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ROLE OF THE SINGLE-NUCLEOTIDE VARIANT rs17492553 OF THE UMAMI RECEPTOR GENE *TAS1R1* IN THE DEVELOPMENT OF METABOLICALLY UNHEALTHY OBESITY IN CHILDREN

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Background. Altered umami taste perception associated with the single nucleotide variant (SNV) in the taste 1 receptor member 1 (*TAS1R1*) gene may contribute to excess fat accumulation and predict the obesity phenotype.

Objective: To determine the risk of developing metabolically unhealthy obesity in children with SNV rs17492553 *TAS1R1*.

Methods. 350 children with obesity aged 6–18 years were examined. Among obese children, two observation subgroups with metabolically unhealthy obesity (MUO, n = 204) and metabolically healthy obesity (MHO, n = 146), were separated. The level of basal glycemia, insulinemia was studied by immunochemical method with electrochemiluminescent detection, high-density lipoproteins and triglycerides – by enzymatic-colorimetric method in the Synevo (Ukraine). SNVs of the *TAS1R1* gene were identified by whole-genome next-generation sequencing in 52 children at the CeGaT laboratory (Germany).

Results. Of the six identified SNVs (rs10864628, rs17492553, rs34160967, rs35118458, rs35375392, rs41278020) of *TAS1R1*, only SNV rs17492553 was associated with the development of MUO, determining an increase in gonadotropins and a decrease in 25-hydroxycalciferol in serum.

Conclusions. Carriers of the CT genotype of SNV rs17492553 *TAS1R1* are 2.73 times more likely to develop metabolically unhealthy obesity than CC homozygotes.

Keywords: children, obesity, single nucleotide variants, taste 1 receptor member 1.

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РОЛЬ ОДНОНУКЛЕОТИДНОГО ВАРІАНТА rs17492553 ГЕНА РЕЦЕПТОРА УМАМІ *TAS1R1* У РОЗВИТКУ МЕТАБОЛІЧНО НЕЗДОРОВОГО ОЖИРІННЯ У ДІТЕЙ

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Актуальність. SNV rs17492553 гена *TAS1R1* впливає на сприйняття смаку умамі, що може сприяти розвитку ожиріння.

Мета: оцінити ризик метаболічно нездорового ожиріння (metabolically unhealthy obesity – MUO) у дітей із варіантом гена *TAS1R1*.

Методи. Обстежено 350 дітей (6–18 років) з ожирінням: 204 з MUO та 146 з метаболічно здоровим типом (metabolically healthy obesity – MHO). Показники глікемії, інсуліну та ліпідного профілю визначали методами Synevo. Секвенування генома 52 дітей проведено в лабораторії CeGaT (Німеччина).

Результати. Серед шести виявлених SNV лише rs17492553 корелював із MUO. Він асоціювався з підвищенням рівнів гонадотропінів та зниженням вітаміну D (25-гідроксикальциферолу) в сироватці.

Висновки. Носії CT-генотипу rs17492553 мають ризик розвитку MUO у 2,73 раза вищий, ніж CC-гомозиготи.

Ключові слова: діти, ожиріння, однонуклеотидні варіанти, рецептор смаку 1 член 1.

Introduction

The increase in the prevalence of obesity in children observed in recent decades is becoming alarming. It has been demonstrated that 45.7% of children under five years of age are overweight. At the same time, it has been established that overweight and obesity in children are associated with a high risk of developing type 2 diabetes mellitus, dyslipidemia, cardiovascular diseases, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea/hypopnea syndrome, psychosocial disorders, and some types of cancer [1; 2; 3].

Altered taste perception of food products is a significant factor contributing to the development of obesity. Today, five basic tastes are recognized, such as sweet, salty, sour, bitter and umami. A candidate for the sixth basic taste is the taste of kokumi (rich taste, enhanced taste) [4].

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Стаття поширюється на умовах ліцензії

The Japanese word "umami" means "pleasant taste". The umami taste is characterized as a "savory, meaty, brothy" taste experienced when eating meat, shellfish, soy sauce, tomatoes, mushrooms, and some cheeses. The term "umami" was first proposed in 1908 by Japanese chemist and professor at Tokyo Imperial University Kikunae Ikeda while studying dashi, a traditional Japanese broth. Umami was recognized as a basic taste in 2009. The prototypical compound that causes umami in humans is monosodium glutamate (MSG), which has the ability to enhance the taste of food [5; 6; 7]. The recognition of umami taste involves type 1 taste receptor proteins T1R1 and T1R3, the genes for which – *TAS1R1* and *TAS1R3* (taste 1 receptor member 1 and 3) – are located on chromosome 1. The T1R1 and T1R3 proteins form a heterodimeric receptor T1R1/T1R3, which belongs to the superfamily of seven-helix transmembrane receptors, is associated with the G protein and mediates the perception of L-glutamate and other 5'-ribonucleotides, such as guanosine monophosphate and inosine monophosphate. In rodents, the chemosensory receptor T1r1/T1r3 functions as a receptor for L-amino acids (alanine, asparagine, glycine, glutamine, methionine, serine, threonine, cysteine) [7; 8; 9]. Also involved in the perception of umami taste are taste-specific metabotropic glutamate receptors 1–4 (GRM 1–4) [6].

It is known that stimulation of chemoreceptors that recognize the umami taste reliably increases appetite [5]. Genetically determined disturbances in umami taste perception may be one of the most important factors that contribute to both excessive adipose tissue accumulation in children and obesity-associated metabolic disorders [10; 11]. It has been demonstrated that activation of heterodimeric T1R1/T1R3 receptors is associated with the expression of 328 genes, including genes encoding transcription factors such as *BACH2, EBF1, GATA1, GBX1, GCM1, KLF7, MZF1*. It is known that early B-cell factor 1 (EBF1), kruppel-like factor 7 (KLF7) [12], myeloid zinc finger 1 (MZF1) [13] are involved in the development of obesity or its complications.

In all likelihood, the change in the level of umami taste perception, which is associated with *TAS1R1* gene variants, may contribute to excessive accumulation of adipose tissue and predetermine the obesity phenotype.

The aim of our study was to determine the risk of developing metabolically unhealthy obesity in children with the rs17492553 variant of the *TAS1R1* gene.

Materials and Methods

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 (protocol No. 7 dated December 11, 2019 and protocol No. 4 dated September 2, 2020). We obtained formal written informed consent from the parents of the children to participate in the study. Data were collected from January 2020 to February 2024.

Study design

Study design: observational, analytical, longitudinal, cohort study. Research standard: STREGA (https://www.equator-network.org/). Inclusion criteria: children with polygenic obesity (BMI ≥97th percentile) 6–18 years old. Exclusion criteria: children with monogenic and/or syndromic obesity, pregnancy.

350 children with obesity aged 6–18 years were examined. The first group (n=204) was represented by children with MUO. The second group (n=146) consisted 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 ≥5.6 mmol/L and/or according to the recommendations of the IDEFICS Study, the level of basal insulinemia is more than 90 percentiles; 2) high-density lipoprotein cholesterol (HDL-C) ≤ 1.03 mmol/L or less than 10th percentile of the age norm; 3) triglycerides (TG) ≥1.7 mmol/L or more than the 90th percentile of the age norm; 4) systolic blood pressure (SBP) and Diastolic blood pressure (DBP) above the 90th percentile for a given age, gender and height [14; 15].

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 90th 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.

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) [14].

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 Synevo.

To study the role of pro-inflammatory markers in the development of meta-inflammation in children with obesity, the serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6) were determined in Synevo. IL-1β was detected by the immunochemical method with chemiluminescence immunoassay (CLIA). Analyzer and test-system: Immulite (Siemens AG), Germany. The reference value of IL-1β 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 pg/mL.

From the first and second groups, 52 samples for WGS 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. The sample population examined by whole genome sequencing (NGS, Illumina CSPro®, 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 protocol: Sbeadex DNA

Purification Kit, customized CeGaT version (Biosearch Technologies, LGC). Average amount of DNA (μg) 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 x 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. 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. ABRA, version 2.18 and GenotypeHarmonizer v.1.4.20 were used for local realignment of reads in target regions to improve more accurate detection of indels in the genome during variant detection (https://github.com/molgenis/systemsgenetics/).

We used ClinVar Version 20200316, InterVar gnomeAd Version 3.0 and dbnsfp Version 35c for clinical and functional variant annotation and GWAS catalog database annotation (https://www.ncbi.nlm.nih.gov/clinvar/).

Reference sequence obtained from the National Center for Biotechnology Information RefSeq database (https://www.ncbi.nlm.nih.gov/refseq/).

Statistical analysis

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

For statistical processing of the materials studied, normality of data distribution was rechecked according to the Shapiro-Wilk test (SW-W), the homogeneity of variances – according to the Fisher test (F). The arithmetic mean with the error of the mean value (M±m) was used to describe quantitative traits with a normal distribution; the standard deviation (SD) to describe the variation in the traits and the 95% confidence interval (95% CI), sequential Wald analysis with calculation of Relative Risk (RR), to define the range of the population means.

The relationship between indicators was determined using Spearman correlation analysis. The reliability assessment of the difference of means in multiple comparisons for quantitative traits with a normal distribution was carried out by one-way analysis of variance (ANOVA) with a posteriori pairwise comparisons according to the Tukey test. Intergroup comparisons of statistical characteristics were performed taking into account the law of distribution using parametric and non-parametric criteria: assessment of the probability of differences in means for unrelated samples – according to Student's criteria (t) in the Welch modification (R Studio, Version 1.0.136, 2016). Only statistically significant results were taken into account ($p < 0.05$).

Research results and their discussion

As a result of whole-genome sequencing, we identified the presence of six single nucleotide variants (SNV) of the TAS1R1 gene in children with obesity: rs10864628, rs17492553, rs34160967, rs35118458, rs35375392, rs41278020. A brief description of the SNVs identified in children with obesity is presented in Table 1.

According to our data, of all identified variants of the *TAS1R1* gene, only the intronic SNV rs17492553 was associated with the development of MUO (Table 2).

It was found that the occurrence of MUO is significantly associated with the heterozygous genotype CT SNV rs17492553 of the *TAS1R1* gene. The relative risk of developing MUO in heterozygotes of SNV rs17492553 of the *TAS1R1* gene was 2.73.

It is interesting that in children with the CT genotype of SNV rs17492553 of the *TAS1R1* gene, the values of the parameters characterizing the endocrine function of adipose tissue, the level of meta-inflammation activity, glucose and lipid metabolism, and the state of the endocrine system were practically no different from those in children with the CC genotype of the SNV rs17492553 variant of the *TAS1R1* gene, with the exception of the content of luteinizing hormone (LH) and 25-hydroxycalciferol in the blood serum (Table 3).

Children with the CT genotype of the *TAS1R1* gene demonstrate more pronounced signs of adipose tissue dysfunction, meta-inflammation, insulin resistance, dyslipidemia, and altered hormonal profile compared to children with the CC genotype.

Thyroid-stimulating hormone (TSH), somatotropic hormone, insulin-like growth factor 1 (IGF-1), prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS) were statistically significantly higher in children with the CT genotype (all $p < 0.01$).

A characteristic finding of children with the CT genotype of SNV rs17492553 of the *TAS1R1* gene was a deficiency of 25-hydroxycalciferol ($p < 0.05$).

The *TAS1R1* gene is located on the short arm of chromosome 1 p36.23 in close proximity to the genes encoding nucleolar protein 9 (NOL9) and zinc finger and BTB domain containing 48 (ZBTB48) [16]. The *TAS1R1* gene is formed by 22,577 base pairs that organize 6 exons encoding the T1R1 protein. The amino acid sequence of the T1R1 protein consists of 841 amino acid residues. The secondary structure of the T1R1 protein is characterized by the presence of seven transmembrane helices that form a heptahelical domain and a large extracellular N-terminus. The *TAS1R1* gene is expressed in type II cells in both the fungiform and circumvallate papillae of the tongue, where it is likely involved in various excitatory signal transduction mechanisms. In addition, the *TAS1R1* gene is expressed in cells of various extraoral tissues, which allows it to participate in the regulation of various body functions. Variability in the level of umami taste perception may be based on SNVs of the *TAS1R1* and *TAS1R3* genes, which determine either the expression level or the functional activity of the heterodimeric T1R1/T1R3 chemoreceptor [17]. We identified 5 missense and one intronic SNV of the *TAS1R1* gene in children with obesity (Fig. 1).

We have demonstrated for the first time that the heterozygous state of CT SNV rs17492553 of the *TAS1R1* gene is associated with the risk of developing MUO in children. It is known that CC homozygotes and CT heterozygotes of the intronic variant rs17492553 of the *TAS1R1* gene have a higher level of umami taste perception, on average, by 40%, than TT homozygotes.

Table 1

Characteristics of SNV of the TAS1R1 gene in obesity phenotypes in children

dbSNV	Position	GnomAD _maxPOP	Ref/Alt	AF HOMp NFE, %	Zygosity (proportion) HOMp/ HET/HOMn, %)		SNV type	Nucleotide change	Pathogenic contribution by CADD (GRCh38)	RawScore	Clinical significance by ClinGen Allele Registry
					MUO	MHO					
rs35375392	6615444	AFR	G/A	0.005	0/6.5/93.5	0/0/100	missense	c.11G > A	6.92	0.65	VUS
rs41278020	6631106	NFE	C/T	0.02	0/6.5/93.5	0/9.5/90.5	missense	c.329C > T	2.23	0.19	VUS
rs10864628	6635231	EAS	A/G	99.9	100/0/0	100/0/0	missense	c.1039A > G	1.66	0.11	Benign
rs34160967	6635306	EAS	G/A	0	0/0/100	0/14/86	missense	c.1114G > A	9.55	0.93	VUS
rs17492553*	6636461	AMR	C/T	51.3	33.4/28.6/38	19.4/58/22.6	intronic	2 CNV: c.499–14C > T; c.1261-14C>T	0.96	–0.03	VUS
rs35118458	6637056	NFE	G/A	0.03	0/0/100	0/14/86	missense	2 CNV: c.758G > A; c.1520G > A	0.62	–0.14	VUS

Note: GnomAD_maxPOP – frequency distribution of *TAS1R1* mutations. AFR, NFE, AMR, SAS, EAS represent countries in Africa, non-Finnish Europe, America, South and East Asia; Nucleotide change consequence – functional consequence of the variation in relation to the transcript. Ref – reference allele; Alt – alternative allele. Nucleotide change and position relative to the coding sequence of the affected transcript in the HGVS nomenclature: c. CDS Position Reference Base > Alternative base. Example: c. 223A > T (c. – interpretation for the coding DNA sequence: the first nucleotide of the translation start codon of the coding reference DNA sequence). CADD (Combined Annotation Dependent Depletion) – combined annotation dependent depletion; VUS (Variant of unknown significance) – variant of unknown significance * – SNV *TAS1R1* associated with MUO.

Table 2

Genotypes of SNV rs17492553 of the *TAS1R1* gene in children with different types of obesity

Genotypes of SNV rs17492553 of the *TAS1R1* gene	Types of obesity (%)		P
	MHO	MUO	
CC	40	22	0.92
CT	30	56	0.03
TT	30	22	0.74

Table 3

Comparative characteristics of the state of various systems in children with different genotypes of SNV rs17492553 of the *TAS1R1* gene

Biomarkers of obesity	Children with the CC genotype (M ± SD)	Children with the CT genotype (M ± SD)	p
Endocrine function of adipose tissue			
Leptin, ng/ml	32.037 ± 5.023	43.73 ± 4.715	< 0.001
Adiponectin, mcg/ml	6.200 ± 1.200	5.454 ± 0.895	0.049
Meta-inflammation activity			
IL-6, pg/ml	4.061 ± 0.677	4.921 ± 1.040	**0.003**
IL-1β, pg/ml	4.189 ± 0.896	3.637 ± 0.674	0.051
C-reactive protein, mg/l	4.550 ± 1.012	5.278 ± 1.077	**0.041**
Glucose metabolism			
Fasting glucose, mmol/l	4.965 ± 0.138	5.072 ± 0.173	**0.040**
Basal insulin, μUnits/ml	21.472 ± 3.611	26.620 ± 2.495	**< 0.001**
HOMA index, before treatment, %	4.709 ± 0.825	6.008 ± 0.617	**< 0.001**
HbA1c, %	5.224 ± 0.178	5.624 ± 0.174	**< 0.001**
Lipid metabolism			
Total cholesterol, mmol/l	4.529 ± 0.261	4.998 ± 0.312	**< 0.001**
Total cholesterol, percentile	85.692 ± 4.508	88.619 ± 3.109	**0.038**
LDL-C, mmol/l	2.709 ± 0.188	3.164 ± 0.309	**< 0.001**
LDL-C, percentile	79.462 ± 7.065	81.524 ± 5.810	0.352
HDL-C, mmol/l	1.199 ± 0.058	1.405 ± 0.123	**< 0.001**
HDL-C, percentile	27.867 ± 3.308	35.417 ± 5.045	**< 0.001**
VLDL-C, mmol/l	0.615 ± 0.088	0.710 ± 0.071	**0.002**
TG, mmol/l	1.245 ± 0.191	1.381 ± 0.182	**0.036**
TG, percentile	81.200 ± 4.960	85.417 ± 2.588	**0.007**
Atherogenicity coefficient, UI	2.962 ± 0.296	2.868 ± 0.89	0.637
Endocrine system			
Thyroid stimulating hormone, μIU/ml	2.845 ± 0.439	3.613 ± 1.047	**0.003**
freeT4, ng/dl	1.156 ± 0.077	1.126 ± 0.056	0.204
freeT3, ng/dl	3.650 ± 2.350	3.644 ± 0.540	0.992
Antibody to thyroid peroxidase, IU/ml	76.171 ± 65.524	45.024 ± 21.900	0.094
Cortisol, μg/dl	17.000 ± 1.400	11.356 ± 2.901	**< 0.001**
Somatotropic hormone ng/ml	0.490 ± 0.435	1.300 ± 1.215	**0.006**
Insulin-like growth factor 1, ng/ml	277.000 ± 11.000	312.667 ± 49.347	**0.002**
Prolactin, ng/ml	12.190 ± 4.510	16.381 ± 4.176	**0.007**
Luteinizing hormone, μIU/ml	1.125 ± 0.614	3.897 ± 1.094	**< 0.001**
Follicle stimulating hormone, μIU/ml	2.213 ± 0.636	3.149 ± 0.751	**< 0.001**
Free testosterone, nmol/l	1.675 ± 0.235	1.580 ± 0.362	0.327
Dehydroepiandrosterone sulfate, μg/dl	193.500 ± 9.500	280.167 ± 32.532	**< 0.001**
Other metabolites			
Uric acid, μmol/L	297.250 ± 28.675	377.333 ± 43.030	**< 0.001**
25-hydroxycalciferol, ng/mL	22.397 ± 2.062	14.278 ± 1.271	**< 0.001**

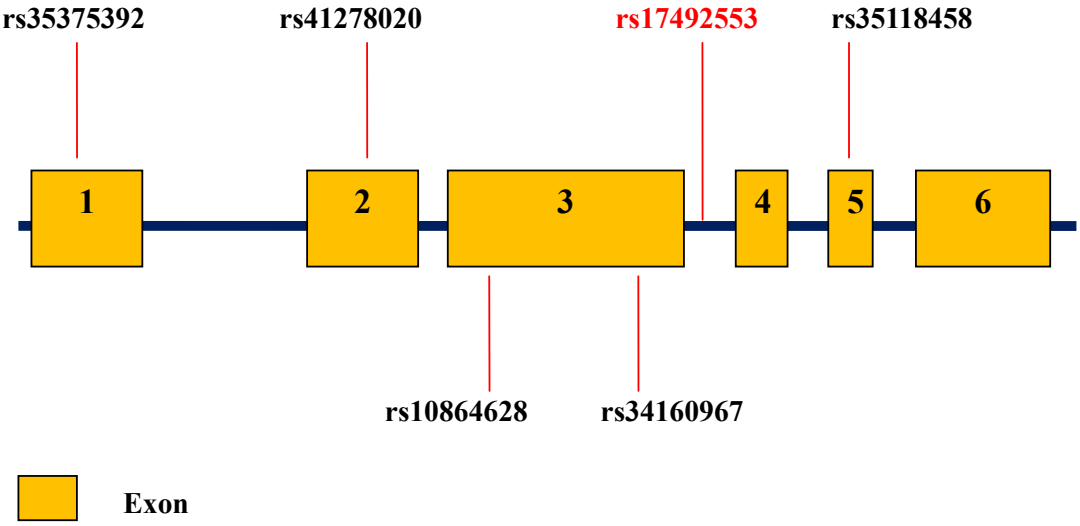


Fig. 1. Localization of SNV in the *TAS1R1* gene in obese children

In all likelihood, the T allele of SNV rs17492553 causes alternative splicing of exon 3 of the *TAS1R1* gene, which is accompanied by the generation of non-functional forms of mature mRNA. A decrease in the sensitivity of T1R1/T1R3 receptors may be accompanied by a change in the activity of genes associated with lipid metabolism. In particular, it has been demonstrated that *Tas1r1* gene knockout mice, compared with wild-type mice, show a slower increase in fat mass and adipocyte size, as well as a lower level of triglyceride and total cholesterol concentration in liver tissue [17].

Lu Ma [17] and colleagues believe that knockout of the *Tas1r1* gene in experimental animals leads to suppression of lipogenesis gene expression in adipose and liver tissues and increased lipid catabolism. It has also been shown that T1R1/T1R3 receptors are involved in carbohydrate metabolism and autophagy regulation. Thus, amino acid excitation of T1R1/T1R3 receptors leads to activation of MAPK1-MAPK3-associated signaling pathways and mammalian target of rapamycin complex 1 (mTORC1). Activation of MAPK1-MAPK3-associated signaling pathways of pancreatic β-cells induces insulin secretion. Knockout of the *TAS1R1* gene of pancreatic β-cells is accompanied by a significant decrease in MAPK1-MAPK3 activity and amino acid-induced insulin production. Under conditions of nutrient excess and activation of T1R1/T1R3 receptors, mTORC1 activation prevents autophagy initiation. *Tas1r1* knockout cells have enhanced potency of autophagy mechanisms. *Tas1r3* knockout mice exhibit high levels of autophagy in cardiomyocytes, skeletal muscle myocytes, and hepatocytes [18].

It remains unclear how the heterozygous state of SNV rs17492553 of the *TAS1R1* gene leads to the occurrence of metabolic disorders. It is possible that in individuals with the CT genotype of the intronic variant rs17492553 of the *TAS1R1* gene, which maintains a physiological level of sensitivity to umami-flavored foods, activation of T1R1/T1R3 receptors leads to altered taste preferences, which causes increased consumption of high-calorie foods. In particular, it has been demonstrated that carriers of the GG genotype of SNV rs34160967 of the *TAS1R1* gene consume significantly more high-calorie and fatty foods compared to carriers of the A allele [19]. MSG intake has also been shown to increase appetite and food intake, which may lead to weight gain [20].

We have established for the first time that the CT SNV rs17492553 genotype of the *TAS1R1* gene is accompanied by a deficiency of 25-hydroxycalciferol.

Conclusions

Genetic variants of SNV rs17492553 of the *TAS1R1* gene mediate the development of metabolically unhealthy obesity in children. Carriers of the CT-genotype SNV rs17492553 of the *TAS1R1* gene are 2.73 times more likely to develop metabolically unhealthy obesity than CC homozygotes.

The CT-genotype SNV rs17492553 of the *TAS1R1* gene is associated with a deficiency of 25-hydroxycalciferol.

When organizing medical observation of children with the CT-genotype SNV rs17492553 of the *TAS1R1* gene, it is necessary to monitor body weight dynamics and the level of vitamin D.

Conflict of interest. The authors declare no conflict of interest.

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