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GENETIC ASSOCIATIONS OF OBSTRUCTIVE SLEEP APNOEA SYNDROME IN CHILDREN WITH OBESITY

O. Abaturov[1], A. Nikulina[1], D. Dikhtyarenko[2]

1 - Dnipro State Medical University, Dnipro, Ukraine
2 - Municipal educational institution Scientific medical lyceum "Dnipro" Dnipro regional council
anna.nikulina.201381@gmail.com

Background. Observance of sleep hygiene together with rational nutrition and dosed physical activity contribute to the quality and duration of life. The aim of the study: to determine the contribution of single-nucleotide gene variants associated with the risk of obstructive sleep apnea syndrome in metabolically unhealthy obesity in children. Materials and methods. 52 obese children aged 14-18 years were examined by the method of complete genome sequencing (CeGat, Germany). Results. In the absence of SNV rs2307111 nucleotide substitution of the POC5 gene, the probability of developing obstructive sleep apnea syndrome in MUO increases 5 times (95% CI 1.22 - 20.48), p=0.025. Conclusions: TT SNV rs2307111 POC5 is highly associated with the presence of MUO and OSAS in children.

Key words: *genetic associations, single nucleotide gene variants, obstructive sleep apnea syndrome, obesity, children*

ГЕНЕТИЧНІ АСОЦІАЦІЇ СИНДРОМУ ОБСТРУКТИВНОГО АПНОЕ УВІ СНІ У ДІТЕЙ З ОЖИРІННЯМ

О. Абатуров[1], А. Нікуліна[1], Д. Діхтяренко[2]

1 - ДДМУ, Дніпро, Україна
2 - Комунальний заклад освіти «Науково-медичний ліцей «Дніпро» Дніпропетровської обласної ради

Актуальність. Дотримання гігієни сну разом із раціональним харчуванням та дозованою фізичною активністю сприяють якості та тривалості життя. Мета визначити внесок однонуклеотидних варіантів генів (single nucleotide variants – SNV), асоційованих з ризиком синдрому обструктивного апное уві сні при ожирінні у дітей. Матеріали та методи. Методом повного геномного секвенування (CeGat, Німеччина) обстежено 52 дитини з ожирінням віком 14-18 років. Результати. За відсутності нуклеотидної заміни SNV rs2307111 гена POC5 – вірогідність формування синдрому обструктивного апное уві сні при МУО зростає в 5 разів (95% ДІ 1,22 – 20,48), p=0,025. Висновки: Високо асоційованими із МУО та OSAS у дітей є TT SNV rs2307111 POC5.

Ключові слова: *генетичні асоціації, однонуклеотидні варіанти генів, синдром обструктивного апное уві сні, ожиріння, діти*

INTRODUCTION

The prevalence of obesity in children has now reached epidemic proportions [1;2]. Obesity has been shown to be strongly associated with the development of various sleep disorders, including obstructive sleep apnea syndrome (OSAS). An increase in body mass index (BMI) by just one standard deviation increases the risk of developing OSAS (Odds Ratio: 2.21) [3]. The combination of obesity and OSA contributes to the development of insulin resistance, arterial hypertension, and other metabolic disorders in childhood [4; 5].

The genome plays a key role in the initiation and maintenance of sleep and wakefulness. It has been demonstrated that features of sleep patterns, such as sleep duration, excessive sleepiness, early awakening or late falling asleep, are characterized by a high degree of hereditary predisposition, and external stressors are more likely to induce the development of sleep disorders in individuals with a genetic predisposition. To date, genes involved in neurotransmission have been identified; signaling pathways that are involved in the processes of sleep and wakefulness; regulation of the circadian rhythm of the body's physiological activity. Genome-wide association studies (GWAS) have made it possible to establish associations of numerous single nucleotide variants (SNVs) of various genes with the risk of developing sleep disorders. According to the results of transcriptional research, sleep is accompanied by significant changes in the expression level of many genes, as well as the activity of metabolism and the functioning of all physiological systems of the body. Tissue cells with a high level of metabolism, in particular the brain, have a special need for the restorative effect of sleep. It has been demonstrated that the synaptic scaling of neuronal networks is directly proportional to the duration and quality of sleep.

GWAS studies have identified a number of genes whose mutations are highly associated with human body weight. One of the groups of obesogenic genes is the centriolar protein gene (POC5) [6; 7]. It has also been demonstrated that single nucleotide variants (SNV) of the POC5 gene are associated with the risk of snoring. In particular, it was shown that SNV rs2307111 of the POC5 gene is associated with a high probability of developing

snoring, as a cardinal feature of OSAS [8; 9].

To date, the contribution of SNV genes to the development of OSAS in children with obesity is practically unknown. Therefore, the aim of this study was to determine the contribution of single nucleotide variants of genes associated with the risk of obstructive sleep apnea syndrome in children with obesity.

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 (meeting minutes No. 18 of April 18, 2024).

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

Inclusion criteria: children with polygenic obesity (BMI≥95th percentiles) 14-18 years old. Exclusion criteria: children with monogenic and/or syndromic obesity, pregnancy.

52 children with obesity aged 14-18 years were examined. The first group (n=31) was represented by children with metabolically unhealthy obesity (MUO). The second group (n=21) consolidated of children with metabolically healthy obesity (MHO). All children underwent a general clinical, immunobiochemical examination (Synevo, Ukraine). The criteria for the inclusion of children in the group of MUO were the recommendations of the IDEFICS consortium (Identification and prevention of Dietary and lifestyle-induced health effects in children and infants Study).

Screening for the high risk of developing obstructive sleep apnea syndrome was carried out according to the Berlin questionnaire [10].

Using the method of complete genome sequencing (CeGat, Germany), 52 children aged 14-18 years with obesity were examined. 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 [11]. 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 [12] ABRA, version 2.18 and Genotype Harmonizer 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 [13].

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

To describe quantitative characteristics with a normal distribution, the arithmetic mean with an error of the mean value (M±m) was used. In the course of the research, the mathematical apparatus for testing statistical hypotheses was used using variational analysis, ROC analysis. The basis for testing statistical hypotheses was the so-called feature conjugation tables. Only statistically significant results ($p<0.05$) were taken into account.

RESULTS AND ITS DISCUSSION

A high risk of OSAS was noted in 48.39% (±8.98%) of children with MUO and in 19.05% (±8.78%) of children with MHO, $p<0.05$. Student's t-test value: 2.34. Differences are statistically significant ($p<0.05$). The number of degrees of freedom f=50. The critical value of the Student's t-criterion=2.009, at the level of significance α=0.05.

As a result of the testing of statistical hypotheses based on the conjugation table of traits from 743 SNVs of 86 candidate genes studied, the greatest association with a high risk of OSAS in MUO was found for the SNV of the POC5 gene. Among obese children, 10 SNV POC5 were identified (rs17563610, rs17563686, rs17649248, rs17672542, rs2047059, rs2307111, rs34678567, rs35130836, rs35898774, rs888788). CC SNV rs2307111 genotype of the POC5 gene was significantly more common in patients with MHO and no OSAS risk ($p<0.02$). In the absence of nucleotide substitution SNV rs2307111 gene POC5 <1.0 - the probability of forming MUO with obstructive sleep apnea syndrome increases by 5 times (95% CI 1.22 - 20.48), p=0.025.

Based on the results of GWAS and analysis of data from the UK Biobank, Adrián I Campos and colleagues in 2020 identified 42 genomic loci (containing 120 genes) associated with snoring. It was shown that SNVs rs10878269, rs11018488, rs11409890, rs12119849, rs12429765, rs13251292, rs145367119, rs17060460, rs17151229, rs180107, rs202110996, rs2049045, rs2207944, rs227727, rs2307111, rs2664299, rs34732995, rs34811474, rs4744369, rs4976269, rs4987719, rs57222984, rs592333, rs59502288, rs6054427, rs6099273, rs61597598, rs725861, rs74936745, rs773118143, rs7829639, rs796856741, rs80093081, rs8069947, rs8108822, rs947612, rs9583546, rs9900496 are associated with the risk of snoring. It was found that SNV of the genes DLEU7, MSRB3, POC5, which are expressed in the brain, cerebellum, legges, blood and intestines, are most significantly associated with the development of snoring.

Peng Zhou et al. [14] found that SNVs in the POC5 gene are associated with both increased body mass index and an increased risk of developing OSAS. Centriolar protein, the gene for which is located on chromosome 5q13.3 [15], is an estrogen-dependent protein that is involved in cell cycle progression and in the elongation of

centrioles, which are cellular microtubular structures located at the poles of the cell division spindle [16]. POC5-mediated development of adiposopathy is likely associated with disorders of cell division or cilia formation; and the occurrence of snoring may be associated with disturbances in the transmission of the signal associated with the estrogen-related receptor-α (ERR-α) [17; 18].

CONCLUSIONS

TT SNV rs2307111 genotype of the POC5 gene is highly associated with the presence of MUO and the development of OSAS in children.

Conflict of Interest: The authors declare that they have no conflict of interest.

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