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Association analysis of gene polymorphisms *COL1A*, *MCT1*, *COL12A1* with sports hernia in football players

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Sports hernias are diagnosed in over 80% of athletes presenting with chronic groin pain. The genotype distributions of the examined polymorphisms were studied in 95 football players, all males, using the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire. DNA extracted from buccal epithelium. Statistical calculations were performed in the R statistical environment (r-project.org) and Odds ratios (OR) were used to estimate genotype associations. Multifactor dimensionality reduction was used to identify multiple sports hernia susceptibility loci.Two single nucleotide polymorphisms MCT1 rs1049434 and COL1A1 rs1800012 are associated with sports hernias (63% testing accuracy shown by random forest). According to the HAGOS questionnaire outcomes, exercise-related pain, reduced mobility, and range of motion in the groin and thigh are typically associated with sports hernia diagnosis (75% testing accuracy shown by random forest).The combination of genetic research and HAGOS questionnaire helped obtain a sensitivity of 93% for the detection of sports hernia. Active engagement in sport is the most important risk factor for sports hernia, so the identification genes SNP in footballers may contribute to taking timely preventive actions. This study is the first demonstration of an association between sports hernia and COL1A1 rs1800012 genotype. The study discovered a synergistic interaction between the indicated polymorphism and the gene polymorphism MCT1 rs1049434. Further investigations are required to study the association between COL12A1 rs240736 gene SNP and sports hernia.

Key words: single nucleotide polymorphism; genetics;sports hernia; football player; COL1A; MCT1; COL12A1.

INTRODUCTION

The study of polymorphism of various genes has recently significantly improved the prediction and treatment of various diseases. However, the study of gene polymorphism, including the detection of genes associated with sports injuries, remains poorly understood, and the polymorphisms of genes associated with sports hernias have not been identified yet. Therefore, early diagnosis and appropriate treatment can be challenging in the management of sports hernia.

Sports hernia is not a common groin injury, accounting for just up to 4% of all injuries to the hip and groin in high-profile male football players. Almost 50% of sports hernias in high-profile male football players result in more than a 4-week cessation of training as well as participation in football matches, and the injury time is almost double that of the injuries to the adductors [1].

However, a considerable number of studies suggest the association between specific genetic polymorphisms and elite athletic performance [2-5]. The *COL1A1* (G→T) gene determines collagen formation in cartilage, bone, skin and connective tissue. Moreover, collagen is the main structural component of tendons and ligaments. In the current study, it has been found

that genetic variants in the *COL1A1* gene, which encodes various collagen types, are associated with reduced risk of sports-related injuries. The *MCT1* gene influences the lactate transport capacity and the intensity of sports performance, particularly *rs1049434* polymorphism that has been related to athletic performance [6-10], injuries and body composition in football players [11, 12]. The association of the *COL12* gene with the risk of sports injury and the presence of sports hernia has not been described in the literature, so it is necessary to establish whether the polymorphism of the *COL12* gene can be used to predict sports hernia in football players. Carriers of the minor MCT1T allele have lactate transport rates reduced by 60-65% [13] and higher blood lactate accumulation during high-intensity circuit weight training, compared with carriers of the *MCT1*A allele [14]. Based on the known relationship between blood lactate accumulation and the *MCT1* T allele and the assumption that football players, who had greater lactate transport rates, demonstrated a higher capacity to maintain their performance at intense effort levels, it was hypothesized that the *MCT1* A1470T polymorphism could be associated with sports hernia. Therefore, the purpose of the study is to determine *MCT1 rs1049434*, *COL1A1 rs1800012*, *COL12A1 rs240736* SNPs association with a risk of sports hernias in football players.

METHODS

Participants: The buccal epithelium collected from 95 football players, all males and high-profile football players between ages 17 and 33, who were examined on the basis of the Department of General Surgery No. 2 at O.O. Bogomoletz National Medical University. The athletes included 41 football players with pain in the groin at the time of inclusion (experimental group) and 54 healthy youth football players (control group). Additional research methods were also used: assessment of anamnesis data; the HAGOS questionnaire; general clinical examination, inguinal examination; instrumental methods - ultrasound and MRI of the groin (Fig. 1).

The Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire was used in this study. The HAGOS is a measure of pain and function in athletes, and reference values have already been obtained in football players. It consists of six subscales that are scored separately: «Pain» (P) - 10 items; «Symptoms» (S) - 7 items; «Physical function in daily living» (A) - 5 items; «Physical function in sport and recreation» (SP) - 8 items; «Participation in physical activities» (SP) - 2 items and «hip and/or groin-related quality of life» (Q) - 5 items. Each question gets a score from 0 to 4, where 0 indicates no problem. Raw scores are then transformed to a 0-100 scale, with zero representing extreme hip and/or groin issues and 100 representing no hip and/or groin pain; scores between 0 and 100 represent the percentage of the total possible score achieved [15]. The duration of the study was 1 year.

DNA collection and isolation. Genotyping: The buccal epithelium was collected from all

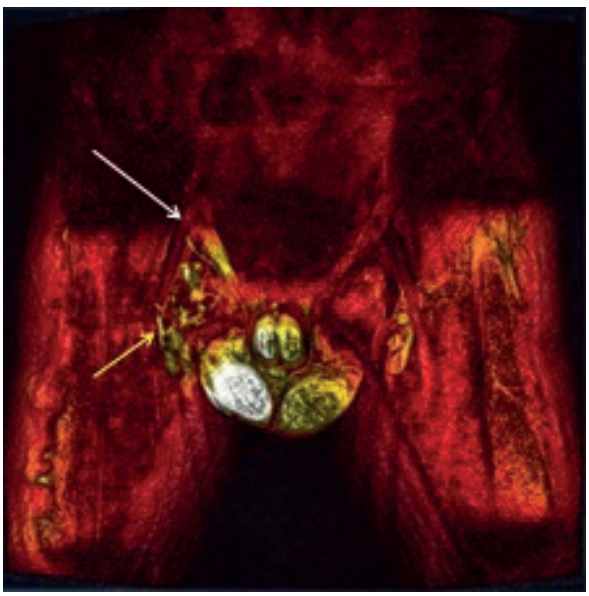

Fig. 1. MRI groin scan in a patient with sports hernia. The white arrow indicate increased MR signal intensity observed from the structures of the inguinal canal, yellow arrow indicates increased lymph nodes on the side of groin pain

football players and treated with means of a set of reagents NeoPrep DNA ("NeoPrep DNA", Ukraine). All DNA samples were genotyped using an allelic determination assay on a 7500 Fast Real-Time PCR System ("Applied Biosystems", "Foster City", USA) with TaqMan probes. For the discrimination of the *MCT1 rs1049434, COL1A1 rs1800012, COL12A1 rs240736* TaqMan® Pre-designed SNP Genotyping Assays were used 7500 Fast Real-Time PCR System ("Applied Biosystems", USA; assay ID: C_2017662_30, C_7477170_30,C_3278190_10). According to the literature data, we found a significant role of these genes *COL1A1, MTC1*and *COL12A1* in the occurrence of sports hernia (Table).

The study of the findings was performed using the Random Forest as given in the R library (r-project.org) and Odds ratios (OR) were used to estimate genotype associations. Random forest can accommodate thousands of independent variables and have been demonstrated to be among the most accurate statistical learning methods and are capable of generating metrics ofthe feature's importance.Multifactor dimensionality reduction (MDR) (https://ritchielab.org/research/research-areas/genetic-architecture-of-complex-traits/methods/mdr) [16] was used to identify multiple sports hernia susceptibility loci.The multinomial logistic regression analysis was conducted to assess the association between a genotype and the risk of sports hernia. In each case, the analysis was carried out by comparing the *MCT1 rs1049434*, *COL1A1 rs1800012*, *COL12A1 rs240736* SNPs with the HAGOS questionnaire results. Finally, the results were analyzed and recommendations were developed for athletes with a set of polymorphisms associated with the risk of sports hernia.All results were considered statistically significant at $P < 0.05$.

Ethics: The design of the study was approved by the commission on bioethical examination and ethics of scientific research at O.O. Bogomoletz Institute of Physiology, NAS of Ukraine (Protocol No.3/20 as of April 25, 2020). The research did not contain an increased risk for the subjects of the study. It was performed taking into account the existing bioethical norms and scientific standards for conducting clinical trials involving patients and in accordance with the ethical standards of the Helsinki Declaration.

RESULTS AND DISCUSSION

According to the results of the HAGOS questionnaire we found that the symptoms of groin pain in football players affect their participation in physical activities, SP = 63.3% in the experimental group compared to controls SP = 96.18% ($P < 0.05$).Also in the experimental group, the football players with sports hernia showed a decrease in daily physical activity (A) by 18.91% compared to the football players in the control group, A = 78.78% and A = 97.69%, respectively($P < 0.05$) and groin pain (P) was revealed 6.16 times more often in the experimental group than in the control group, P = 7.29 and P = 1.13 respectively

Genetic variants associated with groin disruption injury [24]

Gene	Biological function	Genotype	RS Number refSNP Cluster ID Numbers
MTC1	Lactic acid clearance Muscle fatigue	A→T	rs 1049434
COL1A1	Collagen formation in cartilage, bone, skin, connective tissue	G→T	rs 1800012
COL12A1	Maintain extracellular matrix integrity in load-bearing connective tissues of the locomotory system	A→G	rs 240736

(P < 0.05).Additionally, the presence of sports hernia significantly worsens the performance of football players during physical activity (PA): PA = 2.71 (65.25%) in the experimental group and PA = 0.44 (94.44%) (P < 0.05) and affects their quality of life (Q):Q = 8.34 (57.07%) in the experimental group and Q = 0.96 (95.19%) in the control group respectively (P < 0.05). Thus, according to the HAGOS questionnaire outcomes, the index of reduced mobility and range of motion,as well as exercise-related pain in the groin and thigh, should be typically associated with sports hernia diagnosis. The sensitivity of the model is 75% (Fig. 2).

In the study, the three SNPs, related to the risk of sports hernias in football players, were analyzed, and it was found that male participants with the genotype G/G (n = 30) and T/G (n = 11) within *COL1A1 rs1800012* complained of groin pain more frequently compared participants with the genotype T/T. For *COL1A1 rs1800012*, there was an association between males with the TT: n = 9 in the control group and n = 0 in the experimental group genotype sodecreased risks of sports hernias compared to those male

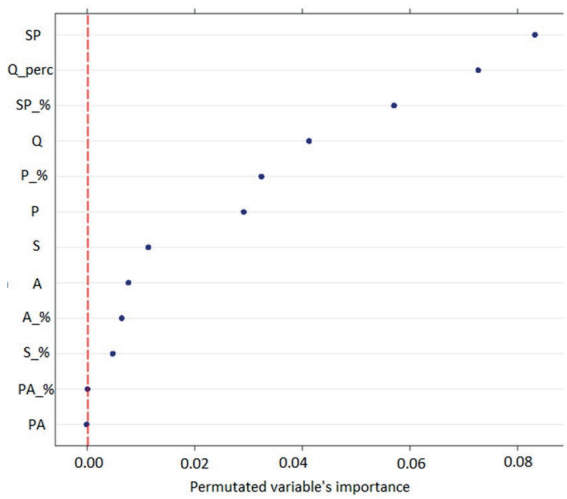

Fig. 2.Selection of predictors by the relevance of their impact. The predictors to the right of the vertical line have the greatest impact on the risk of sports hernia. SP - physical function in sport and recreation, Q - hip and/or groin-related quality of life, P - pain, S - symptoms, and less significant indicators are: PA - participation in physical activities, A - function on a daily basis

football players with the G/G(OR = 1.0;95% CI – 1.0-1.0): n = 35 in the control group and n = 30 in the experimental group genotype and T/G(OR = 1.28; 95%CI –0.48-3.49): n = 10 in the control group and n = 11 in the experimental group genotype (P < 0.05) (Fig. 3).

The second SNP *rs 1049434* within T/T genotype of the MTC1 gene was found to be associated with the less risk of sports hernia (OR = 0.14; 95% CI – 0.01-1.03), T/T (n = 2) in football players with groin pain compared to the healthy players T/T (n = 11) genotype (P > 0.05). No significant association was found between genotypes A/A (n = 3) and A/A (n = 4) genotypes (OR = 1.0; 95% CI – 1.0-1.0) and A/T (n = 40) and A/T (n = 35) (OR = 0.66; 95% CI – 0.12-3.17) in males in the control group and in the experimental group (Fig. 4a).

There was no association established between sports hernia and the *rs 240736* SNP of the *COL12A1* gene due to the relatively small population of male football players in both groups (P > 0.05). Moreover, the G/G genotype was found in 6 males in the control group and in 3 males with sports hernias in the experimental group (OR = 0.78;95% CI (0.15-3.3). The *COL12A1 rs240736* A/A genotype was observed in 20 football players with sports hernia compared to 31 healthy football players without any complaints of exercise-related groin

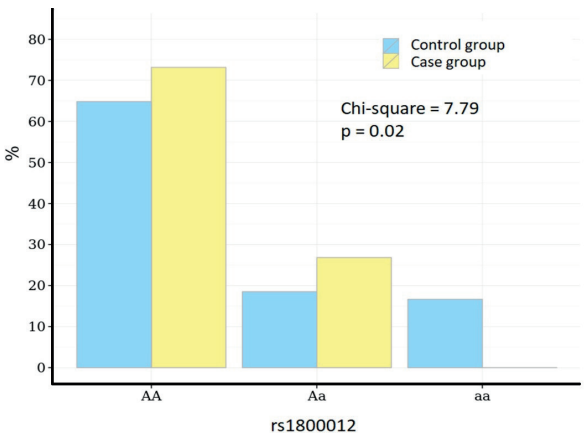

Fig. 3. The distributions of genotypes of *COL1A1 rs1800012* in a group with sports hernia and control group

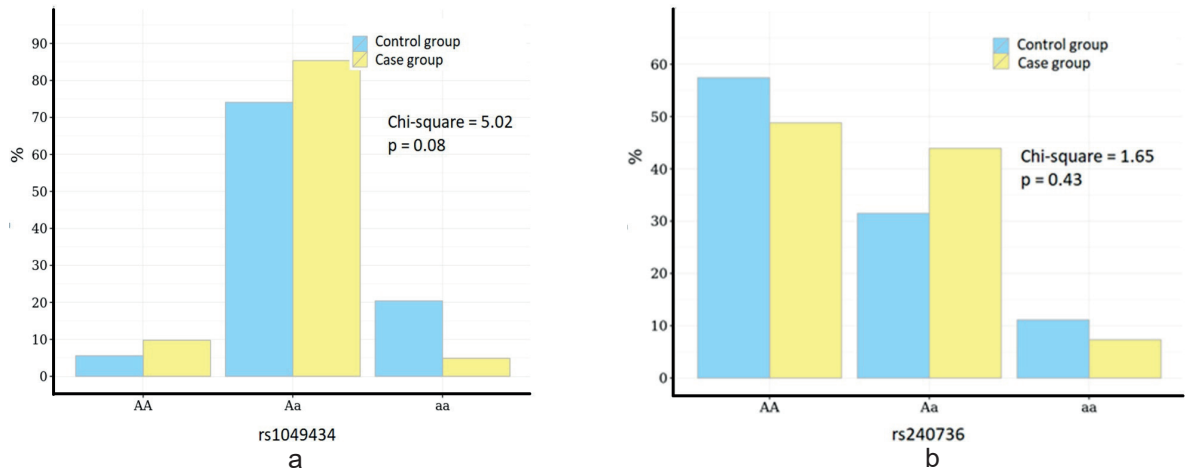

Fig. 4. The distributions of genotypes of *MCT1 rs1049434*(a) and *COL12A1 rs240736* (b) in a group with sports hernia and control group

pain (OR = 1.0;95% CI (1.0-1.0) (Fig. 4b).

It was found that the polymorphism of the gene *COL1A1 rs1800012* (G → T) was the most significant predictor among the identified polymorphisms, and the minor homozygote could be associated with a decreased risk of the disease ($P < 0.05$). It was established that the *MCT1* gene polymorphism *rs1049434* (A → T) was the second significant predictor, which was also included in the mathematical model ($P > 0.05$). The TT genotype of this variant was shown to be associated with a reduced risk of sports hernia, so it was found more in the control group than in the experimental group ($P < 0.05$). An algorithm for a complex analysis of the genetic data helped establish a synergistic relationship between these three polymorphisms (Fig. 5).

The comparative analysis of the findings obtained in the experimental and control groups revealed an increased frequency of the *COL1A1* G/G genotype in sports hernia patients ($P < 0.05$). Specifically, the T/T genotype of *COL1A1 rs180012* and *MTC1 rs1049434* was associated with a lower risk of sports hernia. According to the HAGOS questionnaire outcomes, reduced mobility and range of motion, as well as exercise-related pain in the groin and thigh, should be typically associated with sports hernia diagnosis (75% testing accuracy shown by random forest). These symptoms result in decreased quality of life as well as influence professional performance. The combination of genetic research and HAGOS questionnaire helped obtain a sensitivity of 93% by random forest for the detection of sports hernia. The major risk factors of its development include physical activity and identification of all three gene polymorphisms *MCT1 rs1049434, COL1A1 rs1800012, COL12A1 rs240736* (Fig. 6).

Our findings provide insight into the etiology of sports hernia development and highlight

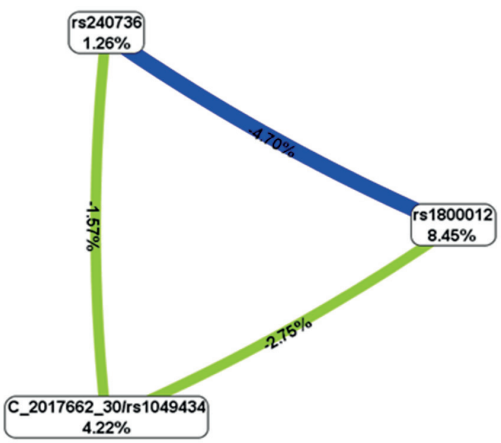

Fig. 5. SNPs interaction graph-model. The interaction model describes the percent of entropy that is explained by each factor. The correlation is depicted as a dark blue line and as light green lines between SNPs accompanied by a negative percent of entropy

genetic pathways for studies of sports hernia occurrence and its treatment [17, 18]. Connective tissues within the inguinal canal are made up of collagen, elastic fibers, and components of the extracellular matrix. Fibers of collagen type I are a major constituent of bundles in tendons and ligaments. Collins et al. [19, 20] suggested that the *COL1A1* TT polymorphism could be associated with a reduced rate of anterior cruciate ligament rupture, shoulder dislocation, and Achilles tendinopathy. Khoschnau et al. [21] evaluated the protective role of the *COL1A1* TT polymorphism in ligament, tendon and other soft tissue injuries.Other suggested that genetic deficiencies of these components may lead to a tendinopathies [23].A major factor for muscle fatigue after intense power exercise is the rates of lactic acid removal. A variant in the *MCT1* gene affects the lactate transport capacity, and thus the intensity of sports performance. Cupeiro R. et al. [22] investigated that carriers for *MCT1* A1470T polymorphism showed higher lactate accumulations than non-carriers during high intensity CWT.

The most important finding of this study is that there are significant associations existing between sports hernia and genetic polymorphisms *MCT1 rs1049434, COL1A1 rs1800012, COL12A1 rs240736*. For the first time, future research should be aimed at the application of sports genetics and the development of genetic performance tests for determining genetic suitability for specific team positions and roles as well as for gaining insights into the athlete development in various sports or physical activities.

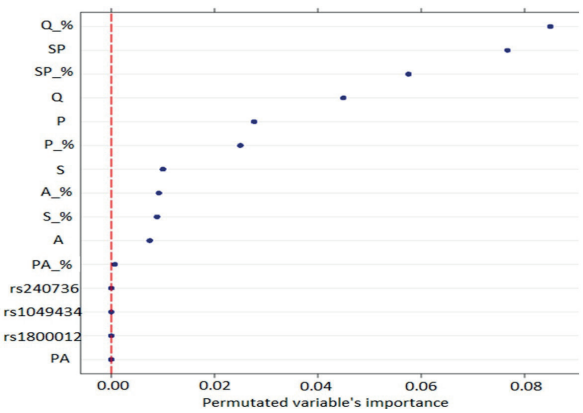

Fig. 6. A variable importance graph of 3 SNPs indicates that 3 SNPs *COL1A1 rs1800012* (G→T), *MCT1 rs1049434* (A→T),*COL12A1 rs240736* (A→G) achieved importance score by crossing the vertical dashed line for sports hernia. Q - hip and/or groin-related quality of life; SP - physical function in sport and recreation; P - pain; S - symptoms;A-function on a daily basis; PA - participation in physical activities

CONCLUSIONS

The association between gene polymorphisms and the risk of developing sports hernias in football players was established for the first time. It was found that the polymorphism of the gene *COL1A1 rs1800012* (G → T) was one the most significant predictor for the sports hernia ($P < 0.05$).The study discovered a synergistic interaction between the indicated polymorphism and the gene polymorphism *MCT1rs1049434* (A→T), which was included in the mathematical model and rated as the second most important predictor ($P > 0.05$).

Further investigations are required to study the association between *COL12A1* gene SNPs and sports hernia. The practical significance of the obtained findings is that a personalized approach to the treatment of football players with sports hernia will be developed and implemented, taking into account the clinical and genetic prognosis of the response to the treatment. The individuals found to be at risk for sports hernias are advised to modify their sports activities to reduce the risk. Thus, physical activity and sports performance phenotype can be optimized.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВИЯВЛЕННЯ ПОЛІМОРФІЗМІВ ГЕНІВ *COL1A1, MCT1, COL12A* ПРИ СПОРТИВНІЙ ГРИЖІ У ФУТБОЛІСТІВ

Спортивна грижа діагностується у 80% спортсменів з хронічними болями в пахвинній ділянці. Нами вивчено зв'язок між виникненням спортивної грижі та поліморфізмами, які було досліджено з букального епітелію 95 футболістів чоловічої статі, а також проведено оцінку якості життя за опитувальником HAGOS. Статистичні розрахунки проводили у пакеті R (r-project.org), для аналізу генотипів оцінювали відношення шансів. Визначено два однонуклеотидні поліморфізми *MCT1 rs1049434* та *COL1A1 rs1800012*, які пов'язані зі спортивною грижею (63% за методом random forest). Біль під час фізичних вправ та обмеження рухів у пахвинній ділянці та стегні мають найбільший вплив на якість життя футболіста відповідно до результатів опитування HAGOS (75% за методом random forest). При поєднанні генетичного дослідження та анкетування отримано до 93% за методом random forest для виявлення спортивної грижі. Активні заняття спортом є фактором ризику її виникнення, а виявлення поліморфізмів генів SNP *MCT1 rs1049434, COL1A1 rs1800012, COL12A1 rs240736* може сприяти наданню спортсменам своєчасних профілактичних заходів. У дослідженні вперше визначено зв'язок між спортивною грижею та *COL1A1 rs1800012*.Дослідження виявило синергічну взаємодію поліморфізмами генів *COL1A1 rs1800012* та *MCT1 rs1049434*.

Ключові слова: однонуклеотидний поліморфізм; генетика; спортивна грижа; футболіст; *COL1A; MCT1; COL12A1*.

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ВИЯВЛЕНИЕ ПОЛИМОРФИЗМОВ ГЕНОВ *COL1A1, MCT1, COL12A1* ПРИ СПОРТИВНОЙ ГРЫЖИ У ФУТБОЛИСТОВ

Спортивная грыжа диагностируется у 80% спортсменов с хроническими болями в паховой области. Нами изучена связь между возникновением спортивной грыжи и полиморфизмами из букального эпителия 95 футболистов мужского пола, также проведена оценка качества жизни по анкетированию HAGOS. Статистические расчеты проводили в среде R (r-project.org), для анализа ассоциаций генотипов оценивали отношения шансов.Определены два однонуклеотидные полиморфизмы *MCT1 rs1049434 и COL1A1 rs1800012*, связанные со спортивной грыжей (63% по методу random forest). Боль во время физических упражнений и ограничение объема движений в паховой области и бедре имеют наибольшее влияние на качество жизни футболиста согласно результатам опроса HAGOS (75% по методу random forest). При сочетании генетического исследования и анкетирования получено до 93% по методу random forest для выявления спортивной грыжи. Активные занятия спортом являются весомым фактором риска ее возникновения, а выявление полиморфизмов генов *MCT1 rs1049434, COL1A1 rs1800012, COL12A1 rs240736* может способствовать своевременным профилактическим мероприятиям. В исследовании впервые определено значение между спортивной грыжей и *COL1A1 rs1800012*. Также выявлено синергическое взаимодействие между полиморфизмов генов *COL1A1 rs1800012 и MCT1 rs1049434*.

Ключевые слова: однонуклеотидный полиморфизм; генетика; спортивная грыжа; футболист; *COL1A; MCT1; COL12A1*.

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