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The polymorphisms of UCP1 genes associated with fat metabolism, obesity and diabetes

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Abstract Uncoupling protein 1 (UCP1), a 32-kDa protein located in the inner mitochondrial membrane, is abundant in brown adipose tissue, as a proton transporter in mitochondria inner membrane which uncouples oxidative metabolism from ATP synthesis and dissipates energy through the heat. UCP1 has been reported to play important roles for energy homeostasis in rodents and neonate of larger mammals including human. Recently, numerous candidate genes were searched to determine the genetic factors implicated in the pathogenesis of obesity, related metabolic disorders and diabetes. UCP-1, which plays a major role in thermogenesis, was suggested to be one of the candidates. This review summarizes data supporting the existence of brown adipocytes and the role of UCP1 in energy dissipation in adult humans, and the genetic variety association with the fat metabolism, obesity and diabetes.

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Introduction

Corrent, obesity is a global health problem, as it is associated frequently with type 2 diabetes (T2D) mellitus and cardiovascular disease and also decreases longevity. In the etiology of obesity, the contribution of the thermoregulatory mechanisms to body weight regulation appears to be critical in homeothermic animals [56, 64, 83]. Obesity, a multifactorial disorder with both environmental and genetic influences, is basically late-onset and its incidence apparently increases with age, being prominent after the age of 20–30 years [52]. However, some studies [33, 99, 103, 104, 110] indicated that most familial aggregation of obesity is caused by genetic influence rather than by shared environment. A family history of T2D are all risk factors for T2D in humans [112]. Both obesity and insulin secretion show high heritabilities, thus suggesting a genetic contribution to these traits and would increase diabetes risk [2, 15, 28]. For this reason, a number of studies have focused on the genes related to thermogenesis, such as those encoding adrenergic receptors (AR) and uncoupling proteins (UCP), have been considered as candidate genes for human obesity and T2D [11, 12, 49, 78].

The UCP1 a 32-kilodalton protein located in the inner mitochondrial membrane has been known to be mainly expressed in brown adipose tissue (BAT), in which UCP1 allows protons to re-enter the matrix, bypassing the ATP synthase. The usually low proton conductance of the membrane is increased, which results in an acceleration of mitochondrial respiration. The dissipation of the proton electrochemical gradient leads to an uncoupled respiration

and heat production, the main function of BAT [76]. UCP1 expression is strongly induced when thermogenesis is required [84]. Involvement of BAT in cold-induced thermogenesis is well established and data from rodents have also demonstrated its role in diet-induced thermogenesis (DIT) [85, 98]. UCP-1 had been thought to be expressed only in brown adipose tissue before; however, it was recently reported that UCP-1 mRNA and/or protein were detected in the white adipose tissue of mouse and humans [6, 21], in human skeletal muscle [72] and in human longitudinal smooth muscle layers [75], in mammalian islet cells [90], in rat and mouse thymocytes [1]. UCP1 in resistance against diet-induced obesity was postulated from the results of studies on transgenic mice [50, 60, 65] and plays an important role in thermogenesis and energy expenditure and is implicated in the pathogenesis of obesity and metabolic disorders in human [6, 21, 37, 63].

The human UCP-1 gene has been located on a long arm of chromosome 4 [9], and the first genetic polymorphism of UCP-1, a *BclI* restriction fragment length polymorphism, was found from Quebec Family Study in 1994 [78], and its molecular nature was elucidated to be an A → G point mutation in -3826 position from the TATA box in the 5′-flanking region of UCP-1 gene (A-3826G) [10]. Until now, many association studies were conducted in various populations to elucidate the association of A-3826G polymorphism with obesity phenotypes, diabetes mellitus and lipid/lipoprotein-related disease [31, 42, 77, 78]. The polymorphisms, A-1766G and A-112C at the 5′-flanking region and Ala64Thr polymorphism in exon 2 of UCP-1 gene were found and shown to be associated with body fat accumulation and body weight gain or body mass index (BMI) as well [26, 32, 43, 44]. This review summarizes data supporting the existence of brown adipocytes and the role of UCP1 in energy dissipation in adult humans, and the genetic variety association with the fat metabolism, obesity and diabetes.

Expression of UCP1 protein and its mRNA

Uncoupling protein 1 was identified in BAT in the mid 1970s, and its cDNA was cloned in 1984. It has since been found to reside in the inner mitochondrial membrane in BAT [36]. It has a tripartite structure, consisting of three repeated domains about 100 residues each, with three extended polar matrix loops, and six intramembranes domains. The N- and C- terminals both face the intermembranous space [24].

Uncoupling protein 1 had been thought to be expressed only in rodents and human infants before, however, UCP-1 protein and (/or) its mRNA expression were detected from periadrenal and perirenal adipose tissue of adult human [21], and from perirenal fat of adult patients with pheochromocytoma [6], and from axillary [59], perirenal [21, 57, 59], omental and subcutaneous adipose tissue of human infants, children and adults [21, 57, 59] and from single adipocytes (dispersed BAT) of white adipose tissue (WAT) [6] or by reinduction in response to certain stimuli as chronic cold exposure [62], chronic sympathetic stimulation [21, 82], presence of pheochromocytoma [5, 21, 59, 82], alcoholism [54], sudden infant death syndrome [54] or hibernoma [114], and around neck arteries and in the pericardium of outdoor workers [38] as well as long-term alcohol consumers [37]. Esterbauer et al. [16] measured UCP-1 mRNA level in adipose tissues obtained from fat biopsy of 153 morbid obese subjects, and found that UCP-1 mRNA expression levels in adipose tissues were significantly lower in morbidly obese individuals than in lean controls. Furthermore, UCP-1 mRNA expression has been detected in skeletal muscle [72] and in longitudinal smooth muscle layers [75], in mammalian islet cells and associated with acute insulin response to glucose in African American families [90]. Recently, it has been demonstrate that UCP1 is present in rat and mouse thymocytes, they conclude that ablation of UCP1 in thymocytes effects susceptibility of thymocytes to apoptosis [1]. However, the physiological functions of UCP1 in theses tissue and organs are not established as well as in BAT. Future work will determine the role of UCP-1 in muscle tissue, islet cells and thymus function.

BAT thermogenesis and functions of UCP1

Himms-Hagen and Desautels [35] showed that BAT metabolism played a role in obesity development, and that obese mice had a defect in the mechanisms necessary for the activation of BAT thermogenesis. It was hypothesised that this defect might be the reason for obesity in the ob/ob mouse. Later the hypothesis gained support by many studies, that defective BAT thermogenesis is involved in the development of obesity in most rodent models, and activation of BAT thermogenesis reduces weight gain in these animals [105, 107]. Rodents with genetic forms of obesity have decreased brown fat sympathetic activity and decreased thermogenesis [34]. Transgenic mice with decreased brown fat mass are characterized by obesity, initially in the absence of hyperphagia, but later in life they develop hyperphagia, indicating a major role of brown fat on energy balance and food intake [8, 65]. Furthermore, it also has been demonstrated that these mice are glucose intolerant and insulin resistant [25]. Although the amount of BAT is reported to be decreased in human adult, it is still responsible for 1–2% of the energy expenditure, preventing a weight gain of 1–2 kg/year [7, 45, 58]. This small portion of energy expenditure can increase the risk for obesity and related metabolic disorders when accumulated for decades [81]. It is obvious, that BAT is a thermogenic organ, present in almost all mammals where it is a major site of

cold-induced non-shivering thermogensis as well as contributing to diet-induced thermogenesis [88].

Non-shivering thermogenesis, for the maintenance of homeothermy, is the main function of BAT. This is particularly important in small and newborn mammals as well as for arousal of hibernators [106]. In rodents, BAT dissipates energy as heat in response to cold exposure or to excessive ingestion of energy (DIT) [86]. The thermogenic response to food intake includes two categories of thermogenesis, an obligatory component related to the energy cost of assimilating nutrients, and an adaptive component [34, 87]. The adaptive DIT represents loss of energy resulting in a decrease in energetic efficiency. It is stimulated by hyperphagia but it depends on age, genotype, environmental temperature, response to nutrient imbalances and other factors [101, 102]. The thermogenic activity of BAT is dependent on its amount, its UCP1 content, and the degree of stimulation by the sympathetic nervous system [106].

It has been demonstrated that thermogenesis in BAT is due to UCP1. UCP1 is exclusively expressed in brown adipocytes, where the gene expression is increased by cold, adrenergic stimulation, β3-agonists, retinoids and thyroid hormone [96]. Only in BAT, UCP1 does affect heat production. It dissipates a proton-motive force by mediating H+ backflow. A schematic diagram indicating the principle of uncoupling in BAT is depicted in Fig. 1 [47, 74]. UCP1 is a major thermogenetic factor and activator when mitochondria are largely uncoupled and the ATP: ADP ratio is low [48]. The presence of UCP1 has been used as the diagnostic criterion to identify BAT [27]. Transgenic mice that overexpress UCP1 in WAT were created (aP2-UCP1 mice) [50]. These mice express a thermogenically active UCP1 and have reduced white fat stores [4, 51], but they present BAT atrophy and homozygous animals are cold-sensitive [100]. Mice expressing the diphtheria toxin in BAT were also developed (UCP-DTA mice) [65]. The expression of the diphtheria toxin under UCP1 promoter control induces specific BAT atrophy. Transgenic mice show a decrease in their internal temperature after cold exposure, which is indicative of BAT dysfunction. Furthermore, these mice gain excessive weight and develop diseases related to obesity (insulin resistance, hyperinsulinaemia, hyperglycaemia, and hyperlipidaemia observed in non-insulin-dependent diabetes mellitus) [25, 65]. The hyperphagia of these animals is still subject to debate [46, 65, 68], and measurements of metabolic rate and body temperature show that these transgenic mice have a lower body temperature, around 0.9°C less [46]. The attenuated body temperature could be responsible for obesity development more than hyperphagia. UCP1 is responsible for NST, for the maintenance of homeothermy, is the main function of BAT. This is particularly important in small and newborn mammals as well as for arousal of hibernators in infants and small mammals [13, 91, 106]. It has been suggested that the UCP1 system in BAT could act as an important site of facultative energy expenditure and provide a defence against obesity [20].

Furthermore, UCP1 is considered to influence anionic fatty acids, so they are able to return in a protonated form via the lipid bilayer. The overall cycle leads to H+ translocation [40, 97] and, hence, to uncoupling. Indeed, UCP1 can be regarded as a pure anion transporter, strictly specific for monovalent unipolar anions [39]. It might participate in futile cycling of unipolar ketocarboxylates under certain physiological conditions while expelling these anions from the matrix. The cycle is completed on their return via the pyruvate carrier in an H+ symport mode [40].

The genetic organization and variants of UCP1 in human beings

In human beings, as showed in Fig. 1, UCP1 is located on chromosome 4 and has relatively six exons. Several single nucleotide polymorphism (SNP), such as A-3826G SNP in

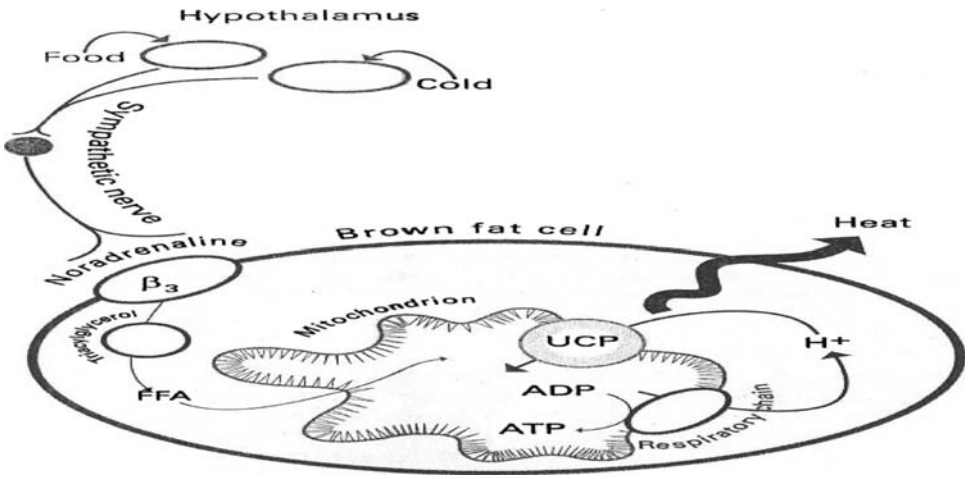

Fig. 1 Schematic diagram illustrating how BAT generates heat: The UCP in the brown fat cell allows protons (H^+) to leak and to pass through the inner mitochondrial membrane when activated by cold and diet, thereby decreasing the proton gradient needed to drive synthesis of ATP and free fatty acid [Adapted from 14, 74]

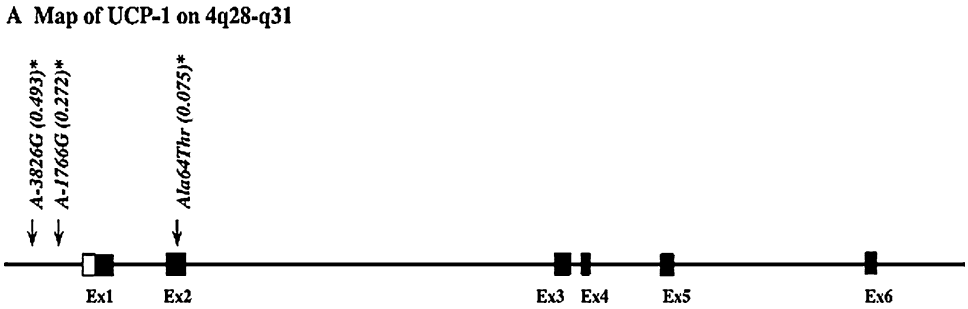

Fig. 2 SNP-map of A the UCP1 genomic region [Adapted from 94]

the promoter, A-1766G polymorphism at the 5′ flanking region,Ala64Thr G/A at +1068 position from the transcription start site, in exon 2 of UCP1 (Fig. 2), have been elsewhere reported to associate with obesity phenotypes, diabetes mellitus and lipid/lipoprotein-related disease, body fat accumulation and body weight gain or body mass index (BMI) [26, 31, 32, 42, 43, 55, 77, 78].

Genetic variation in the promoter of UCP1 gene

Most association studies about the physiological effects of UCP-1 genetic polymorphism were focused on A-3826G, and many studies were conducted in various populations to elucidate the association of this polymorphism with obesity, biochemical parameters and diabetes. Oppert et al. [78] analyzing with among 261 Canadians for 12 year follow-up, a genetic polymorphism of UCP-1 (*BclI* restriction fragment length polymorphism) was found from Quebec family study. The frequent A/G substitution at position -3826 upstream of the UCP1 gene has been related for long time to obesity and weight gain in 261 Canadians. This was the first study to find an association between BMI and the G variant of UCP-1 in Caucasians [78]. Its molecular nature was elucidated to be an A → G point mutation in -3826 position in the 50 flanking region of UCP-1 gene [10]. Following, many association studies were conducted in various populations to elucidate the association of this polymorphism with obesity phenotypes, diabetes mellitus and lipid/lipoprotein-related disease, but the results were controversial.

The -3826G allele (GG genotype or G type) UCP-1 has been associated with reduced UCP-1 mRNA expression [16] indicating that the polymorphism is of functional importance. It has been reported that that obese women with the -3826G allele were more likely to gain weight over time [78], and a greater frequency of the G variant was found in subjects with Type II diabetes [12] and less likely to lose weight [19]. Kogure et al. [49] reported that 113 Japanese obese subjects were treated with a combined low-calorie diet and exercise for 3 months and the decrease in body weight (BW) was less in obese subjects with -3826G-allele carrier than -3826A-allele carrier, although the food intake, exercise, and initial BMI were similar in these groups. Similarly, study investigating Japanese men (53 lean, 126 overweight) found that subjects who were heterozygous for the G variant had increased BMI [29]. The -3826G allele of UCP-1 was associated with lower BW loss by low calorie diet in French overweight subjects [19], increased BMI, and increased serum glucose level in 526 overweight Australian women [31], reduced postprandial thermogenesis and could have adverse effects on the regulation of BW in healthy boys and may easily become obese as a consequence of abundant fat intake over a long period of time [70], an increased BW and BMI in premenopausal women and with changes over a period of 4 years in postmenopausal women [67]. It has been reported that UCP1-3826G allele frequency was higher in men than in women and in obese women than in non-obese women, base on the 160 obese and/or non-obese men and 172 women in Spain. Their results agree with the previously reported association between UCP1 -3826G allele and obesity [80]. However, in the study of Nakano et al. [73] with 251 young Japanese indicated that, the carriers of the AG heterozygote showed higher BMI than those with other genotypes.

Furthermore, an association was observed between fasting glucose and -3826G variant in women with T2D. The mechanism by which genetic variation of UCP-1 is involved in T2D is not certain but fatty acid metabolism could be involved [31]. The genetic variation of UCP-1 association with the obesity, BMI and BW changes could results from the fat metabolism disorders. Esterbauer et al. [16] reported that AG type of UCP-1 gene was associated with significantly lower high density lipoprotein (HDL) cholesterol level compared A type, even though it was not significantly associated with BMI, diastolic blood pressure (DBP), glucose, total cholesterol, and triglycerides in 153 obese Austrian subjects. Proenza et al. [79] showed that BMI-related increase of cholesterol level was associated with A-3826G polymorphism of the UCP-1 in 271 Turkish subjects. Subjects with the GG type showed significantly more increase in cholesterol levels according to the degree of obesity than AA and AG types. The G allele carrier or GG genotype of the UCP-1 gene was associated with lower HDL cholesterol levels compared to the AA or AG/AA genotype [42]. In agreement with the study of Oh et al. [77] with 90 Korean obese subjects, showed that, DBP and

low-density lipoprotein (LDL) cholesterol were significantly higher in AG and GG types compared with AA type, whereas HDL cholesterol was significantly lower in GG type compared with other types. Similarly, in a study conducted among 182 postmenopausal Japanese women, although changes in body weight and BMI were not significantly different, HDL cholesterol was significantly decreased in the G allele carriers of the UCP-1 gene [67]. It has been reported that the -3826G allele frequency of UCP1 was higher in men than in women and in obese women than in non-obese women [80]. The A-3826G polymorphism of UCP1 association with cold-induced thermogenesis in healthy children in Japan was investigated by Nagai et al. [71]. They found that the GG allele carriers have a reduced capacity for thermogenesis in response to acute cold exposure, suggesting that such reduced UCP1-linked thermogenesis may have adverse effects on the regulation of body weight. The atherogenic index and LDL/HDL ratio were also significantly higher in subjects with GG type, suggesting higher risks of cardiovascular disease. These results suggest that the G allele of UCP-1 gene has a strong association with increased LDL cholesterol level and is strongly related to the increased risk of metabolic disorders such as hyper-LDL cholesterolemia among severely obese subjects in East Asian population.

Even though the above studies have suggested the associations of A-3826G polymorphism with obesity and related metabolic disorders, controversies remain because other reports do not support them. A-3826G polymorphism was not associated with obesity phenotype in 380 Danes [108] and obesity indices in 985 Swedish subjects [20] and current BMI at baseline nor with any changes in BMI after exercise with healthy 106 Japanese men [41]. Schaffler et al. [92] showed that A-3826G polymorphism does not play a major role in the pathogenesis of obesity and diabetes in 1,020 Caucasian cohort, as well as in the development of obesity among 180 Polish overweight subjects [42]. It has been reported that neither allele nor genotype frequencies of A-3826G SNP were significantly different in diabetes complications [89]. There are no associations between UCP-1 A-3826G polymorphism and HDL cholesterol levels [12, 31, 73, 92], and diabetic nephropathy, nor did observe any difference in urinary albumin excretion rate among carriers of different UCP1 genotypes in 218 diabetic patients with normal urinary albumin excretion rate (AER), 216 with micro- or macroalbuminuria, and in 106 control subjects without a family history of diabetes [61], and age, sex, BMI, or HbA1c level between T2D in Japanese individuals [18]. In contract, the 3826G was also significantly associated with higher HDL cholesterol levels in the Hispanic San Antonio families [90]. In the study of Kotani et al. [55] with 298 healthy Japanese subjects (144 males and 154 females, mean age: 45.2 years), found that the GG genotype of UCP-1 A-3826G polymorphism may independently have a significant protective effect on low HDL cholesterol status. In males, HDL cholesterol levels of the GG genotype were significantly higher than those found in the AA genotype. In females, the occurrence rate of low HDL-cholesterolemia was significantly different by genotype: a low prevalence in the GG genotype.

This discrepancy can be partly explained by the differences in the initial BMI distribution of subjects and different haplotypes. In the study of Shin et al. [94] with Korean overweight female subjects, -3826G allele has been found to contain three haplotypes including ht2[GGG], ht3[GAG], and ht4[GAA]. Among them, ht2[GGG] was associated with increased obesity phenotypes and ht4[GAA] was associated with decreased obesity phenotypes. Ht3[GAG] was associated with the change of waist-hip ratio (WHR) and fat mass induced by very low calorie diet. These three haplotypes with different effects may provide some clues for the explanation of the controversial effects of -3826G allele.

Like UCP1, the β3 adrenergic receptor is expressed in BAT and white adipose tissue and plays an important role in the induction of lipolysis and in the regulation of energy homeostasis in rodents. A missense mutation Trp64Arg (Trp64/b-AR) have identified to associate with weight gain and other obesity-related indices, as well as with insulin sensitivity in different populations [11, 95, 111, 113]. Some studies have showed that a synergistic effect of UCP1 A-3826G polymorphism and the Trp64/b-AR mutation on increased tendency to weight gain [12], on lower basal metabolic rate [109], and on resistance to weight loss [17, 49] or subsequent weight maintenance after a low-calorie diet [17]. In contrast, no influence of the Trp64/b-AR variant was observed in interaction with the UCP1 A-3826G polymorphism in the resistance to a low-calorie diet [19]. There are no associations between either polymorphism and the body mass index and serum triglyceride levels in a Japanese male cohort [29]. Similar results were observed in several metabolic parameters related to obesity or diabetes in a Caucasian population [92]. In the study of Matsushita et al. [67] indicated that the A/G polymorphism of the UCP1 gene is associated with increased BW and BMI in premenopausal women and with changes over a period of 4 years in the levels of TG and HDL in postmenopausal women, but the β3-AR polymorphism showed no apparent affect on these parameters.

The ethnical difference, the age and environmental factors as well synergistic effect of genes might be the reason of the controversial results among the different investigations. Previous studies in Japanese adults [49, 93] revealed that the frequency rate of GG allele carriers accounted for over 20% of their subjects, indicating that the frequency rate of the GG homozygote of the UCP1 gene would be higher in Japanese than in Caucasian

populations [22]. -3826G allele frequency is about 2-fold higher in East Asian (Korean and Japanese) than Caucasian populations. It can be hypothesized that higher G allele frequency of the East Asian population is one of the genetic factors that leads to increased susceptibility to obesity-related metabolic disorders compared with Caucasian populations [21, 67, 72, 77, 111].

On the other hand, there was different BAT distribution in the different race and age subjects. As the distribution of active BAT appears during childhood [30, 58], the role of BAT as well as the function of the UCP1 gene has an impact on facultative energy expenditure for Japanese children. Moreover, previous human studies indicated that a low amount of BAT was associated with abdominal obesity in adult males [53], whereas abundant BAT induced by the stimulation of a cold environment was found among Finnish outdoor workers [38]. These discrepancies can be partly explained by the differences in the initial BMI distribution of subjects as well.

Genetic variation in the 5′ flanking region of UCP1 gene

In the report of Kim et al. [43], A-1766G polymorphism, for the first time, has been found in the sequencing of pooled and individual genomic DNA of Korean subjects at the of the UCP-1 gene. A-1766G was an A → G point mutation at -1,766 bp upstream from the transcription start site of UCP-1 gene and is about 2 kb downstream from A3826G. The effects of new polymorphism on body fat were elucidated among 387 Korean female. AG/GG genotype had a significantly higher WHR, body fat mass, and percent body fat than the AA genotype. There were significant increases in the AG/GG type compared to the AA type in the abdominal subcutaneous fat and the abdominal visceral fat, respectively. It may possibly be located in or near the genomic region which is involved in the transcriptional regulation even though more study is needed to prove it. Similarly, the report of Shin et al. [94], showed that the G allele of A-1766G polymorphism displayed its significant association with higher WHR, body fat mass, percent body fat, and CT-measured abdominal fat area. It also showed tendencies to be associated with higher body weight, BMI, CT-measured thigh fat area.

In the study of Mori et al. [69] have reported to find other polymorphism (-112A > C, rs10011540) in 5′untranslated region. The 112A > C polymorphism was an A → C point mutation at 5′untranslated region relative to the translation start codon. The C allele of -112A > C polymorphism was associated both with susceptibility to type 2 diabetes and with decreased activity of the UCP1 gene promoter. In the study Fukuyama et al. [18], indicated that the -112A > C polymorphism of UCP1 gene was associated with both hepatic lipid content (HLC) and homeostasis model assessment of insulin resistance (HOMA-IR), but not with BMI, visceral fat area, or intramyocellular lipid content (IMCL). Thus, the C allelers of -112A > C had significantly greater IMCL, fasting plasma immunoreactive insulin concentration (FIRI), HOMA-IR, and HLC compare with other genotypes. The -112A > C polymorphism of UCP1 gene, through its effect on UCP1 gene promoter activity, may contribute to the accumulation of hepatic lipid and the development of insulin resistance. Association studies between polymorphisms and detailed information like HLC might provide insight into understanding the pathogenesis of T2D. HLC was previously found to be correlated with insulin resistance as evaluated by a hyperinsulinemic–euglycemic clamp [3, 23]. Together, these observations suggest that the -112A > C polymorphism of UCP1 gene is a determinant of hepatic lipid content, which itself is a determinant of insulin resistance [18].

Genetic variation in exon 2 of UCP-1 gene

Ala64Thr polymorphism which is a G/A SNP at +1,068 position from the transcription start site, in exon 2 of UCP-1 gene was found by Hamann et al. [26]. 64Thr allele was reported to be associated with increased WHR among Caucasian subjects [32]. In contrast, 64Thr allele was associated with lower fatness, WHR, and CT-measured fat tissue areas among 453 overweight Korean female subjects recruited from an obesity clinic [94]. An explanation for this discrepancy is hard to find and more study is needed. 64Thr allele frequency of 7.5% among the Korean female subjects was somewhat lower compared with 12% in Caucasian study. The Caucasian study includes both male and female subjects while Korean study includes only female subjects, and the effects of genetic polymorphism may be different by gender. These controversies about the effects of genetic polymorphism in the 5′ flanking region of UCP-1 suggest that more studies are needed in this genomic region [43]. Luan et al. [66] found that the effects of genetic polymorphism on obesity phenotypes could be changed by nutritional characteristic of population. It may be possible that different diet pattern between Caucasian and Asian population could modulate the effect of genetic polymorphism on obesity phenotypes. The effects of this SNP in Caucasian and Asian population should be further studied [94].

Conclusion

Numerous studies have reported that understanding the mechanisms underlying BAT function and UCP1 induction. UCP1 is a major thermogenetic factor and activator in

response for the NST as well as DIT in BAT. UCP1 had been thought to be expressed only in rodents and human infants before, however, UCP-1 protein and (/or) its mRNA expression were detected from human WAT, skeletal muscle, in longitudinal smooth muscle layers, mammalian islet cells, mouse thymocytes. However, the physilogic fuctions of UCP1 in theses tissue and organs are not estiblished as well as in BAT. Future work will determine the role of UCP-1 in muscle tissue, islet cells and thymus function.

The metabolic disorders are a complicated process that involves environmental, nutritional and genetic factors (ethnical difference, age and gender). Many studies of the polymorphisms of A-3826G, A-1766G, A-112C and Ala64Thr in UCP1 association with obesity phenotypes, diabetes mellitus and lipid/lipoprotein-related disease were conducted mainly focus on the Caucasian and Eastern Asian population (Japanese and Korean). It has been shown that mutations change the activity or expression of either protein could diminish regulated or basal energy expenditure by variety in the coupling of oxidative phosphorylation and impact pancreatic functions and insulin secretion. Up to now, it is not clear whether the contribution is of individual genes to the metabolic disorders, or probably a combination of different genetic variants in several genes affecting metabolism and/or thermogenesis that could explain a greater tendency to the metabolic disorders. It may possibly be located in or near the genomic region which is involved in the transcriptional regulation. Notwithstanding UCP1 role in obesity phenotypes, diabetes mellitus and lipid metabolism were different even contradictory. Taken together, all of these data indicate that the UCP1 gene is an excellent candidate for these diseases. The further studies need to investigate these genetic polymorphisms of UCP1 in various populations to elucidate the molecular and metabolic mechanism of association of these polymorphisms with obesity phenotypes, diabetes mellitus and lipid/lipoprotein-related disease.

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