21th WCIRDC

ASSOCIATIONS OF SINGLE NUCLEOTIDE VARIANTS OF THE *FTO* GENE WITH METABOLIC DISORDERS IN CHILDREN WITH OBESITY

Aleksandr Abaturov MD, DSc , Professor;

Anna Nikulina MD, PhD;

Dmytro Nikulin

Dnipro State Medical University, Ukraine

Background:

According to World Health Organization (WHO) experts worldwide by 2030 more than 1 billion people will be obese. Obesity induces the development of metabolic disorders, which significantly worsen the state of health and can cause premature death. Overweight and obesity are thought to cause 2.8 million deaths each year. A significant contribution to the development of obesity, especially in children, is brought by genetic factors. One of the genes associated with the development of obesity has been identified as a gene associated with fat mass and obesity (fat mass and obesity-associated - *FTO*).

The human *FTO* gene is located on the long arm of chromosome 16 (16q12.2), consists of 9 exons and 8 introns, and encodes RNA demethylase, 2-oxoglutarate (2-OG) Fe(II)-dependent dioxygenase of the AlkB family.

At the same time, associations of single nucleotide variants (SNV) *FTO* with metabolic disorders in obese children remain virtually unexplored.

Objective:

study of associations of SNV of the *FTO* gene with the development of metabolic disorders in children with obesity.

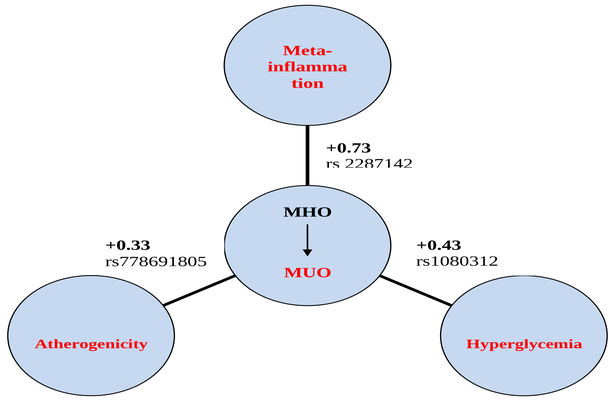

Figure 1. Correlation pleiad of associations of SNVs of the *FTO* gene with the development of metabolic disorders in children with obesity.

Table 1. Characteristics of SNV types of the FTO gene

SNV	Position	GnomAD_maxPOP	Ref	Alt	Consequence	Base Change	CADD	RawScore	Clinical significance (ClinVar)
rs1080312*	53745367	AFR	G	A	intronic	c.45+7226G>A	7.84	0.35	not reported
rs2287142	53945351	EAS	G	A	synonymous	c.60G>A	0.14	-0.44	not reported
rs17823223	53999638	NFE	C	T	intronic	c.230+31617C>T	1.88	-0.05	not reported
rs542356043*	54013348	NFE	G	A	intronic	c.1364+45327G>A	8.63	0.42	not reported
rs778691805*	53859781	NFE	G	T	missense	c.129G>T	17.32	1.68	not reported

Comment: GnomAD_maxPOP – the frequency distribution of *FTO* mutations. AFR, EAS, NFE represent African, East Asian, 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.1 - interpretation for DNA coding sequence). This column is empty if the variant is intergenic; CADD – combined annotation dependent depletion; *- SNV FTO associated with high levels of CADD.

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.

Bioinformatic analysis – demultiplexing of the sequencing reads was performed with Illumina bcl2fastq (version 2.20). Adapters were trimmed with Skewer, version 0.2.2.37 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.

Results

The association with the development of obesity is higher for the A allele rs2287142 (t=2.29) and the T allele SNV rs17823223 (t=6.34) than in healthy individuals (Fig. 1, Table 1). Serum IL-6 level in MHO depends on SNV rs2287142 (r=0.73). Allele A of SNV rs1080312 is associated with basal hyperglycemia (r=0.43) and impaired carbohydrate tolerance (r=0.33), but negatively correlates with low serum cholesterol, low-density lipoprotein cholesterol (LDL-C): r= -0.42, r = -0.39, respectively. The T allele of SNV rs778691805 is associated with a high level of LDL-C in blood serum (r=0.33). The T allele of SNV rs17823223 is negatively associated with basal hyperglycemia (r=-0.51) and directly correlates with high-density lipoprotein cholesterol (r=0.33), $p<0.05$.

Conclusion

In children with obesity, SNV rs2287142 is associated with pro-inflammatory status, and SNV rs1080312, rs17823223, rs778691805 of the *FTO* gene is associated with metabolic markers.

Funding

The work is a fragment of the research work of the Dnipro State Medical University "Prediction of the development of childhood diseases associated with civilization" (No. 0120U101324) financed by the Ministry of Health of Ukraine from the state budget.

Authors' contributions

AA was responsible for the idea and study design, looked over the articles, extracted the data, and interpreted bioinformatics analysis data. DN provided the collection of biological material using dried blood spot shipping kit, AN analyzed the data and interpreted it. Both authors reviewed the paper and approved the final manuscript.

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

Contact

Aleksandr Abaturov, Dnipro State Medical University, Street 9, V. Vernadskogo, 49044, Dnipro, Ukraine, Honored Worker of Science and Technology of Ukraine, MD, Professor, Head of Department of Pediatrics 1 and Medical Genetics, E-mail: alexandrabaturov56@gmail.com. ORCID iD http://orcid.org/ 0000-0001-6291-5386

Anna Nikulina, Dnipro State Medical University", Street 9, V. Vernadskogo, 49044, Dnipro, Ukraine, PhD, Assistant professor of Department of Pediatrics 1 and Medical Genetics, E-mail: anna.nikulina.201381@gmail.com. ORCID iD http://orcid.org/0000-0002-8617-9341. Tel. +380677399385.

***Corresponding author:** Dmytro Nikulin, Dnipro State Medical University, Street 9, V. Vernadskogo, 49044, Dnipro, Ukraine, 5rd year student of the Medical Faculty, E-mail: dn0327481@gmail.com. Tel. +380935809945.

References

1. *Azzam SK, Alsafar H, Sajini AA. FTO m6A Demethylase in Obesity and Cancer: Implications and Underlying Molecular Mechanisms. Int J Mol Sci. 2022 Mar 30;23(7):3800. doi: 10.3390/ijms23073800. .*
2. *Abaturov A, Nikulina A. The role of vitamin D in metabolically unhealthy obesity in children. Child's health. 2023; 18(2):29-35. doi.org/10.22141/2224-0551.18.2.2023.1568.*
3. *Yılmaz B, Gezmen Karadağ M. The current review of adolescent obesity: the role of genetic factors. J Pediatr Endocrinol Metab. 2020 Nov 16;34(2):151-162. doi: 10.1515/jpem-2020-0480.*
4. *Speakman JR. The Fat Mass and Obesity Related' (FTO) gene: Mechanisms of Impact on Obesity and Energy Balance. Curr Obes Rep. 2015 Mar;4(1):73-91. doi: 10.1007/s13679-015-0143-1.*
5. *Lan N, Lu Y, Zhang Y, et al. FTO - A Common Genetic Basis for Obesity and Cancer. Front Genet. 2020 Nov 16;11:559138. doi: 10.3389/fgene.2020.559138.*
6. *Mauer J, Jaffrey SR. FTO, m6 Am , and the hypothesis of reversible epitranscriptomic mRNA modifications. FEBS Lett. 2018 Jun;592(12):2012-2022. doi: 10.1002/1873-3468.13092.*
7. *Yin D, Li Y, Liao X, et al. FTO: a critical role in obesity and obesity-related diseases. Br J Nutr. 2023 Mar 21:1-8. doi: 10.1017/S0007114523000764.*