genetic variants in 127 candidate genes are associated with body weight from 426 positive chromosomal regions; replication of each association in twenty two of these genes are presented in a minimum of five studies, and twelve have been backed by at least ten studies (Rankinen, et al., 2006b).

Candidate genes linked to obesity-related phenotypes can be categorized into three main classes: (1) linked or associated with human obesity; (2) leading to obesity through Mendelian or single gene mutations in humans, and/or; (3) causing obesity in animals. All of which fall into five major groups. First, thriftiness (β-adrenergic receptors 2 (ADRB2) and 3 (ADRB3), and uncoupling proteins 1, 2, and 3 (UCP1, UCP2, and UCP3). Second, (2) hyperphagia (dopamine D2 receptor, DRD2), 5-hydroxytryptamine (serotonin) receptor 2C (HTR2C), LEP, leptin receptor (LEP), MC4R, nuclear receptor subfamily 3, and group C, member 1 (NR3C1). Third, low lipid oxidation ((angiotensin-converting enzyme (ACE)), adiponectin (ADIPOQ), guanine nucleotide binding protein, beta-3 subunit (GNB3), hormone sensitive lipase (LIPE), and low-density lipoprotein receptor (LDLR). Fourth; adipogenesis (peroxisome proliferator-activated receptor gamma (PPARγ), vitamin D receptor (VDR), resistin (RETN), interleukin-6 (IL6), and tumor necrosis factor alpha (TNF)). Fifth, low physical activity (DRD2, MC4R) (Yang et al., 2007; Bouchard, 2007 and Ochoa et al., 2004).

**Beta3-adrenergic receptor gene**

Beta3-adrenergic receptor gene is an obesity gene mapping to chromosome 8P12 and is encoded by the adrenergic receptor (ADR) (USNLMD, 2012). It principally expressed in both white and brown adipose tissue. ADRB3 plays a principal function in energy balance through promoting lipolysis and thermogenesis through the secretion of noradrenaline from the sympathetic nerves triggered by cold temperature and/or food intake (Takenaka et al., 2012) (Michel et al., 2007). Although specific cloning of ADRB3 has been reported from white fat and from several adipose tissue fragments from gall bladder, small intestines, and liver and skeletal muscles (Berkowitz et al., 1995), it is sited predominantly on the surface of both visceral and brown adipose cells (Large et al., 1997).

ADRB3 is a major lipolytic receptor in fat cells as well as the delivery of free fatty acid into the human portal vein (Large et al., 1997; 1995; Lönnqvist et al., 1993). Changes in the adipose tissues and blood glucose levels during and following stress conditions have been assumed to be attributed to endocrine alterations, nonetheless it has been demonstrated that epinephrine release and norepinephrine binding under stress conditions induces the genetic expression of the two main types of ADR; the aADRs and bADRs. Clinical trials have identified several subtypes of adrenergceptors in mammals: α1a, α1b, α1d, α2a, α2b, α2c, and β1, β2, β3 (Giltrow et al., 2011).

The importance of ADR resides in its role in mediating metabolic functions of endogenous catecholamines (Giltrow et al., 2011). Trp64Arg mutation of ADRB3 is associated with lower resting metabolic rate, abdominal obesity and weight gain as well as resistance to weight loss. Adipose cells with ADRB3 of Trp64/Arg64 or Arg64/Arg64 showed two-thirds fold reduced ability to produce intracellular cAMP and lipolytic glycerol compared with those with Trp64/Trp64 (Takenaka et al., 2012; Mitchell et al., 2007).

It has been suggested that ADR should exhibit a wide distribution in mammalian tissues, hence specific RNase protection assays have been undertaken to examine the dispersion of ADR mRNA in human tissues. Adrenergic receptors are expressed in various tissues including heart, lungs, intestines, adipose tissue and several other locations (Berkowitz et al., 1995).

Beta-3 adrenergic receptors belong to G protein-coupled receptors superfamily characterized with the capacity of mediating thermogenic and lipolytic activities, and anti-obesity and anti-diabetic actions as well as motility related functions interpreted by their expression in gastrointestinal tract and prostate (Giltrow et al., 2011). Although beta 3-selective agonists are used as potential
anti-obesity drugs, the role of ADRB3 in normal physiology is unknown yet (Suslic et al., 1995). A missense mutation on codon 64 of the first transmembrane domain (C64T) of the ADRB3 is associated with impaired activity of the ADR, which may result in the swelling of fat cells (Pietri-Rouxel et al., 1997). The sole expression of ADRB3 subtypes is in both brown and white adipose tissue, thus ADRB3 might be fat cell-specific ADRs, (Gilltrow et al., 2011 and Berkowitz et al., 1995). The genetic expression of ADRs between lean and obese humans remains controversial, nevertheless ADRs might be a potential pharmacological target in the management of human obesity (Berkowitz et al., 1995).

Using ligand binding, polymerase chain reaction (PCR), and Northern blot analysis methods have confirmed mRNA expression of ADRB3 genes expressed in an massive number of human tissues including cerebral cortex, cerebellum, liver, gall bladder, pancreas, stomach, small intestine, white and red skeletal muscle, several white fat tissues, left atrium, left ventricle, lung, kidney, prostate, and corpus cavernosa. The characterization of ADRB3 expression in fat and fat free human tissues suggests the potential importance of these receptors not only as specific agonists in the treatment of obesity, but also in physiological functions of several other organs (Berkowitz et al., 1995).

**Proopiomelanocortin gene**

Proopiomelanocortin is a 31 kDa prohormone expressed in the pituitary gland as well as in a range of nonpituitary organs and tumors including melanomas (Bai et al., 2005), and maps to chromosome 2P23.3 (USNLM, 2012). Moreover, it is expressed within the hypothalamic neurons and other brain regions such as striatum, hippocampus and thalamus (Bai et al., 2005). Ten different bioactive peptides is processed by POMC through wide tissue-specific post-translational processing including adrenocorticotropin (ACTH), melanotropins [(α, β, and γ-melanocyte-stimulating hormone(MSH)], lipotropins, and endorphins. These bioactive peptides have a range of functions including pain control, energy balance, melanocyte stimulation, and immune system modulation (Zhang et al., 2010; Pritchard et al., 2002).

The single primary protein precursor translated to perform POMC functions originates from a POMC gene containing 3 exons and 2 introns spliced out to generate POMC mRNA (Rankinen et al., 2006 a, b). POMC gene encodes a precursor polyhormone peptide (O’Donohue and Dorsa, 1982), which undergoes posttranslational cleavage and enters the hypothalamic pathway. This polypeptide is implicated in the regulation of food intake and energy output (Yeo et al., 1998).

The stimulation of the anorexigenic function of POMC is exhibited by its participation in the synthesis of α-MSH after binding to its receptors; MC3R and MC4R (Bai et al., 2005). A substitution mutation (C1032G) in the first introns of POMC gene could alter the transcriptional activity of POMC gene ending with phenotypic effect on body weight. Synthesis of tissue specific ACTH, MSH, endorphins and lipoproteins’ synthesis is stimulated following proteolytic cleavage and posttranslational modifications to act as hormones, neurotransmitters, growth factors, cytokines and biological response modifiers (Slominski et al., 1999).

In addition to the wide expression of POMC in hippocampus, it has been shown that POMC signaling does in part rely on the activation of the HPA axis by parasympathetic nervous system. Nevertheless, potential physiological and adaptive endocrine mechanisms have been suggested to explain the variation in mRNA expression rates of referred neuropeptides in mRNA strands derived from adult and fetal hippocampal cultures. POMC mRNA levels in adults have been reported to exceed fetal levels by more than 8 folds. Henceforth, it has been concluded that these neuropeptides play variable, but significant, roles in hippocampal development by alternating food intake in response to various stimuli during development (Bai et al., 2005); for example short-term pharmacological activation of melanocortin deters obesity caused by diet efficiently in animals. Nonetheless, there was no evidence to explain whether central POMC gene transfer targeted to the hypothalamus or hindbrain nucleus of the solitary track can prevent dietary-induced obesity. Therefore, unlike the hypothalamus, the activation of melanocortin in the brainstem nucleus of the solitary track region effectively reduces chronic dietary obesity (Zhang et al., 2010).

**Leptin gene**

Obese mutation (ob) is a single murine gene mutation first identified in 1950 (Zhang et al., 1994 and Ingalls et al., 1950). It is associated with altered metabolism and increased lipid deposits in adipose tissue. Recessive ob gene mutations in homozygous mice cause both extreme obesity and type 2 diabetes mellitus. The human LEP gene and murine ob gene are homologous (Masuzaki et al, 1995;
Zhang et al., 1994) with about 84% identity at the protein level (Isse et al., 1995). Thus, homology of the *ob* gene product in vertebrates including humans provides evidence that the function *ob* gene is highly preserved. Obese mutation heterozygotes have an improved ability to endure an extended fasting state; heterozygous mutation at *ob* may propose a selective advantage in human populations exposed to energy deprivation. Identification of *ob* provided grounds to examine the pathways, which regulates adiposity and body weight (Zhang et al., 1994).

Leptin gene maps to chromosome 7q31.3 (USNLM, 2012). Leptin is an *ob* gene secreted protein hormone. It is a potent anorexigenic adipocyte-derived peptide hormone (Zhang et al., 1994; Bluher and Mantzoros, 2004), and is known as an obese protein or obesity factor (Isse et al., 1995). *LEP* is one of 12 neurotransmitters known to control eating behavior in the brain by providing a signal to stop eating when human eats sufficient quantity of food (Bluher and Mantzoros, 2004). Since its discovery in 1994; it emerges that *LEP* signaling system is primarily implicated in sustaining adequate energy stores for survival during energy shortage times (Jéquier, 2002) as well as metabolic rate, glucose fluxes, and neuroendocrine effects (Gautron and Elmquist, 2011; Elmquist et al., 1998).

Leptin initiates specific hypothalamic neuronal subpopulations including *POMC* and AgRP neurons containing neuropeptide Y (NPY) neurons. It also triggers many intracellular signaling events, such as the JAK/STAT (Janus kinase/signal transducer and activator of transcription), mitogen-activated protein kinase (MAPK), phosphoinositide kinase-3 (PI3K) and mammalian target of rapamycin (mTOR) pathway. This ultimately translates into reducing energy intake and increasing energy output (Wauman and Tavernier, 2011). Circulating plasma *LEP* rises constantly with increasing mass of the adipose tissue, gender, age, and short-term energy restriction, which may be significant secondary regulators of plasma *LEP* (Ostlund et al., 1996). In addition, *LEP* plays a role in regulating reproductive function, bone homeostasis, and immune function (Wauman and Tavernier, 2011).

The effects of *LEP* at the cellular level are mediated by an isoform of the *LEPR* (*LEPR-b*), which is expressed prominently in the arcuate nucleus (Elmquist et al., 1998). Circulating plasma *LEP* may activate particular nuclear groups in the hypothalamus involved in controlling feeding, body weight, and neuroendocrine function whilst the substrate is available (Campfield et al., 1995). Although *LEP* acts on the brain, the specific anatomic sites and pathways involved in mediating these actions are unclear (Elmquist et al., 1998). Although *LEP* deficiency in both animals and humans causes morbid obesity and diabetes mellitus as well as various neuroendocrine anomalies, the role of *LEP* in the etiology of obesity is only demonstrated in the extremely rare situations of mutations of *LEP* or *LEPR* genes, which result in the absence of the *LEP* signal. *LEP* signal triggers a long-term internal sensation of starvation and, therefore, chronic stimulation of excessive food consumption (Jéquier, 2002). While *LEP* deficiency causes unusual increased appetite for food consumption and, therefore, obesity (Zhang et al., 1994), administration of *LEP* suppresses food intake and reduces body weight (Lönnqvist et al., 1995). This indicates that *LEP* can function directly on neuronal networks, which controls feeding and energy homeostasis (Campfield et al., 1995).

Leptin replacement therapy reduces food consumption, normalized glucose homeostasis, and increased energy output (Gautron and Elmquist, 2011). *LEPR* gene encodes a single transmembrane receptor that belongs to class I cytokine receptors superfamily (Tartaglia, 1997). They have been found in at least six alternatively spliced isoforms in rodents and humans (Chua et al., 1996). The long *LEPR* isoform activates the JAK signal transducer and alters the expression of many hypothalamic neuropeptides (Villanueva and Myers, 2008; Björbaek and Kahn, 2004). Moreover, a single nucleotide mutation in *LEPR* gene (A223G) showed changes in the receptor charge from neutral to positive, a change that leads to changes in receptor function (Crabbe et al., 2006).

**Ghrelin gene**

Ghrelin is a novel 28-amino acid circulating appetite-modulating stomach and neuropeptide; first discovered from the human and rat stomach in 1999 (Zhang et al., 2005; Inui et al., 2004). GHRL maps to chromosome 3P26-P25 (USNLM, 2012). It is derived from a prohormone by posttranslational processing (Zhang et al., 2005). It regulates obesity through central and peripheral mechanisms (Hinney et al., 2002); plasma *GHRL* levels are inversely correlated with body mass index (Tschöp et al., 2001). In addition, a range of functions of *GHRL* including growth hormone release, feeding behavior, and glucose metabolism as well as memory and depression prevention effects have been demonstrated (Sakata and Sakai, 2010). *GHRL* -producing cells were detected in all parts of mammalian GIT including antrum, duodenum, ileum,
cecum, and colon (Sakata and Sakai, 2010), but the major source of circulating GHRL is oxyntic glands of the stomach (Sakata and Sakai, 2010).

GHRL release is regulated by the ghrelin O-acyl transferase enzyme and exerts its effect through the growth hormone secretagogue receptor (GHS1a receptor) (Liu et al., 2011). The release of the growth hormone from the pituitary gland might be managed by both hypothalamic growth-hormone-releasing hormone (GHRH) and GHRL (Kojima et al., 1999). It has been reported that GHRL is involved in a wide range of physiological mechanisms (Liu et al., 2011) such as appetite stimulation, which induces a positive energy balance causing to body weight gain (Inui et al., 2004).

Fasting plasma levels of GHRL are inhibited in individuals with obesity (Hansen et al., 2002) as compared to individuals with anorexia nervosa. Partial weight recovery normalize GHRL plasma levels, which indicates possible GHRL resistance in cachectic states such as those caused by eating disorders. In individuals with anorexia nervosa, the suppression of GHRL release by short-term changes of energy balance is not interrupted and, thus, is independent from long-term changes in energy balance that causes overweight or obesity (Otto et al., 2005).

GHRL may play a role in providing feedback signaling system between food intake and gastric-motor function as well as the central nervous system (Tschöp et al., 2001). Weight loss caused by a reducing diets lead to an increase in plasma GHRL levels. This indicates that GHRL has a role in the long-term body weight management moreover plasma levels of GHRL are reduced substantially following gastric bypass, which may contribute to the weight-reducing effect of the intervention (Cummings et al., 2002).

It has been demonstrated that mutations in the preproghrelin gene are associated with obesity polymorphisms in the region coding for GHRL play a significant role in obesity (Ukkola et al., 2001). Unlike individuals with normal body weight, a mutation at amino acid position 51 (Arg51Gln) of the preproghrelin sequence matching to the last amino acid in mature GHRL has been localized in heterozygous individuals with severe obesity. In addition, the Leu72Met polymorphism of the GHRL gene appears to play a role in predicting obesity in children (Kuzuya et al., 2006). Irregularity of GHRL signaling from the stomach could prompt defects in energy homeostasis and growth as well as associated GIT and neuroendocrine functions (Inui et al., 2004).

To sum up

Non-familial environmental risk factors, gene-gene, and gene-environmental interactions seem to be the most important determinants of the eating behavioral traits. Human nutritional behavior including food intake and eating practices remain the most important environmental risk factor that modulates gene expression (Corella and Ordovas, 2005). It appears that the focus on obesity should be shifted from considering obesity as a main outcome to investigating the possible effect that obesity may have as an effect modifier.

Dynamic energy homeostasis appears to be a basic explanation for the occurrence of obesity. Yet, obesity is a multifactorial complex phenotype when considering the multitude of genetic, biological, psychological, sociocultural, economical and dietary and non-dietary environmental risk factors. All of which affect the dynamic homeostasis between both food intake and energy expenditure and the complex interplay between these risk factors (WHO, 2009).

Hitherto, the process by which energy homeostasis is regulated and the influence of genetic polymorphism on biological systems controlling the pathogenesis of obesity remains to be unraveled and is inadequately examined. Accumulating body of literature in the fields of genomics, nutrigenomics, proteomics, and metabolomics can be used to guide the identification of the obesity-related phenotypes as well as appropriate obesity-related biomarkers. (Paracchini et al., 2005).

Finally, before evaluating the recommended medical and dietary interventions based on required genotype and before raising our expectations with regard to genomic profiling, researchers should embark on validating the clinical usefulness and applications of this approach. Researchers are encouraged to undertake large-scale, well-designed population-based epidemiological studies as well as longitudinal clinical trials testing of multiple genes in obese and lean individuals with epidemiologic data on nutritional behavior (Paracchini et al., 2005).

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<td>Leptin</td>
<td>7q31.3</td>
<td>The adipocyte-specific hormone leptin regulates adipose-tissue mass through hypothalamic effects on satiety and energy expenditure. Exerts negative feedback effects on energy intake.</td>
<td>Potent anorexigenic adipocyte-derived peptide hormone. Mutation in the gene is associated with early-onset obesity. In obesity, leptin loses its ability to inhibit energy intake and increase energy expenditure.</td>
<td>(USNLM, 2012; Enriori et al., 2006; Bluher and Mantzoros, 2004; Green et al., 1995; Zhang et al., 1994)</td>
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<tr>
<td>Ghrelin</td>
<td>3p26-p25</td>
<td>Ghrelin is an endogenous ligand for the growth-hormone secretagogue receptor that stimulates growth hormone release.</td>
<td>Stimulates appetite. Acts as an orexigenic peptide implicated in energy balance mechanisms and weight gain.</td>
<td>(USNLM, 2012; Seim et al., 2007; Garweg et al., 2005; Ukkola et al., 2002).</td>
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<tr>
<td>Beta 3 adrenergic receptor</td>
<td>8p12</td>
<td>principally expressed in both white and brown adipose tissue. Act as a regulator of energy expenditure and lipolysis</td>
<td>Plays a key role in the regulation of energy homeostasis by increasing lipolysis and thermogenesis. Mediating metabolic functions of endogenous catecholamines. Promotes lipolysis and thermogenesis. Mutations associated with lower resting metabolic rate, abdominal obesity, weight gain, and difficulty losing weight.</td>
<td>(USNLM, 2012; Takenaka et al., 2012; Giltrow et al., 2011; Mitchell et al., 2007; Large et al., 1997).</td>
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<tr>
<td>Pro-opiomelanocortin</td>
<td>2p23.3</td>
<td>Ten functionally different peptides can be derived from POMC via extensive tissue-specific post-translational processing. These peptides play crucial roles in numerous biological processes such as pain, energy homeostasis, melanocyte stimulation, and immune modulation.</td>
<td>Bioactive peptides derived from POMC act as endogenous ligands for the melanocortin-4 receptor, a key molecule underlying appetite control and energy balance. Defective processing of POMC may disrupt appropriate melanocortin signaling, ultimately resulting in obesity.</td>
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REFERENCES


Ukkola, O., Ravussin, E., Jacobson, P., Snyder, E. E., Hayder A. Al-Domi
العوامل الجينية المعدلة لتأثير العوامل البيئية المسببة للسمنة

حيدر الدوسي

ملخص

تنجم السمنة عن فشل في أنظمة التحكم في وزن الجسم الناجم عن آليات تغذية متعددة، ومتداخلة. تعتبر عملية الإصابة بالسمنة بشكل أساسي على التفاعلات العقد والشباوب بين الأنماط الجينية المتعددة للجينات المرتبطة بالسمنة والتعرض لعوامل الخطر البيئية. تم تحديد وتمييز ما يقرب من 127 من الجينات متعددة الأشكال المتنوعة والمشتركة لدى نزلاء السمنة، ومع ذلك، فإنها ما زالت بحاجة لدراسة علمية قاطعة ومتعددة بها لربط بين العوامل الجينية كعامل لتثبيت العوامل البيئية المختلفة وعلاقة ذلك بأيبن التحكم في وزن الجسم.

تقوم هذه المراجعة العلمية الدقيقة تدريجيًا وجزأً حول الفهم الحالي للأشكال الجينية المتعددة لأهم الجينات التي يعتقد بعلاقتها بالإصابة بالسمنة والتي يمكن أن تعمل كعامل لتأثیر عوامل الخطر البيئية، وبالتحديد جينات الليبيتين والغليتين والمستقبل والأدرنيالين بيتا 3 والبروتوبيلابوليتروتين.

الكلمات الدالة: السمنة، الجينات، الخصوص، نمط الحياة، البيئة.