21th WCIRDC
CONTRIBUTION OF SNV *GLP1R* IN DISEASOME OF METABOLICALLY UNHEALTHY OBESITY

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Background:

Obesity significantly increases the risk of developing diseases such as type 2 diabetes mellitus, metabolically associated fatty liver disease, arterial hypertension, myocardial infarction, stroke, osteoarthritis, obstructive sleep apnea and some types of cancer, thereby contributing to a decrease in both quality and life expectancy. Dysfunction of the glucagon-like peptide 1 (GLP-1)/GLP-1 receptor (*GLP-1R*) axis promotes obesity and metabolic disorders. It has now been demonstrated that among the various molecular systems involved in the regulation of energy balance and eating behavior, the glucagon-like peptide-1 (GLP-1) and GLP-1 receptor (GLP-1R) axis plays one of the key roles. Dysfunction of the GLP-1/GLP-1R axis contributes to the development of obesity and metabolic disorders.

A gastrointestinal GLP-1 peptide that, in response to direct food stimulation, is released from intestinal enteroendocrine cells and excites GLP-1R, which is expressed by various body cells. The *GLP1R* gene (HGNC:4324) is located on the short arm of chromosome 6 (6p21). A decrease in the level of GLP-1 reception, which is caused by single nucleotide variants (SNV) of the *GLP1R* gene, can induce the development of obesity and metabolic disorders.

However, the study of associations with MUO was carried out only for some SNV of the *GLP1R* gene.

Objective:

study the associations of the SNV *GLP1R* gene with pro-inflammatory cytokines and metabolic disorders in children with various obesity phenotypes.

Comment (Table 1). 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: first nucleotide of the translation start codon of the coding DNA reference sequence). This column is empty if the variant is intergenic; CADD – combined annotation dependent depletion; *- SNV *GLP1R* associated with MUO.

Table 1. Characteristics of SNV types of the GLP1R gene

SNV	Position	Variant name and GRCh38 reference sequence file identifier (HGVS)	GnomAD _maxPOP	Ref	Alt	Consequence	Base Change	CADD	RawScore	Clinical significanse (ClinVar)
rs6918287	39033602	6:39065826A>G (NM_002062.5: c.399A>G)	EAS	A	G	synonymous	c.399A>G	9.35	0.49	not reported
rs6923761	39034072	6:39066296G>A (NM_002062.5: c.502G>A	NFE	G	A	missense	c.502G>A	**16.12**	1.47	not reported
rs761386	39046871	6:39079095C>T (NM_002062.5: c.955-17C>T)	AMR	C	T	intronic	c.955-17C>T	4.32	0.10	not reported
rs1042044*	39041502	6:39073726A>C (NM_002062.5: c.526A>C)	AMR	A	C	missense	c.526A>C	**14.9**	1.25	not reported
rs1126476*	39048491	6:39080715A>C (NM_002062.5: c.1200A>C)	AMR	A	C	synonymous	c.1200A>C	**11.53**	0.75	not reported
rs2235868*	39040654	6:39072878A>C (NM_002062.5: c.526A>C)	AMR	A	C	synonymous	c.526A>C	**12.35**	0.85	not reported
rs3765468	39033593	6:39065817G>A (NM_002062.5: c.390G>A)	EAS	G	A	synonymous	c.390G>A	8.41	0.40	not reported
rs61754624*	39034071	6:39066295C>T (NM_002062.5: c.501C>T)	AMR	C	T	synonymous	c.501C>T	0.11	-0.47	likely benign
rs10305420	39016636	6:39048860C>T (NM_002062.5:c.20C>T)	NFE	C	T	missense	c.20C>T	**13.38**	0.99	not reported
rs10305421	39016675	6:39048899G>A (NM_002062.5: c.59G>A)	NFE	G	A	missense	c.59G>A	**22.5**	2.49	not reported
rs10305457*	39034095	6:39066319C>T (NM_002062.5: c.509+16C>T)	AMR	C	T	intronic	c.509+16C>T	0.43	-0.28	not reported
rs10305492	39046794	6:39079018G>A (NM_002062.5: c.946G>A)	NFE	G	A	missense	c.946G>A	**25**	3.51	not reported
rs10305493	39046931	6:39079155C>G (NM_002062.5: c.998C>G)	OTH	C	G	missense	c.998C>G	**26.1**	3.77	not reported
rs1472308929	39033978	6:39066202C>T (NM_002062.5: c.408C>T)	NFE	C	T	synonymous	c.408C>T	9.32	0.49	not reported

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

An association with the development of obesity was noted for T alleles rs61754624 (t=3.33) and rs10305457 (t=2.06); with MUO - for C alleles rs1042044 (t=2.23), rs1126476 (t=2.63), rs2235868 (t=2.82); T alleles rs61754624 (t=3.33), rs10305457 (t=2.06) *GLP1R*, p<0.05. In the MHO group, a correlation was found with the levels of pro-inflammatory markers IL-1β, IL-6 in the presence of the GA genotype SNV rs3765468; with hyperglycemia - GA genotype SNV rs6923761, CC genotype SNV rs1042044, AA rs6918287; hyperinsulinemia - GA genotype SNV rs3765468, GG rs10305421; triglyceridemia - AA rs6918287 of *GLP1R* (Table 1).

Conclusion

SNV rs1042044, rs3765468, rs6923761, rs6918287, and rs10305421 *GLP1R* are associated with the development of MUO in individuals with MHO.

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, AH, DD 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.

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