

The role of genes involved in lipolysis on weight loss program in overweight and obese individuals

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The ability of obese people to reduce weight in the same treatment varied. Genetic make up as well as the behavioral changes are important for the successfulness of the program. One of the most proposed genetic variations that have been reported in many intervention studies was genes that control lipolysis process. This review summarizes studies that were done showing the influence of genetic polymorphisms in lipolysis pathway and weight loss in a weight loss treatment program. Some studies had shown that certain enzymes involved in this process were related to successfulness of weight loss program. Single Nucleotide Polymorphism (SNP) in PLIN (11482G>A) and ADRB3 (Trp64Arg) are the most studied polymorphisms that have effect on weight loss intervention. However, those studies were not conclusive because of limited number of subjects used and controversies in the results. Thus, replication and confirmation on the role of those genes in weight loss are important due to their potential to be used as predictors of the results of the program.

Key Words: lipolysis, SNP, weight loss, obesity

The expert panel of World Health Organization recommends 10% weight loss for obese and overweight individuals especially by lifestyle modification therapy.⁽¹⁾ Although conventional diets, physical activities and behavior modifications have shown its successfulness in reducing weight loss, some people receive no or less benefit from the program.⁽²⁾ One of the important factors that influence the various outcomes of weight loss program is genetic make-up. The idea of proposed “personalized nutrition” as part of future therapy looks at an individual as a whole with variation of ability to adapt to their environment including nutrition and lifestyle. The influence of diet on health and disease might depend on their genetic make up and it is important to address that genetic background is essential to the responsiveness of such therapy. Studies in gene-nutrient interaction had shown that genetic predisposition plays an important role in the development of certain traits including obesity. Using nutrigenomic and nutrigenetic approaches, scientists can now analyze the role of genetic predisposition on the successfulness of certain diet intervention program. The influence of genetic background on weight loss had been discussed before.⁽³⁾ Genetic candidates that are proposed to influence weight loss are involved in energy expenditure, appetite control, adipogenesis, insulin resistance and lipid metabolism.⁽³⁾

Lipolysis is an important step in lipid metabolism that regulates lipid mobilization from fat storage tissues to the other tissues. The importance of genetic variation in lipolysis process and obesity has been argued before. Arner *et al.*⁽⁴⁾ described possible genetic variation in lipolysis pathway that induce development of obesity including polymorphism in $\beta 1-3$ adrenoreceptors, hormone sensitive lipase (HSL) and components of insulin signaling pathway. The review showed less information about signaling pathways

that involved in induction of lipolysis as well as components of lipolysis enzyme. At the moment when the paper published, HSL was mentioned as the only enzyme involved in lipolysis process. To date, there is an increasing knowledge on lipolysis process showing that other enzymes including adipose tissue triglyceride lipase (ATGL) and monoglyceride lipase (MGL) also play an important role in lipolysis process.

Based on the fact that lipolysis in obese and overweight individual is impaired,⁽⁵⁾ there is a growing hypothesis that this insensitivity affects the successfulness of weight loss program. The aim of this review is to summarize reports showing the effect of polymorphisms of genes related lipolysis pathway of human adipose cells on weight loss. Using current available data, the influence of polymorphisms in each component pathway of lipolysis were collected.

Lipolysis Process, Definition and Why It Matters

Lipolysis, which is started in gastrointestinal (GI) system, makes sure that dietary lipid is well absorbed. Lingual lipase, gastric lipase and pancreatic lipase are important enzymes that breakdown dietary lipid in GI track. Lipid is absorbed in its simple structure then transported in the blood stream in the form of lipoprotein and triglyceride (TG) inside chylomicron.⁽⁶⁾ In order to be transported into its target cells through endothelial barrier, lipoprotein lipase breaks down those lipid complexes. The rest of fat metabolites were then transported and stored in adipocytes as TG. After stimulation by several agents (will be discussed), lipolysis is initiated in adipocytes to release fatty acid (FA) from TG (Fig. 1).⁽⁶⁾

Breakdown and re-esterification of FA is a continuous process that is necessary in order to keep a good homeostasis. Regulation of FA is important because if uncontrolled, the increasing level of FA will disrupt integrity of membrane and affect acid-base homeostasis in circulation. Lipotoxicity could happen in the case of increasing harmful bioactive fatty acid in the circulation. Thus, FA should be stored in specific organ as its ester form and released when there is a demand of additional source of energy. FA then can be used as the source of energy in negative energy balance. Although lipolysis process in both adipose and non-adipose tissues is an important part in development of obesity as well as in weight management, this review only focuses on lipolysis that happens in human adipose tissues.⁽⁷⁾

There is a shift of knowledge about lipolysis processes that occurs in adipocytes. Previously it has been described that HSL is the only enzyme that regulates lipolysis in lipid droplet (LD) of adipocytes.⁽⁶⁾ In recent years there is increasing evidence showing that ATGL or adipose triglyceride lipase as well as

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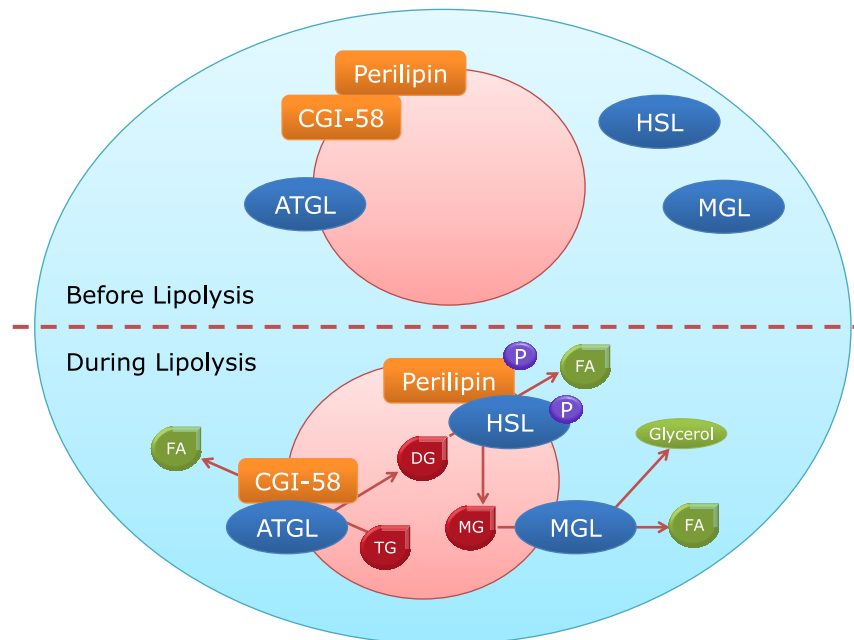


Fig. 1. Perilipin the gatekeeper for lipolysis process. This figure illustrates lipolysis process in adipocyte (blue circle). Perilipin A was attached with CGI-58 at the outer layer of lipid droplet (green circle) before lipolysis induced. Once Perilipin A is phosphorylated, lipolysis induced thus CGI-58 detached with Perilipin A and attached to ATGL. This combination breakdown TG into DG and FA. Phosphorylated Perilipin A and HSL breakdown DG into FA and MG. At the end of lipolysis process MGL breaks down MG into glycerol and FA. ATGL, adipose tissue triglyceride lipase; DG, diglyceride; FA, fatty acid; HSL, hormone sensitive lipase; MG, monoglyceride; MGL, monoglyceride lipase; TG, triglyceride. See online version figure.

MGL are working together in the breakdown of TG into FA and glyceride.⁽⁶⁾ Those enzymes, together with HSL, initiated three important steps of lipolysis. The signal of lipolysis should activate perilipin, the gatekeeper of lipid droplets, and perilipin can attach with HSL. HSL and ATGL mediated lipolysis are responsible for at least 90% of TG hydrolysis process in human adipose tissue.⁽⁸⁾

Perilipin. Perilipin is a part of LD structure in adipocytes. This protein is in the group of so called PAT which is consisted of perilipin, adipose differentiation related protein and TIP-47 (tail interacting protein 47 kDa).⁽⁹⁾ Perilipin is an important regulator of lipolysis in LD and could be activated by phosphorylation by protein kinase A (PKA).⁽¹⁰⁾ This phosphorylation process of perilipin is an important step for lipolysis initiation since it affects activation of two major lipolysis enzymes, HSL and ATGL. In unstimulated state, perilipin was found to be localized together with a protein called CGI-58. *In vitro* studies shown that CGI-58 binds directly to unphosphorylated perilipin and dissociated after perilipin is phosphorylated.^(11,12) The release of CGI-58 is important in further lipolysis process because ATGL requires this protein for its full hydrolysis activity.⁽¹³⁾ The presence of perilipin is also necessary for HSL translocation after PKA activation. Some data showed that HSL requires presence of perilipin in order to get access to LD. This process was done by binding of HSL into NH₂-terminal region of perilipin.^(14,15)

ATGL. ATGL is a newly found lipase involved in adipocytes lipolysis process. This enzyme hydrolyzes TG into DG and FA and this enzymatic activity requires CGI-58 as a co-activator protein.⁽¹³⁾ As β -adrenergic receptor stimulates its downstream pathway via PKA, CGI-58 released from perilipin and attach to ATGL. This is shown that the influence of PKA on ATGL is not direct but via CGI-58. Fasting and glucocorticoid are able to increase expression of this protein but food intake and insulin decrease the expression. However, it has been shown that expression level of this protein, as well as HSL, is not always related to its enzymatic activity.⁽⁶⁾

HSL. This lipase was firstly recognized as enzyme that is regulated by the presence of hormone. HSL was found mostly at white adipose tissue (WAT) and brown adipose tissue (BAT). From an animal study, it has been found that mice without HSL activity retained large amounts of DG in several tissues.⁽¹⁶⁾ This report suggested that HSL is important in hydrolysis of DG instead of TG. As ATGL is important in the initiation of TG breakdown, HSL works at the second process that happens during lipolysis. After being stimulated by β -adrenergic receptor, PKA phosphorylates HSL and perilipin. Those proteins then interact thus give chance for HSL to get into LD and hydrolyze DG.⁽⁶⁾ The end product of this process is MG or monoacylglycerol and fatty acid.

MGL. The last step of TG breakdown is done by MGL which hydrolyzes MG into FA and glycerol. This process occurred in LD and only with the activation of MGL. MGL not only works intracellularly but also extracellularly by taking care of MG derived from lipoprotein lipase (LPL). Studies in mice model showed that lack of this enzyme had an impact on the accumulation of MG in both adipose and non-adipose tissue.⁽¹⁷⁾

Pathways Involved in Lipolysis Process

ATGL, HSL and MGL are important components of lipolysis process in adipocytes. In order to stimulate this machinery, several regulatory pathways have been recognized. The well-known pathway for lipolysis is through adenylyl cyclase (AC) which is activated by stimulus of hormones (especially catecholamine) in β -adrenergic receptor. There are also other pathways that responsible to induce lipolysis in adipocytes, including guanylyl cyclase (GC), mitogen-activated protein kinase (MAPK) and protein kinase C (PKC). Some downstream signals on those pathways interact with each other and possibly induce multiple signaling processes. There are also other downstream pathways that are specific for certain tissue or organism, in this review we only focus on pathways and their downstream molecule on human adipose cells (Fig. 2).⁽⁵⁾

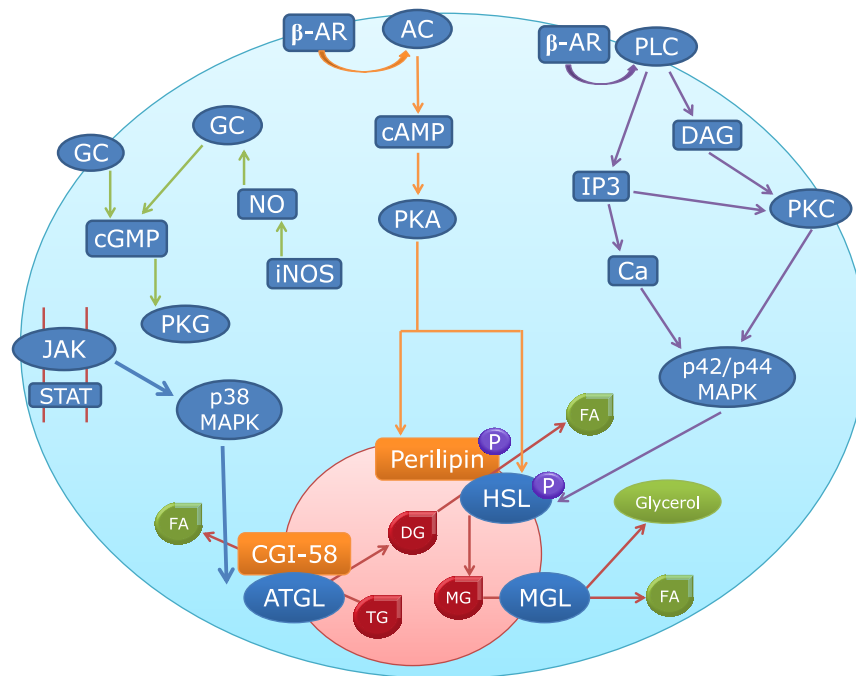


Fig. 2. Lipolysis pathway in human adipose tissue. There are 4 main pathways responsible for regulation of lipolysis process including JAK, GC, β -AR (with AC), and β -AR (with PLC). AC, adenylyl cyclase; β -AR, β -adrenergic receptor; GC, guanylyl cyclase; JAK, Janus Kinase; MAPK, mitogen-activated protein kinase; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, Phospholipase C; STAT, Signal Transducer and Activator of Transcription.

Adenylyl cyclase. Catecholamine is one of the most influential signals that induces lipolysis through AC pathway. This hormone firstly binds β -adrenergic receptor which is located at the surface of adipose tissue. The signal is then followed by activation of AC which increases cAMP concentration and the downstream molecules (PKA). The activated PKA then induces lipolysis by phosphorylation thus followed by translocation of HSL from cytoplasm into LD. PKA is also responsible for phosphorylation of perilipin giving an opportunity for HSL to get in touch with its substrate in LD.⁽¹⁶⁾ There are also several other hormones and proteins that regulate lipolysis via AC pathway. Melanocyte Stimulating Hormone (MSH) has a potent lipolytic effect via AC stimulation by melanocortin receptors.⁽¹⁸⁾ Targeting G-protein-coupled receptor, thyroid-stimulating hormone (TSH) activates AC via activation of G-protein.⁽¹⁹⁾ Studies have shown that TSH treatment *in vitro* not only increases cAMP level but also induces HSL and perilipin phosphorylation.⁽²⁰⁾ *In vivo*, TSH treatment was able to induce lipolysis as seen in increasing level of FA.⁽¹⁵⁾

Phospholipase C. It has been proposed that β -adrenergic stimulation induces lipolysis independently from cAMP pathway. In 3T3-L1 adipocyte, the agonist of β_3 -adrenergic receptor activates p42/p44 MAPK pathway which leads to lipolysis process.⁽²¹⁾ The increasing level of p42/p44 MAPK then stimulates lipolysis via phosphorylation of HSL. Furthermore another study found that this effect worked in acutely and in maximal effective agonist concentration suggesting that this effect only happened when there is a high amount of sympathetic signals to WAT.^(16,21) It has been proposed that induction of lipolysis using PLC pathway is an additional effect to increase the effect of lipolysis during certain kind of physiologic situation human body.⁽²¹⁾

Guanylyl cyclase. Signals that activate GC pathway induce lipolysis through protein kinase G (PKG) activation. One of the most studied regulators of lipolysis via this pathway is arterial natriuretic peptide (ANP) and tumor necrosis factor alpha (TNF- α).⁽²²⁾ It has been shown that ANP induces activation of cGMP.

This process then leads to activation of PKG and induces phosphorylation of perilipin and HSL, leading to further lipolysis process.⁽²³⁾

Mitogen-activated protein kinase. TG hydrolysis in human adipose tissue can also be initiated by leptin. This hormone interacts with lipolysis machinery via its binding to transmembrane receptors.⁽¹⁶⁾ JAK-2 (Janus Kinase-2) is one of the most important candidates in this pathway and this protein is associated with intracellular protein STAT (Signal Transducer and Activator of Transcription).⁽²⁴⁾ Once activated, STAT is activated too and translocated into nucleus and initiates transcription process.⁽²⁴⁾ There is evidence that leptin stimulation did increase ATGL expression.⁽²⁵⁾

Genetic Polymorphisms on Lipolysis Pathways and Weight Loss

The role of genetic make-up and responsiveness to weight loss treatments have been investigated for years. Some SNPs from protein related lipolysis either in exon or intron region have been identified. Although reports from epidemiological studies showed that those SNPs are related to obesity, their relation to weight loss is still controversial. Hereby we reviewed some publications which showed the role of SNPs at the lipolysis pathway and weight changes during weight loss treatment done in recent years.

Perilipin. As mentioned before, perilipin plays an important role in the regulation of lipolysis in adipocytes and regulation of its expression had an impact on the systemic metabolic profiles. A study using genetically modified mice shown that *Perilipin* (*Plin*)^{-/-} knockout increased β -oxidation in adipose tissue as well as muscle and liver.⁽²⁶⁾ The other study shown that *Plin1* knockout mice model were more resistant to obesity compared to wild-type in high-fat diet treatment.⁽²⁷⁾ In this study, they also found that basal and isoproterenol mediated lipolysis was increased. Pietri-Rouxel shown that *Plin*^{-/-} knockout mice had smaller white adipose tissue, higher muscle tissue and elevated basal lipolysis

which explain the importance of this gene in weight regulation.⁽²⁸⁾

Although evidence from animal studies were somewhat convincing, the relationship between PLIN expression and obesity is controversial in human. A study done by Kern *et al.*⁽²⁹⁾ showed that perilipin 1 mRNA was higher in adipose tissue of obese individual while Wang *et al.*⁽³⁰⁾ showed the expression of this gene was lower in severely obese individuals compare to non-obese individuals. Smith and Ordovas⁽³¹⁾ argued that this difference was found due to characteristic of the subjects and degree of obesity that were analyzed. One of the proposed factors that influence the expression of this gene is a genetic variation between individuals. Mottagui-Tabar *et al.*⁽³²⁾ discovered that in a subject with AA (minor allele) genotype in rs894160 of PLIN1 gene had lower adipocyte perilipin content compared to GG genotype.

The role of PLIN polymorphism and obesity had been rigorously investigated. Variation in genetic make up of PLIN is related to many obesity traits including anthropometric profiles, lipid profiles and glucose-related phenotypes.⁽³¹⁾ However, there is limited data on the influence of PLIN genetic variation to weight loss. Intervention studies done from various countries such as The Netherlands, Spain, Korea and Brazil had raised promising results that PLIN could be used as a predictor of weight loss but the results are still being questioned.⁽³³⁻³⁶⁾ Corella *et al.*⁽³³⁾ shown that obese subjects who had A allele of PLIN 11482G>A rs894160 reduced less weight while Jang *et al.*⁽³⁴⁾ showed no effect of this genotype. In Brazilian obese children and adolescents, Deram *et al.*⁽³⁵⁾ found that subjects with T allele of PLIN6 14995A>T rs1052700 reduced more weight after a lifestyle intervention.

It is suspected that differences in weight loss treatment between each study were the reason each finding showed different outcomes. For example, study by Corella *et al.*⁽³³⁾ used 1,200 kcal a day as energy restriction program while Jang *et al.*⁽³⁴⁾ only used 300 kcal reductions a day. This difference could give a big impact in the amount of energy received. In study done by Jang *et al.*⁽³⁴⁾ an individual can have 2,700 kcal a day for his/her daily needs and receive 2,400 kcal for energy restricted diet which already twice as much received by individual from Corella *et al.*⁽³³⁾ The influence of the number of subjects as well as subject distribution among each genotype may also influence the result.

Adrenergic receptor beta 3. One of the major lipolysis signals given by catecholamine is being able to activate α - and β -adrenergic receptors (AR). Subtypes of β -AR (β_1 -AR, β_2 -AR, β_3 -AR) are expressed in several tissues including adipose tissues.^(37,38) ADRB3 is the gene that encodes for β_3 -AR, protein that works as a regulator of lipolysis as well as thermogenesis. From all adrenergic receptor, ADRB3 is the most interesting gene to investigate in terms of the effect of its genetic variance and obesity. In 1995, Clement *et al.*⁽³⁹⁾ introduced miss-sense mutation in ADRB3 gene at codon 64 (Trp64Arg rs4994) to be responsible for weight changes in obese individuals. This mutation replaces tryptophane into arginin thus reduces the ability of receptor to maximally activate cAMP formation. Interestingly, studies found that there is no change in pharmacological properties of this protein.^(40,41)

This finding is supported by both *in vivo* and *in vitro* studies with hypothesis that Trp64Arg rs4994 mutation regulates weight changes via lipolysis process. An interesting study done by Umekawa *et al.*⁽⁴²⁾ showed that Trp64Arg rs4994 mutation lowered lipolytic activity of β_3 -AR in human adipose cells. Fat cells were taken from omental fat depot of 18 patients during hyperectomy. Using L-755,507, a selective human β_3 -AR agonist, lipolytic activity of adipocyte with Trp64Arg rs4994 was detected to be lower than wild type. *In vivo*, this mutation has been shown to be able to control fat oxidation during exercise. From the study, it was reported that healthy young Japanese males with Trp64Arg rs4994 polymorphism in β_3 -AR produce less fat oxidation during exercise.⁽⁴³⁾

Physical exercise is an important part in weight loss program. Together with the fact that individuals with Trp64Arg mutation has less fat consumption leading to assumption that this mutation is responsible for less responsiveness to weight loss treatment. However this is not always supported by human intervention studies. Study in individuals with obesity,⁽⁴⁴⁾ individuals with obesity and type2DM and postmenopausal Japanese women showed that subjects with Trp64Arg rs4994 mutation had less weight reduction after lifestyle intervention.^(45,46) However, other intervention studies showed no significant differences between genotypes after various weight approaches.⁽⁴⁷⁻⁵⁰⁾ Although Tchernof *et al.*⁽⁴⁷⁾ did not observe a significant differences in weight reduction, they found out that intra-abdominal area of subjects after weight loss treatment reduced less in subjects with Trp64Arg mutation compared to wild type.

Adrenergic receptor beta 2. β_2 -AR has been reported to be blunted in obese individuals and the reason of this change is still under investigation.⁽⁵⁾ A study done in women with obesity showed that genetic variability plays an important part in adipose tissue β_2 -AR functioning especially on lipolysis process.⁽⁵¹⁾ In 140 women, it was found that Gln27Glu is related to obesity, the polymorphism itself is not related to β_2 -AR function. However, the other polymorphism, Arg16Gly rs1042713, was related to changes in β_2 -AR function without changing β_2 -AR expression. This was also supported by study by Jocken *et al.*⁽⁵²⁾ by showing that variation in ADRB2 is associated with changes in β_2 -AR mediated lipolysis in overweight and individuals with obesity.

The role of this polymorphism on lipolysis during exercise which theoretically should improve energy usage is potential to influence weight loss. This idea has been investigated before. By comparing 8 obese women with Glu27Glu rs1042714 with 7 obese women with Gln27Gln rs1042714 matched by age, BMI, percentage of body fat mass, waist-to-hip ratio and peak oxygen consumption, Macho-Azcarate *et al.*⁽⁵³⁾ analyzed the role of β_2 -AR polymorphism on lipolysis and fat oxidation. As a result, they found that Glu27Glu rs1042714 polymorphism on β_2 -AR had less lipolysis process during exercise which showed by lower level of glycerol produced.

The influence of Gln27Glu rs1042714 polymorphism of ADRB2 gene on obesity has been reported in a meta-analysis from various ethnic groups including 14,444 subjects. In a study by Jalba *et al.*⁽⁵⁴⁾ stated that Glu27 allele rs1042714 is a significant risk factor for obesity among Asians, Pacific Islanders and American Indians but not Europeans. Recently, there is data shown that polymorphism of ADRB2 gene is also related to weight loss during an energy restricted treatment. Ruiz *et al.*⁽⁵⁵⁾ proved ADRB2 Gln27Glu rs1042714 polymorphism modulated the effect of diet changes to weight and body composition. Subjects who carried Glu allele lost more weight than those without Glu allele. Perhaps Gln27Glu rs1042714 polymorphism is more important than Arg16Gly rs1042713 because from both studies, Arg16Gly rs1042713 has no relationship either with risk obesity or weight changes in energy restricted diet.^(54,55)

Lipolysis Enzymes. There is evidence that the variability of protein at downstream pathway of β -AR signal also plays an important role in regulating lipolysis. Jocken *et al.*⁽⁵⁶⁾ showed that genetic variation in HSL gene (allele 184 i7 and allele 240 i6) influences fat oxidation process via β -AR. This study is supported by Hoffstedt *et al.*⁽⁵⁷⁾ using abdominal subcutaneous fat cells from 117 men and women showing that subjects with allele 5 of the HSLi6 polymorphism had less sensitivity for norepinephrine and cAMP stimulation. There is not much data available to confirm the relationship between HSL polymorphism and weight changes although it is indicated that this polymorphism is related to obesity. A study done in Swedish population showed that people with A5 polymorphism in HSLi6 has increased risk to become obese (Table 1).⁽⁵⁸⁾

Table 1. SNPs on lipolysis related genes and weight loss intervention

| SNPs | Country, Authors (Year) ^(Ref) | Subjects | Intervention | Results |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <i>PLIN</i> | | | | |
| PLIN rs2289487 (6209 T>C); PLIN rs894160 (11482 G>A); PLIN rs2304795 (13041 A>G); PLIN rs1052700 (14995 A>T) | Spain, Corella <i>et al.</i> (2005) ⁽³³⁾ | Obese patients | Energy restriction (1,200 kcal) | Subjects with A allele of PLIN 11482G>A reduced less weight. |
| PLIN rs2289487 (6209 T>C); PLIN rs2304794 (10171 A>T); PLIN rs894160 (11482 G>A); PLIN rs2304795 (13042 A>G); PLIN rs1052700 (14995 A>T) | Korea, Jang <i>et al.</i> (2006) ⁽³⁴⁾ | Non-diabetic overweight-obese | Energy restriction (~300 kcal/day) | No significant differences on weight changes |
| PLIN1 rs2289487 (6209 T>C); PLIN4 rs894160 (11482 G>A); PLIN5 rs2304795 (13041 A>G); PLIN6 rs1052700 (14995 A>T) | Brazil, Deram <i>et al.</i> (2008) ⁽³⁵⁾ | Obese children and adolescents | Lifestyle intervention with balanced diet education. | Subjects with T allele of PLIN6 14995A>T reduced more weight. |
| PLIN1 rs2289487 (T>C); PLIN4 rs894160 (G>A); PLIN6 rs1052700 (A>T) | The Netherlands, Soenen <i>et al.</i> (2009) ⁽³⁶⁾ | Overweight or obese | Very low calorie diet (500 kcal/day for 6 weeks) followed by weight maintenance for a year | Haplotype PLIN1 and PLIN4 influence weight changes during very low calorie diet and weight maintenance. |
| <i>ADRB3</i> | | | | |
| Trp64Arg rs4994 | Japan, Yoshida <i>et al.</i> (1995) ⁽⁴⁴⁾ | Obese women | Low-calorie diet and exercise regimen | Trp64Arg mutation reduced less weight. |
| Trp64Arg rs4994 | Japan, Sakane <i>et al.</i> (1997) ⁽⁴⁵⁾ | Obese women with type2 DM | Low-calorie diet and exercise regime | Trp64Arg mutation reduced less weight. |
| Trp64Arg rs4994 | Finland, Fogelholm <i>et al.</i> (1998) ⁽⁵⁹⁾ | Obese women | Very low calorie diet | Trp64Arg mutation together with A>G mutation in UCP1 reduced less weight. |
| Trp64Arg rs4994 | United States, Tchernof <i>et al.</i> (2000) ⁽⁴⁷⁾ | Obese postmenopausal women | Low calorie diet with 1,200 kcal | Weight loss between genotype was not statistically different. Trp64Arg carriers reduced less intra-abdominal area. |
| Trp64Arg rs4994 | Korea, Kin <i>et al.</i> (2004) ⁽⁴⁸⁾ | Overweight/obese with CAD or metabolic syndrome | Energy restriction (~300 kcal reduction /day) | No significant differences on net weight changes between groups |
| Trp64Arg rs4994 | Japan, Lee <i>et al.</i> (2006) ⁽⁴⁹⁾ | Middle-aged overweight women | Lifestyle modification BW reduction program | No significant differences between groups. |
| Trp64Arg rs4994 | Japan, Shiwaku <i>et al.</i> (2003) ⁽⁴⁶⁾ | Postmenopausal women | 10% reduction calorie intake, exercise and support group | Trp64Arg rs4994 mutation reduced less weight. |
| Trp64Arg rs4994 | Japan, Kuriyama <i>et al.</i> (2008) ⁽⁵⁰⁾ | Overweight Middle-aged Japanese | Diet, exercise and support group therapy | No significant differences between groups. |
| <i>ADRB2</i> | | | | |
| Arg16Gly rs1042713; Gln27Glu rs1042714 | Spain, Ruiz <i>et al.</i> (2011) ⁽⁵⁵⁾ | Obese women | Energy restriction (~600 kcal reduction /day) | 27Glu allele rs1042714 had greater reduction in body weight. There is no effect of Arg16Gly on weight loss. |

Discussion

In this review we summarized studies on the relationship between genetic polymorphisms in lipolysis pathway and weight loss. There was evidence that even polymorphism in one single gene can influence the ability of an individual to response to lipolysis process. In a larger scale, some studies showed that genetic background is associated with weight loss during energy restriction diet or lifestyle intervention.

Until recently, there is not enough evidence showing the importance of these SNPs on weight loss. PLIN and ADRB3 are the most studied gene polymorphisms in terms of their association with weight loss. However, those studies were not conclusive enough because of number of subjects used and controversial in the results of the analysis. Thus, replication and confirmation on the role of those genes are important to be done. Replication is also needed to confirm the role of ADRB2 and HSL polymorphisms on weight changes. This is because several studies had shown that the potential effect of those gene as the predictor of weight loss due to their ability to influence lipolysis process.

However, it is important to keep in mind that there might be an interaction between genes involved in lipolysis process. Thus integration in the analysis of lipolytic related protein is essential. Integration of analysis in these genes might be interesting to see how genes in one single pathway influence the weight changes during lifestyle intervention.

Lifestyle intervention for weight loss program was varied between countries, and sometimes between research institutes

within a country. This of course will lead to confusion because of the phenotypic effect that would be modified due to differences in the treatment. One of the most obvious examples is the weight loss study between Corella *et al.*⁽³³⁾ and Jang *et al.*⁽³⁴⁾ as mentioned previously. Replication of genetic data could be done well if treatment is given in the same manner. It supposed that the effect of Trp64Arg ADRB3 gene polymorphism on weight loss was consistent between race, as shown by study done in Finland and Japan.^(44,45,59)

Based on studies compiled in this review, it is necessary to highlight that genetic profile from proteins involved in lipolysis pathway is potential to be used for the development of personalized diet. The emerging nutrigenomic field has an implication on future diet therapy as it is proposed that tailored diet based on genetic profile could give better impact on diet therapy. This idea was based on the fact that individual responses to diet were varied due to their genes. Data on genetic polymorphism in lipolysis pathway perhaps can help develop formulation on weight loss program for obese individuals.

Conclusion

This paper describe the importance of genetic variation on weight loss in overweight or obese adults and several SNPs were potential to be indicator of weight loss during lifestyle intervention program. PLIN and ADRB3 are the most studied gene polymorphisms and their role on weight loss has been evaluated. There were variation between results because the lifestyle intervention

for weight loss program varied between countries, and sometimes between research institutes within a country. Thus, replication and confirmation on the role genetic variation based on set of genes involved in lipolysis pathway are important to be done in the future.

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Conflict of Interest

There was no conflict of interest in the making of this review, no support from any organisations for the submitted work and no other relationships or activities that could appear to have influenced the submitted work

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