SHORT REVIEW

Advances in athlete genomics in 2019

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Abstract

A literature search revealed that more than 120 genetic markers seemed to be linked to athletic performance. Among them endurance markers: ACTN3 577X, PPARA rs4253778 G, PPARGC1A Gly482 and most widely studied ACE I; power/strength markers: ACTN3 Arg577, AMPD1 Gln12, HIF1A 582Ser, MTHFR rs1801131 C, NOS3 rs2070744 T, PPARG 12Ala and most widely studied ACE D can be taken into consideration as showing positive associations with athlete status. However the genetic architecture of athletic performance seemed to be still the most important challenge and necessary step to full understanding of the background of talent identification both in sport as in dance and other related abilities associated with body movement. On the other hand, the significance of some genetic markers has not been replicated in more than one study.

KEYWORDS: athlete, genetic markers, endurance, power/strenght.

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Physical fitness

Physical fitness (PF) may be defined as the body's ability to perform intensive or long-lasting physical efforts using large muscle groups with maintaining balance of homeostasis. Return of all physiological parameters after completion of an effort goes smoothly to their resting level.

PF is a complex phenotype depending on age, sex, lifestyle, diet, physical activity level, climate and sport or health training. To determine the PF a number of biochemical, physiological, and psychological parameters should be examined. Most often, PF – in particular aerobic capacity – is defined by the maximal oxygen uptake (VO_2max).

Physical fitness is a qualitative trait influenced by abundant components and features of phenotypic variation. Genetic and environmental factors (lifestyle, diet, training) of a given trait may be measured by the heritability coefficient h^2 that shows relative contributions of genetic and non-genetic factors to the total phenotypic variation in a population. In the narrow sense, heritability is a percentage contribution of additive genetic or allelic variation to phenotypic variability. The closer h^2 is to 1 (100%), a given trait is the more genetically determined [13]. On average 66% of the variance in athlete status can be explained by additive genetic factors [1] and are recognized as actually crucial over components of the athletic performance such as strength, power, neuromuscular coordination, endurance, flexibility, psychological traits, and other phenotypes. The resting remaining variance is influenced by non shared environmental factors [7].

Although heritability of athlete status take high values the studies and searching for genetic variants that contribute to success in sport disciplines remain still a challenge. Sports genomics is focusing on the architecture of the genome of elite athletes and historicaly began in the 1998 y after discovery that I/D angiotensin convertase enzyme (ACE) first genetic marker is associated with athletic performance [20].

In recent years a numerous of genetic case-control studies searching for gene variants have been published. In many observations associations with elite athlete status was not confirmed.

Case-control studies involve determining whether one allele is more common in a group of athletes than it is in the general population. It can mean that the allele improve athletic performance. More complicated situation appers in dance since two closely related phenotypes, music [34] and athletic performance [1] contributing different qualities create one consistent "dance" phenotype.

Koutedakis & Jamurtas directly call professional dancers – performing athletes [18].

The challenge in sport genomics is to detect false-positive results, therefore case-control studies should use at least one replication with additional athletic and nonathletic cohorts from different populations [10].

The another approach in sport genomics is cross-sectional association study where examination involved athletes with one genotype/allele show different measures of a trait (lactate, strength, VO_2max, percentage of fast-twitch muscle fibers, cardiac size, etc.) compared to the rest of the analyzed sample.

A new approach is a genome-wide association study (GWAS) that involves rapid scanning several hundred thousand DNA markers of many individuals in searching genetic variations being associated with a certain trait.

A numerous data of evidence indicate that genetic markers may partly explain variability of physical

Table 1. Genetic markers for endurance athlete status

Gene	Polymorphism	Endurance-related marker	Studies with positive results	Studies with negative or controversial results
			Total number of studied athletes	Total number of studied athletes
ACE	Alu I/D (rs4646994)	I	1310	1329
ACTN3	R577X (rs1815739 C/T)	577X	560	3039
ADRA2A	6.7/6.3 kb	6.7 kb	148	–
ADRB1	Ser49Gly (rs1801252 A/G)	49Gly	124	–
ADRB2	Gly16Arg (rs1042713 G/A)	16Arg	629	123
ADRB3	Trp64Arg (rs4994 T/C)	64Arg	100	81
AGTR2	rs11091046 A/C	rs11091046 C	487	–
AQP1	rs1049305 C/G	rs1049305 C	1288	–
AMPD1	Gln12X (rs17602729 C/T)	Gln12	231	84
BDKRB2	+9/9 (exon 1)	9	524	408
	rs1799722 C/T	rs1799722 T	316	–
CKM	A/G NcoI (rs8111989 T/C)	rs1803285 A	176	581
COL5A1	rs12722 C/T (BstUI)	rs12722 T	385	–
	rs71746744 (AGGG/)	rs71746744 AGGG	106	–
COL6A1	rs35796750 T/C	rs35796750 T	661	–
EPAS1 (HIF2A)	rs1867785 A/G	rs1867785 G	451	254
	rs11689011 C/T	rs11689011 T	451	254

GABPB1 (NRF2)	rs12594956 A/C	rs12594956 A	163	–
	rs8031031 C/T	rs8031031 T	74	89
	rs7181866 A/G	rs7181866 G	129	89
GNB3	rs5443 C/T (C825T)	rs5443 T	74	223
HFE	His63Asp (rs1799945 C/G)	63Asp	148	–
HIF1A	Pro582Ser (rs11549465 C/T)	Pro582	316	265
IGF1R	rs1464430 A/C	rs1464430 A	77	–
IL15RA	Asn146Thr (rs2228059 A/C)	rs2228059 A	73	–
KCNJ11	Glu23Lys (rs5219 C/T)	Glu23	282	–
MCT1 (SLC16A1)	Glu490Asp or A1470T (rs1049434 A/T)	Glu490	142	211
NFATC4	Gly160Ala (rs2229309 G/C)	Gly160	694	–
NFIA-AS1	rs1572312 C/A	rs1572312 C	218	–
NOS3	Glu298Asp (rs1799983 G/T)	Glu298	443	–
	$(CA)_n$ repeats	164 bp	316	–
	27 bp repeats (4B/4A)	4B	168	–
	rs2070744 T/C (786 T/C)	rs2070744 T	71	100
PPARA	rs4253778 G/C	rs4253778 G	740	–
PPARD	rs2016520 T/C	rs2016520 C	683	120
	rs1053049 T/C	rs1053049 T	120	–
PPARGC1A	Gly482Ser (rs8192678 G/A)	Gly482	849	508
	rs4697425 A/G	rs4697425 A	127	194
PPARGC1B	Ala203Pro (rs7732671 G/C)	203Pro	578	–
	Arg292Ser (rs11959820 C/A)	292Ser	316	–
PPP3CA	rs3804358 C/G	rs3804358 C	123	100
PPP3CB	rs3763679 C/T	rs3763679 C	123	100
PPP3R1	Promoter 5I/5D	5I	694	–
RBFOX1	rs7191721 G/A	rs7191721 G	218	–
SLC2A4	rs5418 G/A	A	102	–
SOD2	Ala16Val (rs4880 C/T)	C (Ala)	121	508
TFAM	Ser12Thr (rs1937 G/C)	12Thr	588	213
TSHR	rs7144481 T/C	rs7144481 C	218	–
UCP2	Ala55Val (rs660339 C/T)	55Val	694	–
UCP3	rs1800849 C/T	rs1800849 T	877	178
VEGFA	rs2010963 G/C	rs2010963 C	942	–
VEGFR2	His472Gln (rs1870377 T/A)	472Gln	182	–

performance characteristics in response to exercise among individuals [3, 5].

The importance and usefulness of sport-related genetic marker is based on such criteria as total number of studied athletes, frequency of analyzed marker in studied population and type of the polymorphism since missense, non-sense, intronic, etc. polymorphisms that may lead to consequences with different biological effect.

In Tables 1-2 there are presented most frequently investigated and the most important genetic markers associated with endurance (Table 1) and power/strength (speed/strength) athlete status.

Gene markers for endurance athlete status

The ability to perform endurance exercise is influenced by factors relating to cellular metabolism and cardiovascular function: (i) the proportion of slow-twitch fibers in skeletal muscle and (ii) maximal cardiac output which underlie the maximal rate of oxygen consumption (VO_2max).

Factors affecting the VO_2max may be classified to: (1) muscular blood flow, (2) the respiratory system, (3) blood circulation, and (4) muscle metabolism. The 1-3 groups are associated with oxygen transportation to mitochondria, the last one is concerned with oxidative processes in the mitochondria. The most important determinants affecting the VO_2max include: muscular capillary density, the number of mitochondria in myocyte, cardiac output, hemoglobin level, and activity of oxidative enzymes.

Genetic markers associated with endurance include among others: ACE gene that tonic regulatory function in circulatory homeostasis [12, 17, 20, 22], the ADRA2A gene (location: 10q24–q26) mediating the physiological effects of the epinephrine and the norepinephrine [33], AGTR2 rs11091046 C allele (location: Xq22–q23) regulator of skeletal muscle growth and differentiation [21], AQP1 rs1049305 C allele (location: 7p14) responsible for transporting of water across cell membranes [19], AMPD1 Gln12 allele (location: 1p13), which catalyzes the deamination of AMP to IMP in skeletal muscle and it's deficiency may be a cause of exercise-induced myopathy [26], BDKRB2 29 and rs1799722 T allele (location: 14q32.1–q32.2) an endothelium-dependent vasodilator acting via the bradykinin B2 receptor which absence is associated with increased efficiency of muscular contraction [32], calcineurin/NFAT-related genetic markers regulator of skeletal muscle differentiation, hypertrophy, and fiber-type composition, leading to different cardiac/skeletal muscle phenotypes [28], the PPP3CB gene

rs3763679 C/T is associated with resting heart rate [65, 66], CKM rs8111989 A allele (location: 19q13.2–13.3) essential enzyme of energy supply for muscle [29] and the rs8111989 A/G CKM gene polymorphism that is associated with physical performance [27], COL5A1 gene (location: 9q34.2–q34.3) an extracellular matrix protein of elongated fibrils, tendon, ligament, and skin that is associated with improved running performance [24], HIF1A Pro582 allele (location: 14q23.2) responses to hypoxic stimuli and HIF1A Pro/Pro homozygotes are associated with the ability to increase VO_2max through aerobic exercise training [25] and endurance athlete status [8], NOS3 Glu298, 164-bp, 4B and rs2070744 T alleles (location: 7q36) as involved with regulating vascular function that are associated with higher aerobic capacity [8], PPARD rs2016520 C and rs1053049 T alleles as involved in regulation fatty acid oxidation, cholesterol metabolism, and thermogenesis that are associated with enhancing running endurance [31], UCP2 55Val allele and UCP3 rs1800849 T allele as involved in uncoupling OXPHOS from ATP synthesis in certain tissues and regulation of lipid metabolism and energy expenditure Val/Val genotype that is associated with higher exercise efficiency [6].

Some of mentioned above result were not confirmed and this information is enclosed in Table 1.

Gene markers for power/strength athlete status

Despite in exercise physiology power (speed) and strength are recognized as different muscle properties in genetic study these phenotypes are usually regarded in common and described as power/strength (speed/strength) athlete status with the heritability approximately 30-80% [15]. At east 43 genetic markers are associated with power/strength athlete status (Table 2) where some of them seemed characterized more significant effect than others. The mapping of genes that influence to the development of power/strength is complicated task due to the additive character of these abilities and the accumulative effect of multiple genes with an insignificant effect.

Short-lasting efforts being in opposition to long-lasting aerobic efforts reguire developing of maximal force and domination of an anaerobic metabolism. The essential energy carrier in both types of efforts is ATP; however, the sources of ATP resynthesis are different. The ATP deposits in muscles are utilized up a seconds after the beginning of exercise. Thus reactions are activated that supplemented the cellular supplies of ATP independently of the presence of oxygen. The activation of anaerobic ATP sources is fundamental in short-lasting efforts of great

Table 2. Genetic markers for power/strength athlete status

Gene	Polymorphism	Power/strength related marker	Studies with positive results — Total number of studied athletes	Studies with negative or controversial results — Total number of studied athletes
ACE	Alu I/D (rs4646994)	D	385	618
ACTN3	R577X (rs1815739 C/T)	Arg577	1484	498
ADRB2	Gly16Arg (rs1042713 G/A)	Gly16	100	–
	Gln27Glu (rs1042714 C/G)	27Glu	100	–
AGT	Met235Thr (rs699 T/C)	235Thr	163	–
AGTR2	rs11091046 A/C	rs11091046 A	615	–
AMPD1	Gln12X (rs17602729 C/T)	Gln12	510	–
CKM	A/G NcoI (rs8111989 T/C)	rs1803285 G	233	–
CREM	rs1531550 G/A	rs1531550 A	257	–
DMD	rs939787 C/T	rs939787 T	492	–
EPAS1 (HIF2A)	rs1867785 A/G	rs1867785 G	338	–
	rs11689011 C/T	rs11689011 C	338	–
GALNT13	rs10196189 A/G	rs10196189 G	257	–
HIF1A	Pro582Ser (rs11549465 C/T)	582Ser	476	81
IGF1	C-1245T (rs35767 C/T)	rs35767 T	87	–
IGF1R	rs1464430 A/C	rs1464430 C	82	–
IL1RN	VNTR 86 bp (intron 2)	IL1RN*2	205	–
IL6	174 C/G (rs1800795 C/G)	rs1800795 G	211	81
MCT1 (SLC16A1)	Glu490Asp or A1470T (rs1049434 A/T)	490Asp	100	198
MTHFR		A1298C (rs1801131 A/C)	923	–
MTR		A2756G (rs1805087 A/G)	77	–
MTRR		A66G (rs1801394 A/G)	77	–
NOS3		rs2070744 T/C (786 T/C)	192	–
		Glu298Asp (rs1799983 G/T)	29	–
PPARA		rs4253778 G/C	260	81
PPARG	Pro12Ala (rs1801282 C/G)	12Ala	552	–
SOD2	Ala16Val (rs4880 C/T)	C (Ala)	598	–
UCP2	Ala55Val (rs660339 C/T)	Ala55	29	–
VDR	FokI f/F (rs10735810 T/C)	rs10735810 T	125	–

intensity (weightlifting – is an example of static exercises, sprint runs – is an example of dynamic exercises).

In short-time exercises significant propperties of muscles include fiber composition, i.e. the participation of type II fast-twitch fibers which determine contractile power and generate considerable muscle force in a short time and the cross-sectional area of the muscle. Examples of genetic markers that influence power/strength elite status are mentioned below and among others include: ACE D allele (location: 17q23.3) significantly correlated with strength, cross-sectional area of the muscle and an increased percentage of fast-twitch muscle fibers [35], ACTN3 Arg577 allele (location: 11q13.1) that expression is limited to fast muscle responsible for generating force at high velocity, AMPD1 Gln12 allele (location: 1p13) an important regulator of muscle energy metabolism that is associated with faster power decrease in the AMPD-deficient group during the generating the maximal power in the Wingate test [11], DMD rs939787 T allele which is favorable for strength/power performance, HIF1A 582Ser allele (location: 14q23.2) regulator of glycolysis under low-oxygen conditions which is overrepresented in power-oriented athletes [9], IGF1 rs35767 T and IGF1R rs1464430 C allele (location: 12q23.2) playing a role in muscle cell growth that is associated with higher frequency in power-oriented athletes [4], IL1RN*2 allele (location: 2q14.2) taking part in immune and inflammatory responces to exercise may have an advantage in adaptation to high-intensity exercise [23], NOS3 rs2070744 T allele (location: 7q36) nitric oxide synthase gene that generates NO in blood vessels and is associated with power performance, PPARA rs4253778 C allele (location: 22q13.31) that regulates the expression of genes involved in lipid metabolism and is associated with the hypertrophy [16], PPARG 12Ala allele (location: 3p25) regulator of adipogenic and lipogenic processes that is associated with skeletal muscle glucose uptake [30] and greater area of muscle fibers [2], VDR rs10735810 T allele (location: 12q13.11) playing a role in sustaining normocalcemia and has effects on bone and skeletal muscle and being related to the bone mineral density in response to strength training [14].

Conlusions

It has long been recognized that the variability of physical performance traits and the ability to become an elite athlete have a significant genetic background. The number of listed genes that has been associated with various components of physical fitness is long and grows dynamically in each year. The available research results constitute a database which still is being systematized before implementing genetic profiling in sport. These results should also contain data of studies on Polish population where athletes represent various sports. As it is predicted "the next decade will be an exciting period for sports genomics, as we apply the new DNA technologies (whole-genome sequencing, GWAS, epigenomics, transcriptomics, proteomic profiling, etc.) and bioinformatics to further dissect and analyze the genetic effects on human physical ability" [13].

Ahmetov and Fedotovskaya note that "efforts to perform GWAS in the cohorts of athletes are presently underway represent at least athletes from Australia, Canada, Ethiopia, Finland, Germany, Greece, Italy, Jamaica, Japan, Kenya, Poland, Russia, and USA" [1].

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