



EFFECT OF SELECTED POLYMORPHISMS OF GENES LEP, MTHFR AND FTO TO BMI LEVEL AND GENDER-SPECIFICITY

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ABSTRACT

The aim of this study is to investigate the effect of selected polymorphisms LEP (G2548A), MTHFR (C677T) and FTO (*rs1121980*) on body mass index in humans. In the study participated 79 people from Slovakia with some genetic relatedness. Genomic DNA was isolated from the buccal swabs using a commercial kit Qiagen DNA Mini Kit (Qiagen). The detection of SNP polymorphisms in human genes LEP, MTHFR and FTO was performed using molecular genetics methods such as PCR-RFLP and ARMS. The most common genotypes in all 3 polymorphism were found in heterozygous form (for LEP AG = 0.5190, for MTHFR CT = 0.519, for FTO CT = 0.4051). The LEP gene had increased frequency of G allele (0.5506), the MTHFR gene T allele (0.6646) and FTO gene T allele (0.50635). The least frequent genotype in LEP was AA (0.1899), in MTHFR was TT (0.0759), in FTO it was CC (0.2911). According to the results we can assume that the genotypes AA (LEP G2548A), CC (FTO *rs1121980*) and TT (MTHFR C677T) in case of women have a protective effect on the prevalence of obesity, based on BMI, compared to the other genotypes and this polymorphism is gender-specific. Added anthropometric measurements, blood test and extension of the group in the future evaluation could increase the statistical relevance in relation to obesity and gender-specificity.

Keywords: FTO *rs1121980*; LEP G2548A; MTHFR C677T; BMI; gender-specificity

INTRODUCTION

The prevalence of the obesity enormously increases every year as in adult population, same in the children one. As chronic disease, in obesity should be taken into account many of aspects they could influence its incidence, also with non-nutritive origin. Genetic effect should be considered as one from the main factors in relation to obesity and the genetic predisposition as possible influence by a large extent.

Parenthood obesity has shown as big predictor to prevalence of the obesity to their children, as they have 25.2 times greater chance of developing obesity in comparing the children whose parents do not suffer of any forms of obesity. When mother is obese, in 23% of boys and only 16% of girls have the obesity presented but conversely by paternal obesity, the boy has 6.5 times and the girl 40.1 times higher risk of obesity in comparing to the control group. Therefore we can say that children obesity is highly influenced by genetic factors. Obesity parent was most pronounced in boys and paternal obesity, especially among girls. It could be possible that an improvement of environmental factors affecting the parents, could reduce the risk of obesity in their children (Kumar et al., 2010).

The objective of this study was to find a relationship between selected gene polymorphisms and body mass index level considered as one from the obesity linkage. All 3 candidates genes were characterized as possible indicators to higher level of BMI. Numbers of genetic studies have indicated FTO as an important gene for obesity risk in different populations, leading to further development of metabolic disease and diabetes (Mittal, Srivastava A., Srivastava N., 2013).

In research of LEP polymorphism G2548A (Constantin et al., 2010) were found that the G allele carriers had significantly higher leptin and increased risk for developing obesity ($p = 0.013$) were pointed in genotype GG (taking into account the age, sex and BMI). Similar results demonstrated also Ali et al. (2009), when they showed that women with obesity in Tunisian population, which were carriers of the A allele had a significantly lower leptin levels.

Scientific hypothesis

The aim of this study is to investigate the effect of selected polymorphisms LEP (G2548A), MTHFR (C677T) and FTO (*rs1121980*) on body mass index in humans.

MATERIAL AND METHODOLOGY

The target group consisted of people with different age structures and with certain genetic similarity, which created relatedness between individuals. Because of the formation of a general examination of overweight and obesity in humans, there were 79 people evaluated, belonged to 14 families.

Genomic DNA was isolated from the buccal swabs using a commercial kit Qiagen DNA Mini Kit (Qiagen). SNP analysis of genes LEP polymorphism (G2548A) and MTHFR polymorphism (C677T) was performed using molecular genetic PCR-RFLP method (restriction fragment length polymorphism). PCR amplification products observed polymorphism G2548A and C677T and subsequent restriction analysis was carried out following the methodology Mammès et al. (2000) and Deeparani et al. (2009).

The single nucleotide polymorphism rs1121980 in FTO gene was performed by amplification-refractory mutation system (ARMS) analysis of point mutation, following the methodology Shabana and Hasnain (2015).

Followed identification of specific fragment describing the presence of different alleles of the selected SNP polymorphisms was performed by agarose gel electrophoresis.

Age, height, weight were assessed in the target group and then the body mass index (BMI) was calculated according to the following formula:

$$BMI = weight (kg) / body height^2 (m)$$

Basic statistical analysis of gene polymorphism was performed by the following relationships:

1. Alleles frequencies for double allelic system according to the Hardy-Weinberg law

$$p_A = (2 \cdot AA + AB) : 2N \quad q_B = (2 \cdot BB + AB) : 2N$$

p_A , q_B - the frequency of each allele, N - total number of individuals

2. Genotypes frequencies according to the Hardy-Weinberg law

$$(p_A + q_B)^2 = p_A^2 + 2 p_A q_B + q_B^2 = 1$$

3. Genotypic balance was verified by χ^2 – test

$$\chi^2_{(n-1)} = \sum \frac{(e-t)^2}{t}$$

n - total number of phenotypic classes, e - observed number of genotypes, t - theoretical number of genotypes

4. The polymorphic information content (PIC) of Botstein et al., (1980)

$$PIC = 1 - \sum (p^2 + q^2) - \left(\sum_{i=1}^{n-1} \sum_{j=i+1}^n 2p_i^2 p_j^2 \right)$$

5. Heterozygosity (H_e) by Nei, (1978)

$$H_e = 1 - \sum (p^2 - q^2)$$

The relationship of body mass index (BMI) and the polymorphism studied genes was analyzed on the basis of a linear model:

$$BMI_{ijk} = \mu + POHL_i + LEP_j + b(\text{age})_{ijk} + e_{ijk}$$

BMI - body mass index, μ - mean value, $POHL_i$ - fixed effect of sex, LEP_j - fixed effect of genotype (gene LEP), $b(\text{age})_{ijk}$ - effect of age in the form of linear regression, e_{ijk} - residual effect

For the numerical expression of the alleles and genotypes, we used the following substitution: gene LEP (allele A = 0, G allele = 1, genotype AA = 0, genotype AG = 1, the genotype GG = 2), gene MTHFR (allele T = 0, allele C = 1, the genotype TT = 0, 1 = CT genotype, genotype CC = 2), gene FTO (allele C = 0, T allele = 1, genotype CC = 0, genotype CT = 1, TT = 2). Numerical expression of the genes was used because of the expression of genetic predisposition obesity to individuals and families by individual analyzed genes studied separately and also together, based on expected positive or negative effect from the previous studies.

Statistic analysis

Laboratory processing of samples and the DNA analyzes were carried out at the Department of Genetics and Animal Breeding Biology, Slovak University of Agriculture in Nitra. Statistical analysis was performed in the program SAS Enterprise Guide 5.1 and the program SAS 9.2.

RESULTS AND DISCUSSION

Analysis of frequency and basic statistical characteristics

The group consisted of 79 people of people of different age structures, usually with a known family relatedness, including 48 women and 31 men. Tables 1 and 2 show the basic statistical characteristics of the analyzed indicators of the group.

The average age of people was 40.08 years and the mean of BMI was 26.04 kg.m⁻² (79 reviews people). For persons who have reached the minimum age of 20 years the average age of 44.17 years was found and the mean of BMI was 26.97 kg.m⁻² (70 reviews people).

The age structure of the group was very diverse. In the case of man it was from 2 to 79 years and in women from 2 to 74 years. The diverse age structure is justified from the standpoint of families and needed (existence of a joint analysis of one or two generations of ancestors).

According to our results, the age is not a limiting factor in the analysis of the relationship of BMI of the individual genes and polymorphisms. When comparing the body mass index of men (27.09) and women (25.37) of all subjects and average values of subjects who had at least 20 years (male 28.10 and female 26.30) there was a difference of about only 1 point.

In any case, since individual human body measurements are significantly affected by age, also the effect of age was taken into account in the analysis.

The classification of individuals analyzed according to the international classification of underweight, normal weight, overweight and obesity are presented in Table 3.

Table 1 The basic statistical characteristics.

Gender	Indicator	Mean	s _x	min.	max.	n
Men	Weight (kg)	80.85	23.21	14.00	128.00	31
	Height (m)	1.71	0.20	0.88	1.91	31
	BMI (kg.m ⁻²)	27.09	5.35	18.08	39.51	31
	Age (year)	42.29	20.82	2.00	79.00	31
Women	Weight (kg)	69.23	18.29	12.00	113.00	48
	Height (m)	1.64	0.1418.42	0.98	1.80	48
	BMI (kg.m ⁻²)	25.37	5.99	11.15	43.06	48
	Age (year)	38.65	18.42	2.0	74.00	48

Table 2 The basic statistical characteristics (minimal age – 20).

Gender	Indicator	Mean	s _x	min.	max.	n
Men	Weight (kg)	87.80	15.49	64.00	128.00	26
	Height (m)	1.77	0.07	1.55	1.91	26
	BMI (kg.m ⁻²)	28.10	4.87	21.14	39.51	26
	Age (year)	48.65	16.00	20.00	79.00	26
Women	Weight (kg)	73.00	12.96	51.00	113.00	44
	Height (m)	1.67	0.06	1.54	1.80	44
	BMI (kg.m ⁻²)	26.30	5.25	17.86	43.06	44
	Age (year)	41.52	16.37	20.00	74.00	44

Table 3 Classification of overweight and obesity.

BMI (kg.m ⁻²)	Men	%	Women	%	Count	%
< 25	12	38.7	23	47.9	35	44.3
25-30 (<i>overweight</i>)	10	32.3	15	31.3	25	31.6
30 ≥ (<i>obesity</i>)	9	29.0	10	20.8	19	24.1

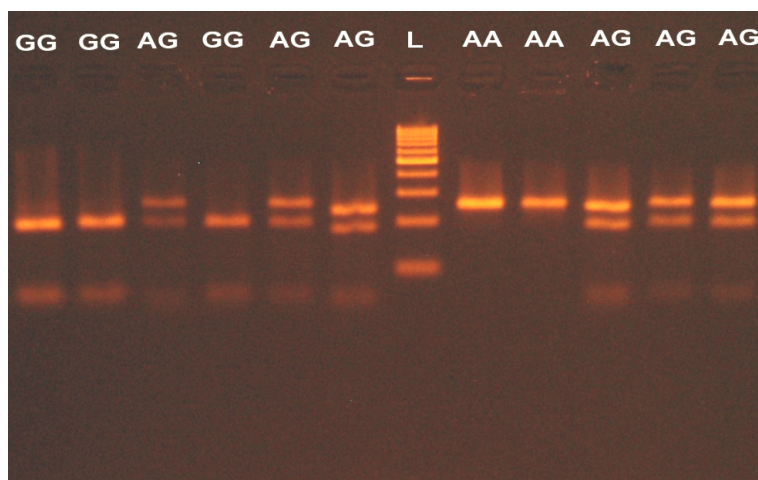


Figure 1 Molecular genetic analysis of the PCR-RFLP for the detection of single nucleotide polymorphism G2548A localized in the gene LEP encoding the leptin.

Note: AA - homozygous genotype (242 bp), AG – heterozygous genotype (242 bp +181 bp +61 bp), GG – homozygous genotype (181 bp +61 bp), L – 100 bp DNA ladder (Thermo Scientific).

Based on the classification of overweight and obesity we can conclude that, overall, 55.7% of people (61.3% men and 52.1% women) we analyzed, suffer from overweight and obesity.

Molecular-genetic analysis of genes LEP (G2548A), MTHFR (C677T), FTO (rs1121980)

Based on the genotyping group of people (79 people) were analyzed gene LEP (G2548A), MTHFR (C677T) and selected polymorphism rs1121980 in FTO gene, in relation to obesity in humans based on BMI values with respect to gender and age.

Statistical analysis of polymorphism of gene LEP (G2548A), MTHFR (C677T), FTO rs1121980

Basic statistical analysis of polymorphisms of individual genes analyzed are presented in Table 4 and shown in Figure 4.

For all polymorphisms was the most frequent heterozygous genotype, for LEP and MTHFR in 51.90% and in FTO in 40.51%.

Testing frequencies of genotypes according to the Hardy-Weinberg law χ^2 test confirmed the maintenance of equilibrium in the evaluated group of people.

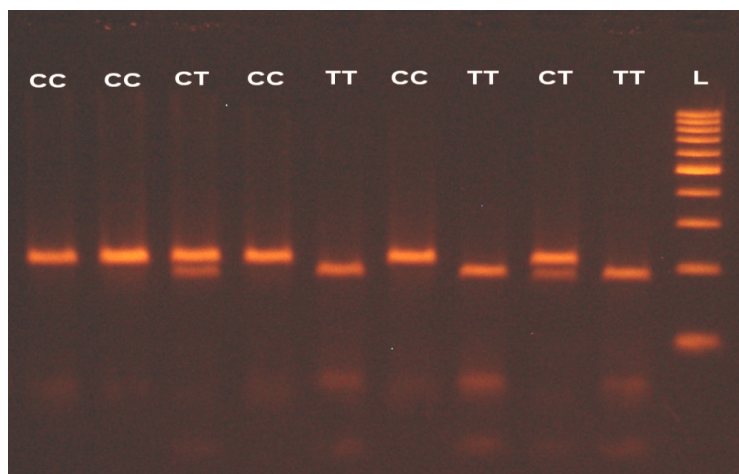


Figure 2 Molecular genetic analysis of the PCR-RFLP for the detection of single nucleotide polymorphism C677T localized in the gene MTHFR.

Note: CC - homozygous genotype (198 bp), CT - heterozygous genotype (198 bp +175 bp +23 bp), TT – homozygous genotype (175 bp +23 bp), L – 100 bp DNA ladder (Thermo Scientific).

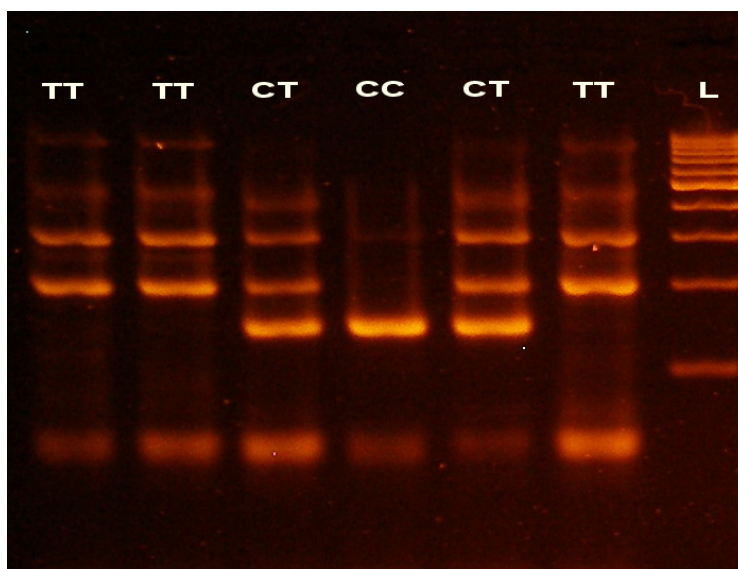


Figure 3 Molecular genetic analysis of the ARMS for the detection of FTO rs1121980.

Note: CC - homozygous genotype (148 bp), CT - heterozygous genotype (208 bp +148 bp +60 bp), TT – homozygous genotyp (208 bp), L – 100 bp DNA ladder (Fermentas), control fragment defined at 311 bp.

Analysis of the relationship of body mass index (BMI) and polymorphisms of genes

Analysis of the relation of body mass index, and the gene polymorphism of the LEP, MTHFR and FTO was made from a linear model [1] referred in the methodology of the research and its comparison is in Figure 5.

The average BMI in relation to age highlighted differences in BMI in different genotypes in the polymorphism G2548A of the LEP gene (AA = 26.88 kg.m⁻², AG = 27.00 kg.m⁻², GG = 27.87 kg.m⁻²) as opposed to values if we do not take account of the age of participants (AA = 25.50 kg.m⁻², AG = 25.35 kg.m⁻², GG = 26.94 kg.m⁻²). We can see increasing tendency from AA to AG genotype if we consider the age.

In MTHFR C677T have been the average BMI lower (CC = 26.18 kg.m⁻², CT = 25.73 kg.m⁻², TT = 24.87 kg.m⁻²) in comparing those with consideration of the age (CC = 27.53 kg.m⁻², CT = 27.05 kg.m⁻²,

TT = 25.89 kg.m⁻²) and the tendency of allele effect is shown the best from all 3 genes.

The average BMI values in FTO rs1121980 (CC = 25.39 kg.m⁻², CT = 24.84 kg.m⁻², TT = 27.62 kg.m⁻²) to those where the age were took to account (CC = 26.88 kg.m⁻², 26.85 kg.m⁻², 27.91 kg.m⁻²). The most abundant difference is in heterozygous genotype, more than 2 kg.m⁻².

The correlation between selected genes and influence to BMI level were not statistically very significant when each from genes were compared separately, however they have together cumulative effect (0.1967) and it is more significant (p = 0.0823). FTO rs1121980 has shown the biggest influence to BMI in comparing the other 2 polymorphisms. With gender consideration comes to decreasing of statistical relevance cause of the decreasing number in each group (M = 31, W = 68).

In gene MTHFR (C677T) has shown variability between genders. Homozygous genotype CC is considered as

Table 4 Frequency of genotypes and alleles of the genes LEP, MTHFR and FTO

Gene	Genotype	Count	Frequencies		PIC	Het.	χ^2 - test
			Genotype	Allele			
LEP G2548A	AA	15	0.1899	A	0.3724	0.519	0.1876
	AG	41	0.519	G			
	GG	23	0.2911	± 0.0386			
MTHFR C677T	CC	32	0.4051	C	0.3465	0.519	2.1264
	CT	41	0.519	T			
	TT	6	0.0759	± 0.0343			
FTO rs1121980	CC	23	0.2911	C	0.375	0.4051	2.8442
	CT	32	0.4051	T			
	TT	24	0.3038	± 0.0434			

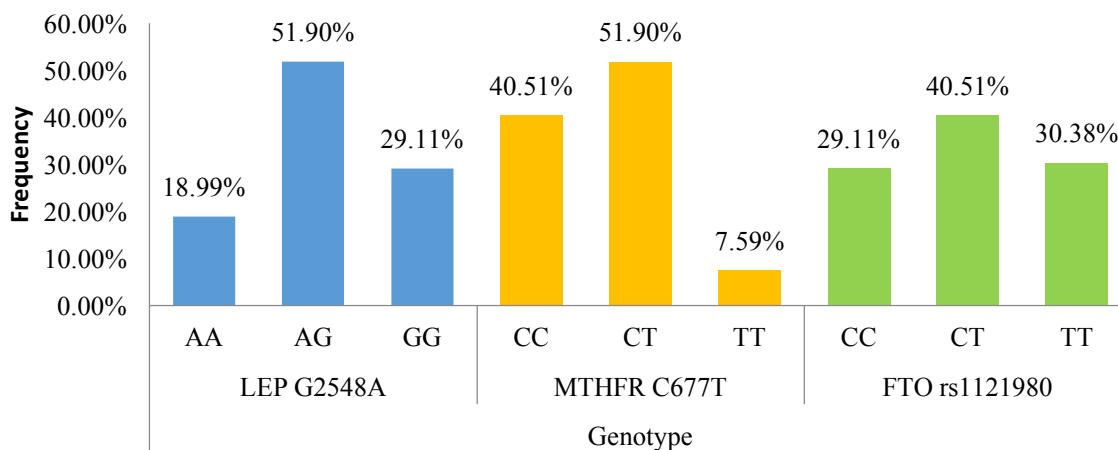
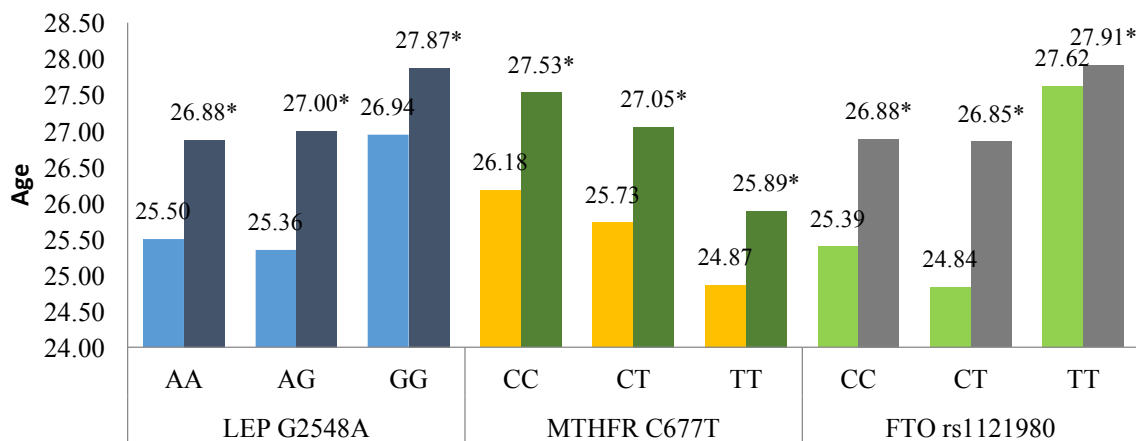


Figure 4 Comparison of frequency LEP G2548, MTHFR C677T and FTO rs1121980 genotypes.



*age took into account

Figure 5 The average of BMI level for LEP G2548A, MTHFR C677T, FTO rs1121980 without and with consideration of age.

protective factor (-0.1100), TT (0.1100), in opposite to women, where is protective genotype TT (-0.1819), CC (0.1819) and the cumulative effect together with LEP and FTO is bigger and more significant ($W = 0.2639$, $p = 0,07$, $M = 0.1163$, $p = 0.53$). With age consideration the protection of TT genotype MTHFR in women is much more relevant (-0.2952) and more significant ($p < 0.05$). In other cases the significant changes were not observed.

With the cumulative effect of the selected genes polymorphisms, using the numerical substitution described in the methodology we can see in Figure 6 the increased

BMI level (28.41 kg.m^{-2}) in case of the worse genotype scenario – 6 risk alleles (LEP – genotype GG, MTHFR – genotype CC, FTO – genotype TT) in comparison with the occurrence just two risk allele (23.49 kg.m^{-2}).

In a study conducted on a population of people in the US, an average BMI of 27.8 kg.m^{-2} was reported (Morland and Evenson, 2008). Dukát (2007) states that in Slovakia, the mean BMI is 26.94 kg.m^{-2} . In comparison with these values the first set of users has only a slightly lower mean BMI. Similar results were recorded in the first group of people by gender. When considering the

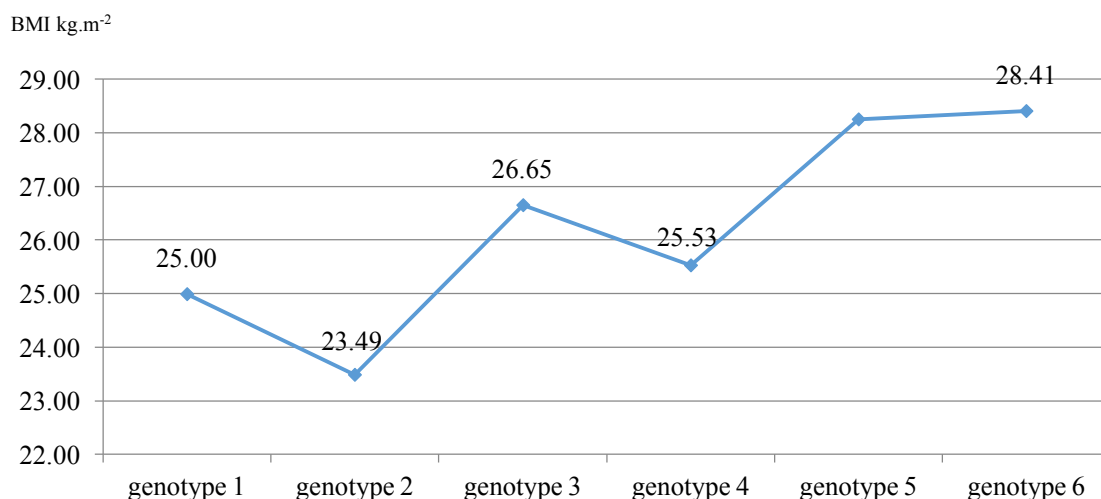


Figure 6 Showing the impact of combinations of alleles of genes and LEP G2548A, MTHFR C677T, FTO rs1121980 on BMI.

minimum age of 20 years, we find the mean of BMI 26.97 kg.m⁻² is virtually identical to the average for Slovakia.

In this study, effect of 3 selected polymorphisms was examined to BMI level in 79 individuals. Our results confirm the findings of **Li et al. (2009)** that the largest effect shown for the FTO locus. Common polymorphism variants have small effects on obesity measures and they have cumulative effects but their predictive value for obesity risk is kindly limited.

Vimalaswaran et al. (2009) have confirmed the effect of polymorphism FTO *rs1121980* to BMI and also to the waist circumference. They found a highly significant association of BMI with allele T and increasing the BMI level in an average 0.40 – 0.66 points per risk allele. They considered bigger effect of the FTO gene variant in less physical active people. The FTO gene has been investigated in the search for gene variants that are mainly related to obesity risk and BMI. Several single nucleotide polymorphisms have been described and one of these is also rs1121980 (**Saldaña-Alvarez et al., 2016**). Also their results support the hypothesis that sex plays an important role in the relationship between FTO SNPs and the obesity development.

Lieskovská (2011) has confirmed negative effect of GG genotype in LEP G2548A gene to BMI level (+2.0499), frequency of A allele (0.46) and G allele (0.54) were similar to our findings (A allele = 0.45, G allele = 0.55). The previous study of **Trakovická et al. (2016)** confirmed the key role of this leptin gene in control of nutritional organism status and indicates the LEP G2548A polymorphism as genetic markers for the level of BMI and obesity related disorders and affirm its significance in genetic evaluation in relation to the lipids metabolism disorders prediction.

Kucukhuseyin et al. (2013) came to finding that owner of the T allele in the MTHFR gene has a protective association for BMI level. This result we found just in group of women (-0.2952, *p* < 0.05), in men group we found the opposite and the T allele has negative effect to BMI (0.2557, *p* = 0.1650). According to **Zhi et al. (2016)** in MTHFR C677T are observed gender-specific

interactions in Chinese Han population what we can confirm also for the European population even with smaller examined group.

CONCLUSION

The results achieved in analysis of the relation for body mass index and polymorphisms studied gene allow us to confirm the hypothesis that the polymorphism of LEP, MTHFR and FTO gene is related to obesity expressed human body mass index (BMI).

In the MTHFR gene (C677T) we observed the gender differences and the protective effect of rariTT genotype in women and CC genotype in men, however cause of low number of frequency TT genotype in the population other observations are needed.

For a more comprehensive evaluation of polymorphisms studied genes and their impact on obesity, we suggest future conduct additional anthropometric measurements, blood tests in connection with the nutritional history and in particular the extension samples of observed people.

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