MOLECULAR GENETIC STUDIES IN THE CONTEXT OF BIOMEDICAL RISKS FOR COSMONAUTS' HEALTH

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Today, genetic studies yield quite a large amount of information about a person, which, in many cases, allows predicting the risks of certain diseases. This gives grounds to believe that such testing can also be applied in the field of manned spaceflights in order to identify candidates best adapted to specific risks. The article examines publications on genetic polymorphisms and their effects on the carrier phenotype, namely, on such manifestations that are of interest in the context of risks arising during long-term space flights. Specific genes are listed and examples of allelic variants are given. Publications describing new molecular methods of monitoring human health are also considered, biomarkers that can be used for research in the interests of regular examination of active astronauts are identified.

Keywords: genetic predisposition, molecular markers, long-term spaceflight risks, cosmonaut selection

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МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКОЕ ТЕСТИРОВАНИЕ В КОНТЕКСТЕ МЕДИКО-БИОЛОГИЧЕСКИХ РИСКОВ ЗДОРОВЬЮ КОСМОНАВТОВ

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Генетические исследования сегодня позволяют получить достаточно большое количество информации о человеке, на основе которой иногда возможно прогнозировать риски возникновения определенных заболеваний. Это дает основания полагать, что подобное тестирование можно применять и в области пилотируемых космических полетов с целью выявления кандидатов, наиболее приспособленных к специфическим рискам. В статье рассмотрены публикации, посвященные генетическим полиморфизмам и их влиянию на фенотип носителя, а именно на проявления, представляющие интерес в контексте рисков, возникающих во время длительных космических полетов. Перечислены конкретные гены и приведены примеры аллельных вариантов. Уделено также внимание публикациям, описывающим новые молекулярные методы наблюдения за здоровьем человека, определены биомаркеры, которые могут быть использованы для исследований в интересах регулярного обследования действующих космонавтов.

Ключевые слова: генетическая предрасположенность, молекулярные маркёры, риски длительных космических полетов, отбор космонавтов

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With the recent advancements in laboratory diagnostic methods, it is now possible to perform genome-wide DNA sequencing with subsequent analysis of the sequences fairly quickly. Theoretically, knowledge of how each of the alleles in the genotype affects phenotype, individually and in combination with other alleles, allows predicting many important parameters, adaptability to given conditions, predisposition to various diseases, as well as body's response to given influences. It is interesting to investigate applicability of the genetic analysis as the source of data used in the process of selection of candidates best fit for the conditions of spaceflight and least exposed to the risks arising from the associated factors, since such people may have significantly extended professional longevity. However, today, there is only a limited number of alleles with known role in the formation of the phenotype, therefore, it is virtually impossible to obtain complete data that would exhaustively describe characteristics of the body. Still, the amount of available information allows selecting alleles that presumably secure advantages in the context of resistance to the classified and other factors of spaceflight. In addition, there are genes for which the effect of allelic variants on the phenotype has not yet been uncovered. Given that this information may become important in the future, this matter can be addressed additionally. We have also reviewed papers describing molecular studies that we recommend conducting before, during, and after the flight, since they provide the most complete information about both health of the cosmonaut and the specific processes occurring in his body.

Studying allelic variants of genes, we decided to divide them into groups depending on how the considered polymorphisms can mitigate or aggravate risks peculiar to long-term spaceflights. For this purpose, we looked into both Russian and foreign sources, with references to the latter mainly collected while analyzing all the risk evidence documents published to the NASA's Human Research Program (HRP NASA) website. As a result, some of the articles are more

than 10 years old, yet, the authors considered it necessary to include them in the review. We have also relied on additional literature and eventually identified genes whose variations can affect susceptibility of future cosmonauts to factors associated with spaceflight factors, and, consequently, their professional longevity.

Genetic polymorphisms in the context of risks associated with long-term spaceflights

In the context of assessment and mitigation of the risks of development of adverse cognitive or behavioral conditions and mental disorders during spaceflight, there have been identified polymorphisms in the circadian CLOCK and NPAS2 genes, which were shown to trigger sleep disorders [1, 2], one of the factors promoting depression. A significant polymorphism was found in 5-HTTLPR, serotonin-transporter-linked promoter region. Individuals with S-allele have been shown to run a higher risk of depression stemming from routine difficulties and obstacles [3]. Allelic variations in the genes of some ionotropic channels, such as AMPA3 (Gria3 glutamate receptor, ionotropic) or P2RX7 (ATP-dependent selective calcium channel), may increase the risk of appearance of suicidal thoughts against the background of antidepressants; they also aggravate depression accordingly [4, 5]. It was also found that, with a certain haplotype, the methylenetetrahydrofolate reductase gene involved in folic acid metabolism can positively correlate with depressive states [6].

In terms of the risk of productivity and health deterioration as a result of lack of sleep, circadian disorders and overwork, the most common were polymorphisms of circadian genes, such as CLOCK, NPAS2 and PERIOD3, in which certain variations may be associated with sleep disorders and, as in the case of PERIOD3, promote differential neurobehavioral vulnerability to acute total sleep deprivation [7–10]. It was found that catechol-O-methyltransferase (COMT) enzyme, which modulates dopaminergic catabolism in the prefrontal cortex, grows three- to four-fold less active if the amino acid sequence contains Val158Met replacement, which translates into greater availability of dopamine at receptors and a higher concentration of cortical dopamine. This COMT polymorphism predicts less efficient functioning of the prefrontal cortex and poor performance of working memory in healthy subjects with a highly active Val allele [11]. Additionally, in people with a Met/Met genotype the markers of homeostatic sleep pressure decrease more rapidly. With chronic partial sleep deprivation in the background, all genotypes demonstrated a comparable pace of cognitive performance deterioration and physiological drowsiness increase [9, 10]. Polymorphisms in the adenosine dezminase (ADA) gene, adenosine receptor (ADORA2A) gene, and human leukocyte antigen (DQB1) gene are associated with various disorders. The latter was found to condition narcolepsy, a sleep disorder characterized by excessive daytime sleepiness, fragmented sleep and shorter REM sleep delay. Individuals with DQB1*0602 polymorphism of the DQB1 gene suffer a sharper drop of homeostatic pressure during sleep; they are generally more drowsy and prone to fatigue. However, chronic partial sleep deprivation caused comparable decline of cognitive abilities and growth of physiological drowsiness in both carriers and non-carriers of this allele. As it turned out, the adenosine deaminase gene plays a part in alteration of duration of slow-wave sleep, contributing to the interindividual variability of the initial sleep level, and the adenosine receptor gene polymorphism is associated with objective and subjective differences in the effects of caffeine on sleep after acute total sleep deprivation [9, 10].

Regarding the assessment and mitigation of the risks associated with use of ineffective or toxic drugs during a long-term spaceflight, the crucially important factor is the metabolizer status, that is, the rate at which a given individual can metabolize a particular drug. Depending on this rate, such individual may need an abnormal dose of the drug, which can be both smaller and larger. Disregarding peculiarities of metabolism can up the risk of overdoses, or, on the contrary, prevent intake of the drug in the amount needed for it to produce the expected therapeutic effect. Metabolizer status depends on an array of allelic variants of genes that encode enzymes and carrier proteins involved in metabolism and drug clearance.

Enzymes of the cytochrome P450 superfamily play a key role in the metabolism of drugs; they are found in many tissues, but are most common in the liver. The main enzymes from this superfamily are the CYP2D6, CYP2C19, and CYP3A4 proteins. They are involved in processing of most medicines used today; for their genes, there have been identified dozens of alleles that can alter enzymatic kinetics, i.e., the rate of a chemical reaction resulting in either a breakdown or a modification of the drug molecules. Thus, the range of rates at which enzyme isoforms work can be very wide, from almost complete loss of activity to the so-called "ultrafast" variants [12–15].

First-aid kits in the US Orbital Segment of the International Space Station (ISS) contains two types of antidepressants, so the haplotypes conditioning the effects of these drugs have also been considered. The researchers found that some of the allelic variants in 5-HTTLPR and 5HTR6 are associated with a better response to antidepressants, while other, on the contrary, degrade drug tolerance [16, 17].

In the context of assessment and mitigation of the risks related to cardiovascular adaptations, previous studies have uncovered significant polymorphisms associated with various cardiovascular pathologies. Thus, C1561T polymorphism of the GCPII gene is an independent risk factor for coronary heart disease, which makes development of this condition 2.71 more likely, while C1420TT polymorphism of the cSHMT gene almost halves the respective risk [18]. Same group of researchers investigated the MTRR gene (encodes methionine synthase reductase), and found one of the allelic variants in the homozygous state to boost oxidative stress, which also increases the risk of coronary heart disease. The findings also included a genome-wide significant interaction of polymorphisms in the loci of the HCN4 and SLC28A1 genes that is associated with an increased risk of atrial fibrillation [19]. The risk of cardiovascular pathologies is also influenced by the level of low-density lipoprotein cholesterol, as well as the total cholesterol level. A group of researchers established that isoforms of ApoE, a protein involved in the metabolism of fat in mammalian organisms, are linked to fluctuations of the blood cholesterol levels, with the specific values thereof above or below the population average depending on the presence of certain alleles [20].

Regarding assessment and mitigation of the risks of spaceflight-associated intracranial pressure growth and neuro-ocular syndrome, there are noteworthy studies that consider higher blood concentrations of single-carbon metabolites (cysteine, etc.) detected in the astronauts that can develop the said syndrome. Based on the data, researchers assumed that variations in the genes of single-carbon metabolism may increase the susceptibility of astronauts to ophthalmological changes. Eventually, they have found that polymorphisms of the MTRR and SHMT1420 genes significantly condition the effect a prolonged mission to the ISS has on the visual analyzer [21]. Another study has shown that carriers of the MTHFR677TT

polymorphism are more likely to suffer from idiopathic internal hypertension [22].

Searching for genetic variants associated with the risk of radiation carcinogenesis, a team of researchers identified a mutation that occurs in 0.4% of the European population in a heterozygous variant. It is a mutation in the gene of a protein that mutated against the background of ataxia-telangiectasia (ATM, serine/threonine protein kinase, recruited and activated by double-strand breaks); this mutation significantly increases the incidence of breast cancer in women carrying heterozygous variant thereof. Compared to the general population, female carriers of the ATM mutation were also found to be at a somewhat higher risk of cancer in general [23]. Overall, the idea of searching for haplotypes that signal lower susceptibility to malignant tumors looks difficult to implement at the moment, since the nature of the respective diseases is complex and multifactorial. However, in the future, cosmonauts will be sent on long-term missions, those to Mars in the first place, which involve a significantly higher risk of malignant tumors than now. In this regard, the data on preferred haplotypes can be extremely useful, so it is worth continuing investigations of this subject matter.

In addition to those described above, there are also unclassified risks that should still be accounted for. For example, researchers have identified polymorphisms of the Hsp70 (heat shock protein) gene that can both protect the carrier from hearing loss caused by prolonged noise exposure and, on the contrary, increase his sensitivity to this environmental factor [24, 25]. Presumably, Hsp70 is released, inter alia, in response to loud sounds with the purpose of shielding hair cells in the inner ear from damage and subsequent death, but the exact mechanism of protection is still unknown. In addition to noise, space flights imply exposure to radiation; presumably, certain alleles of the apolipoprotein gene [26, 27], and the HLA-DRB1*11 allele of the major histocompatibility complex gene, can protect therefrom to some extent [28].

There are allelic variants of genes the effect of which on the risks associated with spaceflight are yet to be investigated, including various replacements in the catalase (CAT) gene sequence. The polymorphisms identified so far produced opposite effects in different populations, but it is certain that they condition hearing loss significantly [29]. It is also necessary to study genes in which polymorphisms can affect predisposition to sarcopenia, including ACE, ACTN3, MSTN, CNTF, VDR, IGF1 [30]. Finally, there is a link between certain haplotypes of various genes and the rate of progression of osteoporosis that should be looked into. Considering the number of genes involved, osteoporosis is an extremely complex disease [31], and the genetic variants or their combinations that would significantly decelerate the associated bone loss are yet to be identified. Currently, there is an expanding list of candidate genes that can be investigated in this connection [32].

Biomarkers enabling monitoring of a cosmonaut's physical condition indicators

Genotype-based screening of cosmonauts is not the only genetics-related issue in the considered field: there is also a demand for ways to monitor health of the cosmonauts with the aim at extending their professional longevity. The arguments below present biomarkers that, monitored, provide a more complete picture of the physical condition of cosmonauts.

Telomere studies

Presumably, the dynamics of telomere length is an informative biomarker showing the state of health of individuals, including cosmonauts, since it reflects the degree of influence of the factors they are exposed to in space. Individual genetic characteristics, nutritional, psychological, and physical stresses, unique environmental conditions (microgravity, cosmic radiation, altered atmosphere of the space station) — all these factors have an effect on a cosmonaut that can be registered by changes in the length of his telomeres.

Studies show that telomere length, which can be influenced by various lifestyle factors, may signal increased rate of aging and onset of age-related diseases, since it is negatively correlated with age. The expression of biomarkers of telomeric dysfunction and DNA damage, such as stathmin (regulates the dynamics of microtubules; disruptions of its operation may translate into uncontrolled assembly of mitotic spindles) and EF1-a (mediates accommodation of aminoacyl-TRNA into the ribosome), increases with age [33]. Long-term (over 5 years) follow-ups have shown that shorter telomeres mean significantly lower survival rate, which is conditioned by higher incidence of cardiovascular and infectious diseases [34]. DNA instability associated with telomere dysfunction (severe shortening) is an early oncogenesis event. Cancer patients were found to have significantly shorter telomeres compared to the control group [35]. In general, there are many factors that influence the length of the telomeres, gender, lifestyle specifics, diet, psychological load, chronic stress, and illnesses. Telomeres also reflect the effects of the environment on the body, with air pollution, ultraviolet and ionizing radiation having an effect on their length [36]; moreover, they are considered to be distinctive signs of radiosensitivity [37]. Telomeres are difficult to sequence with short reads because they are basically tandem repeats, but recent advancements allowed applying long-read sequencing to them, with results thereof showing telomere length and localization of non-canonical repeats [38].

A study that involved 11 astronauts has shown that, both before and after the spaceflight, their telomeres are shorter, and telomerase less active than in the control group (on Earth), but in the course of the space mission, the length of the telomeres increased significantly. The same study has also revealed a correlation between chronic oxidative stress (peculiar to spaceflight) and dynamics of telomere length, as well as a strong connection linking concentrations of inflammatory cytokines (interleukins, IL4, IL10, IL5, IL1a, IL2), chemokines (CCL5, CCL4, CXCL5), and VEGF-1 and telomere lengths before, during, and after the flight [39]. Throughout the year-long mission to the ISS, astronauts had high blood plasma concentration of VEGF-1, which may be associated with the increased expression of HIF-1a that participates in regulation and activation of hTERT, a human telomerase catalytic subunit [40], thus offering an explanation for longer telomeres during spaceflight.

Exosome studies

Exosomes are extracellular vesicles secreted by cells into the external intercellular space. They contain proteins, RNA, peptides and cell-free DNA. The amount of cell-free DNA (cfDNA) is a dynamic and highly responsive indicator that allows assessing the degree of DNA damage, tumor growth, regulatory changes in RNA, and immune response to infections [41].

cfDNA contain traces of nucleosomes, the nuclear architecture, gene structure, and expression of which yield information about their source tissue. In particular, positioning of nucleosomes may point to traces of transcription factors binding, promoter activity, and splicing, ultimately reporting about the processes of gene regulation in the tissue/cell of origin [42].

One study involved two monozygotic male twins, one of whom spent 340 days on the ISS while another stayed on Earth. The analysis of their cfDNA did not reveal a significant difference in the concentration and distribution of DNA length between brothers, and between them and the control group [41]. However, in the course of the study, the blood level of extracellular mitochondrial DNA was found to have been growing in the astronaut throughout the entire mission. The analysis of exosomes circulating in blood plasma also revealed a high content of ubiquitin-independent proteasome proteins in the spacefaring twin. In addition, the exosomes in his samples contained CD14, a proinflammatory monocyte marker, and basigin and integrin β1, which correlate with development of cancerous tumors and inflammation; the control samples in this study did not have these monocyte and proteins [43, 44]. Moreover, BAIAP2 (brain-specific angiogenesis inhibitor 1-associated protein 2) and BAIAP2L1 (brain-specific angiogenesis inhibitor 1-associated protein 2-like protein 1) were identified inside exosomes isolated from plasma samples of the astronaut twin, unlike control samples, which had more proteins associated with regulation of apoptosis and ATP biosynthesis. Three years after the flight, the researchers have registered a correlation between the content of 20S proteasomes and the concentration of exosomes in the astronaut's blood plasma. This protein is an important component of the oxidation-driven degradation mechanism; under oxidative stress, its amount may increase [45, 46]. In addition, a higher content of 20S proteasomes in the exosomal vesicles correlates with pathological processes, such as carcinogenesis, vascular damage, viral infections, and autoimmune diseases. The analysis of plasma exosomes isolated from the astronaut's samples upon his return to Earth revealed a drastically greater amount of circulating particles with untypical types of proteins in them. These changes are unique in comparison with the indicators describing the respective parameters of his twin and the control group of healthy individuals [41]. Since most of the exosomes circulating in plasma originate from immune cells, it is likely that this is a reflection of immune dysfunction associated with spaceflight and subsequent return to normal gravity. The researchers assume that presence of exosomes with brain-specific proteins in the peripheral blood may be the result of alterations in the state of the blood-brain barrier (tight contacts therein) caused by the spaceflight, a phenomenon earlier established for the intestinal epithelial cells [47].

Clonal hematopoiesis studies

Clonal hematopoiesis is faster growth of cells with certain mutations, which ups the risk of hematology and cardiovascular diseases. A study that involved twin astronauts found their blood to contain hematopoietic clones carrying mutations in the TET2 genes (catalyzes the conversion of methylcytosine to 5-hydroxymethylcytosine) and DNMT3A (an enzyme that catalyzes the transfer of methyl groups to CpG methylation sites in DNA) [48]. Both proteins are involved in epigenetic regulation; mutations in their genes often disrupt the amino acid sequence, and they accompany hematological cancers [49]. Such mutations usually occur in old age, while in the astronauts examined they were detected two decades earlier than expected. The factors causing early mutations are not known for certain, but they probably stem from the known working conditions on the ISS and associated with spaceflight. Throughout the mission, one of the twin astronauts exhibited signs of vascular remodeling of the carotid artery, which is a fact deserving a special note. He had a mutation in TET2, which also creates a significant risk of cardiovascular diseases. Thus, monitoring of clonal hematopoiesis, along with other parameters, can be included in the comprehensive assessment of the health status of cosmonauts.

Investigation of the effect of spaceflight on the critically important physiological systems of cosmonauts

Of course, for a more complete molecular examination of cosmonauts, it is necessary to consider as many informative markers as possible, thus assessing the state of all bodily systems. A good illustration of the value of such approach is the case of search for the molecules that reflect the state of the cardiovascular system. This search returned detection of higher concentration of S100A9 (neutrophil myeloid protein, important for the regulation of proinflammatory reactions and immune response) in cosmonauts, and this protein is a new predictor of myocardial infarction in patients with acute coronary syndrome. An increased plasma level of the S100A8/9 heterodimer indicates a higher risk of cardiovascular diseases, and it has also been shown that expression of S100A8/9 grows in human atherosclerotic arteries. It is assumed that the S100A9 protein signals damage to the vascular monolayer endothelial cells and induction of proinflammatory reactions in those cells, which are also confirmed when proteins associated with vascular damage and protecting the endothelium are found in blood plasma [50, 51].

Investigations of the effect of spaceflight on the immune system reveal a high degree of variability of the respective indicators, which points to individual predispositions to this or that immunity alteration triggered in space. However, it was reliably established that spaceflight causes the ratio of IFNu/IL10 to decrease; this ratio affects Th1 and Th2 cells, therefore, its disruption can lead to suppression of the immune response. Also, after the mission, cosmonauts had elevated blood concentration of HSP70, a protein massively expressed upon exposure to various stress factors and capable of protecting monocyte-granulocyte cells [52, 53].

Investigation of bone remodeling in cosmonauts revealed that the subjects most sensitive to microgravity have more TRAP than normal in their blood and less OPG therein. These markers allow conclusions about the degree of bone resorption: TRAP reflects the activity of osteoclasts, and OPG is the inhibitor of osteoclastogenesis [54].

Molecular markers associated with damage to the central nervous system (CNS) are also very interesting. A study [55] has shown the effect of radiation exposure on secretion of neurotrophins, composition of cerebrospinal fluid, and metabolism of microRNAs that play a major regulatory role in the nervous system. MicroRNAs can also be found in exosomes secreted by astrocytes, which is important for the CNS's in the intercellular interactions [55].

CONCLUSION

Summarizing the above, we believe it is necessary to note that the above list of molecular genetic markers is not complete, since investigations of the subject matter continue. However, this list considers the most important and well-studied sections of the genome that correlate with human predispositions to certain diseases associated with spaceflight, as well as other biological markers that, monitored, can underpin a more detailed assessment of the cosmonauts' health. Of course, future will bring new data, and the list will have to be expanded. Perhaps, someday, it will be possible to identify haplotypes best fit for space missions, and consequently consider improvement of

the candidate selection process. The given recommendations are primarily aimed at increasing professional longevity of cosmonauts, and there will be more of them. It should be noted that studying these issues is important as part of the Russian space exploration strategy and concept, which involve creation of technological capacities needed for interplanetary flights to Mars and asteroids. Development of the system/means of assessment and mitigation of medical risks faced by crews is integral to this effort. The value of such research increases dramatically in the context of manned deep space expeditions that, compared to low-orbit missions, imply longer exposure to the factors of spaceflight, which have a more intense effect. Thus, the importance of studying the subject matter considered in this work will grow exponentially in the future, therefore, the basis for the respective research activities should be laid in the present time.

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