ORIGINAL PAPER

Taste preferences and obesity

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ABSTRACT

Introduction: Genetically determined violation of taste preferences leads to inversion of taste perception and overeating, distorting the homeostatic feedback of the peripheral energy status with hedonic centers, causing obesity. According to previous research the gene *TAS2R38* (taste 2 receptor member 38) has the greatest contribution to the development of metabolically unhealthy obesity (MUO).

Aim of the study was to study the role of the single nucleotide variant (SNV) gene *TAS2R38* in the development of MUO in children.

Material and methods: 205 obese children 6-18 years old were examined by clinical and laboratory methods, including anthropometric, immunobiochemical, and psychological, using the Food and Beverage Preference Questionnaire (FBPQ) and next-generation sequencing. The main group ($n = 124$) consisted of children with MUO, according to the recommendations of the expert group of the IDEFICS, 2014. The control group ($n = 81$) consisted of children with metabolically healthy obesity. The following statistical methods were used: analysis of variance, odds ratio, Spearman's correlation analysis, Wald's sequential analysis.

Results: The level of the mean preference for bitter food in the main group was 2.75 ±0.15 points, while in the control group it was 3.24 ±0.14 points; Student's test, $t = 2.39$, $p < 0.02$. The analysis of food diaries in children showed a positive correlation between the daily rejection of fresh vegetables and the development of MUO ($p = 0.32$) with a prognostic coefficient of 2.7; $p < 0.05$. Three SNVs of the *TAS2R38* gene (missense mutations) were diagnosed. The probability of detecting the heterozygous C/G variant of the rs713598 genotype of *TAS2R38* in the main group was 1.75 times higher than in the control group ($p < 0.05$).

Conclusions: Low taste preferences for bitter foods are associated with the development of MUO in children. rs713598 (C/G) has the greatest association with the development of metabolically unhealthy obesity among the SNVs of the *TAS2R38* gene we have identified.

KEY WORDS:

obesity, children, taste preferences, single nucleotide variants, taste 2 receptor member 38.

INTRODUCTION

Taste sensations determine the differentiated choice of food products necessary for the life of the human body. The formation of taste preferences depends on numerous exogenous (nutritional education, national, family characteristics of cooking, dietary environment, food availability, social status, and others) and endogenous factors (genetic, epigenetic determinants, age, emotional, cognitive development, nutritional experience, individual characteristics of the microbiome intestines, food digestion and others). However, the preference in choosing food products that have a specific taste is largely determined by the peculiarities of the functioning of genes that encode certain taste receptors [1, 2]. Taste reception is associated with the functioning of various genes: sweet taste reception with genes *TAS1R2*, *TAS1R3* and *GNAT3*; umami taste with the genes *TAS1R1*, *TAS1R3*; bitter taste with

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the *TAS2R38* gene; sour taste with the genes *PKD2L1*, *ACCN2*, *PKD1L3* and *ACCN1*; salty taste with the genes *SCNN1B* and *TRPV1* [3].

It has been demonstrated that changes in the activity of taste reception can be associated with single nucleotide variants (SNVs) of taste genes and epigenetic influences that affect the expression of taste genes [4]. Changes in the functioning of taste buds are accompanied not only by a change in the spectrum of taste preferences, but also by metabolic deviations [5].

Genetically determined taste preferences for a particular taste of food (sweet, salty, sour, bitter, fatty) determine the type of eating behavior and metabolic phenotype of an individual. In particular, they can be involved in the development of obesity [6, 7]. Extraoral taste buds affect digestion processes, intestinal motility, and hormone secretion, determine the level of the satiety threshold, and participate in the regulation of energy balance and in the development of adipose tissue [8].

Changes in taste sensitivity and taste preferences may be associated with the development of metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO). The MUO phenotype is the main predictor of metabolically associated diseases: type 2 diabetes, arterial hypertension, polycystic ovary syndrome, and metabolically related liver and bone diseases [7, 9]. According to the results of genetic studies [10, 11], the development of obesity is associated with SNV genes for bitter taste receptors, in particular, the *TAS2R38* gene (member of 38 taste receptors 2). The *TAS2R38* gene (gene ID: 5726; location: 7q34) encodes a seven-membrane receptor associated with the G-protein, which controls the taste reception of molecules that contain thiourea (glucosinolates and phenylthiocarbamide) [12].

It has been demonstrated that SNVs of the *TAS2R38* gene are associated with the body mass index (BMI) level [13]. It was also found that the risk of developing severe metabolic syndrome is strongly associated with SNV rs1726866 (G>A) of the *TAS2R38* gene, and body weight and BMI are inversely proportional to the level of taste perception of bitter food [14]. Despite the existence of many scientific studies investigating various factors that determine the role of taste preferences in the development of body weight, the contribution of SNVs (rs10246939, rs1726866, rs713598) of the *TAS2R38* gene to the development of MUO in children has not been sufficiently studied.

MATERIAL AND METHODS

The observational, ongoing, randomized, case-control study examined 205 obese children aged 6-18 years in the Children's Endocrinology Department of CNE Dnipro Clinical Hospital No. 9 of the Dnipro City Council. For the examination of children, the consent of their parents was obtained. Participants provided written informed consent, and research protocols and procedures were ap-

proved according to the ethical standards of the Helsinki Declaration and by the Human Research Ethics Committee of Dnipro State Medical University (meeting minutes No. 7 of December 11, 2019 and meeting minutes No. 5 of September 3, 2020).

Inclusion criteria: children with polygenic obesity (BMI ≥ 95th percentile) 6-18 years old.

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

For inclusion in the main observation group, the presence of abdominal obesity and two of the following criteria were taken into account: 1) fasting glycemia ≥ 5.6 mmol/l [10]; 2) high-density lipoproteins (HDL) ≤ 1.03 mmol/l or less than 10th percentile of the age norm; 3) triacylglycerides (TAG) ≥ 1.7 mmol/l or more than the 90th percentile of the age norm; 4) systolic blood pressure (SBP) above the 90th percentile for a given age, gender and height [11]. The abdominal type of obesity was determined according to the consensus of the International Diabetes Federation (IDF), based on the waist circumference exceeding the 90th percentile for children 6-15 years old or exceeding 94 cm for boys aged 16-18 years and 80 cm for girls 16-18 years old [12]. The main group (*n* = 124) consisted of patients with MUO. The control group (*n* = 81) consisted of children with MHO.

Clinical and laboratory research methods included anthropometric (waist circumference [WC], height, weight, BMI), manometric (blood pressure measurement) and immunobiochemical methods. To highlight the prevailing modalities of taste preferences for the four most important categories (sweet, fatty, salty and bitter), a questionnaire was carried out using an adapted version of IDEFICS (Identification and prevention of Dietary and lifestyle-induced health EFfects In Children and infantS Study) of the Food and Beverage Preference Questionnaire (FBPQ) on a 5-point scale with the calculation of the average value of the level of taste preference [15] and the analysis of food diaries. In the study of taste preferences for sour taste, we evaluated the child's attitude to natural lemon juice. To interpret the data obtained, we also used a 5-point scale of the FBPQ.

Blood samples were obtained after an overnight fast by venipuncture in vacutainer gel tubes, and serum was separated from cells by centrifugation in the certified laboratory "Synevo" (Dnipro, Ukraine) using an analyzer and a Cobas 6000 test system; Roche Diagnostics (Switzerland). Basal insulin (reference values: 2.6-24.9 μU/ml) was analyzed using the electrochemiluminescence immunoassay method (ECLIA). The analysis of serum glucose was carried out by the hexokinase method; the determination of TAG and HDL cholesterol of blood plasma was carried out by the enzymatic-colorimetric method.

Next-generation sequencing (NGS) was performed by random sampling in 42 children (27 in the main group, 15 in the control group) in the certified laboratory "Ce-Gat" (Tubingen, Germany) using the Infinium Omni-

Express-24 genotyping kit version 1.2 BeadChip (Illumina Inc.) in accordance with the manufacturer's protocol with the relevant quality standards. The amount of double stranded DNA was measured using PicoGreen (Invitrogen Corporation). Allele detection and genotyping were performed in the GenomeStudio genotyping module (Illumina, Inc.). SNVs that were not displayed on autosomal chromosomes were filtered out from the original complete set. SNVs with a minor allele frequency < 0.01 or deviations from the expected Hardy-Weinberg equilibrium ($p < 1.0 \times 10^{-5}$) were removed. Thus, only SNVs that had passed qualitative filtering were left for further analysis.

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 was used for local restructuring of readings in target regions to achieve more accurate detection of indels in the genome. When interpreting the data of bioinformatic analysis, the combined annotated-dependent depletion (CADD) was calculated for each identified non-synonymous SNV of the *TAS2R38* gene [16].

Statistical processing of the results using parametric and nonparametric methods included: analysis of variance with the calculation of Student's *t*-test (*t*); sequential Wald analysis with calculation of the prognostic coefficient (PC); Spearman correlation analysis with calculation of Spearman's rank correlation coefficient (ρ); and the odds ratio (OR) with 95% CI (confidence interval). The critical value of the level of statistical significance (*p*) for all types of analysis was taken at the level of $p < 0.05$ (5%). Statistical processing of the results was performed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 205 children were included (mean age: 12 years; 49% female). In the comparison groups, children did not differ in age and sex, $p > 0.05$. However, the proportion of children with MUO (60.5%) was 1.5 times higher than the proportion of children with MHO (39.5%) in the total cohort of obese children. Children with MHO had a smaller WC than their peers with MUO. At the same time, in patients from the MUO group, arterial hypertension, dyslipidemia in the form of hypertriglyceridemia and basal hyperinsulinemia were recorded significantly more often than in the MHO group (all $p < 0.05$) (Table 1).

When examining the levels of taste preferences in the comparison groups for the five main types of taste, significant differences were noted only in relation to bitter taste. Namely, among children from the main group with

TABLE 1. Clinical indicators of study participants in accordance with obesity phenotype

Variable	MUO (*n* = 124)	MHO (*n* = 81)	*p*-value*
Age, years	12.3 ±0.3	11.9 ±0.2	> 0.05
BMI in percentiles, %	99.4	97.8	> 0.05
WC in girls, cm	91.6 ±3.3	80.5 ±3.1	< 0.05
WC in boys, cm	108.6 ±3.1	97.7 ±4.5	< 0.05
SBP in percentiles, %	95	85	< 0.05
HDL cholesterol, mmol/l	1.42 ±2.1	1.44 ±1.3	> 0.05
TAG, mmol/l	1.3 ±0.02	0.76 ±0.04	< 0.05
Fasting glucose, mmol/l	5.24 ±0.01	5.02 ±0.02	> 0.05
Basal insulin, μU/ml	29.24 ±1.12	13.61 ±1.01	< 0.05

*P-value for the comparisons (means or percentages) between MUO and MHO. Student's t-tests for continuous variables.
MUO – metabolically unhealthy obesity, MHO – metabolically healthy obesity, BMI – body mass index, WC – waist circumference, SBP – systolic blood pressure, HDL – high-density lipoproteins, TAG – triacylglycerides

TABLE 2. Relative risk of developing metabolically unhealthy obesity (MUO) in children 6-18 years old with different single nucleotide variants (SNVs) of the *TAS2R38* gene

SNV type of the gene *TAS2R38*	Relative risk of developing the MUO phenotype
10246939 C/C, HOM[†]	OR = 1.167; 95% DI: 0.09-14.06
10246939 T/C, HET*	OR = 1.193; 95% DI: 0.33-4.28
1726866 A/A, HOM	OR = 0.79; 95% DI: 0.21-2.94
1726866 G/A, HET	OR = 1.33; 95% DI: 0.37-4.76
713598 C/C, HOM	OR = 1.167; 95% DI: 0.09-14.06
713598 C/G, HET	OR = 1.75; 95% DI: 1.10-6.35

HET* – heterozygous variant (single allelic single nucleotide substitution), HOM[†] – homozygous variant (biallelic single nucleotide substitution).

MUO, according to the FBPQ results, the level of taste preferences was lower for this taste modality compared to the control group of children with MHO (*t* = 2.39; $p = 0.022$; critical value *t* = 2.023). There were no statistically significant differences in the comparison groups by gender, age, educational level, and sensory preference for sweet, fatty, sour, and salty tastes, $p > 0.05$.

When analyzing food diaries in the examined patients, a positive correlation was found between the absence of daily consumption of fresh vegetables and the development of MUO (ρ = 0.32) with a PC = 2.7; $p < 0.05$.

Three SNVs of the *TAS2R38* genes were identified among obese patients by NGS: rs10246939, rs1726866, rs713598 with CADD = 9.46; 12.15; 13.24 respectively. The frequency of occurrence of the C/G variant of the rs713598 genotype of the *TAS2R38* gene in the MUO group was 1.75 times higher than in the MHO group, $p < 0.05$. The relative risk of MUO for different SNV genotypes of the *TAS2R38* gene in children 6-18 years old is presented in Table 2.

DISCUSSION

Research results indicate that SNV genes of taste receptors in children, including the *TAS2R38* gene, make a more significant contribution to taste reception than in adults [17]. The most common SNVs of the *TAS2R38* gene are rs714598 G>C (A49P), rs1726866 T>C (V262A), and rs10246939 T>C (I296V). SNV data of the *TAS2R38* gene are associated with different levels of perception of 6-n-propylthiouracil (PROP) and other bitter compounds (e.g., glucosinolates, myrosinase) [7, 18].

SNV rs714598, rs1726866, and rs10246939 of the *TAS2R38* gene determine the variability of three amino acid residues at positions 49, 262, and 296 of the receptor molecule and, respectively, determine the level of sensitivity to bitterness. These SNVs are involved in the formation of two haplotypes. The dominant haplotype (proline-alanine-valine, PAV) has a functionally active allele (Pro49, Ala262, and Val296). The recessive haplotype (alanine-valine-isoleucine, AVI) contains a non-functional allele (Ala49, Val262 and Ile296).

The PAV haplotype is associated with high sensitivity to bitter taste (tasting phenotype). PAV/PAV homozygotes are supertasters of bitter taste. The AVI haplotype is associated with low sensitivity to bitter taste (non-tasting phenotype); the AVI/AVI homozygotes are a group of bitter nontasters. PAV/AVI heterozygotes are characterized by an average level of sensitivity to bitter taste [19].

Studies of the threshold of sensitivity to bitter taste in obese or overweight individuals show varying results, even exactly opposite data. Thus, it has been observed that in obese individuals the level of taste sensitivity to bitterness can be higher [11], lower [14], or similar to the level observed in persons with normal body weight (Table 3) [20].

Changes in the sensitivity to bitter taste associated with the SNV of the *TAS2R38* gene can lead to deviations in the development of body weight [24, 26]. We have demonstrated that the C/G rs713598 genotype of the *TAS2R38* gene increases the risk of switching from MHO to MUO in children. It is known that the C/G rs713598 genotype of the *TAS2R38* gene is associated with a decrease in sensitivity to bitter taste [24]. It is likely that the development of MUO in body-positive children with the C/G rs713598 genotype of the *TAS2R38* gene is due to the fact that the decreased level of sensitivity to bitter taste is accompanied by an increase in the consumption of saturated fatty acids [15, 27].

In contrast to the study of the threshold for sensitivity to bitter taste, the level of taste preferences in children with MUO has hardly been studied [28]. At the same time, in adult individuals, a relationship was detected between SNV rs713598 of the *TAS2R38* gene and food preferences, sensory responses, biochemical parameters, and body composition [10]. In comparison with previous studies, which are based on the use of FBPQ and are mainly devoted to studying the role of sensory preferences for sweet and fatty tastes in the development of excess weight [15], we have identified the contribution of genetically determined taste preferences for bitter, salty and sour foods in the process of converting MHO to MUO in prepubertal children. We found that prepubertal children with MUO and rs713598 C/G genotype showed a significant decrease in the preference for bitter taste. Children with MUO and different SNV genotypes – rs713598, rs10246939, rs1726866 – of the *TAS2R38* gene did not differ in children with MHO in terms of their preference for sweet, fatty, salty and sour tastes. In all likelihood, the formation of taste preferences is determined not only by the level of the threshold of taste sensitivity, but also by the peculiarities of the influence of taste buds on hedonic pathways of appetite regulation, fat metabolism and on the development of visceral adipose tissue. A decrease in the preference for bitter taste, in our opinion, causes a decrease in the consumption of bitter foods, in particular cruciferous vegetables (white cabbage, cauliflower, Peking cabbage, Brussels sprouts, broccoli, radishes, turnips, asparagus, kohlrabi, watercress, spinach, arugula). Patients with MUO compensate for the restriction of vegetable consumption by the consumption of sweet and fatty foods, which contributes to the development of obesity and the occurrence of meta-inflammation of adipose tissue. Also, other authors have reported that SNVs of the *TAS2R38* gene are associated with self-limitation and reduced consumption of cruciferous vegetables [29]. From an evolutionary point of view, limiting the intake of bitter tasting foods prevents potentially toxic substances from entering the child's body, while the presence of preferences for sugary and fatty foods causes excessive consumption of high-calorie foods [30]. Self-limitation of cruciferous vegetable consumption by children may be one of the early clinical signs of a possible transformation of MHO to MUO in body-positive children.

CONCLUSIONS

A feature of the structure of obesity phenotypes is the predominance of 1.5 times the MU phenotype (60.5%) among the body-positive children we examined, which emphasizes the need to introduce preventive measures in this target group aimed at reducing the cardiometabolic risk.

The SNVs rs10246939, rs1726866, rs713598 of the *TAS2R38* gene, which are involved in the perception of taste modalities, contribute to the development of MUO.

Taste preferences for sweet, fatty, sour, and salty foods did not differ between children with MHO and MUO.

A decrease in taste preferences for bitter food increases the risk of MUO development in body-positive children and is associated with SNV of the *TAS2R38* rs713598 gene.

TABLE 3. Associations of disturbances in reception and preferences for bitter taste with obesity in children and adults

Study groups	Bitter taste reception	Bitter taste preferences	Analyzed SNV *TAS2R38*	mRNA *TAS2R38*	Features of metabolism, eating behavior	References
Children 6-18 years old (99 obese and 91 normal weight)	↑	–	–	–	–	[21]
Adults (56 people)	–	–	–	–	No association between taste and weight	[20]
Adults (35 people aged 18-55 years, of whom 20 are obese or overweight [OW/OB] and 15 are of normal body weight [NW])	–	–	–	↑	–	[22]
13 165 children	–	↑	–	–	–	[15]
Adults (average age 35; 52 obese and 52 normal weight)	↓	–	rs1726866, rs10246939	–	–	[23]
Adults (118 individuals)	↓	–	G-allele, rs713598	–	Biochemical parameters and markers of body composition did not differ between individuals with genotypes C/C, C/G, G/G rs713598 of the *TAS2R38* gene	[10]
Adults over 50 years of age with metabolic syndrome (381 people)	↓	–	rs1726866	–	–	[14]
Adults (1338 men and 2229 women)	↓	–	TT genotype, rs10246939	–	Increased fruit intake	[24]
Adults (32 obese persons, 18 with normal body weight)	–	–	rs713598	↑	Incubation with PROP caused delipidation and deactivation of the FASN, PPARγ, and GLUT4 genes	[25]
Adults (out of 175 people; 89.1% are obese)	↑	–	–	–	People with the PAV haplotype consume more sodium, sugar, and saturated fat than people with the AVI haplotype	[26]
Adults (83 individuals; 42 obese individuals and 41 normal weight individuals)	↑	–	rs713598, rs1726866, rs10246939	↑	–	[11]

↑ – high association with the studied parameter in obese individuals, ↓ – low association with the studied parameter in obese individuals.

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DISCLOSURE

The authors declare no conflict of interest.

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