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Significance of the rs754635 variant of the cholecystokinin gene in the development of obesity in children

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So far, the possible influence of single nucleotide variants (SNV) of the cholecystokinin (*CCK*) gene on the likelihood of developing obesity and metabolic disorders in children has not been demonstrated.

The aim of the study SNV associations of the *CCK* gene to predict the probability of obesity and personalize the development trajectory of various metabolic disorders associated with obesity in children.

Materials and methods. 252 obese children aged 6–18 years were examined. The main group (n=152) was represented by children with metabolically unhealthy obesity (MUO). The control group (n=100) consolidated of children with metabolically healthy obesity (MHO). Whole genome sequencing (CeGat, Germany) was performed in 31 children of the main and 21 children of the control group. Serum levels of interleukin-1β were measured using a chemiluminescent immunoassay (CLIA) method, interleukin-6 — by enzyme-linked immunosorbent assay (ELISA), Synevo, Ukraine.

Results. The G allele of SNV rs754635 of the *CCK* gene was significantly more frequent among children with both MHO (t=10.93; p<0.05) and MUO (t=12.96; p<0.05) compared to healthy individuals. The G allele of SNV rs754635 of the *CCK* gene was associated with basal hyperglycemia (r=0.44) and impaired carbohydrate tolerance (r=0.33) in the MHO phenotype and with the atherogenicity index of the lipid spectrum (r=0.40) and was inversely correlated with the level of high-density lipoproteins (HDL) (r=-0.58) in children with MUO phenotype, p<0.05.

Conclusions. The G allele SNV rs754635 of the *CCK* gene is associated with obesity and the development of metabolic disorders.

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. No conflict of interests was declared by the author.

Keywords: cholecystokinin, analysis of single nucleotide gene variants, children, metabolically unhealthy obesity, metabolically healthy obesity.

Значення варіанта rs754635 гена холецистокініну в розвитку ожиріння в дітей

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На сьогодні не доведено впливу однонуклеотидних варіантів (single nucleotide variants — SNV) гена холецистокініну (cholecystokinin — *CCK*) на ймовірність розвитку ожиріння з метаболічними розладами в дітей.

Мета — вивчити асоціації SNV гена *CCK* для прогнозу ймовірності ожиріння та персоналізації траєкторії розвитку різних метаболічних розладів, пов'язаних з ожирінням у дітей.

Матеріали та методи. Обстежено 252 дитини віком 6–18 років з ожирінням. Основну групу (n=152) становили діти з метаболічно нездоровим ожирінням (metabolically unhealthy obesity — MUO). Контрольну групу (n=100) — діти з метаболічно здоровим ожирінням (metabolically healthy obesity — MHO). Проведено повногеномне секвенування («CeGat», Німеччина) у 31 дитини основної та 21 дитини контрольної групи. Рівень інтерлейкіну-1β у сироватці крові визначено методом імунохемілюмінесцентного аналізу, інтерлейкіну-6 — методом імуноферментного аналізу, «Synevo», Україна.

Результати. G-алель SNV rs754635 гена *CCK* вірогідно частіше зустрічався в дітей як з MHO (t=10,93; p<0,05), так і з MUO (t=12,96; p<0,05) порівняно зі здоровими особами. G-алель SNV rs754635 гена *CCK* асоціювався з базальною гіперглікемією (r=0,44) і порушенням толерантності до вуглеводів (r=0,33) при фенотипі MHO та з індексом атерогенності ліпідного спектра (r=0,40) і обернено пропорційно корелював із рівнем ліпопротеїнів високої щільності (r=-0,58) у дітей з фенотипом MUO, p<0,05.

Висновки. Алель G SNV rs754635 гена *CCK* асоціюється з ожирінням і розвитком метаболічних порушень.

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. Автор заявляє про відсутність конфлікту інтересів.

Ключові слова: холецистокінін, аналіз варіантів однонуклеотидного гена, діти, метаболічно нездорове ожиріння, метаболічно здорове ожиріння.

Introduction

Obesity in children is a disease, the development of which depends on a variety of exogenous and endogenous factors. An increase in appetite, which leads to an excess intake of calories in the human body, is due to the predominance of orexigenic over anorexigenic factors [37]. Cholecystokinin (cholecystokinin — CCK) is the first identified enteroendocrine satiety signal molecule that suppresses appetite activity [15]. CCK was first identified by A.C. Ivy, E. Oldberg [19] in 1928 in extracts of the jejunum as «highly purified secretin» (highly purified secretin — HPS),

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inducing gallbladder contraction. Cholecystokinin is a member of a family of regulatory peptides with a conserved C-terminal amino acid sequence Trh-Met-Asp-Phe [40]. The *CCK* gene is located on the short arm of chromosome 3 (3p22.1) [6]. The primary translation product of the *CCK* gene is preprochocystokinin, the molecule of which consists of 115 amino acid residues. After the signal peptide is truncated from preprocholecystokinin, procholecystokinin is formed. As a result of protranslational transformations, CCK peptides of various lengths are formed from prochocystokinin: in endocrine cells — CCK-58, CCK-33, CCK-22, CCK-8 CCK-5; in neurons — CCK-8 and CCK-5. Thus, cholecystokinin is represented by several molecular forms, which are united by the presence of a C-terminal heptapeptide sequence. The predominant form of CCK in the human body is CCK-33 [42]. CCK peptides are predominantly secreted by type I neuroendocrine cells of the small intestinal mucosa and brain neurons. Also, CCK is expressed in the cells of some endocrine glands (corticotrophs and melanotrophs of the pituitary gland, C-cells of the thyroid gland, adrenal brain cells, pancreatic cells), in peripheral nerves; cortical and medullary cells of the kidneys, cardiomyocytes and immunocytes [11,40].

The main stimulus for CCK production is food, especially food rich in proteins (L-amino acids) and fats. CCK peptides realize their biological action through the activation of cholecystokinin A/1 receptors (CCKAR, CCK1R) of afferent neurons of the vagus nerve of the intestine; and B/2 (CCK B/2 receptor — CCKBR, CCK2R) neurons of the central nervous system. CCK peptides, by activating CCK1R afferent neurons of the vagus nerve of the intestine, transmit satiety signals to the hypothalamus, which leads to appetite suppression. Thus, CCK, acting as a satiety signal, activates the anorexigenic signaling pathway, preventing the development of obesity [6,39].

Activation of CCK1R also stimulates gallbladder contraction, pancreatic exocrine secretion, and insulin secretion from pancreatic β-cells of the islets of Langerhans; inhibits the secretion of gastric juice and suppresses gastric emptying. By activating CCK2R in the central nervous system, CCK peptides modulate the activity of the dopamine system, slow down the release of gamma-aminobutyric acid, increase the rate of neuronal excitation, predetermining various behavioral functions, including satiety, anxiety and phobia levels [30,33,35,42]. CCK peptides also stimulate the secretion of calcitonin, glucagon, and in the kidneys can act as natriuretic peptides [40]. CCK peptides have different potency: the contractile effect induced by CCK-8 is approximately 10 times greater than that induced by CCK-33 [5].

Modifications of the C-terminal heptapeptide sequence reduce the affinity of CCK peptides for receptors, which impairs the efficiency of their binding and, as a result, prevents the development of biological effects. Reduced activity of CCK-induced excitation contributes to the development of obesity [5].

It has been established that single nucleotide variants (single nucleotide variant — SNV) of the *CCKAR* receptor gene are associated with the risk of developing obesity [31]. However, a possible effect of *CCK* gene SNV on the likelihood of developing obesity and metabolic disorders in children has not yet been demonstrated.

The ***aim*** of the research — to study SNV associations of the CSK gene to predict the probability of obesity and personalize the development trajectory of various metabolic disorders associated with obesity in children.

Materials and methods of the research

Study design: observational, analytical, longitudinal, cohort study [27].

At the Children's Endocrinology Department of the Communal Non-profit Enterprise «Dnipro City Clinical Hospital No. 9» of the Dnipro City Council, 252 children of the Caucasian group aged 6-18 years with a diagnosis of obesity were examined. To verify the diagnosis, the classification of obesity recommended in clinical practice was used: Order of the Ministry of Health of Ukraine No. 254 of 27.04.2006 «Protocol for the provision of medical care to obese children» and Order of the Ministry of Health of Ukraine No. 1732 of 24.09.2022 About the approval of Standards medical assistance «Obesity in children».

The main group (n=152) was represented by children with metabolically unhealthy obesity (MUO), the control group (n=100) was formed from patients with metabolically healthy obesity (MHO).

Criteria for inclusion in the main group: the presence of abdominal obesity [3] and two of the following criteria (hyperglycemia and/or hyperinsulinemia; dyslipidemia; systolic blood pressure (SBP) and diastolic blood pressure

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(DBP) above the 90th percentile for a given age, gender and height [14].

Anthropometric data were measured by a nurse in the admission department, the child was in underwear and without shoes. Height (m) was measured using Heightronic Digital Stadiometer® to the nearest 0.01 m. Weight (kg) was measured using Tefal Bodysignal body composition analyzer (France). Waist circumference (WC), hip circumference (HC) was measured using a standardized anthropometric tape, measuring the circumference at the midpoint between the top of the iliac crest and the lower part of the lateral rib cage to the nearest 0.01 m. Body Mass Index (BMI) was converted to standardised BMI (BMI SDS) by means of the current World Health Organization (WHO) growth references [34].

SBP and DBP were measured using a digital oscillimetric device, Dinamap ProCare (GE Healthcare).

Inclusion criteria: children with polygenic obesity (BMI ⩾97th percentiles) 6–18 years old.

Exclusion criteria: monogenic and secondary forms of obesity; hereditary syndromes accompanied by obesity; diseases, the treatment of which requires the use of medications that affect the metabolism of carbohydrates and lipids; pregnancy.

Immunochemical examination. The studies were carried out in a certified Synevo laboratory (Dnipro, Ukraine). The material for the study was venous blood.

To study carbohydrate metabolism disorders, the level of basal glycemia and insulinemia was determined by immunochemical testing with electrochemiluminescent detection (ECLIA). Obese children were included in the main group with a glycemic level equal to or greater than 5.6 mmol/L and/or they had an increase in insulinemia >90th percentile according to the percentile curves recommended by the Identification and prevention of Dietary — and lifestyle-induced health EFfects In Children and infantS (IDEFICS) consortium for the European population according to age and gender of the child [12,36].

To study lipid metabolism disorders, the level of high-density lipoproteins (HDL-C), low density lipoproteins (LDL-C) and triglycerides (TG) was determined by the enzymatic-colorimetric method using kits from Roche Diagnostics (Switzerland) on the analyzer Cobas 6000. Obese children were included in the main group with HDL-C⩽1.03 mmol/L or less than 10th percentile of the age norm or an increase in ⩾1.7 mmol/L or more than the 90th percentile of the age norm [13].

Molecular and immunological examination. To study the role of pro-inflammatory markers in the development of meta-inflammation in obesity in children, the levels of IL-1β, IL-6 in blood serum were determined in the certified Synevo laboratory (Dnipro, Ukraine). Interleukin-1β was investigated by immunochemical method with chemiluminescent detection (CLIA). Analyzer and test system: Immulite (Siemens AG), Germany. The reference value was considered the level of IL-1β 0–5 pg/ml. Interleukin-6 was determined by enzyme-linked immunosorbent assay (ELISA) using a Cobas 6000/ Cobas 8000 kit provided by Roche Diagnostics (Switzerland). The reference value was considered the level of IL-6 1.5–7.0 pg/ml.

Molecular genetic testing. To study the contribution of *CCK* SNV variants to the formation of MUO, a molecular genetic examination was carried out using the method of new generation whole genome sequencing (NGS) according to the recommendations of The American College of Medical Genetics and Genomics (ACMG) [9] in 52 patients (31 children from the main group and 21 controls) with venous blood sampling in a certified CeGat laboratory (Tubingen, Germany) using the Illumina CSPro® Certified service provider platform.

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; 2×100 bp. QC values of sequencing, Q30 value: 96.07%.

Bioinformatics 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 [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 [17,25,26,28]. 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 [8,32].

Reference sequence obtained from the National Center for Biotechnology Information RefSeq database [41].

Statistical analysis. Statistical analysis of the obtained results was carried out using a package of application programs Statistica 6.1

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Table 1

Characteristics of SNV types of the *CCK* gene

SNV, ID	Position	GnomAD _maxPOP	Ref	Alt	Consequence	Base Change	CADD	RawScore	Clinical significanse (ClinVar)
rs754635	42305131	NFE	C	G	5_prime_UTR_intronic	c*.-9G>C	3.98	0.08	No data

Notes: GnomAD_maxPOP — the frequency distribution of CCK mutations. NFE represent Non-Finnish European; 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 HGVS nomenclature: c. CDS Position Reference Base > Alternative Base. Example: c.223A>T (c.* — interpretation for DNA coding sequence) [41]. This column is empty if the variant is intergenic; CADD — combined annotation dependent depletion.

Table 2

The frequency of occurrence of major and minor variants of SNV rs754635 of the *CCK* gene in children with different obesity phenotypes

SNV	The frequency of occurrence of major and minor options in healthy individuals (%) [22]		The frequency of occurrence of major and minor variants in patients with obesity (%)				The value of Student's t-test in Welch's modification		
	Allele C	Allele G	MHO		MUO		t_1	t_2	t_3
			Allele C	Allele G	Allele C	Allele G	Allele G		
rs754635	76.9	23.1	10	90	16	84	12.96*	10.93*	1.27

Notes: * — Critical value of Student's t-test modified by Welch >1.97, at which the differences in the compared groups are significant, $p<0.05$; t_1 — Student's test of significance by allele G, modified by Welch in the comparison groups MHO and healthy individuals; t_2 — Student's test of significance by allele G, modified by Welch in the comparison groups MUO and healthy individuals; t_3 — Student's test of significance by allele G, modified by Welch in the MUO and MHO comparison groups.

(No AGAR909E415822FA) with help a personal computer based on an Intel processor Pentium 4. Depending on the test result, parametric and nonparametric statistical methods were used. Correlation analysis was used to analyze 100 indicators of clinical, laboratory-instrumental and molecular genetic examinations in 252 children. To assess the relationship between quantitative traits, correlation analysis was used according to the Pearson method, and between qualitative traits, a non-parametric ranking method was used according to Spearman's analysis (r). Only essential ones were taken into account connections ($p<0.05$).

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 (ethical approval DSMU/EC/19/1107). Time of data collection: January 2020 — February 2023.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Results of the research

As a result of complete genome sequencing in children with obesity, we identified only one SNV of the *CCK* gene, rs754635 (IVS1-7C>G). This SNV is located at the intron 1/exon 2 border of the *CCK* gene, which may lead to a change in the splicing mechanism [22].

The molecular genetic characterization of SNV rs754635 of the *CCK* gene is presented in Table 1.

Associations of SNV rs754635 CCK gene with obesity phenotypes in children. The frequency of occurrence of SNV rs754635 of the *CCK* gene in children with different obesity phenotypes is presented in Table 2.

According to the data obtained, obese children have a significantly higher frequency of the G allele compared to individuals with physiological body weight.

In children with the MHO phenotype, the frequency of the mutated G allele for SNV rs754635 of the *CCK* gene was significantly higher ($t=12.96$; $p<0.05$), as in children with the MUO phenotype ($t=10.93$; $p<0.05$), than the frequency of this polymorphism among healthy persons.

According to the analysis, the frequency of the G allele for SNV rs754635 of the *CCK* gene in children with the studied obesity phenotypes was not statistically significant ($t=1.27$, $p<0.05$).

Associations of CCK gene SNV rs754635 with inflammatory activity. According to the results of correlation analysis, the level of production of pro-inflammatory cytokines in obese children did not depend on the SNV rs754635 genotype of the *CCK* gene.

Associations of SNV rs754635 of the CCK gene with disorders of carbohydrate metabolism. Correlation analysis showed the presence of a relationship between SNV rs754635 of the *CCK* gene and indicators of carbohydrate metabolism in patients with the obesity MHO phenotype. It was found that the presence of the G allele was moderately associated with fasting hyperglycemia

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(r=0.44) and impaired carbohydrate tolerance (r=0.33).

Associations of SNV rs754635 of the CCK gene with lipid metabolism disorders. We have found that the G SNV rs754635 allele of the *CCK* gene in children with the MHO phenotype is inversely related to the level of HDL-C in blood serum (r=-0.58) and directly proportional to the atherogenic index of the lipid spectrum (r=0.40) in children with the MUO phenotype.

Discussion

According to the results of complete genome sequencing, obese children, regardless of the obesity phenotype, have a high frequency of occurrence of SNV rs754635 of the *CCK* gene. Mariaelisa Graff et al. [16] found an association of SNV rs754635 of the *CCK* gene with BMI in adults. According to the results of complete genome sequencing, obese children, regardless of the obesity phenotype, have a high frequency of occurrence of SNV rs754635 of the *CCK* gene. Mariaelisa Graff et al. [16] found an association of SNV rs754635 of the *CCK* gene with BMI in adults.

Of interest is the fact that patients with MHO have higher serum levels of CCK and insulin than those with the MUO phenotype [29]. In all likelihood, the lack of excitation of CCK-associated signaling pathways is associated with the development of metabolic disorders. We have shown for the first time the association of SNV rs754635 of the *CCK* gene with metabolic disorders in obese children. Thus, carriers of the G allele SNV rs754635 of the *CCK* gene with the MHO phenotype are characterized by a moderate tendency to fasting hyperglycemia and impaired carbohydrate tolerance. It is known that an increase in the production of the biologically active form of CCK-8 in the duodenum reduces the level of glucose secretion, regardless of the level of insulin, the reduction of CCK-induced excitation due to CCK deficiency or cholecystokinin resistance may contribute to the occurrence of hyperglycemia [4,7]. Introduction of CCK to experimental animals reduces the level of glycemia, stimulates proliferation and prevents apoptosis of β-cells of the islets of Langerhans of the pancreas [20,23,24].

Also, we have shown that in carriers of the G allele SNV rs754635 of the *CCK* gene with the MHO phenotype, a decrease in the concentration of HDL-C is observed, and with the MUO phenotype, a higher level of atherogenicity of the blood serum lipid spectrum is characteristic. Aditya J Desai et al. [11] demonstrated that a decrease in the activity of CCK-associated signaling pathways correlates with elevated serum triglyceride levels in individuals with normal body weight and low concentrations of HDL-C in patients with obesity and diabetes mellitus. The authors suggest that these effects are due to a decrease in CCK1R sensitivity due to an increase in the level of cholesterol in the cell membrane in obese patients. On the other hand, it has been shown that CCK in experimental animals contributes to hypercholesterolemia, hypertriglyceridemia as a result of increased lipid reabsorption from the intestinal lumen. The authors believe that CCK stimulates the secretion of bile from the gallbladder into the small intestine and the secretion of lipases by the pancreas. Bile salts, by forming amphipathic micelles, emulsify fats, allowing pancreatic lipases to gain access to cholesterol ester molecules. Hydrolysis of cholesterol esters by lipases leads to the formation of free cholesterol and fatty acids, which are absorbed by enterocytes and transported to the peripheral bloodstream [44,45]. Also, CCK stimulates the CD36 fatty acid translocase, promoting fatty acid uptake by duodenal enterocytes [10]. *CCK* gene knockout (CCK-KO) mice show decreased activity of Apo B48 chylomicron secretion, lipid transport to the lymphatic system, and triglyceride uptake in response to intraduodenal lipid administration [21]. The contradiction of the results of the study of the effect of CCK on the lipid spectrum of peripheral blood is probably due to the different strength of the effect of CCK on the reabsorption of lipids from the intestinal lumen and the process of absorption of lipids by adipocytes of adipose tissue. It is known that when entering the bloodstream, chylomicron triglycerides are hydrolyzed to free fatty acids by the action of lipoprotein lipase. Most of the released fatty acids and all monoacylglycerols are directly transported to the adipose tissue cells. Adrián Plaza et al. [38] showed that CCK-8 reduces the level of angiopoietin-like protein-4 (angiopoietin-like protein-4 — ANGTPL-4), represses the expression of ANGPTL-4 in white adipose tissue and simultaneously increases the activity of lipoprotein lipase, which promotes the release of fatty acids and their absorption by target cells, in particular adipocytes. In our opinion, carriers of the G allele of SNV rs754635 probably have a lack of biological activity of CCK peptides, which can prevent both lipid reabsorption from the intestinal

lumen and lipid accumulation in adipose tissue. It is possible that CCK peptides in individuals with the G allele of SNV rs754635 contribute more to the reabsorption of lipids from the intestinal lumen than to the absorption of lipids by adipocytes, which leads to a violation of the lipid spectrum in the blood serum.

Conclusions

The presence of the G allele SNV rs754635 of the *CCK* gene in children is associated with the development of obesity and metabolic disorders induced by obesity.

The presence of the C allele SNV rs754635 of the *CCK* gene prevents the formation of metabolic disorders in children.

The rs754635 variants of the *CCK* gene are associated with certain features of carbohydrate and lipid metabolism in obese children. Children with the CG/GG SNV rs754635 genotype and the MHO phenotype are characterized by a higher level of basal hyperglycemia, fasting hyperglycemia and impaired carbohydrate tolerance, and those with the MUO phenotype have a high level of atherogenicity.

Determination of the SNV rs754635 genotype of the *CCK* gene will make it possible to predict the likelihood of obesity and to personalize the development trajectory of various metabolic disorders associated with obesity in children.

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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.

No conflict of interests was declared by the author.

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