

Genetic basis of hemodynamic response to controlled physical activity assessment in the elderly

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Abstract:

Examining the genetic basis for hemodynamic responses to controlled physical activity in the elderly holds both scientific and practical significance within the realm of physical culture and sports, thereby expanding avenues for further investigation. The primary objective of this study was to assess the correlation between polymorphisms in select metabolic genes and the hemodynamic parameters of elderly individuals, both at rest and following controlled physical activity. The research involved 99 participants aged between 60 and 67, regularly engaging in physical training within a sports and recreation complex. During the initial phase, blood samples were collected from all subjects to analyze polymorphisms in four genes: synaptotagmin (SYT 10, rs6488162), branched-chain amino acid transaminase 1 gene (BCAT 1, rs4963772), a gene responsible for a protein interacting with alpha-synuclein (SNCAIP, rs4836027), and the ubiquinone oxidoreductase A11 subunit gene (NDUFA11, rs12974440). The study of gene polymorphisms was carried out by real-time polymerase chain reaction. At the second stage, all subjects were tested using the six-minute walking technique at the maximum pace. The distance covered was recorded in meters. Before and immediately after the stress testing, the heart rate and the level of systolic and diastolic blood pressure were recorded by noninvasive tonometry. Based on these hemodynamic parameters, the predominant nature of the autonomic nervous system response to dosed physical activity was evaluated. **Results.** As a result of the research, we found that polymorphisms of metabolic profile genes play an essential role in human body functional response formation. On the one hand, some genotypes of the genes ST 10, BCAT1, SNCAIP and DUFA 11 are involved in determining the nature of the autonomic response to physical activity in the elderly people. On the other hand, the relationship of polymorphisms of most of these genes with both indicators of systemic hemodynamics in a calm state and their dynamics after performing stress testing in the form of a six-minute walk has been established. **Conclusions.** The established peculiarities of genetic determination and hemodynamic response at rest and after dosed physical activity expand the field of knowledge of this issue. The results obtained can be used in other scientific research in the field of physical culture and sports.

Key Words: physical activity, genetic polymorphisms, cardiovascular system, stress testing

Introduction

The current trend of the world's population aging makes it necessary to actively promote physical activity and a healthy lifestyle in the strategy of improving the life quality of elderly people (Björ et al., 2019; Adamakis, 2021). Along with physical activity, the role of the genetic factor in determining a person's biological age, the duration and quality of his/her life, as well as in the aging rates formation is indisputable (Rutten-Jacobs et al., 2018; Prysiazniuk et al., 2018). It should be noted that there are significant differences in the abilities of specific elderly people to play sports. Researchers have established different levels of their physical endurance and speed-strength characteristics (De Almeida et al., 2022; Martusevich et al., 2023). When a person performs physical training, the leading role is assigned to the state of hemodynamic parameters of the cardiovascular system (Lacombe et al., 2019; Shinichiro Morishita et al., 2021). With age, a person has a deterioration in the hemodynamic characteristics of the cardiovascular system associated with unfavorable age-related changes in the heart muscle and arterial vessels. It reduces the reserve capacity of the cardiorespiratory system and significantly complicates the performance of physical activity by elderly people. In some cases, it can lead to negative health consequences when doing physical exercise or sports.

The revealed significant differences in the indicators of elderly people's physical fitness are interrelated with a variety of genetic determinants. These include the regulation of cellular metabolism, the enzyme profile of an individual, polymorphisms of endurance genes (Jeffries et al., 2014).

It remains unclear which genes can directly or indirectly participate in physical activity performance. The most likely are genes affecting the processes of neuromuscular mobility, the state of muscle mass, the processes of vagotonia and sympathotonia. In particular, the relationship of metabolism with the effectiveness of physical activity characterizes the state of transaminase genes of branched-chain amino acids BCAT site (Lynch et al., 2015). Experimental data indicate that a violation of transamination of branched chain amino acids in mice causes a violation of malate/aspartate metabolism. It leads to a decrease in certain amino acids formation, as well as an increase in the ratio of lactate and pyruvate, ammonia in skeletal muscles, which affects the mechanism of physical performance regulation.

It is known that the polymorphism of the ACE I/D gene is largely associated with the level of a person's physical activity (Yoshihara et al., 2009). A significant contribution to the formation and maintenance of physical performance has been established for genetic polymorphisms of endothelial NO synthase (Teixeira et al., 2016) and aldehyde dehydrogenase (DeAlmeida et al., 2022). Moreover, these effects are mainly observed in women. It indicates the need for mandatory consideration of the gene polymorphism peculiarities in women. At the same time, the role of polymorphism of genes encoding receptor structures remains controversial. In particular, A. Bjor et al. (2019) found no coupling of physical activity and expression of the vitamin D receptor in elderly people. However, a study by Colovati et al., (2020), demonstrated the association of polymorphism of the Apo lipoprotein E gene with physical performance in people over 60 years of age. In the context of the regulatory systems coupling (neuro-immuno-endocrine regulation circuits) during physical training, it is of interest to consider the genetic determination of interleukin synthesis, in particular, the alpha-actin isoform 3 gene (Romero-Blanco et al., 2021) in maintaining an individual's physical performance.

In general, it should be concluded that the genetic determinacy of physical performance in elderly people is currently shown by functional indicators. However, the role of polymorphisms of genes encoding age-dependent metabolism is not fully disclosed. In particular, the impact of genetic determination on the hemodynamics of elderly people has not been fully studied. We believe that studying this issue will make it possible to make adjustments to personalized physical activity for the elderly. It will ensure an effective increase in the duration and quality of life.

Research aim. To evaluate some metabolic genes polymorphisms relationship with hemodynamic parameters of elderly people's body at rest and after dosed physical activity.

Materials & Methods

The research involved 99 people aged 60-67 inclusive. The ratio of men and women was 33:66, respectively. All the surveyed were engaged in regular physical training for at least 6 months in the conditions of the Sport and Recreation Complex of the city of Chelyabinsk, Russia. All persons who participated in the experiment were included in the research on the basis of medical documentation provided to the doctor of the Sports and Recreation Complex. The condition for inclusion in the examination was the absence of severe chronic pathology, as well as the mandatory signing of informed consent. The research was approved in 2022 by the Local Ethics Committee of the National Research University.

At the first stage, blood samples were obtained from all subjects to study polymorphisms of 4 genes:

- *the synaptotagmin gene* (SYT 10, rs6488162), which encodes membrane proteins in the membranes of synapses. It is assumed that this gene is involved in the processes of phospholipid binding and syntaxin;

- *branched chain amino acid transaminase 1 gene* (BCAT 1, rs4963772) having cytosolic and mitochondrial forms. It is assumed that the expression of the gene in question is associated with parameters characterizing the pumping function of the heart, in particular, heart rate, as well as recovery processes (Lynch et al., 2015);

- *a gene encoding a protein interacting with alpha-synuclein* (SNCAIP, rs4836027). The product of this gene can play a significant role in neurodegenerative processes, including in Alzheimer's disease. It is assumed that polymorphisms of this gene have an effect on sympathetic stimulation of the heart muscle and, consequently, on the heart rate and its dynamics during exercise (Jeffries et al., 2014);

- *ubiquinone oxidoreductase A11 subunit gene* (NDUFA11, rs12974440) encoding a subunit of membrane-bound mitochondrial complex I. On this basis, it affects energy metabolism, and complex I deficiency is the most common defect of the respiratory chain, clinically manifested by severe neonatal lactic acidosis, various combinations of neurological, cardiac, hepatic and renal disorders (encephalopathy, cardiomyopathy, some forms of Parkinson's disease (Peverelli et al., 2019). There are data in the literature on the potential association of polymorphisms of this gene with heart rate variability (Knapp-Wilson et al., 2021).

The study of gene polymorphisms was carried out by real-time polymerase chain reaction.

At the second stage, all subjects were tested using the six-minute walking technique (Nezhkina et al., 2022). The motor test included continuous walking at the maximum pace for 6 minutes. In case of feeling serious discomfort, the test was immediately interrupted. The distance covered by each participant of the

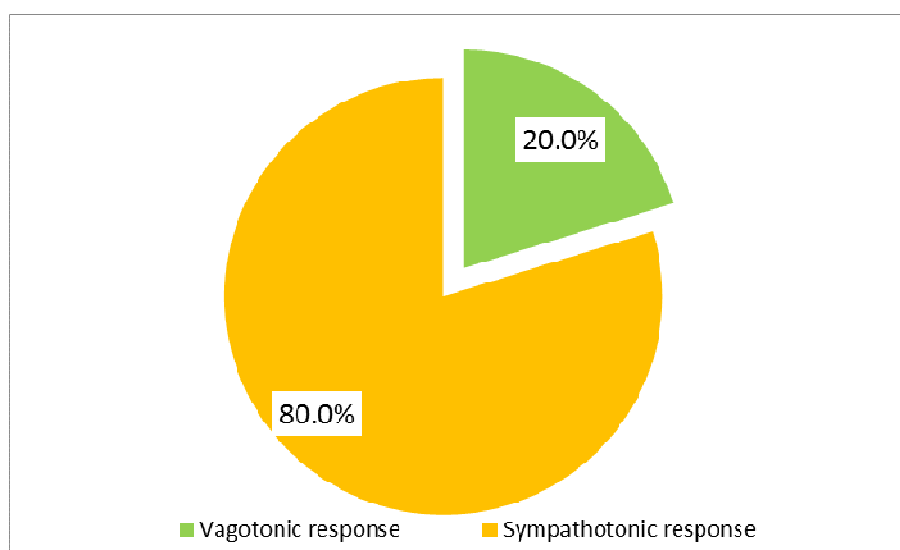
research in meters was recorded. Also, before and immediately after the completion of the stress testing, the heart rate, beats per minute and the level of systolic and diastolic blood pressure were recorded by noninvasive tonometry, mmHg. Based on these and other hemodynamic parameters, the predominant nature of the vegetative-vascular response to standard physical activity was evaluated.

The obtained data were statistically processed and correlation analysis was performed in the Excel for Windows 2016 and Statistica 10.1 software packages.

Results

Based on the stress testing performed using a six-minute walk, two reaction variants were identified, which are associated with the predominant activation of the sympathetic or parasympathetic parts of the autonomic nervous system. At the same time, their ratio in the group of elderly people was not the same, Figure 1. Most of the examined persons (about 80% of the total group) were classified as persons with a sympathotonic type. Taking into account the established division of the subjects according to the prevailing type of regulation, a hypothesis was formed about the possible relationship between the type of reaction to physical activity and the polymorphism of metabolic genes.

Fig. 1. Distribution of the surveyed elderly people by the nature of the response to the test physical activity



We found that the structure of genetic polymorphisms for four metabolic genes (SYT 10, BCAT 1, SNCAIP and NDUFA 11) depends on the nature of the vegetative response to physical activity, Figures 2-5. In particular, according to the synaptotagmin gene, the CT genotype clearly prevails in vagotonics, and CC and TT are minor variants.

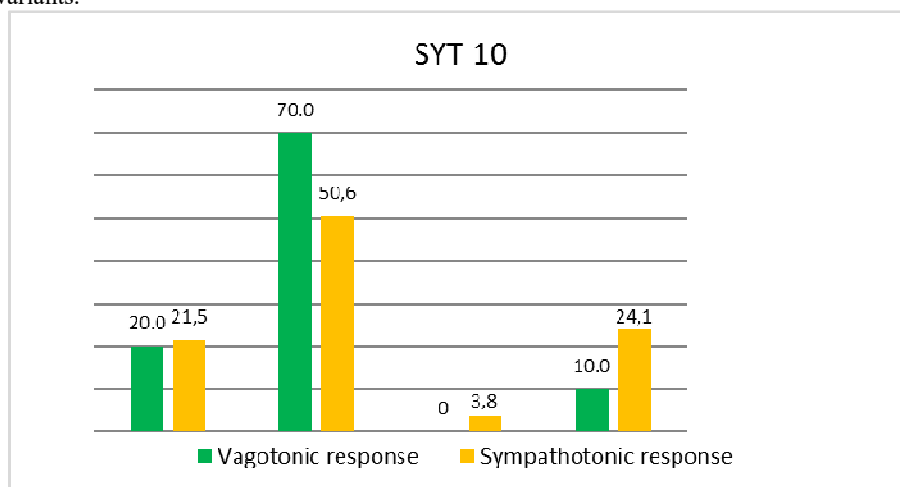


Fig. 2. The structure of the synaptotagmin gene (SYT 10) polymorphisms depending on the response to the six-minute walk test, %

With the predominance of sympathetic myocardial stimulation, a more uniform distribution of the structure of polymorphisms with a moderate prevalence of the CT variant was recorded (about 50% of elderly people with a sympathotonic response to physical activity), Figure 2.

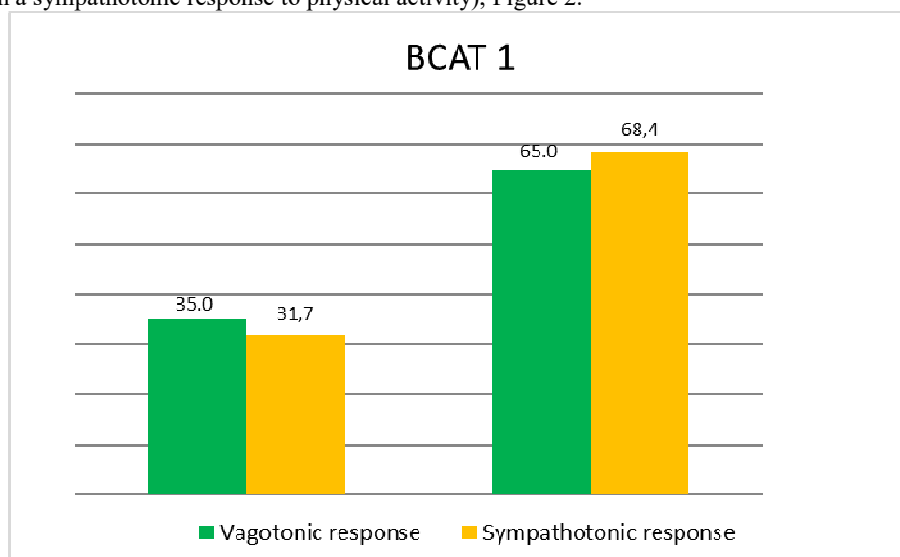


Fig. 3. The structure of the transaminase 1 gene of branched chain amino acids (BCAT 1) polymorphisms depending on the response to the six-minute walk test, %

The least pronounced dependence on the type of cardiorythm autonomic regulation was revealed for the branched chain amino acid transaminase 1 gene, Figure 3. We found only a slight increase in the prevalence of the GG genotype in people with sympathictonia. Interesting data were obtained for a protein gene interacting with alpha-synuclein, Figure 4.

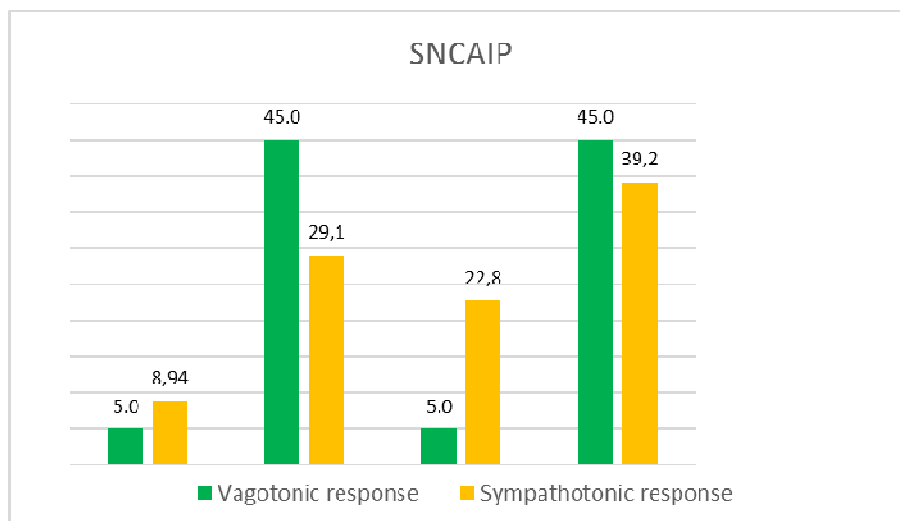


Fig. 4. The structure of the protein interacting with alpha-synuclein (SNCAIP) gene polymorphisms depending on the response to the six-minute walk test, %

Thus, in elderly people with vagotonic nature of the response to stress testing, two unambiguously prevailing variants of the genotype were identified – CT and TT with approximately equal prevalence. On the contrary, in individuals with sympathictonia, most genotypes showed a more uniform structure. In this case, a moderate predominance of the TT genotype was recorded, but a high frequency was found for CT and TC polymorphisms. In the representatives of both selected groups, the CC genotype was the minor variant.

An assessment of the prevalence of the ubiquinone oxidoreductase (NDUFA11) subunit A 11 gene polymorphisms allowed us to establish that the GG variant is more common in elderly people with sympathotonic responses to physical activity than in vagotonics, Figure 5.

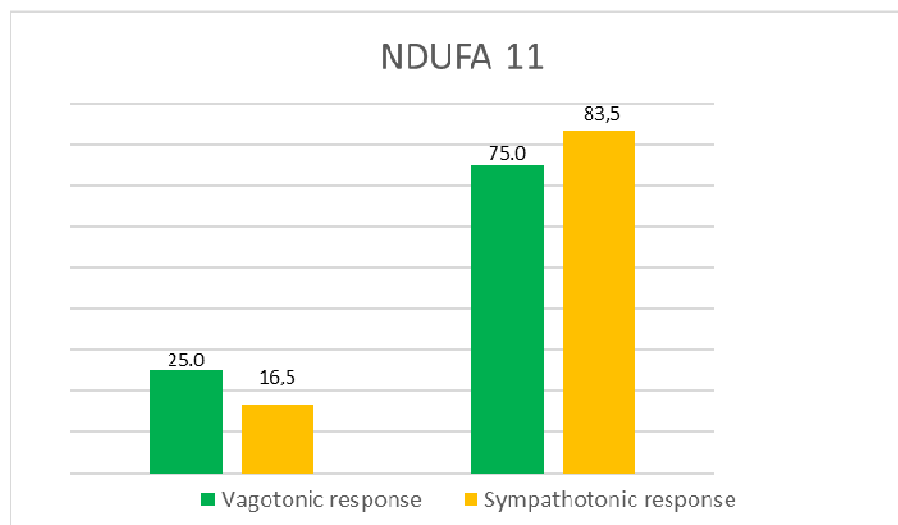


Fig. 5. The structure of the A 11 ubiquinone oxidoreductase (NDUFA11) subunit gene polymorphisms depending on the response to the six-minute walk test, %

At the last stage of the research, we studied the potential coupling of the identified genetic polymorphisms with the functional hemodynamic parameters of the elderly, both in the initial state and after performing a functional test in the form of a six-minute walk technique, Table. We established that there is a genetic determination of the considered parameters of systemic hemodynamics before and after the completion of testing. It was revealed that in a calm state, the heart rate and the level of diastolic pressure in the examined people are associated with polymorphisms of all the evaluated genes, and this trend was most pronounced for the synaptotagmin gene and the branched-chain amino acid transaminase 1 gene. The role of these polymorphisms persisted after the physical activity completion.

Table. Assessment of the genetic polymorphism coupling with hemodynamic parameters during the six-minute walking test (based on the correlation analysis results)

Gene	Before testing	After testing
SYT 10	Diastolic blood pressure ($r = -0.35$), heart rate ($r = -0.37$)	Diastolic blood pressure ($r = -0.33$), heart rate ($r = -0.34$)
BCAT 1	Diastolic blood pressure ($r = -0.35$), systolic blood pressure ($r = -0.43$)	Diastolic blood pressure ($r = +0.32$), systolic blood pressure ($r = -0.31$)
SNCAIP	Heart rate ($r = -0.32$)	Heart rate ($r = -0.34$)
NDUFA11	Diastolic blood pressure ($r = +0.31$)	-

A less significant role in providing a hemodynamic response to a functional test was played by polymorphisms of the genes of the protein associated with alpha-synuclein and the gene of the A11 ubiquinone oxidoreductase subunit, and the latter did not show any statistically significant correlations with the parameters of systemic hemodynamics in elderly subjects after stress testing.

Dicussion

Currently, demographers note an increase in the proportion of old, elderly and senile people in the population, which requires the improvement of existing and the development of new methods and approaches aimed at maintaining a high level of elderly people's health and quality of life (Björ et al., 2019; Adamakis, 2021).

It is known that an important role in maintaining and strengthening health is given to physical activity of a person of any age (Bakiko et al., 2020; Chekhovska et al., 2020). At the same time, researchers found differences in the state of motor qualities in elderly people, which were explained, among other things, by the presence of genetic determinants, in particular, by the peculiarities of cellular metabolism regulation, the enzyme profile of the individual, and endurance genes polymorphism (Jeffries et al., 2014). Researchers have found that the polymorphism of the ACE I/D gene is to some extent associated with the level of aerobic physical activity of a person (Yoshihara et al., 2009). Subsequently, an important role in the physical performance formation and maintenance of endothelial NO-synthase genetic varieties (Teixeira et al., 2016) and aldehyde dehydrogenase (DeAlmeida et al., 2022) was confirmed. Despite the study of many issues of the genetic relationship with

human physical activity, the determination of some genes with hemodynamic parameters at rest and after performing dosed physical activity by the elderly remained not fully studied.

Our research allowed us to establish an inverse correlation of the SYT 10 gene with systolic and diastolic blood pressure and heart rate in elderly people. This relationship was recorded both at rest and after dosed physical activity in the form of a six-minute walk. Our data on the genetic determination of the SYT 10 gene do not contradict the studies of van deVegte et al. (2019), who proved the multidirectional effect of this gene on the duration of the cardiac cycle when a person performs physical activity.

We have also established an inverse correlation in the BCAT 1 gene with systolic and diastolic blood pressure at rest. However, after physical activity, a direct correlation with diastolic blood pressure and an inverse correlation with systolic blood pressure is recorded. It characterizes an increase in pulse blood pressure, which confirms the conclusions of Lynch et al. (2015) about the relationship of this gene with the pumping function of the heart. An improvement in the pumping function of the heart may indicate an increase in the tolerance of the human cardiovascular system to physical activity.

An inverse correlation between the SNCAIP gene and the heart rate in elderly people at rest and after a dosed six-minute walk was established in our research, which confirms the opinion of Jeffries et al. (2014) on the stimulating effect of this gene on the sympathetic autonomic nervous system during cardiac contraction.

In the NDUFA11 gene, we have established a correlation relationship only with diastolic blood pressure at rest. After physical activity, no such relationship has been established.

The research complements the conclusions of scientists on the genetic determination of physical activity and hemodynamic response to graduated exercise in the elderly.

Conclusions

The research made it possible to show that polymorphisms of metabolic profile genes play an essential role in the formation of the functional response of the human body. On the one hand, some genotypes of the genes SYT 10, BCAT 1, SNCAIP and NDUFA 11 are involved in determining the nature of the autonomic response to physical activity in the elderly. On the other hand, the relationship of polymorphisms of most of these genes with both indicators of systemic hemodynamics in a calm state and their dynamics after performing stress testing in the form of a six-minute walk has been established.

The peculiarities of genetic determination and hemodynamic response revealed in elderly people at rest and after dosed physical activity expand the field of knowledge of this issue. The data obtained in the research course can be used in other scientific research related to physical culture and sports and have applied significance.

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Conflicts of interest. The authors declare no conflict of interest.

References:

- Adamakis, M. (2021). Physical activity, sleep and weight management in the COVID-19 era: a case report. *Journal of Physical Education and Sport, Vol. 21 (1)*, 8, 60-65. DOI:10.7752/jpes.2021.01008
- Bakiko, I., Savchuk, S., Dmitruk, V., Radchenko, O., & Nikolaev, S. (2020). Assessment of the physical health of students of middle and upper grades. *Journal of Physical Education and Sport, Vol 20* (Supplement issue 1), Art 39, 286-290. DOI:10.7752/jpes.2020.s1039
- Björ, A., Ribom, E., Johansson, G., Scragg, R., Mellström, D., Grundberg, E., Ohlsson, C., Karlsson, M., Ljunggren, Ö. & Kindmark A. (2019). Variations in the vitamin D receptor gene are not associated with measures of muscle strength, physical performance, or falls in elderly men. Data from MrOS Sweden. *J Steroid Biochem Mol Biol.*, 187, 160-165. DOI:10.1016/j.jsbmb.2018.11.014
- Chekhovska, M., Shevtsiv, L., Zhdanova, O., Chekhovska, L. (2020). Fitness in school physical education lessons. *Journal of Physical Education and Sport, Vol. 20* (Supplement issue 1), Art 60, 420-424. DOI:10.7752/jpes.2020.s1060
- Colovati, M. E. S., Novais, I. P., Zampol, M., Mendes, G. D., Cernach, M. C. S. & Zanesco, A. (2020). Interaction between physical exercise and APOE gene polymorphism on cognitive function in older people. *Braz J Med Biol Res.*, 54(2), e10098. DOI:10.1590/1414-431X202010098
- De Almeida, K. Y., Saito, M., Homma, H., Mochizuki, Y., Saito, A., Deguchi, M., Kozuma, A., Okamoto, T., Nakazato, K. & Kikuchi, N. (2022). ALDH2 gene polymorphism is associated with fitness in the elderly Japanese population. *J Physiol Anthropol.*, 41(1), 38. DOI:10.1186/s40101-022-00312-1
- Jeffries, M. A., Donica, M., Baker, L. W., Stevenson, M.E., Annan, A. C., Humphrey, M. B., James, J. A. & Sawalha, A. H. (2014). Genome-wide DNA methylation study identifies significant epigenomic changes in osteoarthritic cartilage. *Arthritis Rheumatol.*, 66(10), 2804-2815. DOI:10.1002/art.38762
- Knapp-Wilson, A., Pereira, G. C., Buzzard, E., Ford, H. C., Richardson, A., Corey, R. A., Neal, C., Verkade, P., Halestrap, A. P., Gold, V. A. M., Kuwabara, P. E., & Collinson, I. (2021). Maintenance of complex I and

- its supercomplexes by NDUF-11 is essential for mitochondrial structure, function and health. *Journal of cell science*, 134(13), jcs258399. DOI:10.1242/jcs.258399
- Lacombe, J., Armstrong, M., Wright, L., & Foster, C. (2019). The impact of physical activity and an additional behavioural risk factor on cardiovascular disease, cancer and all-cause mortality: a systematic review. *BMC Public Health*, 19(1), 900. DOI:10.1186/s12889-019-7030-8
- Lynch, C. J., Kimball, S. R., Xu, Y., Salzberg, A. C. & Kawasawa, Y. I. (2015). Global deletion of BCATm increases expression of skeletal muscle genes associated with protein turnover. *Physiol Genomics*, 47(11), 569-580. DOI:10.1152/physiolgenomics.00055.2015
- Martusevich, A., Bocharin, I., Guryanov, M., Romanova, E., Kolokoltsev, M., Vyazovichenko, Yu., Lobastova, R., Smirnov, S., Balashkevich, N. & Redi, E. (2023) Metabolic monitoring to assess the response of the body to physical loads. *Journal of Physical Education and Sport*, 23(6), 1401-1406. DOI:10.7752/jpes.2023.06171
- Nezhkina, N., Sokolovskaia, S., Fomin, F., Chueva, T., Fomin, E., Bocharin, I., Balashkevich, N., Kolokoltsev, M., Romanova, E. & Martusevich, A. (2022). The state of vegetative status and adaptive reserve to physical activity in the elderly. *Journal of Physical Education and Sport*, 22(11), 2688-2693. DOI: 10.7752/jpes.2022.11342
- Peeverelli, L., Legati, A., Lamantea, E., Nasca, A., Lerario, A., Galimberti, V., Ghezzi, D. & Lamperti, C. (2019). New missense variants of NDUFA11 associated with late-onset myopathy. *Muscle Nerve*, 60(2), E11-E14. DOI:10.1002/mus.26511
- Prysiashniuk, S., Tolubko, V., Oleniev, D., Parczewskyy, Y., Prontenko, K., Grihan, G., & Zhyrnov, O. (2018). The influence of physical activities on biological age parameters of the first-year female students from the special medical department. *Journal of Physical Education and Sport*, 18(2), Art 81, 561-564. DOI:10.7752/jpes.2018.02081
- Romero-Blanco, C., Artiga González, M. J., Gómez-Cabello, A., Vila-Maldonado, S., Casajús, J. A., Ara, I. & Aznar, S. (2021). ACTN3 R577X polymorphism related to sarcopenia and physical fitness in active older women. *Climacteric*, 24(1), 89-94. DOI:10.1080/13697137.2020.1776248
- Rutten-Jacobs, L. C., Larsson, S. C., Malik R., Rannikmäe, K., Sudlow, C. L., Dichgans, M., Markus, H.S. & Traylor, M. (2018). Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants. *BMJ*, 363, k4168. DOI:10.1136/bmj.k4168
- Shinichiro Morishita, Atsuhiko Tsubaki, Kazuki Hotta, Sho Kojima, Daichi Sato, Akihito Shirayama, Yuki Ito, & Hideaki Onishi (2021). Relationship Between the Borg Scale Rating of Perceived Exertion and Leg-Muscle Deoxygenation During Incremental Exercise in Healthy Adults. *Adv Exp Med Biol.*, 1269, 95-99. DOI: 10.1007/978-3-030-48238-1_15
- Teixeira, T. G., Tibana, R. A., Nascimento, D. D., de Sousa, N. M., de Souza, V. C., Vieira, D. C., Nóbrega, O. T., de Almeida, J. A., Navalta, J. & Prestes J. (2016). Endothelial nitric oxide synthase Glu298Asp gene polymorphism influences body composition and biochemical parameters but not the nitric oxide response to eccentric resistance exercise in elderly obese women. *Clin Physiol Funct Imaging.*, 36(6), 482-489. DOI:10.1111/cpf.12255
- Van de Vegte, Y. J., Tegegne, B. S., Verweij, N., Snieder, H. & van der Harst, P. (2019). Genetics and the heart rate response to exercise. *Cell Mol Life Sci.*, 76(12), 2391-2409. DOI:10.1007/s00018-019-03079-4
- Yoshihara, A., Tobina, T., Yamaga, T., Ayabe, M., Yoshitake, Y., Kimura, Y., Shimada, M., Nishimuta, M., Nakagawa, N., Ohashi, M., Hanada, N., Tanaka, H., Kiyonaga, A. & Miyazaki, H. (2009). Physical function is weakly associated with angiotensin-converting enzyme gene I/D polymorphism in elderly Japanese subjects. *Gerontology*, 55(4), 387-392. DOI:10.1159/000222429