

## GENETIC FACTORS IN OBESITY

The rapidly increasing prevalence of obesity in the population in recent decades is an important public health issue because it increases the risk of diabetes, heart disease, stroke and other serious diseases. Its causes include excessive consumption of high-calorie foods, as well as a sedentary lifestyle. It has been proven that, in addition to energy imbalance, 40–70% of the development of obesity is influenced by hereditary factors. As a rule, obesity results from the interaction of certain gene polymorphisms with the environment. Only a small number of cases of obesity are the result of the presence of mutations in certain genes (monogenic obesity), causing Mendelian syndromes with a very low frequency in the population. This review describes the genetic causes of obesity, including syndromal, monogenic and polygenic causes.

**Keywords:** Obesity, genes, polymorphisms.

**Introduction.** Obesity is a source of chronic energy imbalance in a person who constantly receives more carbohydrates from food than is necessary to fuel the metabolic and physical functions of the body. The rapidly growing prevalence of obesity is characterized by free access to a high-calorie product and a simultaneous decrease in physical activity. Also, as a result of the severe acute respiratory syndrome 2 (SARS-CoV-2) pandemic, which causes a new coronavirus disease COVID-19, quarantine restrictions were introduced around the world [2], which caused changes in lifestyle, diet, as well as the occurrence of hypodynamia, which in turn led to the occurrence of energy consumption and the incidence of obesity [27]. Various studies show that minor changes in body weight over relatively long periods of time increase body weight and eventually approach a significant increase in body weight [18; 40]. If current reserves are maintained, 1 billion adults (nearly 20% of the world's population) are expected to be obese by 2025. Of particular concern is the global rise in obesity among children and adolescents; more than 7% were obese in 2016 compared to less than 1% in 1975 [49].

In recent years, the prevalence of obesity in Asian countries has been steadily increasing due to unbalanced diet and lack of exercise. The Asian type of obesity is different and is characterized by high body fat and low skeletal muscle mass. At the same time, there is excessive ac-

cumulation of fat in the abdomen and liver (non-alcoholic fatty liver disease), which is associated with an increased cardiometabolic risk [6].

In the Russian Federation, the share of the population belonging to the Mongoloid race and of Mongolo-Caucasoid mixed origin is about 9%. If the majority of the population of the European part of Russia belongs to the Caucasoid race, then in the Asian part of the country the proportion of representatives of the Mongoloid race increases significantly. Representatives of various Asian ethnic groups live on the territory of the Russian Federation, such as the Yakuts and Buryats, representing the two largest Siberian ethnic groups.

In recent years, the Republic of Sakha (Yakutia) has seen an increase in the prevalence of obesity, which is associated with the loss of traditional methods of managing and the transition of the indigenous population from the usual protein-lipid type of nutrition to the carbohydrate-lipid type [13]. Sofronova S.I. and co-authors conducted a study to determine the prevalence of overweight and obesity among representatives of the indigenous population of Yakutia (Evenks, Dolgans, Evenks, Yukaghirs, Chukchis, Yakuts) living in the northern uluses. 37.8% of Yakuts are overweight, they found that obesity is more common in men. A strong relationship has been found between BMI and systolic blood pressure. Yakuts and Evenks had higher mean systolic blood pressure than other ethnic groups [11]. Marinova L.G. et al. studied children living in Yakutsk and found a high prevalence of first-degree obesity, mostly in boys. Abdominal obesity was observed in 86% of children. One case of metabolic syndrome has been reported. In the work done, there is no information about the ethnicity of the children participating in the study [5].

Obesity is associated with premature mortality and is a major public health threat, accounting for a significant portion

of the burden of noncommunicable diseases worldwide. Diabetes mellitus, dyslipidemia, hypertension, non-alcoholic fatty liver disease, cardiovascular disease, cancer [10;12] and severe COVID-19 are more common as the main risk factor for a large number of serious complications in obese people, which lead to higher adult mortality rates.

It has been proven that, in addition to energy imbalance, 40–70% of the development of obesity is influenced by hereditary factors [9]. As a consequence, genetic approaches can be used to characterize the underlying physiological and molecular mechanisms that control body weight. Since 2007, genome-wide association studies (GWAS) have identified about 250 genes associated with obesity [47].

### Monogenic and syndromic obesity.

There are about 30 Mendelian disorders with obesity as a clinical feature, often in association with mental retardation, dysmorphic features, and organ-specific developmental anomalies (eg, pleiotropic syndromes) [41]. Monogenic obesity is inherited according to the Mendelian type and, as a rule, rare, early and severe. Mutations in the genes of leptin (*LEP*), leptin receptor (*LEPR*), type 4 melanocortin receptors (*MC4R*), proopiomelanocortin (*POMC*), prohormone convertase 1 (*PCSK1*), brain-derived neurotrophic factor (*BDNF*), and type tyrosine kinase receptor lead to the development of monogenic obesity. 2 (*NTRK2*), the *SIM1* gene, and the Ras suppressor kinase type 2 gene (*KSR2*). Mutations in these genes impair appetite control and lead to hyperphagia, which ultimately leads to obesity [7]. Defects in the *MC4R* gene are the most common known monogenic form of childhood obesity, accounting for about 6% of cases of monogenic obesity.

Syndromic obesity is when obesity occurs in the clinical context of a particular set of associated clinical phenotypes. This is obesity caused by chromosomal rearrangements such as Prader-Willi

syndrome, WAGR syndrome, SIM1 syndrome and pleiotropic syndromes, including Bardet-Biedl syndrome, Fragile X syndrome, Cohen syndrome, etc. [47]. Children with syndromal obesity have extreme obesity, physical dysmorphism, and mental retardation, some of them with indeterminate neuroendocrine abnormalities. It is the latter anomaly that is thought to be responsible for adverse effects on the function of the hypothalamus, which serves as the brain center of appetite that regulates energy balance through food intake and energy expenditure, as a result, children with syndromal obesity are usually characterized by severe hyperphagia and a decrease in satiety, which contributes to weight gain [45].

**Polygenic obesity.** The most common form of obesity is polygenic obesity. A number of obesity-prone gene loci have been identified in various populations using the GWAS approach. The GWAS approach helps to identify common SNPs that contribute to a relatively low risk (measured by odds ratio [OR]<1.5) of the growth of complex diseases and phenotypes, including phenotypes associated with obesity, such as diabetes and hypertension [42].

One of the first obesity genes detected by GWAS in European patients with type 2 diabetes is the *FTO* gene. The researchers identified important SNPs in the first intron of *FTO* that were associated with obesity. These initial screenings were carried out in 2007 among the European population [14; 23;48], and then confirmed in other populations, including Hispanics [46], East Asians [32], Africans [21] of the Middle East [20; 26]. Previously, we also confirmed the association of this gene with obesity in the Yakut population [1; 28]. The *FTO* gene is involved in the regulation of the diet, encodes a protein involved in energy metabolism and affecting metabolism in general [4]. According to the results of the studies, allele A of the *FTO* gene is associated with reduced lipolysis, lack of satiety after an adequate meal, and impaired appetite control. The phenotypic manifestation of the A allele of the *FTO* gene is overweight, obesity due to overeating.

The *PPAR* family genes are mediated through specific receptors called *PPARs*, which belong to the steroid hormone receptor superfamily. *PPARs* affect the expression of target genes involved in cell proliferation, cell differentiation, as well as in immune and inflammatory responses [38]. Three closely related subtypes (alpha, beta/delta and gamma) have been identified. *PPAR* proteins are able to bind to various ligands, including

fatty acids, drugs (fibrates, thiazolidinediones) [43]. Members of the *PPAR* family have distinct tissue distribution patterns and tissue-specific functions. *PPAR-α* is predominantly present in the liver, where it plays an important role in the regulation of nutrient metabolism by stimulating the uptake and oxidation of fatty acids. *PPAR-γ* is mainly expressed in adipose tissue. It is induced during adipocyte differentiation and is a regulator of fat cell formation and lipid accumulation. *PPAR-δ* is abundantly expressed throughout the body and is thought to be involved in adipogenesis and energy metabolism [22].

*PPARα* is activated by various natural agonists, including unsaturated fatty acids and eicosanoids, while fibrate preparations act as synthetic agonists. In the liver, *PPARα* plays a key role in fatty acid catabolism by upregulating numerous genes involved in mitochondrial fatty acid oxidation, peroxisomal fatty acid oxidation, and many other aspects of cellular fatty acid metabolism [30]. Regulates the expression of genes encoding enzymes and transport proteins that control lipid homeostasis, which ultimately leads to stimulation of FA oxidation and improved lipoprotein metabolism [19]. This gene may be specifically involved in the lipolytic process and in weight loss induced by an exercise program [35].

The *PPARG2* protein is abundant in fat cells and plays a key role in their formation. The main function of this protein is the activation of genes associated with fat accumulation, differentiation of adipose tissue cells and myoblasts. It stimulates the differentiation of adipose tissue resident preadipocytes into adipocytes and promotes the mobilization of circulating bone marrow progenitor cells into white adipose tissue and their subsequent differentiation into adipocytes [29]. It plays an important role in the formation of the sensitivity of various tissues to insulin. It is the *PPARG2* gene that determines lipid metabolism [36]. The *PPARG* gene counteracts obesity-induced inflammation by controlling the inflammatory response either by downregulating pro-inflammatory genes or by influencing lipid metabolism. The ability to reduce inflammatory cell infiltration further highlights the central role of *PPARG* in obesity-induced inflammation. During the inflammation process, *PPARG* can direct cells to adipocyte differentiation, which leads to the maintenance of inflammation genes in a suppressed state in adipose tissue in obesity [31].

The function of *PPARD* is to regulate genes associated with fat accumulation (triglyceride synthesis), differentiation

of adipocytes (fat cells) and myoblasts, insulin sensitivity, osteoblast and osteoclast activity (growth regulation) [37]. Also, *PPARD* is directly related to the development of obesity, is involved in wound healing, cell growth, and lipoprotein metabolism. Participates in the control of peroxisome proliferation, which are responsible for fatty acid oxidation and energy metabolism, is expressed in many tissues and organs. By stimulating fatty acid oxidation, *PPAR β/δ* activation results in fat mass loss in various mouse models of obesity [33]. In addition to enhancing fatty acid oxidation, *PPAR β/δ* activation in muscle also increases the number of type I muscle fibers, leading to increased endurance [39].

The intestinal fatty acid binding protein *FABP2* binds saturated and unsaturated long-chain fatty acids and is involved in the synthesis of triglyceride-rich lipoproteins [44]. The affinity of *FABP2* for long chain fatty acids is doubled when the Ala54Thr polymorphism is present in the *FABP2* gene. Ala54Thr polymorphism increases triglyceride (TG) secretion and free fatty acid transport in vitro [34]. In a study by Baier L.J. et al. (1996) found that this polymorphism affects lipid transport and secretion. They suggest that individuals expressing the Thr54 genotype process more long-chain fatty acids into chylomicron triglycerides than individuals with the Ala54 genotype. Either or both of these processes will result in a decrease in the rate of insulin-mediated glucose uptake and an increase in the rate of insulin release from pancreatic β-cells, consistent with the observed insulin resistance and hyperinsulinemia found in subjects with the Thr54 genotype [17].

The leptin receptor (*LEPR*) gene, which secretes a single transmembrane cytokine protein located on chromosome 1p31, plays a critical role in the regulation of body weight by stimulating energy expenditure and inhibiting food intake. Mutations in the *LEPR* gene are associated with monogenic forms of severe early obesity and hyperphagia. Numerous studies in various populations have confirmed the association of Q223R (rs1137101) polymorphism with obesity rates [15; 16; 50].

The Q223R polymorphism reduces leptin binding and thus impairs leptin signaling, thus playing an important role in the pathogenesis of obesity through its direct effects on lipid and glucose metabolism, adipose tissue metabolism, body fat control, and cardiovascular function.

Increased appetite is the driving force behind weight gain. A large amount of literature data indicates that changes in

the hormone ghrelin play an important role in fluctuations in appetite after eating [24; 25]. Ghrelin is the gut hormone with the strongest orexigenic signal that helps the body respond to changes in metabolic status by binding to growth hormone secretion-stimulating receptors (GHSR) [3]. It is synthesized predominantly in the stomach and is found in the bloodstream of healthy individuals. The minor allele 178C>A of the polymorphic *GHRL* gene is associated with obesity, the effect occurs due to an increase in the level of ghrelin, forming an early feeling of hunger [8].

**Conclusion.** Considering the genetic causes and understanding the growing evidence of epigenetic changes influencing the growing epidemic of obesity provide valuable tools in the treatment of obesity. The ability to identify individuals at high risk could facilitate targeted obesity prevention strategies with increased impact and cost-effectiveness.

## Reference

1. Pavlova N.I. [et al.] Associatsiya polimorfizma rs9939609 gena FTO s razvitiem ozhireniya v populatsii yakutov [Association of polymorphism rs9939609 of the FTO gene with the development of obesity in the Yakut population]. *Sovremennye problemy nauki i obrazovaniya* [Modern problems of science and education. 2018; 5 (In Russ.).] DOI:10.17513/spno.28020]
2. Vsemirnaya organizatsiya zdoravohraneniya. VOZ ob'yavlyayet vspyshku COVID-19 pandemii. 2020 g. [Elektronnyy resurs] / Vsemirnaya organizatsiya zdoravohraneniya [World Health Organization. Coronavirus disease (COVID-19) pandemic [Electronic resource] (In Russ.).] <https://www.who.int/europe/emergencies/situations/covid-19>
3. Artemenko Yu. S. [et al.] Geneticheskie markery ozhireniya i svyazannyh s nim reproduktivnyh oslozhenij: sovremennoe sostoyanie problema [Genetic markers of obesity and related reproductive complications: current state of the problem]. *Akusherstvo i ginekologiya: Novosti. Mneniya. Obucheniya* [Obstetrics and Gynecology : News. Opinions. Learning. 2021; 3 (9): 48-55 (In Russ.).] <https://doi.org/10.33029/2303-9698-2021-9-3suppl-48-55>
4. Kochetova O.V., Viktorova T.V. Genetika i epigenetika ozhireniya [Genetics and epigenetics of obesity]. *Uspekhi sovremennoy biologii* [Advances in modern biology. 2015; 2: 128-138 (In Russ.).]
5. Marinova L.G., Savvina N.V., Savvina I.L. Ozhirenie u detej YAKUTII: social'no-gigienicheskie aspekty i klinicheskaya karakteristika [Obesity in children of Yakutia: social and hygienic aspects and clinical characteristics]. *YAKUTSKIY MEDITSINSKIY zhurnal* [Yakut medical journal. 2015; 3 (51): 51-53 (In Russ.).]
6. Dedov I.I. [et al.] Mezhdisciplinarnye klinicheskie rekomendatsii «Lechenie ozhireniya i komorbidnyh zabolevanij» [Interdisciplinary clinical guidelines "Treatment of obesity and comorbid diseases"]. *Ozhirenie i metabolism* [Obesity and metabolism. 2021; 1 (18): 5-99 (In Russ.).] <https://doi.org/10.14341/omet12714>
7. Mikhaleva O. G., Bardymova T. P., Berezina M. V. Monogennye formy ozhireniya [Monogenic forms of obesity]. *Sibirskiy meditsinskiy zhurnal* [Siberian Medical Journal. 2014; 6 (129): 5-11 (In Russ.).]
8. Lifshits G.I. [et al.] Nekotorye molekulyarno-geneticheskie mekhanizmy formirovaniya ozhireniya i metabolicheskogo sindroma [Some molecular genetic mechanisms of the formation of obesity and metabolic syndrome]. *Farmakogenetika i farmakogenomika* [Pharmacogenetics and pharmacogenomics. 2017; 1:5-9 (In Russ.).]
9. Dedov I.I. [et al.] Ozhirenie [Obesity]. *Consilium Medicum*. 2021; 4 (23): 311-325 (In Russ.).] <https://doi.org/10.26442/20751753.2021.4.200832>
10. Berishvili A.I. [et al.] Ozhirenie i rak molochnoj zhelezy [Obesity and breast cancer]. *Opuholi zhenskoy reproduktivnoy sistemy* [Tumors of the female reproductive system. 2022; 3(18): 40-51 (In Russ.).] <https://doi.org/10.17650/1994-4098-2022-18-3-40-51>
11. Sofronova S.I. [et al.] Ocenka izbytochnoy massy tela i ozhireniya u korennoy naseleniya na severe YAKUTII v zavisimosti ot etnicheskoy prinadlezhnosti [Evaluation of overweight and obesity among the indigenous population in the north of Yakutia, depending on ethnicity]. *Yakut medical journal*. 2019; 2 (66): 76-79 DOI 10.25789/YMJ.2019.66.23]
12. Statsenko M.E. [et al.] Rol' giperurikemii v razvitiy nealkogol'noy zhirovoj bolezni pečeni [The role of hyperuricemia in the development of non-alcoholic fatty liver disease]. *Vestnik Volgogradskogo gosudarstvennogo meditsinskogo universiteta* [Bulletin of Volgogradsky state medical university. 2022; 2 (19): 33-42 (In Russ.).] doi: 10.19163/1994-9480-2022-19-2-33-42]
13. Sevostyanova E.V. Osobennosti lipidnogo i uglevodnogo metabolizma cheloveka na Severe (literaturny obzor) [Peculiarities of lipid and carbohydrate metabolism in humans in the North (literature review)]. *Byulleten' sibirskoy medicine* [Bulletin of Siberian Medicine. 2013; 1 (12): 93-100 (In Russ.).]
14. Frayling, T.M.; Timpson, N.J.; Weedon, M.N.; Zeggini, E.; Freathy, R.M.; Lindgren, C.M.; Perry, J.R.; Elliott, K.S.; Lango, H.; Rayner, N.W.; et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007; 316: 889-894. doi: 10.1126/science.1141634.
15. Bender N, Allemann N, Marek D, Vollenweider P, Waeber G, Mooser V, Egger M, Bochud M. Association between variants of the leptin receptor gene (LEPR) and overweight: a systematic review and an analysis of the CoLaus study. *PLoS One*. 2011; 6(10): e26157. DOI: 10.1371/journal.pone.0026157
16. Illangasekera YA, Kumarasiri PVR, Fernando DJ, Dalton CF. Association of the leptin receptor Q223R (rs1137101) polymorphism with obesity measures in Sri Lankans. *BMC Res Notes*. 2020; 13(1): 34. doi: 10.1186/s13104-020-4898-4.
17. Baier LJ, Bogardus C, Sacchettini JC. A Polymorphism in the human intestinal fatty acid binding protein alters fatty acid transport across Caco-2 cells. *J Biol Chem*. 1996; 271(18): 10892-10896. DOI: 10.1074/jbc.271.18.10892
18. Bhutani S., Cooper J. A., Vandellen M.R. Self-reported changes in energy balance behaviors during COVID-19 related home confinement: A Cross-Sectional Study. *American Journal of Health Behavior*. 2021; 45(4): 756-770. DOI: 10.5993/AJHB.45.4.14
19. Lawrence JW, Li Y, Chen S, DeLuca JG, Berger JP, Umbenhauer DR, Moller DE, Zhou G. Differential gene regulation in human versus rodent hepatocytes by peroxisome proliferator-activated receptor (PPAR)  $\alpha$ . PPAR $\alpha$  fails to induce peroxisome proliferation-associated genes in human cells independently of the level of receptor expression. *Journal of Biological Chemistry*. 2001; 276(34): 31521-31527. doi: 10.1074/jbc.M103306200.
20. Khan S.M., Chehadeh S.E.H., Abdulrahman M., Osman W., Al Safar H. Establishing a genetic link between FTO and VDR gene polymorphisms and obesity in the Emirati population. *BMC Med. Genet*. 2018; 19: 11. doi: 10.1186/s12881-018-0522-z.
21. Adeyemo A, Chen G, Zhou J, Shriner D, Doumatey A, Huang H, Rotimi C. FTO genetic variation and association with obesity in West Africans and African Americans. *Diabetes*. 2010; 59(6): 1549-54. DOI: 10.2337/db09-1252
22. Wagener A., Goessling H.F., Schmitt A.O., Mauer S., Gruber A. D., Reinhardt R., Brockmann G. A. Genetic and diet effects on Ppar- $\alpha$  and Ppar- $\gamma$  signaling pathways in the Berlin Fat Mouse Inbred line with genetic predisposition for obesity. *Lipids Health Dis*. 2010; 9: 99 <https://doi.org/10.1186/1476-511X-9-99>
23. Scuteri A., Sanna S., Chen W.-M., Uda M., Albai G., Strait J., Najjar S., Nagaraja R., Orrù M., Usala G., et al. Genome-Wide Association Scan Shows Genetic Variants in the FTO Gene Are Associated with Obesity-Related Traits. *PLoS Genet*. 2007; 3: e115. doi: 10.1371/journal.pgen.0030115.
24. Makris MC, Alexandrou A, Papatsoutsos EG, Maltz G, Tsilimigras DI, Guerron AD, Morris D. Ghrelin and Obesity: Identifying Gaps and Dispelling Myths. A Reappraisal. *In Vivo*. 2017; 31(6): 1047-1050. doi: 10.21873/in vivo.11168.
25. Wren A.M., Seal L.J., Cohen M.A., Brynes A.E., Frost G.S., Murphy K.G., Dhillo W.S., Ghatei M.A., Bloom S.R. Ghrelin enhances appetite and increases food intake in humans *J Clin Endocrinol Metab*. 2001;86(12): 5992. doi: 10.1210/jcem.86.12.8111.
26. Chehadeh S.E.H., Osman W., Nazar S., Jerman L., Alghafri A., et al. Implication of genetic variants in overweight and obesity susceptibility among the young Arab population of the United Arab Emirates. *Gene*. 2020; 739: 144509. DOI: 10.1016/j.gene.2020.144509
27. Daniel M.M., Liboredo J.C., Anastácio L.R., Souza T.C.M., Oliveira L.A., Della Lucia C.M., Ferreira L.G. Incidence and Associated Factors of Weight Gain During the Covid-19 Pandemic. *Frontiers in Nutrition*. *Front Nutr*. 2022; 9: 818632. doi: 10.3389/fnut.2022.818632.
28. Pavlova N. I., Kurtanov Kh. A., Diakonova A. T., Solovyeva N. A., Sydykova L. A., Aleksandrova T. N., Solovyeva Y. A. Interrelation of the FTO rs9939609 SNP and the DAT1 rs27072 SNP with Body Mass Index and Degree of Obesity in the Population of Yakutsk. *International Journal of Biomedicine*. 2019; 9(3): 210-215. DOI: 10.21103/Article9(3)\_OA4
29. Lauterbach M.A.R., Wunderlich F.T. Macrophage function obesity-induced inflammation and insulin resistance. *Pflugers Arch. Eur. J. Physiol*. 2017; 469: 385-396 doi: 10.1007/s00424-017-1955-5.
30. Mandard S, Müller M, Kersten S. Peroxisome proliferator-activated receptor  $\alpha$  target genes. *Cellular and Molecular Life Sciences*. 2004; 61(4): 393-416. doi: 10.1007/s00018-003-3216-3.
31. Gao Z., Xu X., Li Y., Sun K., Yang M., Zhang Q., Wang S., Lin Y., Lou L., Wu A., Liu W., Nie B. Mechanistic insight into PPAR $\alpha$  and Tregs in atherosclerotic immune inflammation. *Front. Pharmacol*. 2021; 12. Article 750078. doi: 10.3389/fphar.2021.750078.
32. Wen W., Cho Y.-S., Zheng W., Dorajoo R.,

Kato N., Qi L., Chen C.-H., Delahanty R.J., Oka-da Y. Meta-analysis identifies common variants associated with body mass index in east Asians. *Nat. Genet.* 2012; 44: 307–311 doi: 10.1038/ng.1087.

33. Wang Y-X, Lee C-H, Tiep S, et al. Peroxisome-proliferator-activated receptor  $\delta$  activates fat metabolism to prevent obesity. *Cell.* 2003; 113(2): 159–170. doi: 10.1016/s0092-8674(03)00269-1.

34. Garcés Da Silva MF, Guarín YA, Carrero Y, Stekman H, Núñez Bello ML, Hernández C, Apitz R, Fernández-Mestre M, Camejo G. Postprandial Hypertriglyceridemia Is Associated with the Variant 54 Threonine FABP2 Gene. *Journal of Cardiovascular Development and Disease.* 2018; 5(3): P.47. doi: 10.3390/jcdd5030047.

35. Cardoso G. A., Ribeiro M. D., Sousa B. R. V., de Oliveira Y., Sena K.F., Batista J.R. E., Almeida A.E. M., Filho J.M., Silva R. S. B., Persuhn D.C., Silva A. S. PPAR $\alpha$  Gene Is Involved in Body Composition Variation in Response to an Aerobic Training Program in Overweight/Obese. *PPAR Research.* 2021; Article ID 8880042: 9. doi: 10.1155/2021/8880042

36. Darwish N. M., Gouda W., Almutairi S.M., Elshikh M.S., Morcos G.N.B. PPARG expression patterns and correlations in obesity. *Journal of King Saud University – Science.* 2022; 34 (6): 102116

37. Stienstra R, Duval C, Müller M, Kersten S. PPARs, Obesity, and Inflammation. *PPAR Res.* 2007; 95974. doi: 10.1155/2007/95974.

38. Bocher V, Pineda-Torra I, Fruchart J-C, Staels B. PPARs: transcription factors controlling lipid and lipoprotein metabolism. *Annals of the New York Academy of Sciences.* 2002; 967: 7–18. DOI: 10.1111/j.1749-6632.2002.tb04258.x

39. Wang Y-X, Zhang C-L, Yu RT, et al. Regulation of muscle fiber type and running endurance by PPAR $\delta$ . *PLoS Biology.* 2004; 2(10): e294. doi: 10.1371/journal.pbio.0020294

40. Schoeller D.A. The effect of holiday weight gain on body weight. *Physiol Behav.* 2014; 134: 66–69. doi: 10.1016/j.physbeh.2014.03.018.

41. Shawky R. M., Sadik D. I. Genetics of obesity. *Egyptian Journal of Medical Human Genetics.* 2012; 13(1): 11–17 <https://doi.org/10.1016/j.ejmhg.2011.08.005>

42. Singh R. K., Kumar P., Mahalingam K. Molecular genetics of human obesity: A comprehensive review. *Comptes Rendus Biologies.* 2017; 340 (2): 87–108. doi: 10.1016/j.crv.2016.11.007.

43. Smith SA. Peroxisomal proliferate-activated receptors and the regulation of lipid oxidation and adipogenesis/ *Biochemical Society Transactions.* 1997; 25(4): 1242–1248. doi: 10.1042/bst0251242.

44. Switala K, Leonska-Duniec A. Physical activity and gene association with human obesity // *Balt J Health Phys Act.* 2021. № 13(4). P. 99–111. doi: 10.29359/BJHPA.13.4.10

45. Garver W.S., Newman S.B., Gonzales-Pacheco D.M. et al. The genetics of childhood obesity and interaction with dietary macronutrients. *Genes Nutr.* 2013; 8:

271–287. doi: 10.1007/s12263-013-0339-5.

46. Villalobos-Comparán M., Flores-Dorantes M.T., Molina T.V., Rodríguez-Cruz M., Ulloa A.C.G., Robles L., Huertas-Vázquez A., Saucedo-Villarreal N., López-Alarcón M., Sánchez-Muñoz F., et al. The FTO Gene Is Associated with Adulthood Obesity in the Mexican Population. *Obesity.* 2008; 16: 2296–2301. doi: 10.1038/oby.2008.367.

47. Tirthani E, Said MS, Rehman A. *Genetics and Obesity.* StatPearls Publishing. 2022. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK573068/>

48. Dina C., Meyre D., Gallina S., Durand E., Körner A., Jacobson P., Carlsson L.M.S., Kiess W., Vatin V., Lecoer C., et al. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat. Genet.* 2007; 39(6): 724–6. doi: 10.1038/ng2048.

49. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults / *NCD Risk Factor Collaboration (NCD-RisC).* *Lancet.* 2017; 390 (10113): 2627–2642. doi: 10.1016/S0140-6736(17)32129-3

50. Yiannakouris N. The Q223R polymorphism of the leptin receptor gene is significantly associated with obesity and predicts a small percentage of body weight and body composition variability. *J Clin Endocrinol Metab.* 2010; 86(9): 4434–9 doi: 10.1210/jcem.86.9.7842.

DOI 10.25789/YMJ.2023.82.25

УДК 571.27+612.821.2+612.821.5

## A.A.Gulyaev, K.A. Drobyaskina, I.A. Sinyakin, T.A. Batalova NEUROINFLAMMATION AND BRAIN FUNCTION: POSSIBLE IMPLICATIONS IN CHILDREN INFECTED WITH COVID-19

**GULYAEV Artem Alexandrovich** – 6 year-course student of the Amur State Medical Academy, 610 group, Medical Faculty, Blagoveshchensk, Amur State Medical Academy of the Ministry of Health of Russia, e-mail: Superstar533129@gmail.com; **DROBYASKINA Ksenia Anatolyevna** – 3 year-course student of the Amur State Medical Academy, 321 group, Pediatric Faculty, Blagoveshchensk, Amur State Medical Academy, e-mail: drobyaskinak@gmail.com; **SINYAKIN Ivan Alekseevich** – 5 year-course student of the Amur State Medical Academy, 505 group, Medical Faculty, assistant-researcher of the Laboratory of mechanisms of etiopathogenesis and restorative processes of the respiratory system in non-specific lung diseases of the Far Eastern Scientific Center of Physiology and Pathology of Respiration, Blagoveshchensk, the Amur State Medical Academy, e-mail: sinyakin.ivan2016@yandex.ru; **BATALOVA Tatyana Anatolyevna** – Professor, Doctor of Biological Sciences, Head. Department of Physiology and Pathophysiology of the Amur State Medical Academy, Blagoveshchensk, Amur State Medical Academy, e-mail: batalova\_ta@mail.ru.

COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affects children differently than adults, with milder symptoms. However, several cases of neurological manifestations with neuroinflammatory syndromes, such as multisystem inflammatory syndrome (MIS-C), have been reported following infection. As with other viral infections such as rubella, influenza, and cytomegalovirus, SARS-CoV-2 causes a massive release of pro-inflammatory cytokines that affect microglial function, which can be critical for brain development. Along with viral induction of neuroinflammation, other non-infectious conditions may interact to cause additional inflammation, such as imbalances in fatty acid and polyunsaturated fatty acid diets and alcohol consumption during pregnancy. In addition, transient thyrotoxicosis caused by SARS-CoV-2 has been reported, with secondary autoimmune hypothyroidism that may go unnoticed during pregnancy. Together, these factors may represent an additional risk of infection by influencing neurodevelopmental mechanisms such as synaptic pruning and the formation of neuronal ensembles. In this review, we discuss these conditions to consider and the possible occurrence of neurodevelopmental disorders in children infected with COVID-19.

**Keywords:** neuroinflammation, children, COVID-19, synapse formation, brain development, nutrition.

**Introduction.** COVID-19 is a systemic disease caused by severe acute respiratory syndrome coronavirus 2, which belongs to the betacoronavirus genus [3]. The most common neurological symptoms in response to SARS-CoV-2 infection include: headache, anosmia, impaired consciousness, infectious encephalopathies, and neuroinflammatory syndromes such as acute demyelinating

encephalomyelitis [1]. A biomarker study (NfL, intraaxonal marker of neuronal injury; glial fibrillar acidic protein; GFAP, marker of astrocytic activation/damage) also provided evidence of neuronal damage and glial cell activation in patients with COVID-19 [39], strongly suggesting that SARS-CoV-2 has neurotropic activity. In addition, SARS-CoV-2 has been shown to be able to infect human neu-