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## Single-nucleotide variant rs1800139 of the LRP1 gene as a factor in the development of obesity in children

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In the development of postnatal obesity and associated metabolic disorders, genetic features occupy a prominent place among various obesogenic factors. One of the genes that controls adipogenesis and determines the development of adipose tissue is the human low-density lipoprotein receptor-related protein 1 (*LRP1*) gene.

**The aim:** study of the frequency of SNVs of the *LRP1* gene in children with different phenotypes of obesity.

**Materials and methods.** 253 obese children aged 6–18 years were examined. The main group (n=153) was made up of children with metabolically unhealthy obesity (MUO) according to IDEFICS 2014 criteria. The control group (n=100) was made up of children with metabolically healthy obesity (MHO). All children underwent a general clinical, immunobiochemical examination (Synevo, Ukraine). Whole-genome sequencing (CeGat, Germany) was performed in 31 children of the primary and 21 children of the control group. Static analysis: variational analysis, Wald analysis, calculation of  $\chi^2$ , Kramer's independence test, Spearman's correlation analysis, ROC analysis.

**Results.** As a result of testing statistical hypotheses based on the conjugation table of features from 743 SNVs of 86 candidate genes studied, the greatest association with MUO was found in SNV rs1800139 *LRP1* ( $V=0.44$ ). In patients with MHO, the CC genotype was significantly less common ( $p<0.05$ ) and the TT genotype of SNV rs1800139 of the *LRP1* gene was more often registered than in the general human population ( $p<0.02$ ). In patients with MUO, both homozygous genotypes of SNV rs1800139 of the *LRP1* gene occurred significantly less frequently than in the general human population ( $p<0.05$ ). Among patients with MUO, the TT genotype of SNV rs1800139 of the *LRP1* gene occurred significantly less often compared to the group of patients with MHO ( $p<0.01$ ).

**Conclusions.** The CT genotype SNV rs1800139 of the *LRP1* gene is highly associated with the presence of MUO and the development of dyslipidemia in children.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution mentioned in the work. Informed consent of parents or their guardians was obtained for conducting research. The authors declare no conflict of interest.

**Keywords:** low-density lipoprotein receptor-related protein 1 gene, analysis of single nucleotide gene variants, children, metabolically unhealthy obesity, metabolically healthy obesity.

### Однонуклеотидний варіант rs1800139 гена *LRP1*, як фактор розвитку ожиріння у дітей

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У розвитку постнатального ожиріння та пов'язаних із ним метаболічних порушень генетичні особливості посідають чільне місце серед різноманітних обесогенних факторів. Одним із генів, який контролює адипогенез та зумовлює розвиток жирової тканини, є ген протеїну, спорідненого з рецептором ліпопротеїнів низької щільності 1 типу (LDL receptor related protein 1 — *LRP1*) людини.

**Мета** — вивчення частоти зустрічальності SNV гена *LRP1* у дітей з різними фенотипами ожиріння.

**Матеріали і методи.** Обстежено 253 дитини з ожирінням віком 6–18 років. Основну групу (n=153) представили діти з метаболічно нездоровим ожирінням (metabolically unhealthy obesity — MUO) згідно критеріїв IDEFICS 2014. Контрольну групу (n=100) склали діти з метаболічно здоровим ожирінням (metabolically healthy obesity — MHO). Всім дітям було проведено загальноклінічне, імунобіохімічне дослідження (Synevo, Україна). Проведено повногеномне секвенування (CeGat, Німеччина) у 31 дитини основної та 21 дитини контрольної групи. Статистичний аналіз: варіаційний аналіз, аналіз Вальда, підрахунок критерію незалежності  $\chi^2$ , Крамера, кореляційний аналіз Спірмена, ROC -аналіз.

**Результати.** В результаті перевірки статистичних гіпотез на основі таблиці спряженості ознак з 743 одностановковими варіантами (single nucleotide variants — SNV) 86 генів-кандидатів, що вивчались, найбільша асоціація з MUO виявлена у SNV rs1800139 *LRP1* ( $V=0.44$ ). У хворих з MHO достовірно рідше зустрічався генотип CC ( $p<0,05$ ) і частіше генотип TT SNV rs1800139 гена *LRP1*, ніж у загальній людській популяції ( $p<0,02$ ). У той час як у хворих з MUO обидва гомозиготні генотипи SNV rs1800139 гена *LRP1* зустрічалися достовірно рідше, ніж у загальній людській популяції ( $p<0,05$ ). Серед хворих на MUO достовірно рідше зустрічався генотип TT SNV rs1800139 гена *LRP1*, порівняно з групою хворих на MHO ( $p<0,01$ ).

**Висновки:** Високо асоційованими з наявністю MUO та розвитком дисліпідемії у дітей є генотип CT SNV rs1800139 гена *LRP1*.

Дослідження проведено відповідно до принципів Гельсінської декларації. Протокол дослідження затверджено місцевим комітетом із питань етики зазначеної в роботі установи. На проведення дослідження отримано інформовану згоду батьків або осіб, які їх замінюють. Автори заявляють про відсутність конфлікту інтересів.

**Ключові слова:** ген протеїну, спорідненого з рецептором ліпопротеїнів низької щільності 1 типу, аналіз одностановкових варіантів гена, діти, метаболічно нездорове ожиріння, метаболічно здорове ожиріння.

## Introduction

The prevalence of obesity in children has been increasing over the past decades in almost all countries of the world. Obesity that occurs during childhood is highly associated with the development of metabolic disorders that pose a threat to health and significantly reduce human life expectancy. In the development of postnatal obesity and associated metabolic disorders, among various obesogenic factors, the leading place is occupied by genetic characteristics [1,6,7,20,29].

One of the genes that controls adipogenesis and determines the development of adipose tissue is the human low-density lipoprotein receptor-related protein 1 (LDL receptor related protein 1 – *LRP1*) gene, or CD91, which is located on human chromosome 12q13–14. The *LRP1* receptor differs from other receptors of the human low-density lipoprotein family by its special role in the uptake of vitamin K1 through endocytosis of chylomicron remnants [2,19,41].

The *LRP1* protein is a multifunctional endocytic transmembrane protein of the low-density lipoprotein receptor family that is particularly highly expressed in adipocytes and hypothalamic neurons. The *LRP1* receptor binds and internalizes more than 75 biologically diverse ligands. It must be emphasized that the *LRP1* protein is a key regulator of the adipogenic process. It has been established that the expression of the *LRP1* gene is directly proportional to the value of body mass index (BMI) [9,16].

The level of *LRP1* gene expression activity is associated with multidirectional effects on adipose tissue. On the other hand, silencing of the *LRP1* gene in 3T3F442A preadipocytes using is RNA is accompanied by suppression of the expression of adipocyte differentiation markers PPAR $\gamma$ , HSL and aP2 and leads to depletion of the intracellular lipid pool. Cessation of *LRP1* expression in mature adipocytes induces an increase in the process of basal lipolysis. While the development of obesity is accompanied by increased expression of the *LRP1* gene in human tissues. [31]. On the other hand, deficiency of *LRP1* expression in GABAergic neurons is accompanied by increased appetite and causes obesity [38]. It has been demonstrated that *LRP1* is the main regulator of leptin transport in the brain, and therefore deletion of the *LRP1* gene leads to leptin resistance and hyperphagia, which causes the development of obesity [39].

The *LRP1* receptor mediates hepatocyte internalization of lipids carried by postprandial chylomicron remnants by binding to apolipoprotein E, lipoprotein lipase, and hepatic lipase. Adipocyte *LRP1* gene knockout mice exhibited delayed postprandial lipid clearance, decreased fat stores, improved glucose tolerance, and decreased body weight compared to wild-type mice [3,5,10].

The *LRP1* protein is involved not only in lipid but also in carbohydrate metabolism. In particular, *LRP1* is involved in insulin receptor trafficking and intracellular signaling activity. Also, the GLUT2 transporter in hepatocytes, the GLUT4 transporter in adipocytes, as well as the GLUT3 and GLUT4 transporters in neurons are translocated to the cytoplasmic membrane of the cell in an *LRP1*-dependent manner after insulin stimulation [3,17].

At the same time, the clinical significance of single nucleotide variants (SNV) of the *LRP1* gene in the development of obesity and metabolic disorders in children remains a virtually unstudied phenomenon.

**The aim** of the study was to study the frequency of occurrence of SNVs of the *LRP1* gene in children with various obesity phenotypes.

## Materials and methods of the research

**Study design:** observational, analytical, longitudinal, cohort study.

**Time of data collection:** January 2020 – February 2023.

**Inclusion criteria:** children with polygenic obesity (BMI $\geq$ 97th percentiles) 6–18 years old.

**Exclusion criteria:** children with monogenic and/or syndromic obesity, pregnancy.

253 children with obesity aged 6–18 years were examined. The first group (n=153) was represented by children with metabolically unhealthy obesity (MUO). The second group (n=100) consolidated of children with metabolically healthy obesity (MHO). For inclusion in the first observation group, the presence of abdominal obesity and two of the presented criteria were taken into account:

1) fasting glycemia  $\geq$ 5.6 mmol/L [12] and/or according to the recommendations of the IDEFICS Study, the level of basal insulinemia is more than 90 percentile [35];

2) high density lipoprotein cholesterol (HDL-C)  $\leq$ 1.03 mmol/L or less than 10<sup>th</sup> percentile of the age norm [13];

3) triglycerides (TG)  $\geq$ 1.7 mmol/L or more than the 90<sup>th</sup> percentile of the age norm;

4) systolic blood pressure (SBP) and diastolic blood pressure (DBP) above the 90<sup>th</sup> percentile for a given age, gender and height [14].

The abdominal type of obesity was determined according to the consensus of the International Diabetes Federation (IDF), based on the excess of the waist circumference over the 90<sup>th</sup> percentile for children 6–15 years old or more than 94 cm for boys aged 16–18 years and more than 80 cm for girls 16–18 years old [4].

To study carbohydrate metabolism disorders, the level of basal glycemia and insulinemia was determined by the immunochemical testing method with electrochemiluminescent detection (ECLIA), in the certified Synevo Laboratory (Dnipro, Ukraine), followed by the calculation of the generally accepted marker of insulin resistance (HOMA-IR) [12,35].

To study lipid metabolism disorders, the level of HDL-C and TG was determined by the enzymatic-colorimetric method using kits from Roche Diagnostics (Switzerland) on a Cobas 6000 analyzer in the certified Synevo Laboratory (Dnipro, Ukraine).

To study the role of pro-inflammatory markers in the development of meta-inflammation in children with obesity, the serum levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6) were determined in the certified Synevo Laboratory (Dnipro, Ukraine). IL-1 $\beta$  was detected by the immunochemical method with chemiluminescence immunoassay (CLIA). Analyzer and test – system: Immulite (Siemens AG), Germany. The reference value of IL-1 $\beta$  level was 0–5 pg/ml. IL-6 was determined by an enzyme-linked immunosorbent assay (ELISA) using a Cobas 6000/Cobas 8000 kit provided by Roche Diagnostics (Switzerland). The reference value of IL-6 level was 1.5–7.0 pg/ml.

From the first and second groups, 52 samples for whole genome sequencing were selected by limited randomization for an unbalanced distribution with a distribution coefficient of 1.5 between baseline and selective subgroups with different obesity phenotypes [28].

The sample population examined by whole genome sequencing (NGS, Illumina CPro®, CeGat, Germany) consisted of 31 children of the first and 21 children of the second group and was qualitatively homogeneous in relation to the general population.

*Material for research:* venous blood. Starting material: dried blood spot cards. For DNA extraction from blood cards, we use the following pro-

ocol: Sbeadex DNA Purification Kit, customized CeGat version (Biosearch Technologies, LGC). Average amount of DNA ( $\mu$ g) in samples – 0.875. Library Preparation: Quantity used 50 ng. Library Preparation Kit: Twist Human Core Exome plus Kit (Twist Bioscience). Sequencing parameters: NovaSeq 6000; 2 $\times$ 100 bp.

Bioinformatic analysis – demultiplexing of the sequencing reads was performed with Illumina bcl2fastq (version 2.20). Adapters were trimmed with Skewer, version 0.2.2 [18]. DNA-Seq: Trimmed raw reads were aligned to the human reference genome (hg19-cegat) using the Burrows–Wheeler Aligner, BWA – mem version 0.7.17-cegat [24] ABRA, version 2.18 and GenotypeHarmonizer v.1.4.20 were used for local restructuring of readings in target regions to improve more accurate detection of indels in the genome during mutagenesis [32].

We used ClinVar Version 20200316 [22], InterVar gnomeAd Version 3.0 [21] and dbNSFP Version 4.1 [30] for clinical and functional variant annotation and GWAS catalog database annotation [8].

Reference sequence obtained from the National Center for Biotechnology Information RefSeq database (<http://www.ncbi.nlm.nih.gov/RefSeq/>) [27].

Statistical analysis of the obtained results was carried out using a package of application programs Statistica 6.1 (No AGAR909E415822FA) with help a personal computer based on an Intel processor Pentium 4.

The data were checked for compliance with the Gaussian law using the Shapiro–Wilk test, based on regression of ordinal statistics; equality of variances – according to the Fisher criterion. To describe quantitative characteristics with a normal distribution, the arithmetic mean with an error of the mean value ( $M \pm m$ ) was used.

In the course of the research, the mathematical apparatus for testing statistical hypotheses was used using variational analysis, Wald analysis, the  $\chi^2$  (chi-square) independence criterion, Cramer, Spearman correlation analysis, ROC analysis. The basis for testing statistical hypotheses was the so-called feature conjugation tables.

Intergroup comparisons of statistical characteristics were carried out taking into account the distribution law using parametric and non-parametric criteria: assessment of the probability of differences in mean values for unrelated samples – according to Student's t tests as modi-

Table 1

Data from clinical and paraclinic observation of children with different obesity phenotypes

Indicator	Metabolically unhealthy obesity (n=153), M±m	Metabolically healthy obesity (n=100), M±m	Probability, p
BMI in percentiles	99.54±0.21	98.74±0.29	0.12
The presence of extreme obesity stage 2 (120–139% over the 95 <sup>th</sup> percentile), %	19±3.92	16.1±3.68	0.06
The presence of extreme obesity stage 3 (over 140% of the 95 <sup>th</sup> percentile), %	32.3±4.66	0	<b>0.00001</b>
Waist circumference in percentiles	96.65±0.42	93.38±0.82	<b>0.0004</b>
Systolic blood pressure in percentiles	83.77±3.05	71.38±3.96	<b>0.014</b>
Diastolic blood pressure in percentiles	87.48±2.75	66.33±4.09	<b>0.0006</b>
High-density lipoprotein cholesterol in percentiles	30.83±4.04	32.81±2.79	0.68
Triglycerides in percentiles	87.7±2.28	80.33±3.63	<b>0.04</b>
Fasting blood glucose level, mmol/L	4.15± 0.37	3.36±0.48	0.2
Basal insulin, µU/ml	29.47±1.14	12.53±1.44	<b>0.00001</b>
Interleukin-6, pg/ml	3.4±0.82	1.04±0.22	<b>0.007</b>

Table 2

List of SNV genes associated with MUO

N	SNVs of genes associated with MUO	Cramér's criterion, V
1.	rs1800139 <i>LRP1</i> ( <i>LDL receptor related protein 1</i> )	0.44
2.	rs2307111 <i>POC5</i> ( <i>POC5 centriolar protein</i> )	0.40
3.	rs61775167 <i>MACO1</i> ( <i>macoilin 1</i> )	0.39
4.	rs3790435 <i>LEPR</i> ( <i>leptin receptor</i> )	0.38
5.	rs17563686 <i>POC5</i> ( <i>POC5 centriolar protein</i> )	0.37
6.	rs2047059 <i>POC5</i> ( <i>POC5 centriolar protein</i> )	0.37
7.	rs9465994 <i>CDKAL1</i> ( <i>CDK5 regulatory subunit associated protein 1 like 1</i> )	0.36
8.	rs877611 <i>TRPV1</i> ( <i>transient receptor potential cation channel subfamily V member 1</i> )	0.36
9.	rs1800191 <i>LRP1</i> ( <i>LDL receptor related protein 1</i> )	0.34
10.	rs3173798 <i>CD36</i> ( <i>CD36 molecule (CD36 blood group)</i> )	0.29
11.	rs2230374 <i>ITPR2</i> ( <i>inositol 1,4,5-trisphosphate receptor type 2</i> )	0.28
12.	rs1801282 <i>PPARG</i> ( <i>peroxisome proliferator activated receptor gamma</i> )	0.28
13.	rs12623857 <i>PAX3</i> ( <i>paired box 3</i> )	0.28

fied by Welch (R Studio, Version 1.0.136, 2016). Only statistically significant results ( $p < 0.05$ ) were taken into account.

**Ethical approval.** Participants provided written informed consent, and research protocols and procedures were approved according to the ethical standards of the Helsinki Declaration 2013 and by the Human Research Ethics Committee of Dnipro State Medical University, Ukraine (meeting minutes No. 7 of December 11, 2019 and minutes from meeting No. 4 of September 2, 2020). We obtained formal written informed consent from the parents of the children to participate in the study.

### Results of the research

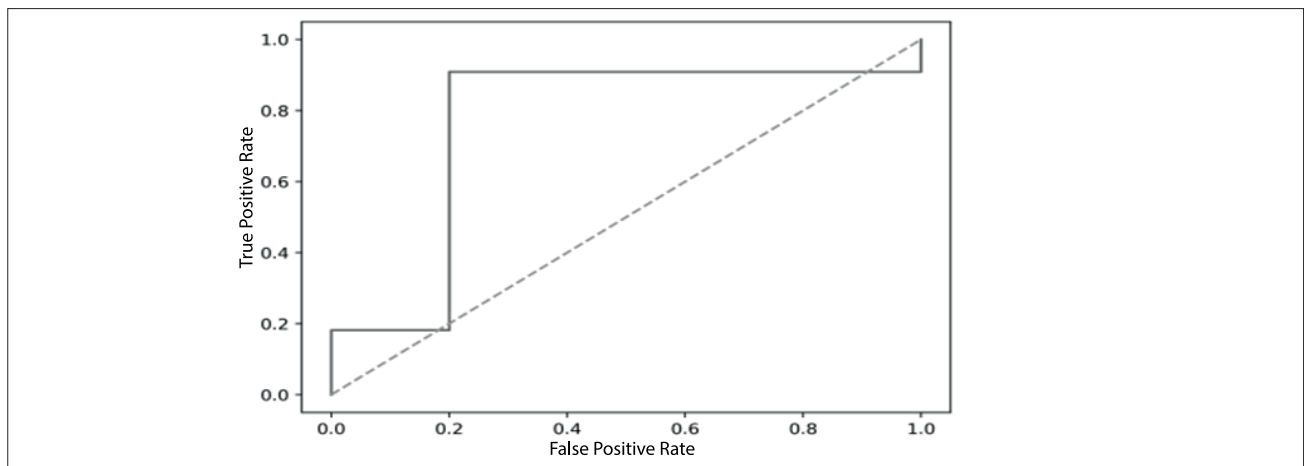
Based on the clinical and paraclinical examination of children, we formed observation

groups for obesity phenotypes, the characteristics of which are presented in Table 1.

Significant differences among children in the comparison groups were characterized by the presence of a greater proportion of children with the MUO phenotype, who had an extreme type of obesity of the 3rd degree, abdominal obesity, increased SBP/DAP, triglyceridemia, hyperglycemia, basal insulinemia, as well as an increase in the level of pro-inflammatory cytokines in blood serum.

As a result of testing statistical hypotheses based on the conjugation table of features of 743 SNVs of 86 candidate genes that were studied (*DNM3*, *NRXN3*, *COBLL1*, *BDNF*, *STK33*, *PTBP2*, *MTCH2*, *ZNF169*, *KLF9*, *LPP*, *GP2*, *LY86*, *SLC39A8*, *SLC6A14*, *TNNI3K*, *MC4R*, *SIGLECL1*, *NUDT3*,





**Fig. 1.** The ROC curve for the logistic regression method demonstrates the validity of predicting MUO associated with SNV rs1800139 *LRP1*, rs2307111 *POC5*, rs61775167 *MACO1*, rs3790435 *LEPR*, rs17563686 *POC5*, rs2047059 *POC5*, rs9465994 *CDKAL1*, rs877611 *TRPV1*, rs1800191 *LRP1*, rs3173798 *CD36*, rs2230374 *ITPR2*, rs1801282 *PPARG*, rs12623857 *PAX3*.

*POC5*, *CDKAL1*, *MAP2K5*, *QPCTL*, *PCSK1*, *ADCY9*, *NEGR1*, *RNF223*, *CCK*, *ZNRF3*, *SEC16B*, *NISCH*, *TMEM212*, *CPEB4*, *VEGFA*, *DNAJC27*, *BCDIN3D*, *ITPR2*, *SH2B1*, *ETV5*, *PAX3*, *TBX15*, *FTO*, *PPARG*, *GLP1R*, *ADRB2*, *ADRB3*, *AGRP*, *CARTPT*, *ENPP1*, *GHRL*, *NR0B2*, *SDC3*, *UCP3*, *APOC3*, *ACE*, *ADIPOQ*, *ApoA1*, *APoA2*, *ApoA5*, *APOB*, *ApoE*, *CD36*, *FABP2*, *TRPV1*, *SLC2A2*, *INS*, *INSIG2*, *LCT*, *LEPR*, *LRP1*, *PPARA*, *TAS1R1*, *TAS2R19*, *TAS2R38*, *KCNJ2*, *TAS2R5*, *FADS1*, *NR1H3*, *MGAT1*, *DYRK1B*, *IL6*, *MRAP2*, *FGF21*, *GALNT2*, *MACO1*, *APOBR*, *PNPLA3*), we obtained a list of SNVs of genes associated with MUO (Table 2), for which the hypothesis of independence was rejected by calculating the strength of this dependence – the Cramér's V test.

For the list of SNVs of genes associated with MUO from Table 2, the Cramér's V criterion varies from 0.28 to 0.44, depending on the selected single-nucleotide variant. These indicators can be considered an indicator of moderate or even relatively high interdependence of mutation indicators and obesity phenotype.

ROC-analysis of the task of classification of favorable and unfavorable prognosis of obesity phenotypes by the method of logistic regression demonstrated: Accuracy – 0.83%, Sensitivity – 0.83%, Specificity – 0.57%. To verify the property of correctly distinguishing different phenotypes of obesity, the ROC-curve constructed as a whole is shown in Fig. 1.

As a result of a full-genome study, we identified 51 SNVs of the *LRP1* gene in obese patients (Table 4).

Among the 51 SNVs of the *LRP1* gene, rs1800139 ( $V=0.44$ ) and rs1800191 ( $V=0.34$ ) contribute the most to the development of MUO. The frequency

of SNV of the *LRP1* gene in children with different phenotypes of obesity is presented in Table 5.

The distribution of patients with different obesity phenotypes by genotype of SNV rs1800139 of the *LRP1* gene is presented in Table 6.

In patients with MHO, the CC genotype was significantly less common ( $p<0.05$ ), and the TT genotype of SNV rs1800139 of the *LRP1* gene was significantly less common ( $p<0.02$ ) than in the general human population. While in patients with MUO, both homozygous genotypes of SNV rs1800139 of the *LRP1* gene were significantly less common than in the general human population ( $p<0.05$ ). Among patients with MUO, the TT genotype of SNV rs1800139 of the *LRP1* gene was significantly less common compared to the group of patients with MHO ( $p<0.01$ ). It can be assumed that the CC genotype of SNV rs1800139 of the *LRP1* gene is protective, preventing the development of obesity, the CT genotype of SNV rs1800139 of the *LRP1* gene is associated with the development of metabolic disorders, and the TT genotype of SNV rs1800139 of the *LRP1* gene is associated with the development of obesity, but prevents the occurrence of metabolic disorders.

The CC genotype of SNV rs1800139 of the *LRP1* gene is associated with a low level of risk of developing both MHO and MUO (Relative risk (RR)=0.45, 0.15, respectively), and the CC genotype of SNV rs1800139 of the *LRP1* gene is associated with a high level of risk of developing MHO (RR =1.78) and a low level of MUO formation (RR =0.60).

Individuals with MHO and genotype CT SNV rs1800139 of the *LRP1* gene have a 2.32-fold increased risk of MUO formation (RR=2.32; Diagnostic coefficient (DC)=+3.66)

Table 2

List of SNV genes associated with MUO

N	SNV	Position	GnomAD_maxPOP	Ref	Alt	Consequence	Base Change	CADD	Raw Score	Clinical significance (gnomAD browser)
1.	rs11172124	57594955	AMR	G	A	intronic	c.10345+19G>A	0.645	-0,129	Not Reported
2.	rs113379328	57587039	SAS	G	A	missense	c.7636G>A	9.184	0,892	Likely benign
3.	rs1140648	57593101	SAS	G	A	synonymous	c.9783G>A	13.71	1,42	Benign
4.	rs1252748027	57594202	EAS	T	A	intronic	c.10015-23T>A	0.55	-0,17	Not Reported
5.	rs12814239	57569478	NFE	C	T	synonymous	c.3783C>T	1.65	0,11	Benign
6.	rs1308286524	57594215	EAS	T	A	intronic	c.10015-10T>A	6.50	0,60	Not Reported
7.	rs1335360405	57594196	SAS	A	C	intronic	c.10015-29A>C	0.94	-0,03	Not Reported
8.	rs138034669	57605824	EAS	A	C	intronic	c.13349+24A>C	14.50	1,55	Not Reported
9.	rs138348495	57587056	SAS	G	A	synonymous	c.7653G>A	2.14	0,18	Benign
10.	rs138980324	57588198	NFE	C	T	synonymous	c.7980C>T	6.86	0,64	Likely benign
11.	rs139916336	57593101	SAS	G	A	synonymous	c.9783G>A	13.71	1,42	Benign/Likely benign
12.	rs141991304	57599466	NFE	G	A	splice_region	c.11590+6G>A	8.34	0,80	Not Reported
13.	rs150340911	57587715	NFE	G	A	missense	c.7838G>A	3.53	0,32	Benign/Likely benign
14.	rs1799986	57535266	NFE	C	T	synonymous	c.300C>T	4.97	0,45	Benign
15.	rs1800127	57539082	NFE	C	T	missense	c.650C>T	1.99	0,16	Not Reported
16.	rs1800137	57548466	EAS	C	T	synonymous	c.1209C>T	14.02	1,47	Benign
17.	rs1800138	57579420	NFE	C	T	synonymous	c.6570C>T	4.65	0,42	Benign
18.	rs1800139*	57585144	SAS	C	T	synonymous	c.7278C>T	7.22	0,68	Benign
19.	rs1800141	57588433	EAS	G	A	synonymous	c.8142G>A	3.31	0,30	Benign
20.	rs1800142	57589067	NFE	C	T	synonymous	c.8322C>T	7.38	0,70	Benign/Likely benign
21.	rs1800154	57589659	AFR	C	T	synonymous	c.8574C>T	13.53	1,39	Benign
22.	rs1800156	57590797	AFR	C	T	synonymous	c.8925C>T	7.69	0,73	Benign
23.	rs1800158	57593204	EAS	A	G	intronic	c.9865+21A>G	4.55	0,41	Benign
24.	rs1800166	57591458	AFR	C	T	intronic	c.9282+11C>T	25	4,36	Benign
25.	rs1800180	57569513	AMR	G	A	intronic	c.3793+25G>A	25.1	4,37	Benign
26.	rs1800188	57588491	EAS	C	T	intronic	c.8191+9C>T	0.45	-0,22	Benign
27.	rs1800189	57589865	SAS	C	T	splice region	c.8702-5C>T	2.81	0,26	Benign
28.	rs1800191*	57590758	AFR	C	T	splice region	c.8893-7C>T	5.87	0,54	Benign
29.	rs1800194	57567762	AFR	C	T	splice_region	c.3546C>T	1.82	0,14	Benign
30.	rs190093413	57596324	EAS	C	T	splice_region	c.10711+4C>T	2.08	0,17	Benign
31.	rs199538567	57588130	NFE	C	T	splice_region	c.7919-7C>T	10.05	0,98	Not Reported
32.	rs199541546	57532232	NFE	C	T	intronic	c.68-10C>T	11.58	1,12	Not Reported
33.	rs200442207	57569424	NFE	C	T	synonymous	c.3729C>T	10.90	1,05	Not Reported
34.	rs2228187	57571249	NFE	C	T	synonymous	c.4236C>T	5.67	0,51	Benign
35.	rs34423990	57577722	AFR	G	A	intronic	c.5929+30G>A	35	6,80	Not Reported
36.	rs34554486	57588127	EAS	C	T	intronic	c.7919-10C>T	13.39	1,37	Benign
37.	rs34574998	57548364	AFR	T	C	synonymous	c.1107T>C	1.81	0,14	Not Reported
38.	rs34577247	57578673	NFE	G	A	missense	c.6238G>A	0.60	-0,15	Benign
39.	rs34790089	57561993	NFE	C	T	intronic	c.2995+686C>T	5.88	0,54	Not Reported
40.	rs35021926	57606059	AFR	G	A	intronic	c.13494+15G>A	11.24	1,09	Benign
41.	rs35031168	57539194	AFR	G	A	synonymous	c.762G>A	0.37	-0,26	Benign
42.	rs36095408	57522830	NFE	C	G	intronic	c.67+16C>G	20.6	2,86	Not Reported
43.	rs367965913	57560017	SAS	C	T	intronic	c.2797+25C>T	2.36	0,21	Not Reported
44.	rs371256123	57593777	OTH	G	A	missense	c.9983G>A	12.8	1,29	Not Reported
45.	rs6581127	57581028	EAS	C	G	intronic	c.6842-22C>G	30	5,32	Benign
46.	rs7308552	57590735	EAS	T	C	intronic	c.8893-30T>C	2.45	1,22	Benign
47.	rs7308698	57590869	EAS	T	C	synonymous	c.8997T>C	0.93	-0,04	Benign
48.	rs7397167	57589784	EAS	A	C	splice region	c.8699A>C	12.14	1,19	Benign
49.	rs746675318	57579495	NFE	G	A	synonymous	c.6645G>A	1.93	0,16	Not Reported
50.	rs76589759	57548605	EAS	C	T	intronic	c.1227+121C>T	17.07	2,07	Not Reported
51.	rs79365493	57567723	EAS	C	T	synonymous	c.3507C>T	1.95	0,16	Benign

Notes: GnomAD\_maxPOP – the frequency distribution of *LRP1* mutations. AFR, NFE, AMR, SAS, EAS represent African, Non-Finnish European, American, South Asian, East Asian; Ref – reference allele; Alt – alternative allele; Consequence – functional consequence of the variation in relation to the transcript. The nucleotide change and position relative to the coding sequence of the affected transcript in Human Genome Variation Society (HGVS) nomenclature: c. CDS Position Reference Base &gt; Alternative Base. Example: c.223A>T (c. – interpretation for DNA coding sequence: first nucleotide of the translation start codon of the coding DNA reference sequence) [34]. This column is empty if the variant is intergenic; CADD – combined annotation dependent depletion; \* – SNV *LRP1* associated with MUO.

Table 5

The frequency of occurrence of SNV *LRP1* gene in children with different obesity phenotypes

SNV	gnomAD browser		Frequency of occurrence of major and minor variants (%)			
	Popmax AF (HOMP), %	AF NFE, (HOMP), %	MHO		MUO	
			(HOMN), %	(HOMP), %	(HOMN), %	(HOMP), %
rs11172124	24	25	57.1	42.9	51.6	48.4
rs113379328	0.03	0.04	95.2	4.8	100	0
rs1140648	65	68	9.5	90.5	3.2	96.8
rs1252748027	1	2	100	0	100	0
rs12814239	5	6	100	0	87.1	12.9
rs1308286524	0.01	0.01	100	0	100	0
rs1335360405	0.03	0.03	100	0	100	0
rs138034669	0	0	95.2	4.8	96.8	3.2
rs138348495	0.07	0.07	100	0	96.8	3.2
rs138980324	0.02	0.03	95.2	4.8	100	0
rs139916336	0.07	0.09	100	0	96.8	3.2
rs141991304	0.01	0.01	95.2	4.8	100	0
rs150340911	0.02	0.01	95.2	4.8	93.5	6.5
rs1799986	14	15	66.7	33.3	77.4	22.6
rs1800127	2	2	85.7	14.3	87.1	12.9
rs1800137	3	2	100	0	96.8	3.2
rs1800138	0.1	0.1	95.2	4.8	100	0
<b>rs1800139</b>	<b>66</b>	<b>69</b>	<b>9.5</b>	<b>90.5</b>	<b>3.2</b>	<b>96.8</b>
rs1800141	3	3	100	0	83.9	16.1
rs1800142	0.7	0.9	100	0	96.8	3.2
rs1800154	33	31	57.1	42.9	32.3	67.7
rs1800156	33	30	57.1	42.9	32.3	67.7
rs1800158	34	26	100	0	83.9	16.1
rs1800166	33	31	57.1	42.9	32.3	67.7
rs1800180	32	31	57.1	42.9	29	71
rs1800188	39	26	100	0	83.9	16.1
rs1800189	66	69	9.5	90.5	3.2	96.8
<b>rs1800191</b>	<b>33</b>	<b>31</b>	<b>57.1</b>	<b>42.9</b>	<b>29</b>	<b>71</b>
rs1800194	33	31	57.1	42.9	25.8	74.2
rs190093413	0.1	0	100	0	96.8	3.2
rs199538567	0	0	100	0	96.8	3.2
rs199541546	0.2	0.2	95.2	4.8	96.8	3.2
rs200442207	0	0	100	0	96.8	3.2
rs2228187	0.1	1	100	0	96.8	3.2
rs34423990	0.06	0	95.2	4.8	96.8	3.2
rs34554486	37	26	95.2	4.8	96.8	3.2
rs34574998	0.1	0	90	10	83.9	16.1
rs34577247	20	20	95.2	4.8	96.8	3.2
rs34790089	22	35	95.2	4.8	83.9	16.1
rs35021926	1	0.7	100	0	83.9	16.1
rs35031168	0	0	100	0	96.8	3.2
rs36095408	0.6	0.7	100	0	96.8	3.2
rs367965913	0	0	100	0	90.3	3.2
rs371256123	0	0	100	0	96.8	3.2
rs6581127	99	99	100	0	96.8	3.2
rs7308552	99	99	100	0	100	0
rs7308698	99	99	100	0	100	0
rs7397167	99	100	100	0	100	0
rs746675318	0	0	95.2	4.8	100	0
rs76589759	0.06	0	95.2	4.8	100	0
rs79365493	0.01	0	95.2	4.8	96.8	3.2

Notes: **HOMP** – homozygous variant (biallelic single nucleotide substitution), **HOMN** – homozygous variant (absence of nucleotide substitutions); **Popmax AF** – Maximum population allele frequency in the genome (gnomAD browser); **AF NFE** – Allele frequency for Non-Finnish Europeans in the genome (gnomAD browser).

Table 6

Frequency of occurrence of SNV rs1800139 genotypes of the LRP1 gene in patients with various obesity phenotypes

Genotype	Obesity phenotype		General population prevalence [24]
	MHO	MUO	
CC	9.5%	3.2%	20.9%
CT	33.4%	77.4%	47.0%
TT	57.1%	19.4%	32.1%

and a 1.4-fold increased risk (RR=1.4; DC=+1.42) the level of HDL-C in blood serum less than the 25th percentile for age is more common.

### Discussion

Obesity, especially during childhood, is a critical factor that determines the general state of health and carries the risk of developing metabolic disorders. It has been demonstrated that SNVs of the *LRP1* gene are associated with the occurrence of obesity and its unfavorable phenotype – MUO. For the first time, we showed the following SNVs of the *LRP1* gene in children with obesity: rs11172124, c.10345+19G>A; rs1252748027, c.10015-23T>A; rs1308286524, c.10015-10T>A; rs1335360405, c.10015-29A>C; rs138034669, c.13349+24A>C; rs141991304, c.11590+6G>A; rs1800127, c.650C>T; rs199538567, c.7919-7C>T; rs199541546, c.68-10C>T; rs200442207, c.3729C>T; rs34423990, c.5929+30G>A; rs34574998, c.1107T>C; rs34790089, c.2995+686C>T; rs36095408, c.67+16C>G; rs367965913, c.2797+25C>T; rs371256123, c.9983G>A; rs746675318, c.6645G>A; rs76589759, c.1227+121C>T. We did not identify a single case of SNV rs715948, c.667C>T of the *LRP1* gene in the examined obese children. Karen E. Smith et al. [37] demonstrated the presence of a relationship between SNV rs715948 of the *LRP1* gene and BMI. It is known that variants of the *LRP1* gene determine the level of absorption of chylomicron residues. In particular, most minor alleles are associated with increased chylomicron uptake. However, the association

between the rs715948 variant of the *LRP1* gene and a high level of BMI in humans, according to A.C. Frazier–Wood et al. [15], is not associated with chylomicron uptake activity. According to N. Vučinić et al. [40] SNV rs715948, c.667C>T of the *LRP1* gene is associated with the development of metabolic syndrome in adults of the Serbian population. The authors showed that the presence of the T allele increases the likelihood of developing metabolic syndrome by 4.76 times compared to carriers of the C allele of SNV rs715948, c.667C>T of the *LRP1* gene.

We found that the most significant polymorphism among 51 SNVs of the *LRP1* gene, associated with the formation of various obesity phenotypes, is the rs1800139 variant (CADD)=7.22. It was shown that the CT genotype of SNV rs1800139 of the *LRP1* gene increases the risk of developing MUO by 2.32 times and is associated with a low level of HDL-C in the blood serum. The rs1800139 polymorphism is located in exon 44 of the *LRP1* gene and encodes a region of the protein that interacts with the inhibitory site of coagulation factor Xa, Fig. 2 [23].

Considering that SNV rs1800139 of the *LRP1* gene is a synonymous variant that does not change the amino acid sequence, it is believed that the effect of SNV rs1800139 of the *LRP1* gene on the functional activity of the LRP1 protein is due to changes in mRNA stability. It has been shown that the mRNA read from the C variant rs1800139 of the *LRP1* gene has a higher level of stability than the transcript of the T variant rs1800139 of the *LRP1* gene [23]. A decrease in the level of stability

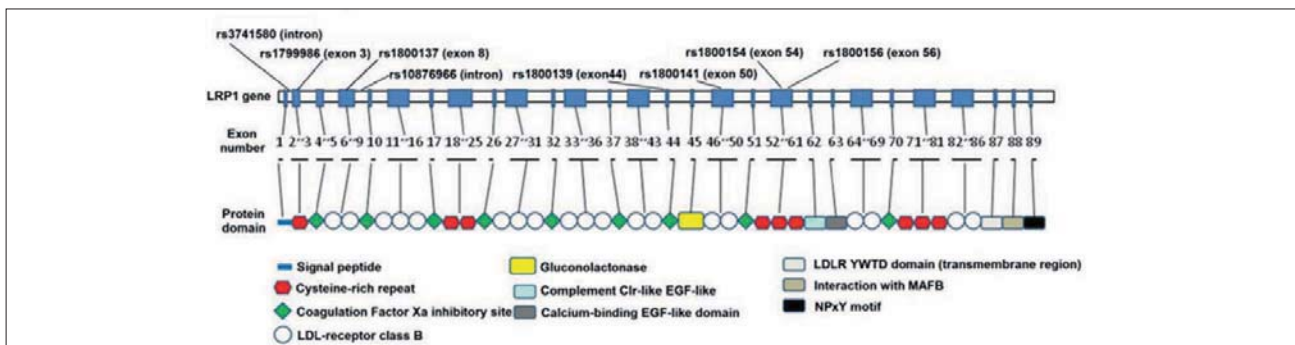


Fig. 2. Structure of the *LRP1* gene [23]



of the *LRP1* gene transcript leads to insufficiency of LRP1 protein synthesis. In particular, it has been demonstrated that warfarin stable dose (WSD) variability depends on SNV rs1800139 of the *LRP1* gene. According to multivariate analysis, SNV rs1800139 of the *LRP1* gene accounts for 5.9% of the WSD variability. The C allele of SNV rs1800139 of the *LRP1* gene is associated with a lower, and the T allele of SNV rs1800139 of the *LRP1* gene is associated with a higher WSD [25]. It has been shown that the LRP1 protein can both promote and prevent the development of atherosclerosis. In particular, LRP1 of macrophages, which play a key role in all stages of atherosclerosis from the formation of atherosclerotic plaques to their rupture, on the one hand can prevent the development of atherosclerosis by enhancing efferocytosis, and on the other hand, accelerate the progression of atherosclerosis by facilitating the absorption of atherogenic particles such as oxidized lipoproteins, causing vascular inflammation [9,33].

We believe that in TT homozygotes, a decrease in the likelihood of metabolic disorders during the development of obesity is due to a decrease in the stability of *LRP1* mRNA. It is also known that SNV rs1800139 of the *LRP1* gene is an expression quantitative trait locus (QTL), which regulates the expression of the constitutive nuclear receptor gene NR1I3 (nuclear receptor subfamily 1 group I member 3) [25]. The constitutive receptor NR1I3 has been identified as the central coordinator of the response to xenobiotic or endobiotic stress. In addition, activation of the NR1I3 receptor leads to a decrease in serum glucose levels by stimulating the mechanisms of glucose uptake by hepatocytes and increasing tissue sensitivity to the action of insulin. Also, a high level of activity of the NR1I3 receptor prevents the development of hepatosteatosis by

inhibiting lipogenesis and inducing the process of  $\beta$ -oxidation of fats [36,42].

It is likely that insufficient expression of the NR1I3 receptor, which is caused by the influence of SNV rs1800139 of the *LRP1* gene, can cause the development of metabolic disorders in obese children.

## Conclusions

Among the population of obese children, there is a wide range of diverse SNVs of the *LRP1* gene, among which SNV rs1800139 makes the greatest contribution to the development of the MUO phenotype.

The CT genotype of SNV rs1800139 of the *LRP1* gene is associated with a high risk of developing the MUO phenotype and the development of dyslipidemia.

The CC genotype of SNV rs1800139 of the *LRP1* gene is associated with a low risk of developing obesity, and the TT genotype of SNV rs1800139 of the *LRP1* gene is associated with a low risk of metabolic disorders.

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**Data availability.** The datasets used and/or analyzed during the current study are open from the corresponding author on reasonable request.

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