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Polymorphic locus rs555621 of the *FSHB* gene is association with the obesity in women

Introduction

- One of the most important medical and social problems in the world at present is obesity. According to the WHO, in 2016, more than 1.9 billion adults over the age of 18 were overweight, of which over 650 million were obese.

- Obesity is more common among women than among men (15% of women and 11% of men). Obesity and overweight are known major risk factors for cardiovascular (heart disease, hypertension, stroke), endocrine (diabetes), musculoskeletal (osteoarthritis), oncology (cancers of breast, endometrial, kidney, prostate, etc.), etc. diseases.

- Genetic factors are involved in the formation of obesity and one of the candidate genes for obesity are genes associated with the age of menarche. It is believed that women with early menarche have a higher risk of developing obesity and polymorphisms associated with early menarche may also be risky for the obesity development.

The aim of the study

To study the association of the menarche-correlated rs555621 *FSHB* gene with the obesity in women

Materials and Methods

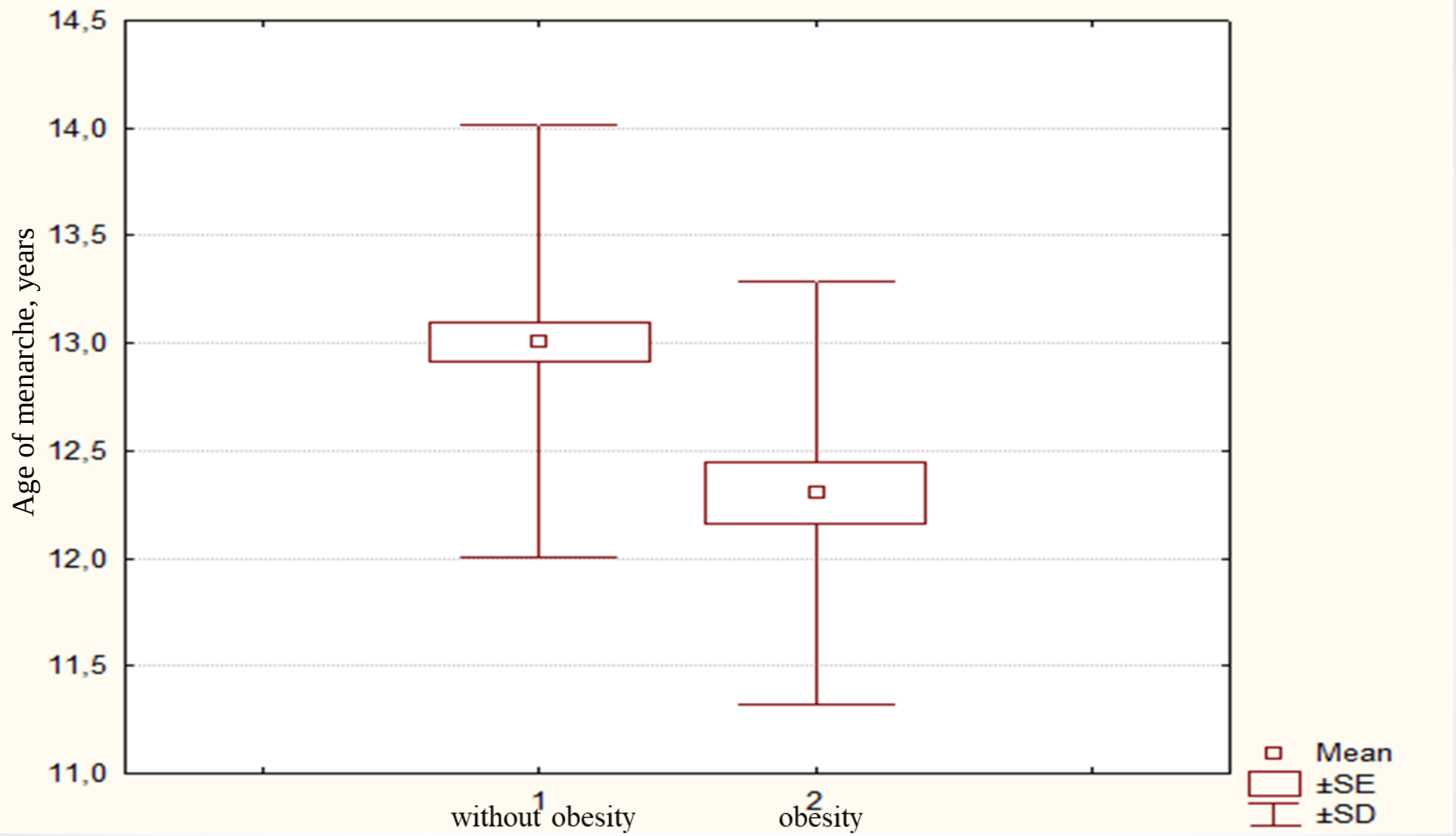
171 women aged 20-30 years, of Russian nationality, living in the Belgorod region, born in the Central region of Russia for the period 1985-1995, without severe somatic diseases.
Studied parameters: age, year of birth, age of menarche, weight, height, BMI

125 women with normal BMI
(BMI=18.5-24.99)

46 women with obesity
(BMI>30)

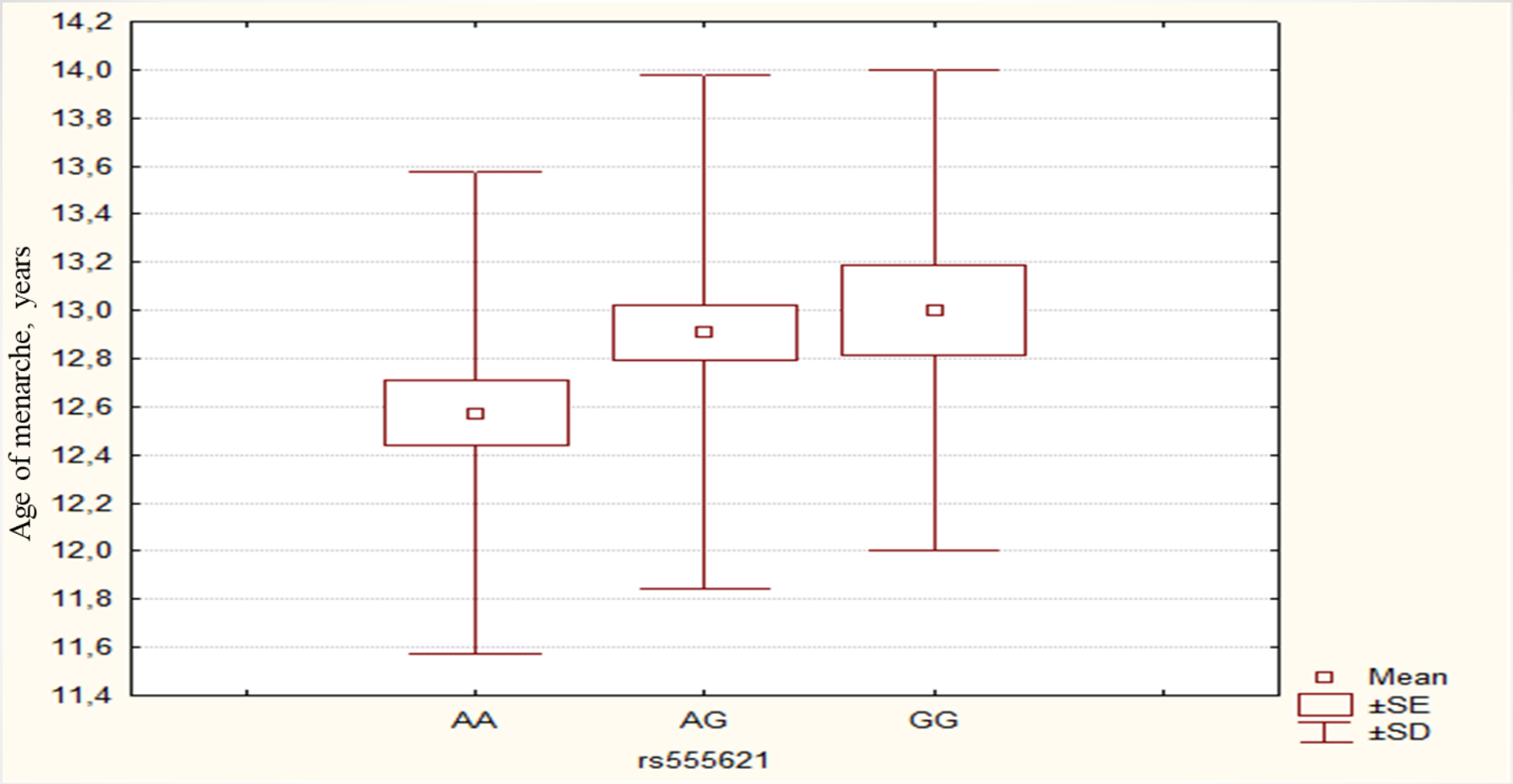
- The SNP rs555621 of the *FSHB* gene was genotyped by CFX-96 Real-Time System (Bio-Rad).
- The associations of the rs555621 *FSHB* with the age of menarche (log-linear regression analysis was used) and obesity (logistic regression analysis was used) in the gPLINK program were studied.
- Additive, recessive and dominant genetic models were tested with correction for covariates (age, BMI in the analysis of menarche age and age, menarche age in the analysis of BMI) and multiple comparisons (permutation testing was used at a statistically significant level of $p_{perm}<0.05$).
- The regulatory potential of the rs555621 *FSHB* was studied *in silico* using Haploreg and GTExportal databases.

The average age of menarche in obese and non-obese women



Women with obesity are characterized by an earlier (by 0.7 years, $p<0.001$) onset of menarche. Using logistic regression analysis, it was found that early menarche is a risk factor for obesity (OR= 0.49, 95% CI 0.34-0.71, $p<0.001$).

The age of menarche in women depending on the genotypes of the rs555621 *FSHB*



The rs555621 of the *FSHB* was associated with the age of menarche according additive (β = 0.233±0.116, p_{perm} =0.05) and dominant (β = 0.357±0.170, p_{perm} =0.05) models with correction for covariates (age and BMI). In women who have one or two G allele rs555621 in the genotype (genotypes AG and GG respectively), menarche occurs 0.34 years or 0.43 years later compared to women whose genotype does not have this allele (genotype AA).

Association of the SNP rs555621 *FSHB* with obesity in women

Alleles, genotypes (genetic model)	Obesity (n=46) abc.(%)	Control (n=125) abc.(%)	OR (95%CI)	p
A	64 (69.56%)	132 (52.80%)	2.04 (1.19-3.51)	**0.009**
G	28 (30.44%)	118 (47.20%)	0.49 (0.28-0.84)	
AA	23 (50.00%)	31 (24.80%)	3.03 (1.41-6.53)	**0.004**
AG	18 (39.13%)	70 (56.00%)	0.51 (0.24-1.06)	0.07
GG	5 (10.87%)	24 (19.20%)	0.51 (0.16-1.55)	0.29
AA vs. AG vs. GG (additive model)	0.51 (0.29-0.89)			**0.02**
AA vs. AG + GG (dominant model)	0.38 (0.18-0.79)			**0.009**
AA + AG vs. GG (recessive model)	0.57 (0.20-1.66)			0.30

- It was found that among obese women, the frequency of the AA rs555621 genotype is 2.01 times higher than in non-obese women (p=0.004). Also, the frequency of the rs555621 A allele is 1.32 times higher among obese women compared to non-obese women (p=0.009). These genetic variants are risk factors for obesity (OR=3.03 for genotype AA and OR=2.04 for allele A).
- The rs555621 of the *FSHB* is associated with the obesity in women according additive (OR=0.51 95% CI 0.29-0.89, p_{perm} =0.02) and dominant (OR=0.38 95% CI 0.18-0.79, p_{perm} =0.009) models with correction for covariates (age and menarche age).

Association of the rs555621 *FSHB* with the level of expression (**eQTL**) and alternative splicing (**sQTL**) of genes in various organs and tissues

Gene	ref allele	alt allele	β	p	Organs
eQTL					
ARL14EP	A	G	0.20	4.5e-10	Thyroid
ARL14EP	A	G	0.19	0.0000024	Brain - Caudate (basal ganglia)
ARL14EP	A	G	0.32	0.0000024	Ovary
ARL14EP	A	G	0.19	0.0000025	Brain - Cortex
ARL14EP	A	G	0.29	0.0000053	Pituitary
ARL14EP	A	G	0.15	0.00001	Adipose - Subcutaneous
RPL12P30	A	G	0.16	0.00035	Thyroid
sQTL					
ARL14EP	A	G	0.35	2.4e-14	Muscle - Skeletal
ARL14EP	A	G	0.38	5.7e-12	Thyroid
ARL14EP	A	G	0.33	1.6e-10	Adipose - Subcutaneous
ARL14EP	A	G	0.34	8.9e-9	Adrenal Gland
ARL14EP	A	G	0.33	2.6e-8	Adipose - Visceral (Omentum)
ARL14EP	A	G	0.38	0.0000093	Pituitary
ARL14EP	A	G	0.35	2.4e-14	Muscle - Skeletal

- The significant regulatory potential of the rs555621 *FSHB* has been established: it is located in the regions of modified histone proteins (H3K27ac and H3K9ac) marking "active" enhancers (H9 cells cell culture) and "active" promoters (primary-peripheral blood mono-nuclear cells).
- The SNP rs555621 was associated with the expression of the *RPL12P30* gene in the thyroid and the *ARL14EP* gene in various parts of the brain (cortex, basal ganglia, pituitary), thyroid, ovaries, subcutaneous adipose tissue.
- The rs555621 was linked with the level of alternative splicing of the *ARL14EP* gene transcript in the pituitary, muscle tissue, thyroid , adrenal glands, visceral and subcutaneous adipose tissue.

Conclusion

In our study, it was found that rs555621 polymorphism of the *FSHB* gene was associated with the age of menarche and obesity in women in Russian residents of the Central region of Russia. The allele G rs555621 *FSHB* was linked with late menarche (β = 0.233- 0.357) and has a protective value in the development of obesity (OR=0.38-0.51), whereas the AA genotype rs555621 was associated with early menarche and was a risk factor for obesity (OR=3.03).The rs555621 *FSHB* has been correlated with an increased level of expression of the *ARL14EP* and *RPL12P30* genes and a high level of alternative splicing of the *ARL14EP* gene transcript in various organs important for the formation of menarche and the development of obesity (brain, thyroid gland, adipose tissue, etc.)