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YOUNG "ATHLETE'S HEARTS" AND ISOLATED SYSTOLIC HYPERTENSION: CAN "ATHLETE'S GENES" UNDERLIE THEIR RELATIONSHIP? RESULTS FROM THE PILOT STUDY

Kolomeichuk S.N.[1,4], Putilov A.A.[2], Meigal A.Yu.[3], Morozov A.V.[4], Budkevich E.V.[5], Markov A.A.[1], Gubin D.G.[1,6]

[1] Tyumen State Medical University (Odesskaya, 54, Tyumen 625023, Russian Federation)
[2] Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (Butlerova 5A, Moscow 117485, Russian Federation)
[3] Institute of High Biomedical Technologies, Petrozavodsk State University (Prosp. Lenina, 33, Petrozavodsk 185910, Russian Federation)
[4] Institute of Biology, Karelian Research Centre, Russian Academy of Sciences (Pushkinskaya str., 11, Petrozavodsk 185910, Russian Federation)
[5] North Caucasus Federal University (Pushkina str., 1, Stavropol 355017, Russian Federation)
[6] Tyumen Cardiology Research Center (Melnikaite str., 111, Tyumen 625026, Russian Federation)

RESUME

Introduction. *Engaging in intense aerobic exercises can lead to a specific, non-pathological condition known as isolated systolic hypertension or "athlete's heart", characterized by elevated systolic blood pressure. The side effects of the heart's response to intense training can be attributed to individual genetic factors.*
The aim. *To analyze a minimal set of polymorphic gene variants in relation to personal differences in hemodynamic parameters among athletes and a control group of untrained individuals.*
Methods. *The study cohort comprised 98 participants who met the specified inclusion criteria. All subjects were male individuals aged between 18 and 30 years, actively engaged in professional sports for a minimum of four years and free from serious medical conditions. Individuals were examined at Republican Autonomous Healthcare Institution of Karelia "Medical and Physical Education Dispensary" and grouped according to sports disciplines. Comprehensive measurements of key anthropometric parameters were conducted, along with an assessment of the functional state of the cardiovascular system at rest. The genetic analysis was performed using DNA extracted from blood samples. ACTN3, ACE, PPARA and BDKRB2 gene variants associated with heart development and functioning were studied by PCR. Statistical analysis was performed using the statistical package SPSS version 22.0 (IBM, Armonk, USA).*
Results. *I/D ACE gene variant was distinctly associated with power-oriented training compared to speed-oriented and endurance-oriented athletes. The combination of dominant alleles from studied genes occurred to be predictor of higher systolic blood pressure in power-oriented athletes.*
Conclusion. *We found that genetic variants may affect to the development of training-specific and mostly disadvantageous characteristics of body composition. Three polymorphic gene variants could independently predict heart remodeling and future health complications in young athletes.*

Key words: *blood pressure parameters; athlete's training; heart adaptation; genetic markers; athletic performance*

Corresponding author:
Sergey N. Kolomeichuk,
e-mail:
sergey_kolomeychuk@rambler.ru

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СИНДРОМ «СПОРТИВНОГО СЕРДЦА» У МОЛОДЫХ СПОРТСМЕНОВ И ИЗОЛИРОВАННАЯ СИСТОЛИЧЕСКАЯ ГИПЕРТЕНЗИЯ: МОГУТ ЛИ «СПОРТИВНЫЕ ГЕНЫ» ЛЕЖАТЬ В ОСНОВЕ ИХ ВЗАИМОСВЯЗИ? РЕЗУЛЬТАТЫ ПИЛОТНОГО ИССЛЕДОВАНИЯ

Коломейчук С.Н.[1,4], Путилов А.А.[2], Мейгал А.Ю.[3], Морозов А.В.[4], Будкевич Е.В.[5], Марков А.А.[1], Губин Д.Г.[1,6]

[1] Тюменский государственный медицинский университет (625023, г. Тюмень, ул. Одесская, 54, Россия)
[2] Институт высшей нервной деятельности и нейрофизиологии РАН (117485, г. Москва, Бутлерова, 5А, Россия)
[3] Институт высоких биомедицинских технологий Петрозаводского государственного университета (185910, г. Петрозаводск, пр. Ленина, 33, Россия)
[4] Институт биологии Карельского научного центра РАН (185910, г. Петрозаводск, ул., Пушкинская 11, Россия)
[5] Северо-Кавказский федеральный университет (355017, г. Ставрополь Пушкина ул., 1, Россия)
[6] Тюменский кардиологический научный центр (625026, г. Тюмень, ул. Мельникайте, 111, Россия)

Автор, ответственный за переписку: **Коломейчук Сергей Николаевич,** e-mail: sergey_kolomeychuk@rambler.ru

РЕЗЮМЕ

Введение. *Занятия интенсивными аэробными упражнениями могут привести к специфическому, непатологическому состоянию, известному как изолированная систолическая гипертензия или «сердце спортсмена», характеризующемуся повышенным систолическим артериальным давлением. Побочные эффекты реакции сердца на интенсивные тренировки могут быть обусловлены индивидуальными генетическими факторами.*

Цель. *Анализ минимального набора полиморфных вариантов генов в связи с индивидуальными различиями гемодинамических параметров у спортсменов и контрольной группы нетренированных лиц.*

Методы. *Критериям включения соответствовали 98 человек. В качестве испытуемых были отобраны лица мужского пола возраст 18–30 лет, профессионально занимающиеся спортом более 4 лет, без серьезных патологий. Участников разделяли на группы согласно основным типам спортивной специализации. Измерялись основные антропометрические параметры, а также оценено функциональное состояние сердечнососудистой системы в состоянии покоя. Генетический анализ проводился с использованием ДНК, выделенной из образцов крови. Варианты генов ACTN3, ACE, PPARA и BDKRB2, ассоциированные с развитием и функционированием сердца, изучали методом ПЦР. Статистический анализ проводился с использованием статистического пакета SPSS версия 22.0 (IBM, Armonk, США).*

Результаты и обсуждение. *Были определены три полиморфных варианта генов (ACTN3 R577X, ACE I/D и BDKRB2 -9/+9), которые достоверно предсказывали значения систолического артериального давления. Полиморфные варианты генов ACE и BDKRB2 ассоциированы с высоким уровнем систолического артериального давления у спортсменов группы силовой направленности. Полиморфный вариант I/D гена ACE был дифференцированно связан с силовыми тренировками по сравнению с тренировками на скорость и выносливость. Сочетание доминантных аллелей четырех генов является предиктором повышенного систолического артериального давления у спортсменов силовой специализации.*

Выводы. *Определенные варианты генов могут влиять на развитие специфических для тренировок и преимущественно неблагоприятных характеристик состава тела. Три полиморфных варианта генов могут независимо предсказывать ремоделирование сердца и будущие осложнения со здоровьем у молодых спортсменов.*

Ключевые слова: *тренированность спортсменов; адаптация сердца; генетические маркеры; показатели артериального давления; спортивные результаты*

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INTRODUCTION

The effects of prolonged, high-intensity exercise on the cardiovascular system remain a subject of considerable debate [1]. Adverse consequences of excessive training may include the development of hypertension and cardiomyopathy. High blood pressure as well termed as hypertension is considered among pivotal risk elements for development of cardiovascular pathologies in human population worldwide [2, 3]. Moreover, it has been associated with left ventricular hypertrophy in professional and elite athletes [4, 5].

It is commonly accepted that regular physical activity has beneficial effects on life longevity and cardiovascular health. Considering intense athletic training as an extreme of physical activity one should expect serious remodeling of cardiovascular system and especially heart. Both power-oriented and endurance-oriented training lead to complex structural and functional remodeling of the heart, resulting in special condition characterized by a high resting cardiac stroke volume and cardiac output, accompanied by low values of peripheral vascular resistance and heart rate [6]. Such state is often referred to as the "athlete's heart", a term originally identified and described by Henchen S. in 1898 [7]. Although diastolic blood pressure stands within the normal range, pulse pressure and systolic blood pressure values often exceed the average range. Indeed, professional athletes are obliged to pass regular health examinations before and after sport events and have blood pressure measurements in the pre-hypertensive range and, occasionally, in the range of stage 1 hypertension [8]. A related phenomenon observed in athletes is "spurious systolic hypertension" [9, 10]. This arises due to an exaggerated amplification of pulse pressure in the arm as a consequence of the progressive decrease in arterial diameter from the heart to the periphery and the corresponding increase in arterial impedance. In contrast to brachial systolic blood pressure, central (aortic) systolic blood pressure typically remains within the normal range [11]. This temporary systolic hypertension may represent an intermediate state between normotensive condition and sustained hypertension [12, 13].

The cause of "athlete's heart" remains a complex issue with a genetic predisposition frequently suggested. While numerous genetic markers associated with athletic performance have been identified in the literature (over 200 sources from 2005–2024 [14, 15]), few have been consistently replicated across studies. Several genetic variants, including *ACTN3* R577*, AMPD1* Gln12*, ACE* D*, NOS3 rs2070744 T*, and *HIF1A* 582Ser, were found to be more prevalent in disciplines focused on power and strength. Conversely, their minor alleles have been attributed to endurance-oriented sports [15]. Notably, in a study examining 31 genetic variants linked to athletic traits, the PPARA rs4253778 C allele and the -9 allele of the *BDKRB2* gene were identified as potential genetic indicators of power/strength and endurance, respectively [16].

To date, investigations exploring the relationship between these polymorphisms and blood pressure in young athletes are either limited or absent. Therefore, this pilot study aimed to determine whether a selected set of well-established athlete's genetic markers (*ACTN3* R577X, *ACE* I/D, *PPARA* G/C, and *BDKRB2* -9/+9), implicated in both performance enhancement and blood pressure regulation, contribute significantly to inter-individual differences in systolic blood pressure among athletes. Furthermore, we sought to explore the possibility that these genetic variants may predispose young athletes to the development of elevated systolic blood pressure.

The following specific hypotheses were tested:

1. Selected *ACTN3, ACE, PPARA*, and *BDKRB2* gene variants might predict inter-individual differences in blood pressure parameters in full cohort and in subgroups of athletes;
2. Elevated systolic blood pressure in athletes is associated with a specific combination of the four genetic variants: the ACTN3 577R and *ACE* D alleles, associated with benefits in power-oriented training, and the PPARA G and BDKRB2-9 alleles, associated with benefits in endurance-oriented training;
3. The association between specific genetic variants and the risk of elevated systolic blood pressure may differ according to sport specialization.

MATERIALS AND METHODS

This work continued research pilot program at Petrozavodsk State University aimed at deciphering genetic aspects in sports. In our case-control study we recruited seventy-four male athletes (25 power-oriented athletes, 24 speed-oriented athletes, 25 endurance-oriented athletes) and twenty-four control untrained volunteers who met the selection criteria. Selection criteria were follows: professional sports experience of more than 4 years at national and international sports events, age 18–30 years old, male gender, absence of drug addiction, doping usage and chronic diseases. The study included male participants belonging to Russian ethnic group. The subjects were categorized based on their primary sports specialization. Key anthropometric measurements (height (cm), weight (kg), fat mass (kg), muscle mass (kg), total body water (kg), bone mass (kg), body mass index (weight-to-height ratio) were taken, alongside assessments of the cardiovascular system's functional state in a steady state. The power-oriented group comprised athletes from boxing, weightlifting, throwing events, wrestling, and powerlifting. The speed-oriented group included all types of runners except for those specializing in endurance events. Meanwhile, the endurance-oriented group consisted of cross-country skiers and long-distance runners.

Trained research assistants at Autonomous Health Institution of the Republic of Karelia "Medical and Physical Therapy Clinic" performed standardized resting blood pressure measurements by using an aneroid sphygmomanometer with an adequate sized cuff to the arm circumference. Reported values were obtained by averaging over three measurements. To determine body's composition,

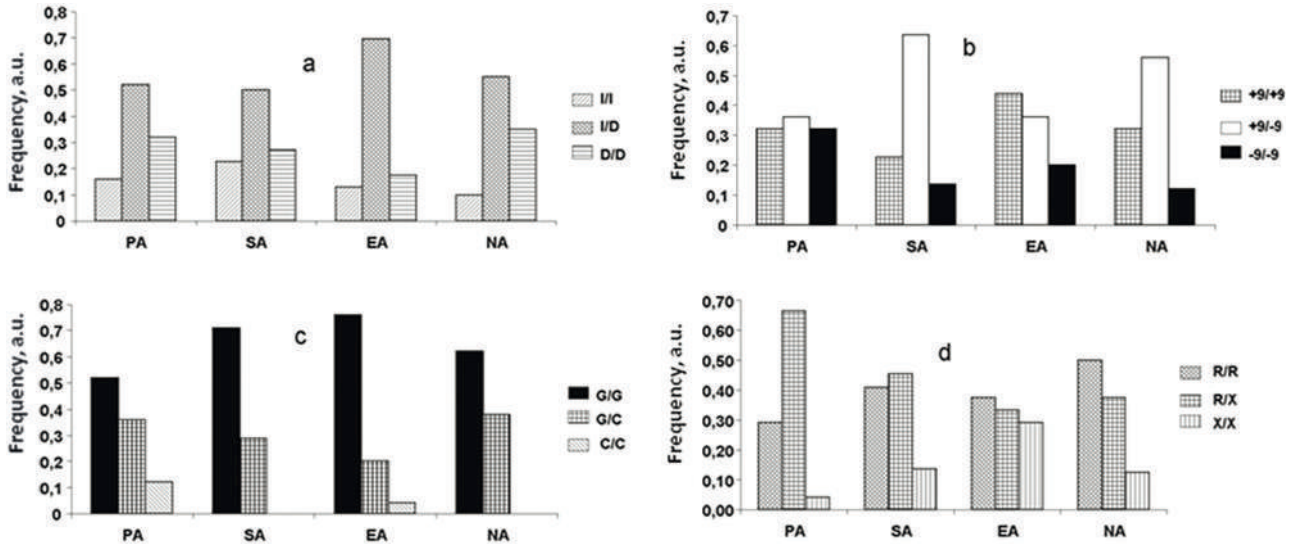
the conventional method of bioelectrical impedance analysis was applied using Tanita's SC330 Body Composition Monitor (Tanita Corporation of America, Inc., Illinois, USA). Resting heart rate was measured during electrocardiographic examination with Polyspectr (Neurosoft, Ivanovo, Russia). Blood was sampled after an overnight fast between 9 a.m. and 10 a.m. It was drawn from an antecubital vein with a 19-gauge needle into sampling tube containing ethylenediaminetetraacetic acid. The serum was segregated within the following two hours, and samples were stored at −70 ºC. Genomic DNA was extracted from 200 microlitres of peripheral blood lymphocytes by DiaGene DNA isolation kit (Dia-M, Moscow, Russia) according to manufacturer's instructions. The study protocol was reviewed and approved by the Joint Review Board of the Institute of Biology Karelian Science Center and Medical Institute at Petrozavodsk State University (Protocol № 21/20/187 from 26.02.2015). It was in agreement to international ethical standards from the Declaration of Helsinki 1975, revised in 2024. Each participant has signed written informed consent.

Genotyping of the *ACTN3 (rs1815739)* gene was performed according to previous study [15]. PCR was also applied to detect the alleles I and D of the *ACE (rs1799752)* gene according to the method described in our previous work [16]. PPARA intron 7 G/C polymorphism (*rs4253778*) was detected as proposed by Ahmetov I.I. [17]. Next, the -9/+9 polymorphism in exon 1 of the *BDKRB2* gene was genotyped according to Williams A.G. [18].

Statistical analyses were performed by SPSS statistical package (IBM, Armonk, NY, USA, version 22.0). Differences between the groups in parameters of body's composition and some other parameters were tested with one-way ANOVAs followed by post hoc analysis (Bonferroni multiple comparison test). The chi-square statistics were calculated to examine the distribution of genotypes into the subgroups with and without a systolic blood pressure of >140 mm Hg combined with a diastolic blood pressure of < 90 mm Hg. Linear regression analyses were performed for predicting blood pressure by 4 genotypes as predictors. In order to detect differences between three genotypes of each gene in four groups, two-way ANCOVAs was run with "Age" as the covariate and two inter-subject factors, "Genotype" (carriage major/minor alleles, respectively) and "Group" (different sport disciplines, and control group). Bonferroni multiple comparison test was used in the post hoc analysis for examination of significance of each pairwise difference. Finally, linear regression analyses were performed for predicting sum of major alleles with blood pressure and age as predictors. Score for sum was explained as follows: 2 – homozygous dominant allele, 1 – heterozygote, 0 – homozygous minor allele and, in sum, each individual was scored as carrying 0–8 dominant/major alleles.

RESULTS

We got the following information from our genotyping analysis. Allele frequencies on polymorphic *ACE I/D* gene variant in Karelian athletes were detected in the following order power-oriented athletes (I/I-15.9 % and D/D-32.4 %) and in the control group (I/I-10 % and D/D-13.2 %) did not differ statistically significantly ($\chi^2 = 2.35$; d.f. = 2, $p = 0.12$) (Fig. 1). The lowest frequencies for homozygotes in allele D were detected in control group in comparison to other participants. Our results correspond to the data of other researchers that the frequency of the *ACE* D/D



a – polymorphic ACE gene variant; b – polymorphic BDKRB2 gene variant; c – polymorphic ACTN3 gene variant; d – polymorphic PPARA gene variant. Data presented as PA – subgroup included power-oriented athletes only (n = 25), speed-oriented training, SA (n = 24), endurance-oriented training, EA (n = 25), and non-athletes, NA (n = 24).

FIG. 1.
Genotype and allele frequencies distribution in studied cohort of individuals

genetic variant is higher in power-oriented athletes compared with the control ones [15]. The distribution of ACE allele and genotype frequencies among athletes did not deviated from the expected values based on the Hardy – Weinberg equilibrium.

The frequency of polymorphism +9/-9 of the *BDKRB2* gene in Karelian athletes +9/-9-31,9 %; +9/-9-36,0 %; -9/-9-32,1 %) and in the control group (+9/+9-32 %; +9/-9-56 %; -9/-9-12 %;) were statistically significantly different ($\chi^2 = 9.37$; d.f. = 2, $p < 0.01$).

The frequency of the *ACTN3* gene R/X genetic marker among analyzed cohort specializing in strength activities (R/R — 28.9 %; R/X — 67.0 %; X/X — 4.0 %) was significantly different from those in the control NA group (R/R — 50.2 %; R/X — 37.3 %; X/X — 13.5 %; $\chi^2 = 21.15$; d.f. = 2, $p < 0.001$), and especially from endurance-oriented group where X/X genotype was equal to 28.9 % (Fig. 1). The distribution of ACTN3 allele and genotype frequencies among athletes deviated from the expected values based on the Hardy – Weinberg equilibrium, suggesting that selection had taken place in the analyzed group.

The frequency of the PPARA G/C polymorphic marker amongst studied sample specializing in power-oriented activities was (G/G — 28.9 %; C/G — 67.0 %; C/C — 12.0 %) was not significantly different from that in the control (G/G — 61.8 %; C/G — 37.9 %; C/C — 0.0 %; $\chi^2 = 3.12$; d.f. = 2, $p > 0.05$) and speed-oriented groups (G/G — 71.2 %; C/G — 28.8 %; G/G — 0.0 %; $\chi^2 = 3.76$; d.f. = 2, $p > 0.05$) respectively. The distribution of PPARA allele and genotype frequencies among athletes deviated from the expected values based on the Hardy – Weinberg equilibrium (Fig. 1).

Information on allele frequencies for all examined hereditary markers was in concordance with earlier discoveries for cohorts in Northern Russia as well as Eastern Europe [14, 15, 16]. However, when athletes were subdivided into the subgroups with and without a systolic blood pressure of > 140 mm Hg (none of the study participants had diastolic blood pressure of > 90 mm Hg), the distribution of phenotypes with and without elevated systolic blood pressure was found to be different in the group of power-oriented training as compared to the groups of speed- and endurance-oriented training (5 and 2 with vs. 20 and 47 without, $\chi^2 = 4.898$, df = 1, $p = 0.027$).

Table 1 shows that the group of athletes with power-oriented training also profoundly differed from other groups (either athletes or non-athletes) in several interrelated morphological and physiological characteristics. When compared to non-athletes, they had higher 1) body weight, 2) percentage of fat, 3) body mass without fat, 4) muscle mass, and 5) body mass index. They also had lower 6) percentage of body water and 7) body impedance. In contrast, they did not show a slower resting heart rate compared to non-athletes while the athletes from two other groups did. Compared to other athletes, they have higher 1) heart rate, 2) body weight, 3) percentage of fat, 4) body mass without fat, and 5) body mass index, and 6) they had a lower percentage of body water (Table 1).

Next we checked whether polymorphic variants could distinctly predict blood pressure in studied participants. It is noteworthy that we obtained divergent results. Our analyses revealed that that major alleles in analyzed genes to be significant predictors of systolic blood pressure and pulse pressure but not diastolic blood pressure (Table 2). To further investigate our hypothesis regarding the most reliable predictors of elevated blood pressure, we conducted regression analyses on both the entire cohort and the subsample of athletes. Specifically, the presence of the R allele of the *ACTN3* gene and the -9 allele of the *BDKRB2* gene predicted elevated levels of systolic blood pressure and pulse pressure, but not of diastolic blood pressure. Carriage the major alleles these genetic markers (R allele of *ACTN3* gene and -9 allele of *BDKRB2* gene) and age could explain almost 24 % of individual variation in pulse pressure values (Fig. 2). It is important to highlight that the major alleles of the *ACE* gene and the *PPARA* gene, which were associated with higher values of systolic and pulse pressure, neither achieve statistical significance in the regression analysis for the entire cohort, nor in the subsample of athletes. Moreover, we found that presence of the major D allele of *ACE* gene was a predictor of systolic blood pressure in power-oriented group of athletes.

Two-way ANCOVAs confirmed the results of regression analyses and, in particular, it clarified the relationship between variation in ACE gene and systolic blood pressure. The significant interaction between the between-subjects factors "ACE" and "Group" was yielded by this analysis. As can be seen in Figure 3A, the pattern for any gene was uniform in that its major allele showed more or less evident positive relationship with systolic blood pressure. However, as shown in Figure 3B, this association with the presence of D allele of the ACE gene was significant only for the power-oriented group of athletes.

To quantify the risk of elevated systolic blood pressure and its correspondence to carriage of major alleles of studied genes, summary rank was computed, indicating occurrence of major alleles in each patient (Table 2).

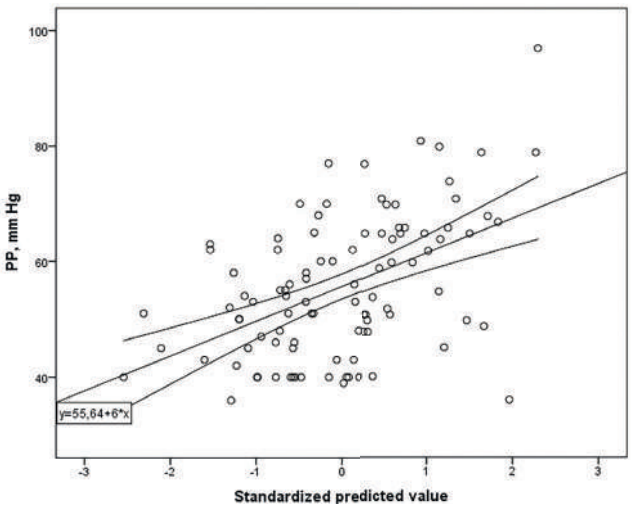


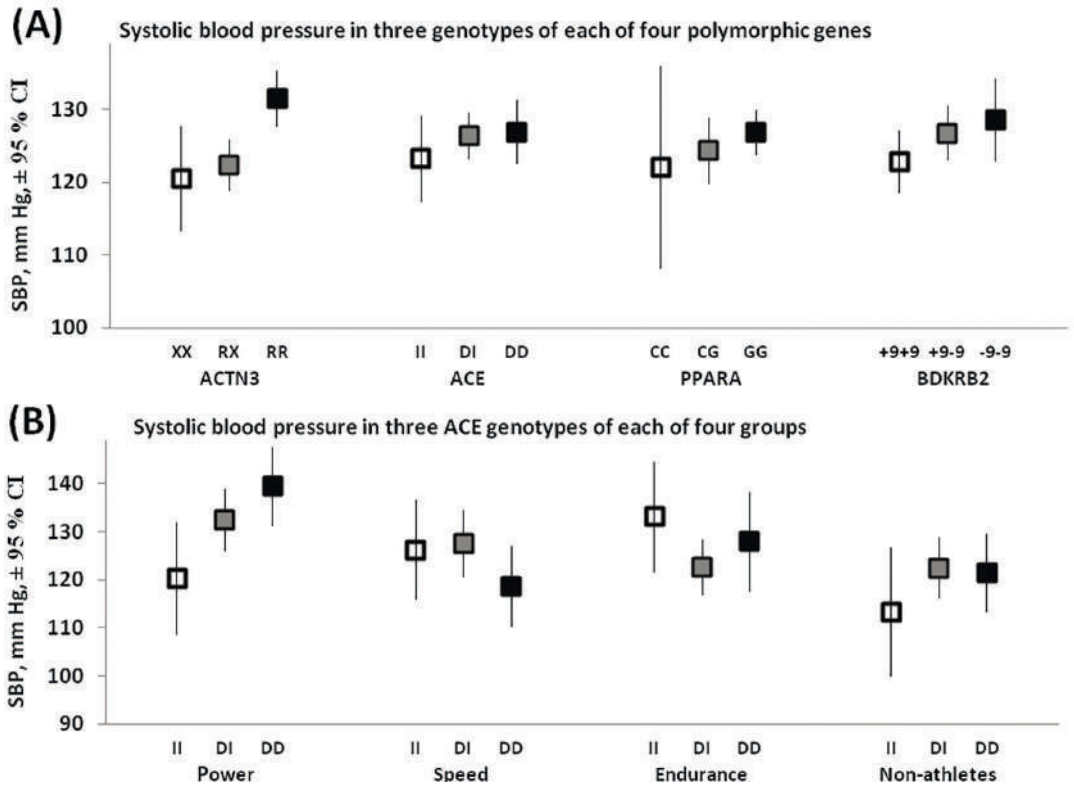
FIG. 2.
Results of predicting pulse pressure (PP) by 7 predictors

TABLE 1

DIFFERENCES BETWEEN ATHLETES GROUPS

Group/Statistics	Mean	Study cohorts			NA	$F_{3/94}$	Pairwise difference	
Variable	SD	PA	SA	EA		*p*	within	between
Age, years	Mean	22.1	20.0	20.1	20.6	2.378	None	None
	SD	3.2	2.8	3.3	2.9	0.075		
Training, years	Mean	6.2	6.6	10.6	0	38.253	PA<EA***, SA<AE**	NA<PA***, SA***, EA***
	SD	3.2	3.9	4.9	0	<0.001		
Status, score	Mean	1.40	1.33	1.56	0	67.802	None	NA<PA***, SA***, EA***
	SD	0.50	0.48	0.51	0	<0.001		
Systolic blood pressure, mm Hg	Mean	132	125	126	121	3.781	None	NA<PA***
	SD	15	9	11	12	0.013		
Diastolic blood pressure, mm Hg	Mean	74	69	68	70	2.073	None	None
	SD	9	9	8	9	0.109		
Pulse pressure, mm Hg	Mean	58	55	58	51	1.986	None	None
	SD	14	13	13	7	0.121		
Sum of major alleles, score	Mean	4.8	4.9	4.6	5.0	0.380	None	None
	SD	1.2	1.6	1.5	1.3	0.769		
Height, cm	Mean	177	179	179	180	0.521	None	None
	SD	7	8	6	6	0.669		
Weight, kg	Mean	84.0	72.9	72.3	68.5	7.137	PA>SA*, EA**	PA>NA***
	SD	17.6	10.0	8.0	10.1	<0.001		
Fat, %	Mean	12.8	8.8	8.5	9.4	8.220	PA>SA***, EA***	PA>NA***
	SD	4.4	2.7	3.0	3.3	<0.001		
Body mass without fat, kg	Mean	72.6	66.4	63.5	61.9	4.262	PA>EA*	PA>NA**
	SD	12.5	8.6	14.1	7.7	0.007		
Muscle mass, kg	Mean	31.4	28.6	28.5	26.7	5.432	None	PA>NA***
	SD	5.4	3.7	3.0	3.3	0.002		
Body water, %	Mean	61.0	64.2	64.1	64.0	7.522	PA<SA***, EA***	PA<NA**
	SD	3.4	2.0	2.1	3.4	<0.001		
Body mass index, kg/m^2	Mean	26.5	22.8	22.5	21.2	17.529	PA>SA***, EA***	PA>NA***
	SD	3.8	1.8	1.8	2.5	<0.001		
Body impedance, Ω	Mean	453	475	481	517	6.124	None	NA>PA***, SA*
	SD	63	38	41	55	<0.001		
Heart rate, beats per minute	Mean	65.6	60.0	57.4	69.3	6.762	PA>EA*,	NA>SA*, EA***
	SD	13.0	8.3	8.0	8.3	<0.001		

Notes. SD: Standard Deviation; Score for Status: 2 – master (master of sport, international class or master of sport or candidate for master of sport), 1 – sportsman (first-class or second-class or third-class sportsman), 0 – non-athlete. Score for sum of major alleles: numbers were assigned for gene variants: 2 – homozygote for the major allele, 1 – heterozygote, 0 – homozygote for the minor allele and, in sum, each individual was scored as carrying 0-8 major alleles; Pairwise difference, within or between: Significance of pairwise difference between three groups within the athlete' subsample (PA, SA, and EA) or between such a group and non-athletes (NA) at ***$p < 0.001$, **$p < 0.01$, and *$p < 0.05$ (*t*-test with Bonferroni correction for multiple comparison).



Estimated marginal means ± Confidence Interval (CI, vertical lines) for each genotype, namely, homozygotes for the minor allele (open squares), heterozygotes (grey squares), and homozygotes for the major allele (filled squares). ***A****. Main effects of factor "Polymorphism" from four two-way ANCOVAs (for each of four genes).* ***B****. Interaction between factors "Polymorphism" and "Group" from the two-way ANCOVA for ACE gene.*

FIG. 3.
Estimated marginal means ± Confidence Interval (CI, vertical lines) for each genotype, namely, homozygotes for the minor allele (open squares), heterozygotes (grey squares), and homozygotes for the major allele (filled squares). A. Main effects of factor "Polymorphism" from four two-way ANCOVAs (for each of four genes). B. Interaction between factors "Polymorphism" and "Group" from the two-way ANCOVA for ACE gene.

TABLE 2

PARAMETERS OF PREDICTING BLOOD PRESSURE

Measure		r/r square	F/*p* ACTN3	Beta/*p*						
				ACTN3	ACE	PPARA	BDKRB2	Status	Training	Age
Systolic	All Athletes	0.4650	3.5	0.2680	0.1010	0.1110	0.1980	0.4090	-0.2600	-0.0660
		0.2160	0.002	0.006	0.308	0.254	0.046	0.002	0.051	0.501
		0.4880	3.0	0.2710	0.0950	0.1140	0.2830	0.1470	-0.3020	-0.0600
		0.2380	0.009	0.017	0.413	0.308	0.014	0.224	0.014	0.58
Diastolic	All Athletes	0.4420	3.1	0.0540	-0.0900	-0.0120	-0.0130	0.2360	-0.3140	0.2690
		0.1950	0.005	0.577	0.371	0.899	0.893	0.073	0.021	<0.001
		0.5140	3.4	0.0560	-0.1070	-0.0760	0.0400	0.1320	-0.2840	0.4140
		0.2640	0.004	0.609	0.35	0.491	0.719	0.267	0.019	0.001
Pulse	All Athletes	0.4890	4.0	0.2310	0.1670	0.1210	0.2100	0.2440	-0.0370	-0.3320
		0.2390	0.001	0.016	0.09	0.207	0.033	0.058	0.773	0.001
		0.4840	2.9	0.2110	0.1600	0.1560	0.2330	0.0460	-0.0860	-0.3390
		0.2350	0.011	0.061	0.173	0.167	0.043	0.704	0.479	0.005

Notes. r: Pearson coefficient of linear correlation; r-square: explained variance; F: F-ratio and p: level of significance (either for F or for beta): Analyzed data presented as All-full cohort (*n*=98), Athletes – subsample of athletes only (*n* = 74). First line: r, F or beta; second line: r-square or *p*-value.

We propose that maximal value calculated as 8 was associated to almost 50 % risk of having systolic blood pressure > 140 mm Hg. On the other hand, this was quite rare occurrence in the overall cohort. For cohort of power-oriented athletes' hazard score was detected at value of 6, indicating a group-specific increase in risk. Individuals with values of 4 or less were considered to have minimal risk. A score of 2 would typically suggest a very low risk; however, no athletes in the power group achieved this score, and it was also uncommon in the other groups, with only two athletes scoring 1 or 2.

As indicated by the results of the final linear regression analysis aimed on predicting sum of major alleles, higher systolic blood pressure but not diastolic blood pressure significantly predicted this sum (Table 3). The association of this sum with either systolic blood pressure or pulse pressure was also significant in non-athletes but the risk to have systolic blood pressure of > 140 mm Hg with increase in number of major alleles remained at a rather low level.

DISCUSSION

Four polymorphic loci were selected for genotyping based on the following previous findings. *ACTN3* R577X and *ACE* I/D were prioritized because the *ACE* I/I and *ACTN3* R577/R577 variants have been consistently linked to endurance and power performance, respectively. The *ACTN3* 577X and *ACE* D variants, in contrast, have shown weaker associations with these traits [19, 20, 21, 22]. Previously we documented lowest values of heart rate variability in the group of athletes homozygous by D allele of *ACE* gene [16]. Therefore, in this exploratory study, we investigated whether some genes involved in heart activity contribute to inter-individual differences in blood pressure parameters among athletes engaged in various sport disciplines.

According to our findings, at least three of the tested polymorphisms (*ACTN3* R577X, *ACE* I/D, and BDKRB2-9/+9) were important predictors of inter-individual variations in systolic blood pressure and pulse pressure, but not

TABLE 3

RESULTS OF REGRESSION ANALYSES AIMED ON PREDICTING SUM OF MAJOR ALLELES

Sample and its subdivisions	All	Athletes					NA
		Athletes	PA	SA	EA	SA+EA	
Three predictors are systolic and diastolic blood pressure plus age							
R	0.384	0.411	0.384	0.471	0.279	0.306	0.526
R^2	0.142	0.169	0.142	0.221	0.041	0.094	0.277
F-ratio	5.408	4.747	5.408	1.897	0.592	1.547	2.555
p for F	0.002	0.005	0.002	0.163	0.627	0.215	0.084
Standardized beta for each of three predictors							
Systolic	0.405	0.419^	0.405^^	0.270	0.303	0.293	0.865
p for *t*	<0.001	<0.001	<0.001	0.188	0.200	0.054	0.015
Diastolic	-0.189	-0.158	-0.189	-0.501	-0.067	-0.174	-0.681
p for *t*	0.093	0.211	0.093	0.074	0.771	0.291	0.051
Age, years	0.155	0.152	0.155	0.452	0.158	0.204	0.168
p for *t*	0.138	0.215	0.138	0.105	0.518	0.231	0.397
Two predictors are pulse pressure and age							
R	0.373	0.391	0.585	0.453	0.247	0.300	0.522
R^2	0.139	0.153	0.342	0.205	0.061	0.090	0.273
F-ratio	7.698	4.422	5.723	2.705	0.714	2.279	3.941
p for F	0.001	0.003	0.010	0.090	0.501	0.114	0.035
Standardized beta for each of two predictors							
Pulse pressure	0.375	0.403	0.584	0.524	0.279	0.341	0.503
p for *t*	<0.001	0.001	0.003	0.033	0.249	0.041	0.013
Age, years	0.185	0.199	0.161	0.368	0.168	0.222	0.155
p for *t*	0.063	0.087	0.363	0.124	0.484	0.182	0.414

Notes. r: Pearson coefficient of linear correlation; r-square: explained variance; F: F-ratio and *p*: level of significance (either for F or for beta): Analyzed data presented as All-full cohort (*n*=98), Athletes – subsample of athletes only (*n* = 74). First line: r, F or beta; second line: r-square or *p*-value.

diastolic blood pressure in athletes. Importantly, previous studies have suggested: (i) a role for *ACTN3* polymorphisms in the maintenance of vascular tone [16, 21, 23], (ii) an increased susceptibility to cardiovascular disease associated with the carriage *ACE* DD allele [24], and (iii) a link between elevated systolic blood pressure in children and carriage of *ACE* DD genotype with the *ACTN3* RR or RX genotypes [22].

It should be mentioned that two other genetic variants, i.e. PPARA rs4253778 G/C associated with endurance orientation, and the forth polymorphism, BDKRB2 –9/-9 was listed among polymorphisms associated with endurance-related performance in, at least, two studies [16, 18]. In the study of Minushkina and colleagues, PPARA genetic variance was linked to presence of left ventricular hypertrophy in patients with hypertension [23]. As for BDKRB2 +9/-9 polymorphism, it was reliably shown that it is involved in modulation of the vascular response to physical activity and significantly associated with left-ventricular growth response [25] as well as with left-ventricular changes in response to antihypertensive treatment [26]. Besides, this polymorphism was associated with left ventricular hypertrophy in hypertension [23] and with blood pressure variations in several studies of specific populations [24, 26, 27].

One of these polymorphisms (*ACE* I/D) was differentially associated with training orientation. It was linked to power-oriented but not to speed- and endurance-oriented training. Such training was characterized by the strongest association with four polymorphisms suggesting that having 6 of 8 maximally possible major alleles led to a 50 % chance to have an elevated systolic blood pressure. The association with polymorphic genes was also significant in non-athletes but did not lead to such profound increase in systolic blood pressure with increase in number of major alleles.

We additionally found that development of elevated systolic blood pressure in the group of athletes trained for power-oriented performance was accompanied by training-specific deviation of the parameters of body's composition from those found in other athletes and non-athletes. It is likely that the changes were not, in general, advantageous for their cardiovascular system. For instance, the athletes of this group have relatively high body mass index that is one of the strongest predictors of hypertension in adults [27].

Therefore, these findings have practical implications, as they suggest the potential for preliminary athletes screening to identify genes involved in development systolic blood pressure in response to intensive power-oriented training.

Surprisingly, one of the four studied genetic variants *PPARA* G/C hasn't shown statistically significant evidence for an association between blood pressure, allele frequency and sport discipline. This may be attributable to the limited sample size of our exploratory study. Furthermore, this polymorphism differed from the other three in that only one previous report suggested its association with individual differences in the regulation of the cardiovascular system, and that study involved patients rather than athletes. In contrast, much more results were reported for three other polymorphisms in the studies of various population including athletes.

We think that it is too early to discuss possible mechanisms underlying the revealed associations of elevated blood pressure with the three polymorphisms, and this exploratory study was not aimed on confirmation of health hazards of elevated systolic blood pressure in athletes. However, the present study, if replicated, seems to provide empirical evidence for association of the underlying genetic variation in "athlete's genes" not only with performance enhancement in the particular sport but also with changes in blood pressure in response to intensive training.

This exploratory study has several limitations. As it has been already mentioned, the sample size is rather small, and the size of the group of non-athletes was smaller compared to the total size of the athlete's subsample. The cross-sectional, non-repeated measures design restricts causal inference. Detailed evaluations of participant's health status and cardiovascular response to exercise were not included. Moreover, a detailed evaluation the interplay between environmental, hereditary, and social parameters driving the observed association between elevated systolic blood pressure and the studied genes is limited by the lack of additional data.

CONCLUSION

We found that certain genetic variants may affect to the development of training-specific and mostly disadvantageous characteristics of body composition. Three polymorphic gene variants could independently predict heart remodeling and future health complications in young athletes.

Conflict of interest

No potential conflict of interest was reported by the authors.

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Information about the authors

Sergey N. Kolomeichuk – Cand. Sc. (Biol.), Head of the Laboratory for Genomics, Proteomics, and Metabolomics, Research Institute of Biomedicine and Biomedical Technologies, Tyumen State Medical University; senior research officer at the Laboratory of Genetics, Institute of Biology, Karelian Research Centre, Russian Academy of Sciences; e-mail: sergey_kolomeychuk@rambler.ru, https://orcid.org/0000-0003-3104-3639

Arcady A. Putilov – Dr. Sc. (Biol.), Leading Researcher at the Laboratory of Sleep/Wake Neurobiology, Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences; e-mail putilov@google.com, https://orcid.org/0000-0003-2779-9046

Alexander Y. Meigal – Dr. Sc. (Med.), Head of the Laboratory of the New Methods in Physiological Research, Institute of High Biomedical Technologies, Petrozavodsk State University; e-mail: meigal@petrsu.ru, https://orcid.org/0000-0003-2088-5101

Artem V. Morozov – leading biologist at the Laboratory of Animal Ecophysiology, Institute of Biology, Karelian Research Centre of the Russian Academy of Sciences; e-mail: artem.morozow@yandex.ru, https://orcid.org/0000-0001-7840-939X

Elena V. Budkevich – Cand. Sc. (Med.), Leading Researcher at the "nanobiotechnology and biophysics" research laboratory, North Caucasus Federal University, e-mail: evbudkevich@ncfu.ru, https://orcid.org/0000-0002-4975-5821

Alexander A. Markov – Cand. Sc. (Med.), Director of the Research Institute of Biomedicine and Biomedical Technologies; Associate Professor of the Department of Medical Prevention and Rehabilitation, Tyumen State Medical University; e-mail: markova@tyumsmu.ru, https://orcid.org/0000-0001-7471-4792

Denis G. Gubin – Dr. Sc. (Biol.), Head of the Laboratory of Chronobiology, Tyumen State Medical University; Leading Researcher, Tyumen Cardiology Research Center; e-mail: dgubin@mail.ru, https://orcid.org/50000-0003-2028-1033