THE 6TH ANNUAL HEART IN DIABETES
SINGLE NUCLEOTIDE VARIANTS OF THE *MCM6* GENE AS A RISK FACTOR FOR METABOLICALLY UNHEALTHY OBESITY IN CHILDREN


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Background:

Lactose maldigestion associated with lactase non-persistence is a trigger for persistent meta-inflammation in metabolically unhealthy obesity (MUO), including arterial hypertension, atherogenic-type dyslipidemia, and insulin resistance.

Recently, more and more data has been accumulating, indicating that it is single nucleotide gene variants (SNV) that make an important contribution to phenotypic differences between people, including personal characteristics in the development of compensatory reactions, and also determine the predisposition to the occurrence of a number of chronic diseases.

Objective:

to study the contribution of single nucleotide variants (SNV) of the gene Minichromosome maintenance complex component 6 (*MCM6*) to the development of MUO in children.

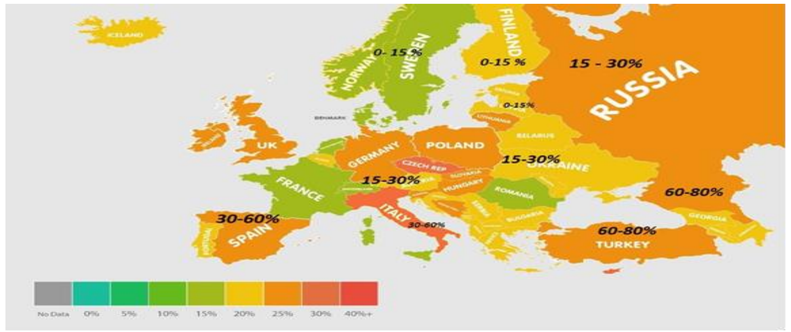

Figure 1. The prevalence of gene-associated lactase non-persistence *MCM6*

Table 1. The ratio of the chances of the influence of the studied risk factors on the development of MUO

The studied sign	OR	95% CI	*p*
The age of the child at the time of examination is from 12 to 17 years	6.00	2.51 - 14.37	***<0.001***
Pathological course of pregnancy in the mother	3.23	1.35 - 7.68	***0.008***
Presence of excess weight at an early age	2.58	1.08 - 6.19	***0.034***
Term of introduction of supplementary food from 0 to 4 months	16.21	0.9 - 291.34	*0.059*
History of pneumonia	6.67	1.81 - 24.5	***0.004***
Transferred chickenpox in the anamnesis	3.79	1.71 - 8.39	***0.001***
Hereditary burden of metabolic syndrome	11.61	3.67 - 36.7	***<0.001***
The average duration of eating from 20 minutes	0.11	0.04 - 0.29	***<0.001***
Serving volume from 1 to 2 palms	0.45	0.08 - 2.59	*0.374*
Prevalence in fast food	2.36	1.09 - 5.08	***0.029***
Daily consumption of up to 2-3 servings of fresh fruits and vegetables	0.20	0.07 - 0.55	***0.002***
Daily consumption of red meat, sausages, potatoes, rice, margarine, sweet drinks	10.95	4.31 - 27.86	***<0.001***
Multiplicity of physical activity - only in physical education classes	1.96	0.83 - 4.65	*0.127*
Non-academic computer/TV time is more than 3 hours	6.87	2.91 - 16.24	***<0.001***
The presence of clinical symptoms of hypolactasia	3.24	1.48 - 7.1	***0.003***
The level of physical development of the child is more than 67.34 percentiles	3.12	1.39 - 7	***0.006***
The presence of acne vulgaris	5.34	1.66 - 17.16	***0.005***
Violation of age norms of initiation of puberty	5.88	2.16 - 15.99	***0.001***
Genotype of the *LCT/MCM6* C/C - 13910 gene	10.75	4.37 - 26.44	***<0.001***
The level of basal insulinemia from 18.36 µOd/ml	93.85	5.51 - 159.54	***0.002***

Materials and methods

152 obese children aged 6-18 years were genotyped for the LCT/MCM6 genes (RT-PCR, Synevo, Ukraine). The main group (n=77) according to the IDEFICS 2014 recommendations was represented by children with MUO. The control group (n=75) consolidated of children with metabolically obesity (MHO).

Additionally, whole genome sequencing (NGS, CeGat, Germany) was performed in 27 children of the main and 15 children of the control group.

To recognize the functional effects of SNV LCT/MCM6 in the development of MUO, nominal data analysis was used - odds ratio (OR), 95% confidence interval (CI), Pearson's correlation coefficients (C), normalized Pearson's coefficient (C'), Cramer's test (V) and linear regression models (r), where p-values less than 0.05 were considered statistically significant. Statistical processing of the results was performed using Microsoft Excel (Office Home Business 2KB4Y-6H9DB-BM47K-749PV-PG3KT) and STATISTICA 6.1 software (StatSoftInc, no. AGAR909E415822FA).

Results

Among obese children, 11 *MCM6* SNVs were identified (rs61752701, rs141448886, rs201537325, rs2289049, rs3087353, rs1057031, rs143348934, rs3087348, rs4988270, rs2070068), Table 1, 2.

The frequency of MUO (r=0.22; p=0.020) and extreme obesity (r=0.22; p=0.022) was higher in children with the "wild" genotype *MCM6*-13910 and was respectively OR 80.0; 95% CI 66.96 - 88.76 and OR 54.0%; 95% CI 40.4 - 67.03, compared with with carriers of mutant genotypes (r=-0,37; p<0,001), Fig. 1. OR at MUO to detect SNV *MCM6* G/A rs105703 - 2.6 95% CI 0.65-10.

Table 2. Characterization of the SNV MCM6 in Obesity Phenotypes in Children

№	Position	n	GnomAD _maxPOP	dbSNP (SNV)	Ref/Alt	Zygosity	Consequence	CADD	RawScore
1	136598550	1	SAS	rs141917101	T/C	HET	intronic	5.239	0.160458
2	136624155	1	AFR	rs2070068	G/A	HET	intronic	7.639	0.333665
3	136602196	1	NFE	rs4988270	G/A	HET	synonymous	8.453	0.405136
4	136624314	1	EAS	rs3087348	A/C	HET	intronic	8.066	0.370008
5	136605608	1	AMR	rs143348934	G/A	HET	intronic	9.362	0.495651
6	**136633962**	**18**	**SAS**	**rs1057031***	**G/A**	**HET/HOM**	**5_prime_UTR**	**9.898**	**0.554078**
7	136623717	1	EAS	rs3087353	C/T	HET	synonymous	11.55	0.749133
8	136624123	1	AFR	rs2289049	G/A	HET	intronic	13.66	1.034057
9	136633927	1	AMR	rs201537325	G/A	HET	synonymous	14.01	1.090330
10	136620315	2	NFE	rs141448886	T/C	HET	missense	23.3	2.866344
11	136627912	1	OTH	rs61752701	G/A	HET	missense	32	4.570014

Conclusion

The greatest contribution to the development of MUO in children is made by the G/A rs1057031 genotype out of 11 SNV *MCM6* diagnosed by us.

A direct correlation between SNV MCM6 G/A rs1057031 (V=0.143; C=0.142; C'=0.201) and MUO risk was moderate (p<0.05).

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.

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