Метаанализ ассоциации полиморфных вариантов генов *FTO, LPL, LIPC, PON1* с риском развития ожирения у детей и подростков

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Аннотация

Целью исследования стало изучение потенциальной взаимосвязи между *PON1 Q192R, LIPC -250G>A, LPL* Ser447Ter, *FTO A23525T* и риском развития ожирения, атеросклероза и диабета у детей и подростков Европы и европейской части России в рамках метаанализа.

Нами было проанализировано 2549 публикаций. В общей сложности в метаанализ было включено 3603 человека, разделенных на группы: дети и подростки с ожирением или избыточной массой тела – 1 877 человек и дети и подростки, составившие контрольную группу, с нормальным весом или дефицитом веса – 1726 человек.

Для rs9939609 гена *FTO* были выявлены повышенные риски развития ожирения для гомозигот по аллелю *A* в 2 раза ($p<0.0001$). Статистически значимые различия для детей и подростков с ожирением и нормальным весом выявлены для доминантной и рецессивной моделей наследования ($p< 0.0001$).

Анализ частот генотипов для мальчиков и девочек выявил статистически значимые различия для гомозигот по аллелю *A* в группе девочек ($p=0.00268$). Статистически значимые различия в группе мальчиков и в группе девочек были выявлены для рецессивной модели наследования. Отношения шансов для генотипа *A23525A* составили 1.74 ($p=0.0022$) и 1.65 ($p=0.0094$) для девочек и мальчиков с ожирением и нормальным весом соответственно.

Ключевые слова: полиморфизм гена, rs9939609, *FTO, LPL, LIPC, PON1*, ожирение детей и подростков

Meta-analysis of the association of polymorphic variants of the *FTO, LPL, LIPC, PON1* genes with the risk of obesity in children and adolescents

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Abstract

Background: To the best of author's knowledge, presently there are no papers on the relationship of polymorphism of the *FTO, LPL, LIPC, PON1* genes with the risk of obesity in children and adolescents. The relevance of this area of research is dictated by the high prevalence of obesity not only in the adult population, but also in children.

The aim of this work is to study the potential relationship between the polymorphisms of the *PON1 Q192R, LIPC -250G> A, LPL Ser447Ter, FTO A23525T* genes and the risk of obesity, atherosclerosis, and diabetes in children and adolescents in Europe and the European part of Russia by means of meta-analysis.

Methods. A systematic review and meta-analysis of the results of 9 case-control studies meeting the selected criteria has been carried out. The meta-analysis included 3603 people, divided into groups: children and adolescents with obesity or overweight — 1,877 people and children and adolescents who made up the control group, with normal weight or underweight — 1,726 people.

Results. For *rs9939609* of the *FTO* gene, a 2-fold increased risk of obesity for homozygotes for allele *A* was revealed ($p < 0.0001$). Statistically significant differences for children and adolescents with obesity and normal weight were found for the dominant and recessive inheritance patterns ($p < 0.0001$).

Conclusions. Analysis of genotype frequencies in girls revealed statistically significant differences for homozygotes for allele *A* ($p = 0.00268$). For the recessive inheritance model, significant differences were found in boys and girls. The odds ratios for the *A23525A* genotype for girls and boys with obesity and normal weight were 1.74 ($p = 0.0022$) and 1.65 ($p = 0.0094$), respectively.

Key words: gene polymorphism *FTO, LPL, LIPC, PON1*, obesity, children and adolescents

Introduction. Paraoxonase 1 (PON1), lipoprotein lipase (LPL), triaglyceride lipase (LIPC) and alpha-ketoglutarate-dependent dioxygenase (FTO) play key roles in lipid metabolism. Genetic variants *PON1 Q192R, LIPC -250G> A, LPL Ser447Ter, FTO A23525T* affect the activity of these proteins and the characteristics of metabolic pathways. Description of these polymorphic variants of the *PON1, LIPC, LPL, FTO* genes and their molecular effect is presented in Table 1.

Table 1 — Characteristics of the loci of the *PON1, LPL, LIPC, FTO* genes (according to the NCBI database).

Gene localization	Alleles	SNP	Protein	Molecular effect of SNP
PON1				
7q21.3	*T>C*	rs662	Gln192Arg	Missense variant in coding position. Decreased gene activity [1]
LIPC				
15q21.3	*-250G>A*	rs2070895	-	Intron variant in 5 'UTR
LPL				
16p13.3	*G>A,C*	rs149551759	Ser447Ter	Exon 14, stop codon
			Ser447Leu	Missense variant
FTO				
16q12.2	*23525T>A*	rs9939609	-	Intron variant. Increased gene expression [2]

According to the gnomAD browser data, the allele frequencies of these SNPs differ in populations around the world (Table 2).

Table 2 — Population frequency of SNV genes *PON1*, *LIPC*, *LPL*, *FTO* according to gnomAD browser [3]

Population	rs662	rs2070895	rs149551759*	rs9939609
Africans / African-Americans	0.6733	0.5139	0.000	0.4823
East Asians	0.6568	0.3916	0.000	0.1309
South Asians	0.3824	0.000	0.000	0.000
Latinos / Latino Americans	0.4941	0.5036	0.000	0.2541
Ashkenazi Jews	0.3075	0.2063	0.000	0.5207
Europeans excluding Finns	0.2806	0.2251	0.0006447	0.4216
Finns	0.2771	0.2837	0.0008792	0.3970
General for women	0.3945	0.3332	0.0005114	0.4197
General for men	0.3708	0.3258	0.0002875	0.4134
General	**0.3816**	**0.3290**	**0.0003899**	**0.4162**
Total number of homozygotes	23 727	2 824	0	2 824
Number of alleles in exomes read	95 101	Not investigated	95	Not investigated

The number of alleles in the genomes read	12 746	13 038	15	13 038

*- for Ser447Leu

For *rs662, rs2070895, rs149551759, rs9939609*, participation in the development of obesity, diabetes, and atherosclerosis in adults for different populations has been shown [4-7]. Taking into account the fact that the clinical manifestations of these diseases are usually noticeable in middle age, the process of atherogenesis is able to start in early childhood [8]. External factors such as diet, lifestyle, hormonal changes affect the phenotypic manifestations of SNP and have to be studied [9, 10].

The aim of the study was to investigate the potential relationship between *PON1 Q192R, LIPC-250G> A, LPL Ser447Ter, FTO A23525T* and the risk of obesity, atherosclerosis and diabetes in children and adolescents in Europe and the European part of Russia by means of meta-analysis.

Materials and research methods

A systematic search was carried out in the PubMed, eLIBRARY.RU and Google Academia databases to search for full-text studies in English and Russian, published before April 2020. The articles were analyzed using the guidelines for systematic reviews and meta-analyzes (PRISMA) [11]. All included studies had to meet the following criteria: 1. Research focused on the role of gene polymorphisms *PON1 Q192R, LIPC -250G> A, LPL Ser447Ter, FTO A23525T* and the risk of obesity, atherosclerosis or diabetes in children and adolescents; 2. studies with a case-control design; 3. the age of the participants included in the experiment is no more than 20 years; 4. studies providing detailed frequencies of genotypes and the total number of studied groups for the territory of Europe and the European part of Russia. The exclusion criteria were:

1. the article is not related to the studied polymorphisms;
2. review article, editorial articles or meta-analysis;
3. basic experimental studies or animal studies;
4. studies without available genotyping data;
5. data on populations that have been in genetic isolation for a long time (for example, Ashkenazi, Icelanders, etc.).

The search was carried out using the following set of keywords (table 3).

Table 3 — Keywords used for research searches.

Atherosclerosis	Diabetes	Obesity
PON1 / LIPC/ LPL/ FTO young subjects atherosclerosis	*PON1 / LIPC/ LPL/ FTO* young subjects diabetes	*PON1 / LIPC/ LPL/ FTO* young subjects overweight obesity
PON1 / LIPC/ LPL/ FTO atherosclerosis children adolescents	*PON1 / LIPC/ LPL/ FTO* diabetes children adolescents	*PON1 / LIPC/ LPL/ FTO* obesity children adolescents
rs662/ rs2070895/ rs149551759/ rs9939609 atherosclerosis children adolescents	rs662/ rs2070895/ rs149551759/ rs9939609 diabetes children adolescents	rs662/ rs2070895/ rs149551759/ rs9939609 obesity children adolescents

Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* atherosclerosis children adolescents	Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* diabetes children adolescents	Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* obesity children adolescents
PON1 / LIPC/ LPL/ FTO atherosclerosis in children and adolescents	*PON1 / LIPC/ LPL/ FTO* diabetes children adolescents	*PON1 / LIPC/ LPL/ FTO* obesity children adolescents
rs662/ rs2070895/ rs149551759/ rs9939609 atherosclerosis in children and adolescents	rs662/ rs2070895/ rs149551759/ rs9939609 diabetes children adolescents	rs662/ rs2070895/ rs149551759/ rs9939609 obesity children adolescents
Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* atherosclerosis in children and adolescents	Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* diabetes children adolescents	Gln192Arg/ *-250G>A/* Ser447Ter/ *A23525T* obesity children adolescents

An initial search in electronic databases yielded 2,549 studies in accordance with the above comprehensive search strategy. A detailed outline of the research selection process is shown in Figure 1. In total, more than 2,500 publications were excluded after careful reading of the titles, abstracts, or full text of the article. Following this procedure, 9 case-control studies were identified that met our criteria. In total, 3,603 people were included in the meta-analysis, divided into groups: children and adolescents with obesity or overweight (BMI) — 1,877 people and children and adolescents who made up the control group, with normal weight or underweight — 1,726 people.

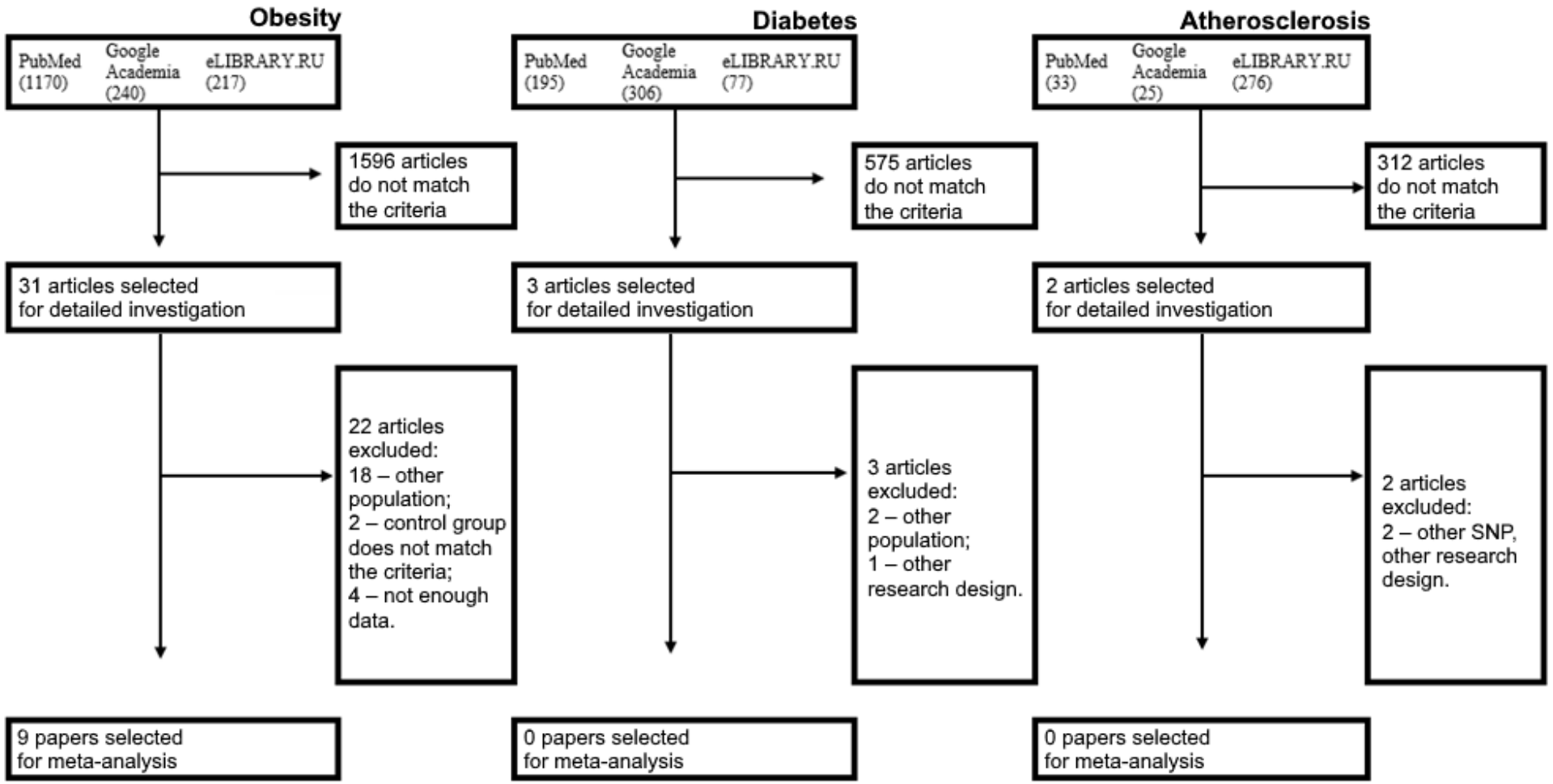

Figure 1. Description of the procedure for searching for publications.

Statistical processing of results

The correspondence of the frequency distribution of genotypes to the Hardy-Weinberg equilibrium and the $\chi 2$ criterion were calculated using the Hardy-Weinberg equilibrium calculator [12]. The odds ratio (OR) was calculated using the SciStat.com program [13]. Differences were regarded as statistically significant at $p < 0.05$. If the authors did not provide detailed data in the article, HWE and OR were additionally calculated. The combined odds ratios were calculated for the dominant and recessive models, since, to the best of author's knowledge, the data on the type of inheritance of the studied polymorphisms has not been found.

Results and discussion

Analysis of data on polymorphisms *rs662, rs2070895, rs149551759, rs9939609* in the development of obesity in children and adolescents.

1627 articles have been found and analyzed by keywords (Table 3) in the PubMed, eLIBRARY.RU and Google Academia databases. Of these, 31 publications were devoted to a case-control study of rs662 and rs9939609 in the development of obesity in children and adolescents. Data on these studies are presented in Table 4. No such studies were found for the gene variants *LIPC-250G> A* and *LPL Ser447Ter*.

The results of a meta-analysis of the association of the rs662 polymorphism of the PON1 gene are presented in the study by Ferré N. et al (Table 5). There were no statistically significant differences for the two groups of children. The authors mention that the presence of the *rs662* polymorphic alley of the *PON1* gene in the genotype cannot be considered as a direct cause-and-effect relationship with the development of obesity. However, the authors note a decrease in plasma *PON1* activity in obese children. In the respective publication, it is concluded that PON1 may play a role in the occurrence and development of metabolic changes in childhood obesity, which leads to diabetes and cardiovascular diseases at a later age [14].

Table 4 — Characteristics of studies investigating the role of rs662 and rs9939609 in the development of obesity in children and adolescents

First author, year	A country	Ethnicity	Diagnosis	Age in years	Sample size, absolute		Inclusion / exclusion criteria in meta-analysis
					Weight deficit / average physical development	Obesity / body mass index	
PON1							
Ferré N., 2013 [14]	Spain	Spaniards	Obesity	12±3	36	110	Meets all criteria
FTO							
Hallman D. M., 2005 [15]	USA, Texas, Louisiana	Non-hispanic whites	-	8-18	1081		Population is of no interest
		African American			478		
Grant SFA, 2008 [16]	USA, Philadelphia	Caucasians	Obesity	2-18	2270	418	Population is of no interest
		African American			1424	578	
Jacobsson J.A., 2008 [17]	Sweden	Swedes	Obesity	6-21	512	450	Meets all criteria
Müller T. D., 2008 [18]	Germany	Germans	Obesity / body mass index	10,71±3,1	178	519	The average age of the participants included in the control group is 24.58 ± 2.56 years
Xi B., 2010 [19]	China	Chinese	Obesity	6-18	2274	1229	Population is of no interest
Bollepalli S, 2010 [20]	USA, Ohio	Non-hispanic whites	-	14.26 ± 2.21	561		Population is of no interest
		African American		14.21 ± 2.15	497		

Okuda M., 2011 [21]	Japan	Japanese	Overweight, including obesity	10-13	133	133	Population is of no interest
Riffo B., 2011 [22]	Chile	American Indians Chile	Obesity	6-11	136	238	Population is of no interest
Zavattari P., 2011 [23]	Italy	Italians	Obesity	10.5±3.3	543	912	The average age of the participants included in the control group is 34 ± -7.1 years
Mangge H., 2011 [24]	Austria	Austrians	Obesity	12,5±3,1	103	268	Meets all criteria
Moleres A., 2012 [25]	Spain	Spaniards	Obesity	6-18	146	208	Meets all criteria
Luczynski W, 2012 [26]	Poland	Poles	Obesity	14.01±3.24	634	199	Meets all criteria
Dwivedi O.P., 2012 [9]	India	Hindus	Obesity / body mass index	11-17	2230	896	Population is of no interest
Pyrzak B., 2012 [27]	Poland	Poles	Obesity	12 - 18	24	136	Meets all criteria
Olza J., 2013 [28]	Spain	Spaniards	Obesity	6-15	241	290	Meets all criteria
Vasan S. K., 2013 [29]	India	Indians of southern India	Obesity	17.1 ± 1.9	1036	181	Population is of no interest
Ibba A., 2013 [30]	Italy	Sardinians	Obesity	4-20	543	412	Meets all criteria
Yang M., 2014 [31]	China	Chinese, cities of Beijing, Tianjin, Chongqing, Hangzhou,	Obesity	7-18	2600	1400	Population is of no interest

		Shanghai and Nanning					
Lazopoulou N., 2015 [32]	Greece	Greeks	Obesity / body mass index	11.08±2.23	151	153	Insufficient data to analyze
Reuter C.P., 2016 [33]	Brazil	Brazilians	Obesity / body mass index	7-17	266	140	Population is of no interest
Zhang M.X., 2017 [34]	China	Han Chinese	Obesity	6-11	531	246	Population is of no interest
Abdelmajed S.S., 2017 [35]	Egypt	Egyptians	Obesity	9.93±3.06	100	100	Population is of no interest
Fu L.W., 2017 [36]	China	Chinese	Obesity	pupils	2306	1196	Population is of no interest
González-Herrera L., 2018 [37]	Mexico	Mexicans	Obesity / body mass index	6-12	303	318	Population is of no interest
Yang Y, 2019 [38]	China	Chinese people of the northwestern part of the country	Obesity	pupils	170	200	Population is of no interest
Bondareva, E.A., 2013 [39]	Russia	The population of the city of Arkhangelsk and the Arkhangelsk region	body mass index	10 -17	66	25	Meets all criteria
Zavyalova L.G., 2011 [40]	Russia	Russians, population of Novosibirsk	Overweight	14-17	530	56	Meets all criteria

Shakirova A.T., 2017 [41]	Russia	Population of the Republic of Tatarstan	body mass index	7-17	81	114	Meets all criteria
Lebedeva E.N., 2019 [42]	Russia	Population of the Orenburg region	body mass index	adolescents	50	50	Insufficient data to analyze
Ubaidullayeva S.A., 2019 [43]	Uzbekistan	Uzbeks	Obesity	No data	54	41	Population is of no interest, insufficient data to analyze

Table 5 — Results of meta-analysis of the association of rs662 polymorphism of the PON1 gene

Genotype	Obesity, absolute	The control, absolute	p	OR (95%CI)
Ferré N., 2013 (Spain, Spanish)				
General inheritance model				
QQ	47	18		1
QR	51	16	0.6	1.22 [0.56 – 2.66]
RR	12	2	0.3	2.23 [0.47 - 11.29]
p=0.31				
Dominant inheritance model				
QQ	47	18	0.45	1
QR+ RR	63	18		1.34 [0.63 – 2.85]
Recessive inheritance model				
QQ+ QR	98	34	0.35	1
RR	12	2		2.08 [0.44 – 9.77]

The study by Huen K. et al was not included in the meta-analysis based on population criteria and the absence of a case-control study design. The study itself has been carried out twice on a cohort of 373 children: at the age of 2 and 5 years, anthropometric measurements were carried out, blood was taken for analysis of the activity of enzymes — participants in lipid metabolism. Genotyping was performed for *rs662* of the *PON1* gene. The direct link between genetic origin and obesity parameters was also examined. It was found that African roots were not significantly associated with higher BMI scores. These findings provide additional evidence that it is important to consider parentage in genetic studies of obesity. Interestingly, the associations observed at ages 2 and 5 were vastly different. For example, the association between rs662 and obesity was stronger and the effect of genetic origin was more pronounced at age 2 years compared with age 5 years [44]. These data are well supported by data from studies of twins and adopted children, demonstrating that the influence of heredity on the development of obesity is lowest at 5 years, when the influence of general environmental factors is strongest [45].

The data of studies for which the frequencies of genotypes and odds ratios for the *rs9939609* polymorphism of the *FTO* gene were calculated are presented in tables (6-8) (general, dominant and recessive inheritance patterns) and in Figure 2. For data in publications by Luczynski W. et al, Pyrzak B. et al and Zavyalova L.G. with colleagues [26, 27, 40] for the genetic variant *23525T>A* of the *FTO* gene, when calculating the distribution of allele and genotype frequencies, a correspondence to the Hardy-Weinberg equilibrium of one of the studied groups has not been found. Therefore, these data were not included in the pooled sample.

Table 6 — Results of meta-analysis of the association of *rs9939609* polymorphism of the *FTO* gene

First author, year	Genotype	Obesity / BMI, abs.	Control, abs.	*p*	OR (95%CI)
Jacobsson, J. A., 2008 [17]	*TT*	133	174		1
	TA	206	244	0.5	1.105 [0.825-1.479]
	AA	111	92		1.58 [1.105-2.255]
	p=0.01638				
Mangge, H., 2011 [24]	*TT*	75	31		1
	TA	118	56	0.6	0.87 [0.515-1.473]
	AA	75	16	0.055	1.9 [0.979-3.836]
	p=0.08425				
Moleres, A., 2012 [25]	*TT*	53	49		1
	TA	106	76	0.3	1.29 [0.792-2.100]
	AA	49	21	**0.01799**	2.16 [1.135-4.099]
	p=0.02076				
Ibba A., 2013 [30]	*TT*	84	183		1
	TA	193	254	**0.00188**	1.65 [1.203-2.277]
	AA	135	106	<**0.0001**	2.775 [1.931-3.987]
	p=<**0.0001**				
Olza, J., 2013 [28]	*TT*	72	90		1
	TA	149	118	**0.02246**	1.58 [1.066-2.338]
	AA	69	33	**0.00023**	2.6 [1.557-4.387]
	p=0.00019				
Bondareva, E.A. [39], 2013	*TT*	4	24		1
	TA	13	32	0.15	2.45 [0.706-8.418]
	AA	8	10	**0.023**	4.8 [1.173-19.637]
	p=0.02408				
Shakirova A.T., 2017 [41]	*TT*	30	34		1
	TA	58	37	0.078	1.78 [0.936-3.373]
	AA	26	10	**0.01424**	2.95 [1.223-7.098]
	p=0.0104				
Pooled data	*TT*	451	585		1
	TA	843	817	**0.00025**	1.34 [1.145-1.564]
	AA	473	288	<**0.0001**	2.13 [1.760-2.579]

	p=<**0.0001**				
Zavyalova L.G., 2011 [40]	*TT*	15	177	PXB for the control group p=0.0067	
	TA	23	321		
	AA	18	92		
Luczynski W, 2012 [26]	*TT*	51	187	For comparison group PXB p=0.001326	
	TA	76	313		
	AA	72	134		
Pyrzak, B., 2012 [27]	*TT*	35	5	PXB for the control group p=0.032089	
	TA	67	6		
	AA	34	13		

Statistically significant differences for the overweight or obese and normal weight groups of children were found for all studies included in the meta-analysis. In the pooled sample, the risk of developing obesity for homozygotes for allele *A* is doubled (p <0.0001). These data are consistent with the data of other researchers obtained for the populations of children in China, Japan, Europe and Africa, Brazil [18, 19, 21, 32, 35, 36, 38, 46, 47].

Table 7 — Results of meta-analysis of the association of *rs9939609* polymorphism of the *FTO* gene for the dominant model

First author, year	Genotype	Obesity / BMI, abs.	Control, abs.	p	OR (95%CI)
Jacobsson, J. A., Danielsson, P., 2008	*TT*	133	174	0.13	1
	TA+AA	317	336		1.23 [0.94 - 1.62]
Mangge, H., 2011	*TT*	75	31	0.69	1
	TA+AA	193	72		1.1 [0.67 - 1.82]
Moleres, A., 2012	*TT*	53	49	0.1	
	TA+AA	155	97		1.48 [0.93 - 2.35]
Ibba A., 2013	*TT*	84	183	<**0.0001**	1
	TA+AA	328	360		1.98 [1.47 - 2.67]
Olza, J., 2013	*TT*	72	90	**0.0019**	1
	TA+AA	218	151		1.8 [1.24 - 2.62]
Bondareva, E.A., 2013	*TT*	4	24	0.07	1
	TA+AA	21	42		3 [0.92 - 9.77]
Shakirova A.T., 2017	*TT*	30	34	**0.0227**	1
	TA+AA	84	47		2.025 [1.10 - 3.72]
Pooled data	*TT*	451	585	< **0.0001**	1
	TA+AA	1316	1105		1.54 [1.33 - 1.79]

Table 8 — Results of a meta-analysis of the association of the rs9939609 polymorphism of the FTO gene for the recessive model

First author, year	Genotype	Obesity / BMI, abs.	Control, abs.	p	OR (95%CI)
Jacobsson, J. A., 2008	*TT+TA*	339	418	**0.0124**	1
	AA	111	92		1.49 [1.09 - 2.03]
Mangge, H., 2011	*TT+TA*	193	87	**0.0139**	1
	AA	75	16		2.11 [1.16 - 3.83]
Moleres, A., 2012	*TT+TA*	159	125	**0.0345**	1
	AA	49	21		1.83 [1.04 - 3.22]
Ibba A., 2013	*TT+TA*	277	437	**<0.0001**	1
	AA	135	106		2 [1.49 - 2.70]
Olza, J., 2013	*TT+TA*	221	208	**0.0036**	1
	AA	69	33		1.97 [1.25 - 3.10]
Bondareva, E.A., 2013	*TT+TA*	17	56	0.08	1
	AA	8	10		2.63 [0.898 - 7.73]
Shakirova A.T., 2017	*TT+TA*	88	71	0.07	1
	AA	26	10		2.1 [0.95 - 4.64]
Pooled data	*TT+TA*	1294	1402	**<0.0001**	1
	AA	473	288		1.78 [1.51 - 2.098]

According to calculations for the dominant model of inheritance, statistically significant differences for the two groups of children were revealed for the studies of Ibba A. et al, Olza J. et al, Shakirova A.T. For a sample common for all studies, the odds ratio for homo- and heterozygous genotypes for the polymorphic allele was 1.54 ($p < 0.0001$) (Table 7).

The risk of developing obesity is increased for the homozygous genotype for allele A according to calculations for the general data ($p < 0.0001$). For the recessive model of inheritance, statistically significant differences were not revealed only for the data of E. A. Bondareva (2013) with colleagues and A. T. Shakirova (2017) with colleagues. According to calculations in the other studies, the risk of obesity is increased by 1.5-2 times for the A23525A genotype (Table 8). These data are consistent with the data obtained for children of the Italian population [23] and the population of children in Uzbekistan [43]. The authors of [43] note that this genotype is 2.5 times more common in the group of obese children than in the control group. At the same time, the T allele, with a low level of relative risk and a high level of reliability, may indicate a protective value. Lebedeva E.N. (2019) [42] and co-authors found that allele A is a risk factor for the development of obesity for both the A23525A genotype and the T23525A genotype in the population of children and adolescents in the Orenburg region [42]. For the population of Chilean American Indian children, there are data indicating a relationship between the A allele of the FTO gene and insulin resistance [22].

In the population of adults in St. Petersburg, it was shown that the T23525T genotype of the FTO gene is more common in metabolically healthy people with obesity. The likelihood of metabolic health decreased in the presence of the A allele rs9939609 [7].

The literature contains data on different risks for *rs9939609* for different populations of children and adolescents. Different risks of obesity for different genetic variants of the *FTO* gene have been identified for Caucasians and African Americans in Ohio, USA [20]. In his work, Grant SFA. et al. performed genotyping for 11 SNPs of the *FTO* gene. An association of different SNPs and haplotypes with the risk of obesity in the groups of Caucasians and African American children was revealed. The researchers argue that the association observed in children is almost identical to that of adults [16]. According to Hallman D. M. et al. the *A / A rs9939609* genotype in the *FTO* gene is associated with a higher body mass index in non-Hispanic whites compared to African Americans in samples from Louisiana and Texas. The association can change with age, with the A / A genotype associated with a larger difference in body mass index in late adolescence than in childhood [15].

For children and adolescents of the Indian population for *rs9939609*, the findings are controversive. According to some data, the *FTO* gene is not associated with general obesity, but a correlation was found with the waist-hip ratio [29]. According to other authors, genetic variants of *FTO* influence the risk of obesity to a greater extent in children than in adults [9].

Endocrinological changes in adolescents can act as external factors influencing the development of obesity. It has been shown that the presence of the A allele of the *FTO* gene in the genotype is associated with a higher body mass index, fat mass index, and leptin concentrations in the blood in children aged 12 years, at the same time, there is a decrease in the association between the ages of 13-14 and its strengthening at the age of 17 [10].

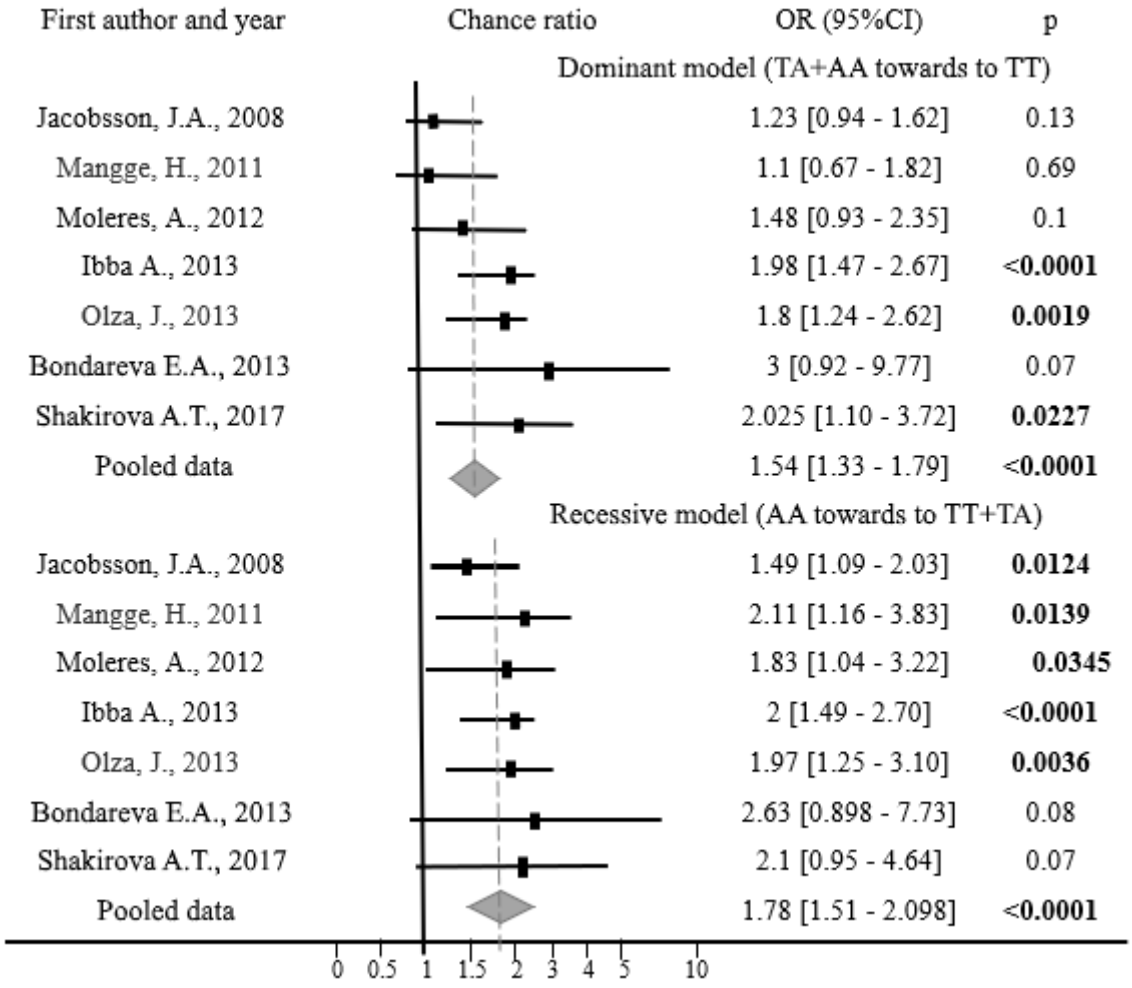

Figure 2. Overall assessment of the odds ratio for dominant and recessive models for the rs9939609 polymorphism of the FTO gene

Jacobsson J. A. et al. and Zavyalova L.G. with colleagues [17, 40] presented data on genotypes for boys and girls for children with obesity and normal weight. Data on odds ratios for general, dominant and recessive inheritance models are presented in Tables 9-11 and in Figure 3. For the group of girls in the study by LG Zavyalova with colleagues, the correspondence with the Hardy-Weinberg equilibrium for the control group was not found, therefore, the genotype data of girls from this study were not included in the pooled sample.

Table 9 — The results of a meta-analysis of the association of the *rs9939609* polymorphism of the FTO gene for boys and girls.

Group	Genotype	Obesity / BMI, abs.	Control, abs.	p	OR (95%CI)

Jacobsson J. A., 2008 (Sweden)					
♀	*TT*	62	94		1
	TA	106	122	0.19	1.32 [0.872-1.991]
	AA	59	44	**0.00563**	2.033 [1.227-3.369]
	p=0.00625				
♂	*TT*	67	80		1
	TA	92	122	0.62	0.9 [0.590-1.374]
	AA	47	48	0.55	1.17 [0.697-1.960]
	p=0.64797				
Zavyalova L.G., 2011 (Russia)					
♀	*TT*	5	101		1
	TA	10	174	0.79	1.16 [0.386-3.492]
	AA	7	58	0.13	2.45 [0.740-8.031]
	p=0.14413				
♂	*TT*	10	76	PXB control group p=0.004935	
	TA	13	147		
	AA	11	34		
Pooled data					
♀	*TT*	67	195		1
	TA	116	296	0.46	1.14 [0.803-1.620]
	AA	66	102	**0.00268**	1.88 [1.243-2.854]
	p=0.004				
♂	*TT*	77	156		1
	TA	105	269	0.19	0.79 [0.555-1.127]
	AA	58	82	0.103	1.43 [0.929-2.210]
	p=0.22				

For the general inheritance model, statistically significant differences were found for groups of girls with obesity and normal weight (OR = 1.88, p = 0.00268). These data are consistent with the data of studies of Mexican and Polish populations of children and adolescents [26, 37].

Table 10 — The results of the meta-analysis of the association of the *rs9939609* polymorphism of the *FTO* gene for boys and girls for the dominant model

Group	Genotype	Obesity / BMI, abs.	Control, abs.	p	OR (95%CI)
Jacobsson J. A., 2008 (Sweden)					
♀	TT	62	94	**0.0375**	1
	TA+ AA	165	166		1.51 [1.02 - 2.22]
♂	TT	67	80	0.905	1
	TA+ AA	139	170		0.98 [0.66 - 1.45]
Zavyalova L.G., 2011 (Russia)					
♀	TT	5	101	0.45	1
	TA+ AA	17	232		1.48 [0.53 - 4.12]
Pooled data					
♀	TT	67	195	0.09	1

	TA+ AA	182	398		1.33 [0.96 - 1.85]
♂	TT	77	156	0.72	1
	TA+AA	163	351		0.94 [0.68 - 1.31]

Table 11 — The results of the meta-analysis of the association of the rs9939609 polymorphism of the FTO gene for boys and girls for a recessive model

Group	Genotype	Obesity / BMI, abs.	Control, abs.	p	OR (95%CI)
Jacobsson, J. A., 2008 (Sweden)					
♀	TT+ TA	168	216	**0.0151**	1
	AA	59	44		1.72 [1.11 - 2.67]
♂	TT+TA	159	202	0.34	1
	AA	47	48		1.24 [0.79 - 1.96]
Zavyalova L.G., 2011 (Russia)					
♀	TT+ TA	15	275	0.098	1
	AA	7	58		2.21 [0.86 - 5.67]
Pooled data					
♀	TT+ TA	183	491	**0.0022**	1
	AA	66	102		1.74 [1.23 - 2.47]
♂	TT+TA	182	425	**0.0094**	1
	AA	58	82		1.65 [1.13 - 2.41]

Statistically significant differences both in the group of boys and in the group of girls were revealed for the recessive inheritance model in the pooled sample. The odds ratios for the *A23525A* genotype were 1.74 (p = 0.0022) and 1.65 (p = 0.0094) for girls and boys with obesity and normal weight, respectively. There were no statistically significant differences for the pooled sample for the dominant model.

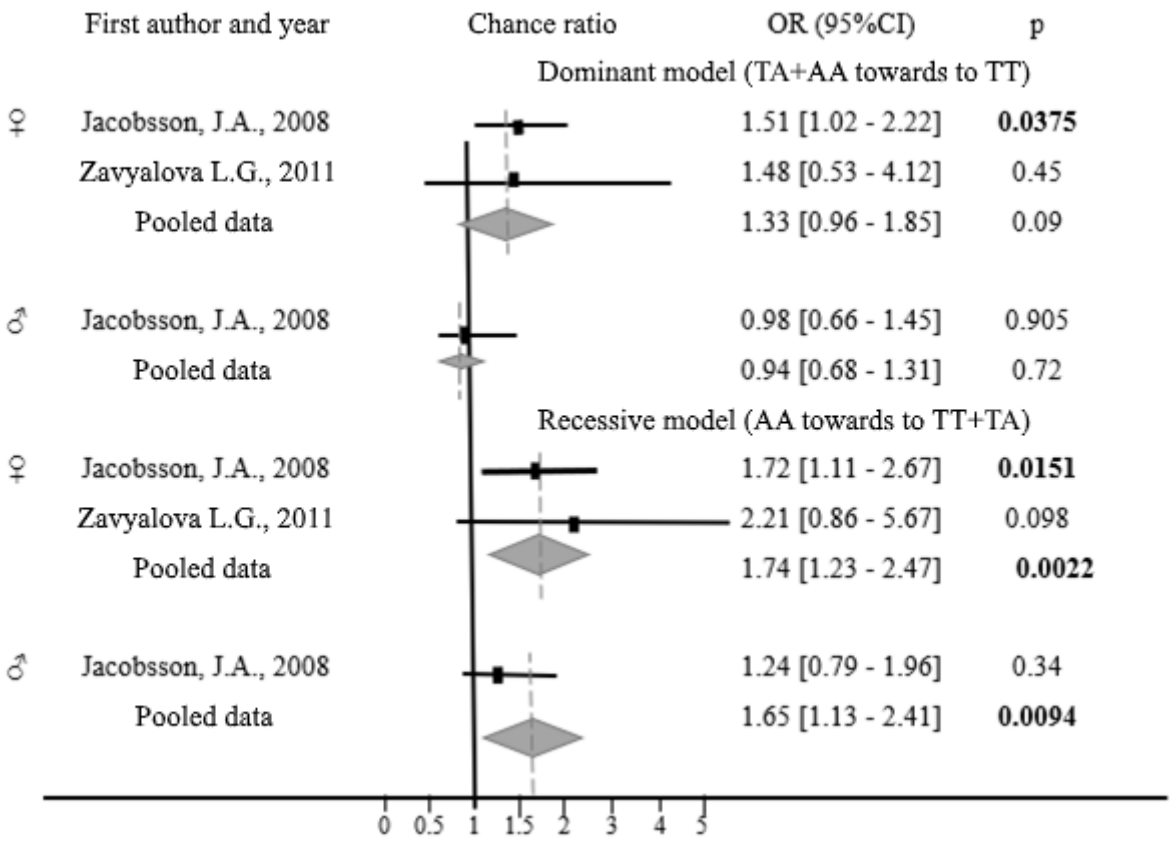

Figure 3. Overall assessment of the odds ratio for the dominant and recessive models for the *rs9939609* polymorphism of the *FTO* gene.

Analysis of data on polymorphisms *rs662, rs2070895, rs149551759, rs9939609* in the development of diabetes in children and adolescents.

On this topic, we analyzed 578 articles, of which only 3 articles were devoted to the study of type I diabetes in children for *rs662* and *rs9939609*. The data from these studies are presented in Table 12.

For genes of lipoprotein lipase and triacylglyceride lipase, data on the carriage of genetic variants *rs2070895, rs149551759* and the development of diabetes in children were not found.

For the *PON1* gene, 2 publications were found that met the required criteria, except for the territorial one [48, 49]. In a study by Fekih O. et al. conclude that the *L55M* and *Q192R PON1* gene polymorphisms can be genetic markers of diabetic nephropathy in type I diabetes, as well as the *LMQQ* and *MMQQ* haplotypes [48]. Gallego P. H. et al. analyzed genotypes for *PON1* gene polymorphisms *Leu54Me* and *Gln192Arg*. According to their studies, it can be argued that these SNPs are involved in the development of complications in type I diabetes. Researchers emphasize the relationship between the *Leu54Met* variants and the increase in plantar fascia thickness, which indicates the involvement of PON1 in the pathogenesis of collagen in diabetes [49]. In their study, Luczyński W. et al. showed that the carriage of the A allele of the *rs9939609*

variant of the *FTO* gene is associated with increased body weight in children with type I diabetes, especially in girls [50]. This article was not included in the meta-analysis due to a different study design.

Table 12 — Data from studies on the development of type I diabetes in children and adolescents for *rs662* and *rs9939609*

First author, year	A country	Ethnicity	Age in years	Sample size, abs.	
				The control	Type I diabetes
PON1					
Fekih O, 2017 [48]	Tunisia	Not specified	12.59 ± 5.38	91	116
Gallego P.H., 2008 [49]	Australia	Caucasians	15.4 ±1.9	172	159
FTO					
Luczyński W., 2014 [50]	Poland	Poles	13.39±3.42	-	1119

Association between genetic variants *rs662, rs2070895, rs149551759, rs9939609* and the risk of atherosclerosis in children and adolescents.

314 articles have been analyzed by keywords: "atherosclerosis in children and adolescents *PON1 FTO LPL LIPC*", "atherosclerosis children teens *PON1 / LPL / FTO / LIPC", "PON1 / LPL / FTO / LIPC* atherosclerosis in children" in the PubMed databases, Google Academia, eLIBRARY.RU. (table 3). There were no articles on the analysis of the *rs662, rs2070895, rs149551759, rs9939609* polymorphisms in the development of atherosclerosis in children and adolescents. Research has focused on the study of atherosclerosis in adults and the elderly.

2 articles were devoted to the search for candidate genes for lipid metabolism disorders in children and adolescents [51, 52] Montali, A. et al studied 283 children of the Italian population 2-18 years old for *LPL* gene polymorphisms *rs1801177, rs268, rs118204078, rs328, p.Ser45Asn* and predisposition to the development of atherogenic dyslipidemia. Based on the results obtained, the authors of the article conclude that the presence of these polymorphisms may contribute to the development of hypertriglyceridemic traits in the subgroup of children with atherogenic dyslipidemia [51]. Agirbasli, M. et al conducted a study among 365 Turkish schoolchildren 12-15 years old to search for candidate genes for lipid levels. The analyzed genes included *LPL (rs328)* and *LIPC* (rs1800588). The children were divided into groups with high and low levels of lipoprotein cholesterol and triglycerides. No statistically significant differences were found for these polymorphisms for these groups [52].

For *PON1*, it was shown that a decrease in its activity in serum is accompanied by an increase in oxidative stress and the risk of atherosclerosis [53].

Conclusion

Thus, based on the results of the meta-analysis, it can be concluded that the *23525T>A* polymorphism of the *FTO* gene is involved in metabolic pathways disorders in children and adolescents in Europe and the European part of Russia. The risk of developing obesity for homozygotes for allele *A* is doubled ($p < 0.0001$). Statistically significant differences for children and adolescents with obesity and normal weight were found for dominant and recessive inheritance patterns ($p < 0.0001$).

An analysis of genotype frequencies for boys and girls revealed statistically significant differences only for homozygotes for allele *A* in the girls group ($p = 0.00268$). Statistically significant differences both in the group of boys and in the group of girls were found for the recessive inheritance model. The odds ratios for the *A23525A* genotype were 1.74 ($p = 0.0022$) and 1.65 ($p = 0.0094$) for girls and boys with obesity and normal weight, respectively.

Based on the data of one publication for *rs662* of the *PON1* gene, no significant differences in the allele frequencies of genotypes for groups of children and adolescents with and without obesity were found.

To the best of authors knowledge, there are no studies of genetic variants *rs662, rs2070895, rs149551759, rs9939609* in children and adolescents in Europe and the European part of Russia and the risk of atherosclerosis and diabetes.

Various genetic factors have an additive effect on changes in body mass index and obesity status in children. An individual who carries more risk alleles in genes associated with obesity has an increased risk of developing obesity [34, 38, 46]. It is likely that many of the individual polymorphisms have only a moderate effect on the risk of obesity, diabetes, or atherosclerosis, but their effects are enhanced in synergism with other genetic and environmental factors [54]. For example, it was shown that the effects of the *rs9939609 FTO* gene are more expressed among children with insufficient level of vitamin D [55]. It is also necessary to take into account the hormonal background of children and adolescents that affect metabolic pathways. In this regard, independent studies of children and adolescents of different age groups are possible [10, 54]. Studies of hereditary factors in the association of obesity with gene polymorphisms associated with the risk of its development among members of the same family is also important. It has been shown that the *rs9939609* association of the *FTO* gene is higher if the student has a mother or a paternal or maternal grandmother is obese [33].

For the *LPL* gene, it was revealed that epigenetic disturbances in the intergenic *LPL* region in the placenta were associated with birth weight, fetal growth, and fat accumulation in childhood, which can lead to metabolic dysfunctions in later life [56].

The genome accumulates different genetic variants over generations. Epigenetic profiles determine which parts of it will be transcribed. Depending on the post-transcriptional regulators, various mature RNAs are formed from the original messenger RNA. Diet has been shown to affect DNA sequence variants, epigenetic profiles, and post-transcriptional regulation [31]. The

influence of food products on the translation process leads to a final set of functional proteins, activated pathways and subsequent metabolites, which constitute the functional gene product. According to nutrigenetics, positive or negative phenotypic effects depend on food and lifestyle (Figure 4). Taste preferences and lifestyle are determined by culturally inherited customs and habits. In addition, diseases of metabolic disorders have been hidden for a long period of time due to food shortages and forced lifestyle. The masking effect is also associated with the Mediterranean diet, which has recently been increasingly mentioned in the literature. Modern living conditions and dietary habits lead to the activation of hidden genes [57]. However, the relationship of specific SNPs affecting metabolism for different ethnic groups needs further study [44, 57].

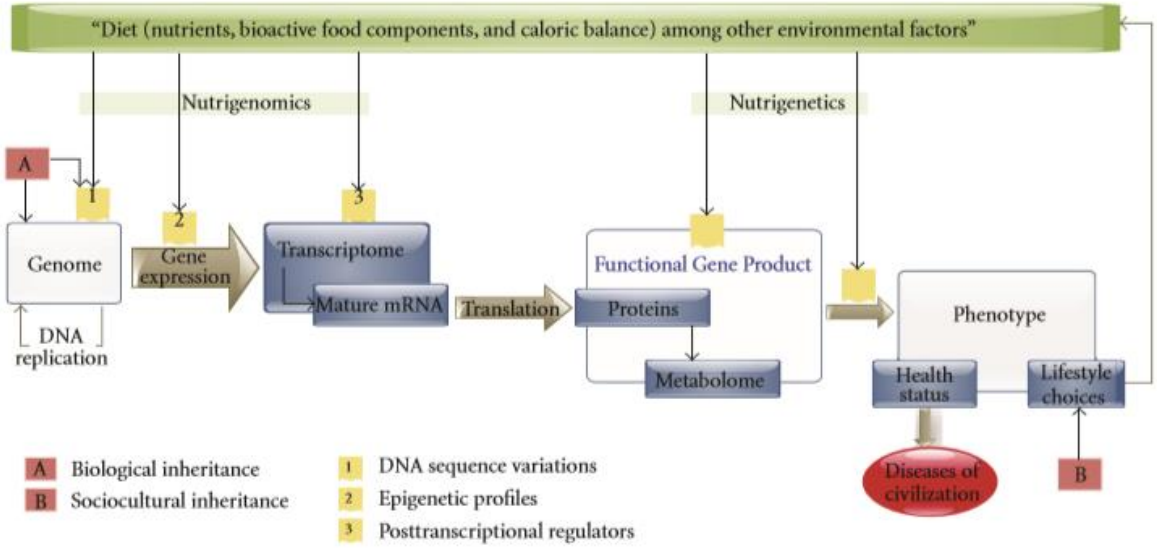

Figure 4. Impact of diet from genotype to phenotype [57].

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Conflicts of interest
No conflict of interests.

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