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Frequency of C825T G protein β3 subunit gene polymorphism and its association with obesity in the Kyrgyz population

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Abstract

Objective: To examine the frequency of C825T G protein β3 subunit gene polymorphism and its association with obesity of ethnic Kyrgyz.

Methods: The study enrolled 210 people, 89 patients (35 females, 54 males) with obesity (BMI ≥ 30 kg/m2) and 121 practically healthy patients (38 females, 83 males) with normal body weight and no signs of type 2 diabetes (group of control), who were not observed before by a cardiologist. The blood pressure, anthropometry, glucose and lipid profile were examined among all subjects. Genomic DNA was extracted from peripheral blood cells. G protein β3 subunit C825T polymorphism was determined by polymerase chain reaction (PCR).

Results: TT and CT genotypes carriers were grouped together in one group because the TT genotype was rare. CT + TT genotype frequency in the group with obesity made 0.72 and was significantly higher than that in the control group - 0.52 (χ2-8.44; P = 0.004; odds ratio - 2.55; 95%CI 1.31-4.23). The statistical analysis revealed that hypertension (45% vs. 31.3%, P = 0.049) and obesity (51.2% vs. 30%, P <0.01) occurred significantly more often in CT + TT genotype carriers than in the CC homozygotes. The results of the multivariate logistic regression analysis showed that the presence of 825T allele (exp β - 2.89; 95% CI 1.25-6.7; P=0.013), along with the occasional consumption of vegetables (exp β - 3.47; 95% CI 1.52-7.94; P=0.003) was the significant risk factor for obesity, regardless of gender, age and level of physical activity. In the construction of the similar regression model for hypertension, the statistically significant role of 825T allele was lost after adjustment for obesity as an independent variable.

Conclusion: G protein β3 subunit gene C825T allele in the Kyrgyz ethnic group has an association with obesity.

Keywords: G protein β3 subunit C825T polymorphism, Obesity, Hypertension

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Introduction

The prevalence of obesity is increasing in both developed and developing countries and is a serious medical and social problem. On the one hand, obesity is recognized as one of the modifiable risk factors for atherosclerosis, and on the other hand, visceral obesity is identified as one of the "triggers" of insulin resistance (IR) and is

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often associated with high blood pressure (arterial hypertension), lipid and carbohydrate disorders, increasing the risk of type 2 diabetes mellitus (DM) [1].

The lifestyle changes with predominance of refined foods, animal fats and carbohydrates in the diet as well as with decreased levels of physical activity are recognized as causes of obesity. However, environmental factors have a greater impact on individuals with a genetic predisposition. It is believed that genetic factors may cause 40% to 70% of the variation in body weight [2] according to the results of various studies and therefore there is an active search for candidate genes responsible for fat and energy metabolism. These include the heterogeneous G protein localized on the cell membrane consisting of α, β and γ subunits that depend on the interaction of receptor activity. Upon activation of a receptor, G protein forms dimers and trimers, which can activate / inhibit intracellular processes such as ion channel activity, phospholipase, adenylate cyclase and other enzymes [3-5]. There are several known genetic polymorphisms of G protein, of which the most clinically significant is C825T polymorphism β3 subunit. The 825T allele is associated with expression of truncated and functionally active dimer of G protein and increased intracellular signal transduction [6]. Clinical studies showed the association of this polymorphism with susceptibility to obesity and hypertension [7-12]. However, the data from different studies are rather contradictory.

The study of genetic markers of obesity in the Kyrgyz ethnic group was not conducted before so that the goal of the present study was to investigate the relationship between C825T polymorphism of G protein β3 subunit with obesity among ethnic Kyrgyz.

Methods

Subjects

The study enrolled 210 people, of whom 89 patients (35 females, 54 males) were with obesity (BMI ≥ 30 kg/m2) and 121 were age- and sex-matched healthy controls (38 females, 83 males) with normal body weight, with no signs of type 2 diabetes, and were not observed before by a cardiologist. The study did not include those with severe cardiovascular (severe heart failure, stroke, etc.) or physical illnesses (chronic hepatitis, hepatic, renal failure, etc.) which could result in a change in body weight, those with chronic alcoholism, cancer, thyroid dysfunction, pregnant women, and people above 70 years old. The authors received consent from all participants.

All persons involved in the study underwent a clinical examination, including chief complaints and medical history, physical examinations and anthropometric measurements (body weight, height, waist circumference [WC], hip circumference [HC], and blood pressure[BP]). Body mass index (BMI) was calculated through the formula: BMI = weight (kg) / height (cm) ^{2}. A BMI of more than 30 kg/m^2 is considered as obese. The metabolic syndrome was defined according to ATP III criteria [13]. All examined persons were also interviewed through the questionnaire of the Finnish Diabetes Association to assess the risk of development of diabetes [14], including questions on vegetables consumption (every day or not every day) and physical activity (more than or less than 30 minutes per day).

Laboratory exam

Biochemical parameters were performed on SYNCHRON CX4 DELTA (Beckman, USA). Blood samples for determination of biochemical and genetic studies were obtained in the morning after fasting for 12 hours. Blood samples were obtained to determine fasting blood glucose and lipid profile (total cholesterol [TC], high density lipoprotein cholesterol [HDL-C], triglycerides [TG]) in the blood. The level of low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald formula [15].

DNA extraction and genetic analysis

DNA was extracted from the blood cells using Nucleon BACC3 kit (Amersham Pharmacia Biotech, Sweden). G protein β3 subunit C825T polymorphism was determined using polymerase chain reaction (PCR) in thermocycler "Hybaid" using specific primers (forward 5'TGA CCC ACT TGC CAC CCG TGC 3 ' and reverse 5'GCA GCA GCC AGG GCT GGC 3) and subsequent restriction of the PCR products by digestion with BseDI enzyme. The resulting restriction fragments were: TT - 268 bp, TC – 268+152+ 116 bp and CC – 152+ 116 bp. Scanning restriction fragments in 3% agarose gel and analysis of the results was performed using image-densitometer GelDoc-It (UVP, USA).

Statistical analysis

Statistical analysis was performed us-

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ing SPSS version 17.0. Comparison of variables with normal distribution was performed using student's t-test, data are presented as mean ± standard deviation. Variables with nonparametric distribution were compared using the Mann-Whitney test, data are presented as median (25%-75%). The relationships between qualitative variables were assessed using chi-square test and the odds ratio (OR) with 95% CI. The logistic regression model with stepwise inclusion of variables was used to identify the main factors influencing the development of obesity in the study group. For all statistical tests P <0.05 was used as the criterion for statistical significance.

Results

The clinical characteristics of patients are shown in Table 1.

There were no statistically significant differences between groups in terms of sex and age. According to the criteria of division of patients into groups, those with obesity had higher BMI and more frequent metabolic syndrome, hypertension with higher systolic and diastolic blood pressure numbers, type 2 diabetes and increased fasting blood sugar as well as higher values of triglycerides and lower concentrations of HDL-cholesterol.

The incidence of G protein β3 subunit C825T polymorphism genotypes and alleles in the two groups is shown in Table 2.

Genotype distribution and allele frequencies followed the Hardy–Weinberg equilibrium. The heterozygous (CT) genotype was frequently reported among the groups. Because homozygous TT genotype was relatively rare (less than 5%), those people with mutant alleles were combined into one group to conduct a statistical analysis. It was revealed that the presence of CT + TT genotype occurred significantly more often in obese patients than in those without obesity. Mutant alley carriers have up to 2.5-fold increased risk of obesity (Figure 1).

It was revealed that the T allele car-

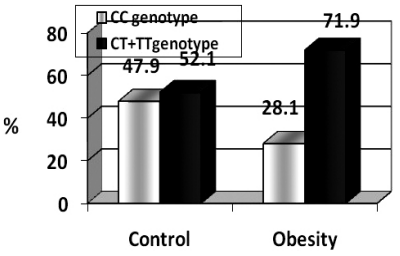

Figure 1. Relationship of G protein β3 subunit C825T polymorphism with obesity
Note: χ^2- 8.44; P = 0.004; OR 2.55 (95% CI 1.31-4.23)

Table 1. Clinical characteristics of patients

Indicators	Control n – 121	Obesity n – 89	p
Sex (male), n (%)	83 (69)	54 (61)	ns
Age, years	50.5±8.03	51.2±7.3	ns
AH; n (%)	15 (12.4)	68 (76.4)	<0.0001
SBP: mm Hg	124±16	149±25	<0.0001
DBP; mm Hg	80±10	93±14	<0.0001
BMI kg/m2,	24.9±2.7	33.0±3.1	<0.0001
Family history on CVD, n (%)	31 (25.6)	30 (33.7)	ns
Type 2 DM; n (%)	0	27(30.3%)	<0.0001
Fasting glucose; mmol/l	5.3±0.7	6.7 ± 2.5	<0.0001
MC, n (%)	31 (25)	71 (78)	<0.0001
TC, mmol/l	5.08±0.96	4.96±1.07	ns
HDL-C; mmol/l	3.2±0.84	3.13±0.85	ns
LDL-C; mmol/l	1.18±0.35	0.98±0.29	<0.0003
TG; mmol/l*	1.21 (0.87-1.7)	1.69 (1.16 – 2.4)	<0.0001

*Data is presented as median (25%-75%). AH = arterial hypertension; DBP = diastolic blood pressure; BMI = body mass index; CHD = coronary heart disease; HDL-C = high density cholesterol; LDL-C = low density cholesterol; MS = metabolic syndrome; TC = total cholesterol; SBP = systolic blood pressure; DM = diabetes mellitus; CVD = cardiovascular diseases; TG = triglycerides.

Table 2. Genotype and allele distribution of G protein β3 subunit C825T polymorphism frequency in the two groups

Genotype	Control	Obesity group (n-210)	Total
CC- genotype	58 (47.9%)	25 (28.1%)	83 (39.5%)
CT -genotype	58 (47.9%)	60 (67.4%)	118 (56.2%)
TT -genotype	5 (4.2%)	4 (4.5%)	9 (4.3%)
C -allele	174 (71.9%)	110 (61.8%)	284 (67.6%)
T -allele	68 (28.1%)	68 (38.2%)	136 (32.4%)

riers had significantly more frequent arterial hypertension. However, subjects of both groups were comparable on the level of blood pressure. Obesity was also more prevalent in patients with the presence of 825T allele with no significant difference between the groups on indicators such as BMI and WC. Abdominal obesity by ATP III criteria occurred more frequently in T allele carriers without statistical significant differences. No significant differences were found for other cardiovascular risk factors, including lipid and carbohydrate metabolism. Analysis of the relationship between the studied polymorphism and hypertension showed that the presence of T allele increased the risk of hypertension to 1.79 times.

Further, to assess the impact of various factors on the development of obesity the logistic regression analysis was performed with obesity as a dependent variable and the factors which may influence obesity development (gender, age, consumption of vegetables [every day or not every day], physical activity [more than or less than 30 minutes a day]and the 825T allele carriers as independent variables.

According to the analysis of the included variables the absence of daily vegetables consumption increased almost 3.5 times the risk of obesity, but the presence of 825T allele increased 2.9 times the risk, regardless of gender, age and level of physical activity (Table 4). In the construction of a similar regression model for hypertension a statistically significant role of 825T allele was lost after adjustment for obesity as an independent variable, which may indicate indirectly an intermediate effect of the 825T allele on blood pressure through the development of obesity.

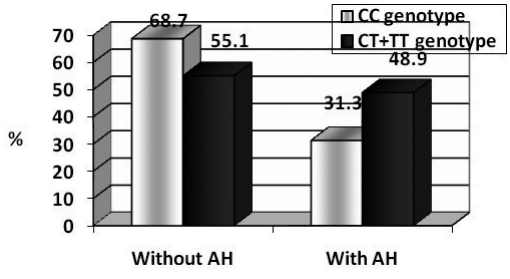

Figure 2. Relationship of G protein β3 subunit C825T polymorphism with arterial hypertension
Note: χ^2- 3.86, P = 0.049; OR 1.79 (95% CI 1.01-3.2)

Table 3. Relationship of risk factors on CVD with G protein β3 subunit C825T polymorphism

Indicators	CC n – 83	CT+TT n - 127	p
Sex (male), n (%)	55 (66.3)	82 (64.6)	ns
Age, years	52.0±8.1	50.1±7.5	ns
AH; n (%)	26 (31.3)	57 (45.0)	<0.05
SBP: mm Hg	132±21	137±25	ns
DBP; mm Hg	84±12	87±14	ns
Obesity, n (%)	24 (28.9)	65 (51.2)	<0.01
BMI kg/m2,	27.7±4.7	28.8±5.1	ns
AO, n (%)	44 (53)	83 (64.8)	ns
WC, cm	95.6 ±12.9	98.4±15.1	ns
FRS on CVD, n (%)	21 (25.3)	40 (31.2)	ns
Type 2 DM; n (%)	11 (13.3)	16 (12.6%)	ns
Fasting glucose; mmol/l	6.15±2.44	5.7 ± 1.36	ns
MC, n (%)	35 (42.1)	67 (52.8)	ns
TC, mmol/l	5.1±0.86	4.96±1.09	ns
HDL-C; mmol/l	3.26±0.79	3.1±0.93	ns
LDL-C; mmol/l	1.11±0.32	1.08±0.36	ns
TG; mmol/l*	1.3 (0.93-1.97)	1.36 (0.95 – 2.1)	ns

*Data is presented as median (25% - 75%). AH = arterial hypertension; AO = abdominal obesity; DBP = diastolic blood pressure; BMI = body mass index; CHD = coronary heart disease; HDL-C = high density cholesterol; LDL-C = low density cholesterol; MS = metabolic syndrome; FRS = family risk score; WC = waist circumstances; TC = total cholesterol; SBP = systolic blood pressure; DM = diabetes mellitus; CVD = cardiovascular diseases; TG = triglycerides

Discussion

G protein plays an important role in metabolic processes by regulating signal transmission from different receptors to the cell surface. Inactive G protein consists of three subunits (α, β, and γ) and is associated with a guanosine triphosphate (GTP) through the α subunit. In activation of the protein a GTP transforms into guanosine diphosphate (GDF) and α subunit separates from β, γ - complex. Depending on α subunit type a various intracellular molecules are activated (αs) or inhibited (αi), triggering a signal transductions cascades [3]. Among others G protein affects key processes such

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Table 4. Summary results of stepwise logistic regression analysis adjusted for obesity

	β	p	expected β	95% CI expected β
Vegetable consumption*	1.25	0.003	3.47	1.52 - 7.94
825T allele carriers	1.06	0.013	2.9	1.25 - 6.70
Sex (male)	2.02	0.16	0.55	0.24 - 1.25
Age	0.011	0.92	1.0	0.95 - 1.06
Physical activity#	0.027	0.87	1.12	0.38 - 3.3

* not every day consumption of vegetables with meals

walking less than 30 minutes a day

as activation / inhibition of adenylate cyclase, different phospholipase isoforms, K +, Na +, Ca + , H + transmembrane flux regulation and the cascade of mitogen-activating protein kinases, etc. [4,5]. Expression of G protein β3 subunit is found in all tissues of the body and is a key component in signal transduction. The gene encoding of the β3 subunit is located on chromosome 12. Replacement of cytosine to thymidine at position 825 does not affect the amino acid sequence of the protein, but leads to the synthesis of truncated β3 subunit, which in turn leads to increased intracellular signals transduction, probably due to the formation of closer β3-αi ties [6].

In our survey group of ethnic Kyrgyz the heterozygous CT genotype was prevailing, homozygous mutant genotype was relatively rare, and the 825T allele frequency was 32.4%. According to the literature 825T allele frequency varies strongly depending on ethnicity and race. Homozygous 825TT genotype was found more often in Africa, where mutant allele frequency varies from 74% to 91% [10]. In Asian populations allele frequency is 46% (42%-55%) on average, in European original population 33% (21%-38%). In the post-Soviet states data on studied polymorphism is available for Russia, where the CC genotype was dominating, the T allele frequency was 21%, and in Uzbekistan, where CC and CT genotypes frequency were similar, the prevalence of T allele was 36% [10].

In our study of the Kyrgyz ethnic group an association was found between G protein β3 subunit 825T allele carriage and obesity. This association was also found in most other studies. Siffert W. et al [10] showed that the odds ratio to identify overweight in TT genotype carriers varies from 2 to 3 on average, and this association was observed in all 3 ethnic populations included in the study: the Europeans (OR = 2.5; 95% CI 1.1-6.1), Asians in the Chinese population (OR = 1.8; 95% CI 1.0-3.1) and the African population (OR=2.7; 95% CI 1.4-5.3). It was also shown that this association in the African population was more pronounced in urban areas than in rural communities, pointing out growing influence of environmental factors on people with a genetic predisposition. The study of pharmacogenetic features revealed a greater reduction in body weight in patients with CT and TT genotypes during non-drug interventions (hypocaloric diet, increased physical activity) [16,17], and in some of them this effect was enhanced by adding sibutramine therapy [17,18].

Possible mechanisms of obesity in 825T allele carriers may be a reduction in lipolytic activity in fat cells in response to catecholamines [19,20] and increased adipogenesis through excessive stimulation through pertussis toxin-sensitive (PTX) - receptors [21,22]. Given the high 825T allele frequency among Asian and African descents, G protein β3 subunit C825T polymorphism is considered to be "energy-saving" polymorphism and its influence on development of obesity is consistent with the theory of Neel J [23] in which the genes are historically responsible for accumulation of adipose tissue currently contribute to obesity, insulin resistance and type 2 diabetes.

In Kyrgyzstan, the prevalence of obesity is increasing, which may also be associated with lifestyle changes. Historically, the Kyrgyz tribes were nomadic and their diet has always been rich with animal origin fats necessary in transitions. Currently, the dietary habits have not changed significantly, but physical activity has decreased. This has led to a significant increase of obesity among the indigenous population, which may be due to the accumulation of unspent energy and lack of genetic protection.

In our study, hypertension was revealed more often in CT + TT genotypes group. However, in the logistic regression analysis a statistically significant role of 825T allele was lost after adjustment for obesity as an independent cofactor, which makes the assumption about indirectly intermediate effect of surveyed polymorphism on blood pressure through

the development of obesity. The relationship between obesity and hypertension is confirmed by numerous studies [1]. The results of research on the relationship between the C825T polymorphism and hypertension are rather contradictory. Some of them support the 825T allele association with the development of hypertension, left ventricular hypertrophy [8,10,24-26] and atherosclerosis [27], while the other are not [28-32]. Basically, positive relationship with T allele was revealed in European populations, while this relationship is significantly loose for Asians. Interestingly, in the Uzbek population, on the contrary, CC genotype was associated with hypertension, and in control group of normotensive patients CC genotype does not occur at all [33]. A meta-analysis of 34 studies including 14,094 patients with hypertension and 17,760 controls showed an increased risk of hypertension of CT + TT genotype carriers to 1.17 times (95% CI 1.06-1.29), and this relationship was significantly higher after the exclusion from the analysis of studies conducted in Asian populations [8].

Possible mechanisms for the development of hypertension in patients with C825T polymorphism are not fully understood. It is assumed that the effect of this polymorphism on the rise in blood pressure is implemented through the slow action mechanisms, perhaps as a result of PTX-receptor hyperactivation and dysregulation of the transmembrane Na +, H + and Ca + ion flux [34]. It was also shown that the G protein β3 subunit 825T allele is associated with low concentrations of renin in the blood [35]. As known, patients with hypertension and reduced levels of renin are characterized by high sensitivity to salt intake from food and water retention in the body. Interestingly, there is salt and water retention in the body in obesity as well. The results of pharmacogenetic studies have shown more pronounced hypotensive effect of thiazide diuretics in 825T allele carriers [36,37], while there was no significant difference in the response to β blockers in CC, CT and TT genotypes carriers [38,39].

Thus, in our study G protein β3 subunit gene C825T allele in the Kyrgyz ethnic group is associated with obesity.

Conflict of interest

The authors declare no conflict of interest.

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