On Sports And Genes

Gili Zilberman-Schapira[1,2,#], Jieming Chen[1,2,#] and Mark Gerstein[1,3,4,*]

[1]*Program in Computational Biology and Bioinformatics;* [2]*Integrated Graduate Program in Physical and Engineering Biology;* [3]*Department of Molecular Biophysics and Biochemistry; and* [4]*Department of Computer Science, Yale University, New Haven, CT 06520*

Received: May 15, 2012 Revised: July 07, 2012 Accepted: July 07, 2012

Abstract: Our genes influence our athletic ability. However, the causal genetic factors and mechanisms, and the extent of their effects, remain largely elusive. Many studies investigate this association between specific genes and athletic performance. Such studies have increased in number over the past few years, as recent developments and patents in DNA sequencing have made large amounts of sequencing data available for such analysis. In this paper, we consider four of the most intensively studied genes in relation to athletic ability: angiotensin I-converting enzyme, alpha-actinin 3, peroxismose proliferator-activator receptor alpha and nitric oxide synthase 3. We investigate the connection between genotype and athletic phenotype in the context of these four genes in various sport fields and across different ethnicities and genders. We do an extensive literature survey on these genes and the polymorphisms (single nucleotide polymorphisms or indels) found to be associated with athletic performance. We also present, for each of these polymorphisms, the allele frequencies in the different ethnicities reported in the pilot phase of the 1000 Genomes Project – arguably the largest human genome-sequencing endeavor to date. We discuss the considerable success, and significant drawbacks, of past research along these lines, and propose interesting directions for future research.

Keywords: Athletic performance, genomics, genomic polymorphisms, elite athletes, angiotensin I-converting enzyme, Alpha-actinin 3, Peroxismose proliferator-activator receptor alpha, Nitric Oxide Synthase 3.

INTRODUCTION

Genetics plays a role in determining an individual's athletic ability (or athletic potential). Although this is a well-known fact, the causal genetic factors and mechanisms, and the extent of their effects still remain largely elusive. Over the past decades, a large number of studies revealed various associations between specific genes and their polymorphisms and physical ability in various sport fields and across different ethnicities and genders. On some of the studied genes, such as the angiotensin I-converting enzyme, significant amounts of data have been collected, and mechanisms explaining their effects on athletic ability have been proposed and analyzed. In contrast, other genes, such as peroxismose proliferator-activator receptor alpha (PPARα), have only received attention in this context fairly recently, and mechanisms explaining this association are still unknown.

Despite all these uncertainties, the connection between genetics and athletic phenotype is indeed alluring. Efforts have been and are still being made to archive earlier research. There are thorough reports of a "human gene map" of such genes related to human performance that are being discussed and made available [1-7]. Our goal in this paper is not then to perform a similar exhaustive enumeration of all the genes and their corresponding studies. Instead, we attempt to offer a different perspective to genetic associations with athletic performance, via a methodical inquiry. Specifically, we consider only four genes for which at least three different studies of elite athletes support association with athletic ability, namely, the angiotensin I-converting enzyme (ACE), α-actinin-3 (ACTN3), nitric oxide synthase 3 (NOS3), and peroxismose proliferator-activator receptor alpha (PPARα). These represent a small but well supported set of genes. We do an extensive literature survey on these genes and the associated polymorphisms (single nucleotide polymorphisms or indels) that have been found to be associated with athletic performance. In addition, we present, for each of these polymorphisms, the allele frequencies in the different ethnicities reported in the 1000 Genomes Project – the most recent large-scale human genome-sequencing endeavor (Table **1**).

*Address correspondence to this author at the Program in Computational Biology and Bioinformatics, Yale University 06520; Tel: 203-432-6105; E-mail: mark.gerstein@yale.edu

#These authors contributed equally

RESULTS

Angiotensin I-Converting Enzyme (ACE)

ACE insertion/deletion (I/D) polymorphism is the earliest evidence that links genetics to elite athletic performance [9]. A plethora of research has been performed in athletes (versus non-athletes) from a variety of sports and from different ethnic backgrounds (Table **2**). This is a 287-base-pair insertion in an *Alu* intronic region of chromosome 17 (long arm 17q23, with dbSNP [10] ID rs4340) has been associated with performance in endurance sports and the corresponding absence of this segment (D) with strength- and power-oriented sports [9]. However, exceptions have also been observed in some studies, particularly looking at some (or a combination of) ethnic groups and sport combinations. Table **2** gives a tabulation of some of this research done to date:

1872-2156/12 $100.00+.00

Table 1. Summary of the Allele Frequencies from the Pilot Phase of the 1000 Genomes Project [8]

Gene	dbSNP ID	Chr	Position	Polymorphism Alleles A/B	Population Allele Frequencies (Number of Individuals)					
					CEU (120)		CHB+JPT (120)		YRI (118)	
					(Allele A)	(Allele B)	(Allele A)	(Allele B)	(Allele A)	(Allele B)
ACE	rs4340	17	58919125	Large indel I/D	--	--	--	--	--	--
ACTN3	rs1815739	11	66084671	SNP C/T	0.492	0.508	0.467	0.533	0.898	0.102
NOS3	rs2070744	7	150321012	SNP C/T	0.442	0.558	0.083	0.917	0.119	0.881
PPARα	rs4253778	22	45009298	SNP C/G	0.175	0.825	--	--	0.831	0.169

Positions are based on NCBI reference genome, build 36. Populations abbreviations: CEU = Caucasians with European ancestry from Utah, CHB = Han Chinese from Beijing, JPT = Japanese individuals from Tokyo, YRI = Yoruba from Ibadan, Nigeria. Unfortunately, the indel from ACE cannot be extracted meaningfully from the pilot phase of the 1000 Genomes data, hence is excluded in this table.

Table 2. This Table Shows a Compilation of Some Research Studies in Relation to Elite Athletic Performance of Gene ACE.

Sample Size (Male/Female/Total)	Ethnic Group(s)	Case Samples	ACE Polymorphism Associated with Athletic Phenotype (I/D)		Study (Year)
			Endurance	Power	
Cases: 33/0/33 Controls: 1906/0/1906	Caucasians	British elite mountaineers (ascension >7000m without using supplemental oxygen)	I	---	[11] (1998)
Cases: --/--/92# Controls: --/--/47#^	Caucasians South Asians (from Nepal, Indian and Bhutan)	Elite mountaineers who climbed > 8000 meters high.	I	---	[12] (2007)
Cases: 43/21/64 Controls: 75/39/114	Caucasians	Australian national rowers	I	D	[13] (1998)
Cases: 48/43/91 Controls: --/--/1906#	British African, Carribeans and Caucasians	British potential Olympic runners	I	D	[14] (1999)
Cases: 232/59/291 Controls: 40/45/85	Kenyans	Elite endurance runners (including Olympic runners, world record holders and Commonwealth champions)	No assoc	---	[15] (2005)
Cases: 57/46/103 Controls: 1248/0/1248*	European and American Caucasians	Elite swimmers	---	D	[16] (2001)
Cases: 21/0/21 Controls: 199/0/199	Mixed (from Canada, Brazil, Italy, Australia, France, Holland, Slovenia, Germany, Czech, Switzerland and Argentina)	Elite long-distance (>5km) swimmers from 2002 Open Water Swimming World Championships in Sharm-el-Shiekh	I	---	[17] (2004)
Cases: 38/33/71 Controls: 49/51/100	Portuguese	Elite and average swimmers	---	D	[18] (2009)
Cases: 6/11/17 Controls: ---	Southeast Asians	Rugby players	II (genotype)	---	[19] (2009))
Cases: 447/0/447 Controls: 199/0/199	Caucasians (of different nationalities)	Participants of the 2000/2001 South African Ironman Triathlons	I	---	[20] (2004)
Cases: 60/56/116 Controls: 156/155/311	Jamaican and Americans with self-classified as >50% African-American	Elite national and international level athletes in sprint (<400m), jump and throw events	---	No assoc	[21] (2010)

(Table 2) contd….

Sample Size (Male/Female/Total)	Ethnic Group(s)	Case Samples	ACE Polymorphism Associated with Athletic Phenotype (I/D)		Study (Year)
			Endurance	Power	
Cases: 141/76/217 Controls: 269/180/449	Russians	Elite athletes from swimming, track-and-field athletics, cross-country skiing and triathlon	I	D	[22] (2001)
Cases: 66/14/80 Controls: 39/41/80	Turkish	Endurance athletes (national or international level) from middle-distance running, basketball, han-dball, football	I	---	[23] (2004)
Cases: 50/30/80 Controls: --/--/523#	Finnish	Finnish national team long distance runners, orienteers, cross-country skiers and triathletes	No assoc	---	[24] (1999)
Cases: 219/185/404 Controls: --/--/1906#	British African, Carribeans and Caucasians	British potential Olympic competi-tors in 19 sports disciplines	No assoc	No assoc	[14] (1999)
Cases: 81/39/120 Controls: 347/338/685	Caucasians	Australian representatives in highly aerobic sports (hockey, cycling, skiing, track and field, swimming, rowing, gymnastics and others)	No assoc	No assoc	[25] (1999)
Cases: 60/56/116 Controls: 156/155/311	Jamaican and Americans with self-classified as >50% African-American	Elite national and international level athletes in sprint (<400m), jump and throw events	---	Depletion of X	[21] (2010)
Cases: 152/41/193 Controls: 167/83/250	Lithuanian Caucasians	Elite Olympic and international level athletes (various endurance and power sports)	D	I	[26] (2011)

'---' denotes that the study does not conduct investigation in that genotype-phenotype relationship.

'^' controls in this study were mountaineers that did not climb more than 8000 meters high, unlike in other studies where the controls were non-athletes.

*There are 6 control groups used in this study, but this number corresponds to a control cohort of British military recruits that the authors deem a better control in terms of age and sample size.

Specific gender makeup in case and/or control cohort were not provided in these studies.

There is also extensive research on the mechanisms through which the ACE I/D is affecting athletic performance. In general, ACE is part of the renin-angiotensin system (RAS) that plays a homeostatic role in the human circulatory system. ACE breaks down vasodilator kinins and promotes vasoconstrictor angiotensin II formation. The presence of the 287-base-pair segment (genotypes II or ID) reduces ACE production, thereby increasing the effects of vasodilators and correspondingly decreasing the effects of vasoconstrictors. This has been proposed as the causative polymorphism for the effect of ACE on the local RASs in myocardiac muscles [27] and skeletal muscles [28], leading to increased vasodilation and therefore substrate delivery to the muscles [29]. In light of this and several other corroboratory high altitude studies, it has since been speculated that the ACE polymorphism might be associated with peak maximal oxygen and metabolic efficiency [30,31].

A very recent postulation has called for an evaluation of the epigenetic regulatory profile of the ACE locus as a more possible route of association with endurance physiology. A follow-up comment to this perspective gave also a very brief overview of the loopholes that perhaps a naïve genetic association has overlooked: for instance, systemic feedback mechanisms and protein structural mechanisms [32-34].

Alpha-Actinin 3 (ACTN3)

The ACTN3 gene is found on chromosome 11. It produces an actin-binding protein – α-actinin-3 – that forms the major component of the Z line where actin thin filaments are cross-linked in fast-twitch muscle fibers cells. Absence of this protein is typically associated with the mutation R577X [35] (ID rs1815739 in dbSNP [10]). These fast-twitch muscles are especially relevant in power events such as weight-lifting and sprinting since they are responsible for force generation at high velocity. However, even though α-actinin-3 is a component of the fast-twitch muscles, lacking it is non-pathogenic [36]. The development of an ACTN3 genetic screen from the same laboratory [37] facilitated Yang *et. al.* [36], in 2003, to link ACTN3 to athletic performance in Caucasians:

1) Comparing elite sprint athletes, elite endurance athletes and non-athletes, the sprinters have significantly higher frequencies of the wild type allele 577R than the other two groups of people.

2) Comparing male and female sprint athletes, there seems to be a higher propensity for a heterozygous genotype of 577RX in the female sprinters, indicating a differential effect of ACTN3 genotype on gender.

This sparked a slew of ACTN3 studies in relation to muscle performance that span across multiple dimensions: nationalities, sports, athletic capabilities and age. There also appears to be a gender-specific distinction in allele frequencies. α-actinin-3 has been shown to influence muscle physiology in women more than in men, with deficiency giving rise to lower muscle strength and fat-free mass (lean muscle mass) [38-40]. In addition, in several studies, the XX genotype (α-actinin-3 deficiency) has been known to be enriched in female endurance athletes as compared to the general population, while there is no such evidence amongst the male endurance athletes (Table **3**), implying an advantageous effect of X allele in women endurance athletes than men.

Table 3. This Table Shows a Compilation of Some Research Studies in Relation to Elite Athletic Performance of ACTN3.

Sample Size (Male/Female/Total)	Ethnic Group (s)	Case Samples	ACTN3 Polymorphism Associated with Athletic Phenotype (I/D)		Study (Year)
			Endurance	Power	
Cases: 72/35/107 (short-distance) 122/72/194 (long-distance) Controls: 134/292/436	Caucasians (Australian)	Sprinters (<800m), short-distance swimmers (<200m), track cyclists, speed skaters, judo athletes Long-distance cyclists, rowers, swimmers (>400m), track athletes (>5000m), cross-country skiers	X	R	[36] (2003)
Cases: --/--/141# Controls: --/--/1060#	Finnish	Elite track and field sprinters and endurance athletes	---	R	[41] (2005)
Cases: 71/4/75 Controls: 461/415/876	Caucasian-Americans and African-Americans	Elite bodybuilders, power lifters and college level strength athletes	---	R	[42] (2007)
Cases: 363/123/486 Controls: 524/673/1197	Russians	Elite athletes from various sports (alpine skiing, artistic gymnastics etc.)	No assoc	R	[43] (2008)
Cases: 293/163/456 Controls: 532/679/1211	Russians	Elite athletes in endurance sports (biathlon, triathlon, cross-country skiing, swimming 1500m etc.)	R	---	[44] (2008)
Cases: --/--/101 Controls: --/--/181	Greeks	Elite track-and-field power and endurance athletes and sprinters	No assoc	R	[45] (2008)
Cases: 119/36/155 Controls: --/--/240	Israeli Caucasians (2:1 ratio of non-Ashkenazi : Ashkenazi)	Elite power and endurance athletes	X	R	[46] (2009)
Cases: 17/18/35 Controls: 31/22/53	Italians	Elite gymnasts	---	R (males only)	[47] (2009)
Cases: 316/0/316 Controls: 304/0/304	Athletes from Germany, US, and Finland	Elite endurance athletes from the Genathlete Project, from sports including cross-country skiing, bi-, triathlon, cycling, running and rowing	No assoc	---	[48] (2010)
Cases: 132/118/250 Controls: 298/152/450	Chinese	Elite endurance athletes from various sports (rowing, marathon, track athletes > 5000m, swimmers > 400m etc.)	X (females only)	---	[49] (2010)
Cases: 152/41/193 Controls: 167/83/250	Lithuanian Caucasians	Elite Olympic and international level athletes (various endurance and power sports)	---	X	[26] (2011)
Cases: 31/35/66 Controls: 243/91/334	Spanish	Elite volleyball players	No assoc	No assoc	[50] (2011)
Cases: 71/44/115 Controls: 595/706/1301	Russian	Elite speed skaters (of different racing distances)	X	R	[51] (2011)
Cases: 105/63/168 Controls: 361/242/603	Chinese (Taiwan)	Elite sprint swimmers (<400m)	---	R (female only)	[52] (2011)

'---' denotes that the study does not conduct investigation in that genotype-phenotype relationship.

Specific gender makeup in case and/or control cohorts were not provided in these studies.

Despite also a wealth literature on non-athletic cohorts, we are particularly interested only in athletic studies. Notably, α-actinin-3 has been shown to be an important genetic factor in elite athletes, required in power or strength performance and has been replicated in numerous studies across diverse ethnicities (Table **3**).

Nitric Oxide Synthase 3 (NOS3)

The NOS3 gene is located on chromosome 7. Two different polymorphisms in the NOS3 gene have been studied in relation to athletic ability. The first is a -786 T/C polymorphism, located 786 bases upstream of the gene in the promoter region, and the second is a Glu894Asp polymorphism, located in the coding region [53-62]. As there are too few significant results associating the Glu894Asp polymorphism with athletic performance, we focus hereafter only on the -786 T/C polymorphism.

The -786 T/C polymorphism in the NOS3 gene (ID rs2070744 in dbSNP [10]) has only fairly recently (less than a decade ago) been considered to be associated with athletic performance. Recent studies along these lines explore how genetic variability in NOS3 affects athletic performance in different sports, primarily among Caucasian European athletes. In a key paper by Gómez-Gallego *et al.* the T allele has been found to be significantly enriched in power athletes compared with the controls and with endurance athletes [59]. In addition, the C allele was found to be overrepresented in elite soccer players, who are regarded to be exhibiting a "mixed" athletic phenotype requiring both endurance and power abilities [60]. A summary of these findings is given in Table **4**.

The C allele in the -786 T/C polymorphism was shown to result in significantly reduced transcription of the NOS3 gene. This results in lower levels of the encoded protein, known as the endothelial nitric oxide synthase (eNOS) and consequently, reduced oxygenation to working tissues. The T allele is associated with increased promoter activity. An increased NO level seems to be beneficial in power sports [61].

A possible mechanism to explain these findings lies in the role of eNOS in the vascular system. The eNOS enzyme catalyzes the conversion of the amino acid L-arginine to L-citrulline and finally to nitric oxide (NO) [60]. NO regulates the vascular tone and facilitates vasodilation, thus increasing blood supply to tissues, e.g. to working muscles. New studies suggest that NO is also involved in glucose uptake in working muscles, a process which can limit the local blood flow and in doing so influence endurance performance [59].

Peroxismose Proliferator-activator Receptor Alpha (PPARα)

The PPARα gene is located on chromosome 22, and encodes the peroxismose proliferator-activator receptor α, which is a ligand-activated transcription factor [63] and a member of the nuclear receptor transcription family [64]. This transcription factor regulates the expression of genes involved in fatty acid metabolism.

Past studies examined the potential association between the intron 7 G/C polymorphism (ID rs4253778 in dbSNP [10]) and athletic performance [63,65–67]. These cohorts examined the different allele frequencies that correspond to athletes in different sport fields, and of different ethnicities, compared with athletic controls, or with healthy active individuals. These findings are summarized in Table **5**. Most of these studies find a significant association between the G allele and endurance traits, as well as an association between the C allele and power athletic traits. A comprehensive study by Ahmetov *et al.* [66] further examined the association of the PPARα polymorphism with athletic ability in more specific categories: different sports fields, athletic levels (from regional to elite level athletes), and gender. While they find similar allele frequencies among male and female athletes, their findings show that there is an increased frequency of the C allele in the power group, and of the G allele in the endurance group.

In Ahmetov *et al.* [66], a possible mechanism for interpreting this association is presented based on muscle fiber-typing of 40 men. They found a significant correlation between the intron 7 G/C polymorphism and the muscle fiber specification. According to their findings, the G allele is associated with an increased proportion of muscle fibers that is beneficial in endurance activity, as these fibers use oxygen in a more efficient manner during continuous muscle activity. Sprinters, in contrast, tend to have a higher proportion of "fast twitching" muscle fibers that endow them with bursts of power.

DISCUSSION

The above literature survey revealed considerable success in uncovering connections between genotype and athletic phenotype. Indeed, many companies have come up with "sport genetics tests" that are based largely on such scientific studies. However, while the notion of linking one's genotype to athletic potential is certainly attractive, our survey also exposed the limitations of these studies, which render some of their conclusions extremely problematic. Specifically, insufficient comparative analyses across genders, ethnicities, and sport fields, greatly limits our ability to draw meaningful conclusions. We now elaborate on these three crucial factors.

The inherent differences in the physiology, psychology and anatomy of males and females clearly play a major role in athletic performance. The genetic association to athletic ability can thus sometimes be gender-specific. For instance, in several occasions ACTN3 has shown an enrichment of XX genotype in female endurance athletes but no such association has been found in male endurance athletes [36,49]. Also, it appears that the muscle physiology is more affected by a deficiency of α-actinin-3 in women than in men [38,39,68]. We have deliberately included the gender constitution in each study, thus demonstrating that many of the research studies (as seen in Tables **2**-**5**) only focus on a single gender or, present the combined results for both genders.

Ethnicity is another important variable to examine. It has already been known that even within a less genetically heterogeneous ancestry, e.g., among Europeans [69], or among

Table 4. This Table Shows a Compilation of Some Research Studies in Relation to Elite Athletic Performance of NOS3.

Sample Size (Male/Female/Total)	Ethnic Group (s)	Case Samples	NOS3 -786 T/C Polymorphism Associated with Athletic Phenotype		Study (Year)
			Endurance	Power	
Cases: 100/--/100 (endurance athletes) 53/--/53 (power athletes) Controls: 100/--/100 (healthy non athletes)	Spanish Caucasians	Endurance: road cyclists and endurance runners. Power: jumpers, throwers and sprinters.	---	T	[59] (2009)
Cases: 29/--/29 (power sports) 53/--/53 (intermittent sports) Controls: 38/--/38	Italian Caucasians	Power sports: sprinters, short distance runners, volleyball players Intermittent sports: football, basketball, hockey.	---	T	[62] (2011)
Cases: 60/--/60 (Soccer players) Controls: 100/--/100 (endurance athletes) 53/--/53 (power athletes) 100/--/100 (healthy non athletes)	Spanish Caucasians	Professional soccer players (considered mixed phenotype) from the best team according to FIFA.	C		[60] (2012)

'---' denotes that the study did not investigate that genotype-phenotype relationship.

Table 5. This Table Shows a Compilation of Some Research Studies in Relation to Elite Athletic Performance of PPARα.

Sample Size (Male/Female/Total)	Ethnic Group(s)	Case Samples	PPARα Intron 7 G/C Polymorphism Associated with Athletic Phenotype		Study (Year)
			Endurance	Power	
Cases: --/--/786 Controls: --/--/1,242	Caucasian Russians	Cases: Aerobic group: swimmers (800-1,500 m), triathletes (3000-5000 m), skaters (4-7 min), cross-country skiers, biathletes, road-cyclist and rowers (predominant aerobic energy production). Anaerobic group: runners (60-400 m), skaters (50-100 m) and weightlifters with predominantly anaerobic energy production. Mixed group: court tennis players, wrestlers, ice hockey players and boxers.	GG No significant difference in the C allele frequency between the mixed group and the controls.	C	[66] (2006)
Cases: 119/36/155 (endurance and sprint athletes) Controls: --/--/240	Israeli Caucasians	74 long distance runners 81 sprinters	GG	No assoc	[65] (2010)
Cases: 55/--/55 rowers (endurance) Controls: 115/--/115	Polish	50 elite rowers and 25 non-elite (regional level) rowers.	G	---	[63] (2011)
Cases: --/--/60 Controls: 181/--/181	Polish Caucasian	Judokas, wrestlers, and boxers (considered mixed phenotype)	G		[67] (2011)

'---' denotes that the study did not investigate that genotype-phenotype relationship.

the Han Chinese [70], there are still discernible differences in the genetic profiles of individuals. Population stratification is therefore a prominent issue to consider in such studies. For instance, a study of Russian athletes revealed an association of R allele to endurance sports (biathlon, triathlon etc.) instead of the X allele, which is the consensus from most studies in ACTN3. In addition, considering different ethnic groups together might lead to wrong conclusions, e.g., an enrichment of an allele in one ethnic group might be canceled out by depletion in another ethnic group. A potential case in point might be the Genathlete study [48] where athletes from Germany, the US and Finland were combined to test for association between ACTN3 and endurance traits (Table **3**). No genetic association was found although in past studies endurance athletes with Caucasian ancestry have been shown consistently to have an association. Understanding the role of ethnicity in genetic association naturally becomes even more complicated when athletes are of mixed ancestry - an increasingly common phenomenon in today's highly globalized world.

There is also the issue of the specific sport field considered. Most studies employ a dichotomy of "endurance-" and "strength-based" sports. Inevitably, the question of deciding where to place sports that require a mixture of both arises, and the answer is often fairly subjective. For instance, some studies use the 200-meter mark in running events to differentiate sprinters [14], whereas other studies use 400 meters [45]. This heterogeneity affects the choice of "case" individuals and deeply impacts the statistical outcome. An interesting observation is that the strongest genetic evidence seems to be derived from the most extreme level of sports: >2km swimming, >7000km climbers without supplemental oxygen, 100-meter dash, etc.

Another glaring limitation of all these studies is the small sample size. This is difficult to overcome, because it is imperative in these studies to include only elite athletes as the test cases. This narrows the human performance spectrum to those only at the highest end. Many of the studies performed examine active elite athletes. Perhaps the recruitment of retired elite athletes (either due to age or to injury) might be able to bolster the ranks.

CURRENT AND FUTURE DEVELOPMENT

Looking forward, as we herald the era of personal genomics, an individual's genome data will potentially be a common commodity. A person's genetic makeup definitely does not define his ultimate destiny, let alone his athletic success. An excellent athlete is born from a strong mental and physical constitution, with that unyielding perseverance and determination to fight for glory. The genetic makeup does, however, provide a basis for nurture – an initial physiological point, in which the ensuing interplay between nature and nurture will stem. Undoubtedly, the knowledge of one's personal genome will make it possible to empower the individual in selecting the optimal environment to nurture nature. Perhaps then, the focus of sports genetics should shift from predicting athletic excellence to injury susceptibility and preventive care so as to identify physiological weaknesses of active athletes and design personal training programs accordingly.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

We thank the Raymond and Beverly Sackler Institute for Biological, Physical and Engineering Sciences for supporting this work.

PATIENT CONSENT

Declared none.

REFERENCES

[1] Pérusse L, Rankinen T, Rauramaa R, *et al.* The human gene map for performance and health-related fitness phenotypes: the 2002 update. Med Sci Sports Exerc 2003;35(8):1248-64.

[2] Rankinen T, Pérusse L, Rauramaa R, *et al.* The human gene map for performance and health-related fitness phenotypes: the 2001 update. Med Sci Sports Exerc 2002;34(8):1219-33.

[3] Rankinen T, Pérusse L, Rauramaa R, *et al.* The human gene map for performance and health-related fitness phenotypes. Med Sci Sports Exerc 2001;33(6):855-67.

[4] Bray MS, Hagberg JM, Pérusse L, *et al.* The Human Gene Map for Performance and Health-Related Fitness Phenotypes. Med Sci Sports Exerc 2009;41(1):35-73.

[5] Wolfarth B, Bray MS, Hagberg JM, *et al.* The human gene map for performance and health-related fitness phenotypes: the 2004 update. Med Sci Sports Exerc 2005;37(6):881-903.

[6] Rankinen T, Bray MS, Hagberg JM, *et al.* The human gene map for performance and health-related fitness phenotypes: the 2005 update. Med Sci Sports Exerc 2006;38(11):1863-88.

[7] Rankinen T, Pérusse L, Rauramaa R, *et al.* The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2003 Update. Med Sci Sports Exerc 2004;36(9):1451-69.

[8] Consortium, Project 1000 G. A map of human genome variation from population-scale sequencing. Nature 2010;467(7319):1061-73.

[9] Woods DR, Humphries SE, Montgomery HE. The ACE I/D polymorphism and human physical performance. Trends Endocrinol Metab 2000;11(10):416-20.

[10] Sherry ST, Ward MH, Kholodov M, *et al.* dbSNP: the NCBI database of genetic variation. Nucleic Acids Res 2001;29(1):308-11.

[11] Montgomery HE, Marshall R, Hemingway H, *et al.* Human gene for physical performance. Nature 1998;393(6682):221-2.

[12] Thompson J, Raitt J, Hutchings L, *et al.* Angiotensin-converting enzyme genotype and successful ascent to extreme high altitude. High Alt Med Biol 2007;8(4):278-85.

[13] Gayagay G, Yu B, Hambly B, *et al.* Elite endurance athletes and the ACE I allele--the role of genes in athletic performance. Hum Genet 1998;103(1):48-50.

[14] Myerson S, Hemingway H, Budget R, *et al.* Human angiotensin I-converting enzyme gene and endurance performance. J Appl Physiol 1999;87(4):1313-6.

[15] Scott RA, Moran C, Wilson RH, *et al.* No association between Angiotensin Converting Enzyme (ACE) gene variation and endurance athlete status in Kenyans. Comp Biochem Physiol, Part A: Mol Integr Physiol 2005;141(2):169-75.

[16] Woods D, Hickman M, Jamshidi Y, *et al.* Elite swimmers and the D allele of the ACE I/D polymorphism. Hum Genet 2001;108(3):230-2.

[17] Tsianos G, Sanders J, Dhamrait S, *et al.* The ACE gene insertion/deletion polymorphism and elite endurance swimming. Eur J Appl Physiol 2004;92(3):360-2.

[18] Costa AM, Silva AJ, Garrido ND, *et al.* Association between ACE D allele and elite short distance swimming. Eur J Appl Physiol 2009;106(6):785-90.

[19] Goh KP, Chew K, Koh A, *et al.* The relationship between ACE gene ID polymorphism and aerobic capacity in Asian rugby players. Singapore Med J 2009;50(10):997-1003.

[20] Collins M, Xenophontos SL, Cariolou MA, *et al.* The ACE Gene and Endurance Performance during the South African Ironman Triathlons. Med Sci Sports Exerc 2004;36(8):1314-20.

[21] Scott RA, Irving R, Irwin L, *et al.* ACTN3 and ACE genotypes in elite Jamaican and US sprinters. Med Sci Sports Exerc 2010;42(1):107-12.

[22] Nazarov IB, Woods DR, Montgomery HE, *et al.* The angiotensin converting enzyme I/D polymorphism in Russian athletes. Eur J Hum Genet 2001;9(10):797-801.

[23] Turgut G, Turgut S, Genc O, *et al.* The angiotensin converting enzyme I/D polymorphism in Turkish athletes and sedentary controls. Acta Medica (Hradec Kralove) 2004;47(2):133-6.

[24] Karjalainen J, Kujala UM, Stolt A, *et al.* Angiotensinogen gene M235T polymorphism predicts left ventricular hypertrophy in endurance athletes. J Am Coll Cardiol 1999;34(2):494-9.

[25] Taylor RR, Mamotte CD, Fallon K, *et al.* Elite athletes and the gene for angiotensin-converting enzyme. J Appl Physiol 1999;87(3):1035-7.

[26] Ginevičienė V, Pranculis A, Jakaitienė A, *et al.* Genetic variation of the human ACE and ACTN3 genes and their association with functional muscle properties in Lithuanian elite athletes. Medicina (Kaunas) 2011;47(5):284-90.

[27] Dzau VJ. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. Circulation 1988;77(6 Pt 2):I4-13.

[28] Dragović T, Minshall R, Jackman HL, *et al.* Kininase II-type enzymes: Their putative role in muscle energy metabolism. Diabetes 1996;45 Suppl 1:S34-7.

[29] Jones A, Woods DR. Skeletal muscle RAS and exercise performance. Int J Biochem Cell Biol 2003;35(6):855-66.

[30] Hernández D, de la Rosa A, Barragán A, *et al.* The ACE/DD genotype is associated with the extent of exercise-induced left ventricular growth in endurance athletes. J Am Coll Cardiol 2003;42(3):527-32.

[31] Kasikcioglu E, Kayserilioglu A, Ciloglu F, *et al.* Angiotensin-converting enzyme gene polymorphism, left ventricular remodeling, and exercise capacity in strength-trained athletes. Heart and Vessels 2004;19(6):287-93.

[32] Raleigh SM. Epigenetic regulation of the ACE gene might be more relevant to endurance physiology than the I/D polymorphism. J Appl Physiol 2011;(November 2011):1082-3.

[33] Danser a HJ, Vagula MC, Rawding R, *et al.* Commentaries on viewpoint: epigenetic regulation of the ACE gene might be more relevant to endurance physiology than the I/D polymorphism. J Appl Physiol 2012;112(6):1084-5.

[34] Raleigh SM. Last word on viewpoint: epigenetic regulation of the ACE gene might be more relevant to endurance physiology than the I/D polymorphism. J Appl Physiol 2012;112(6):1086.

[35] North KN, Yang N, Wattanasirichaigoon D, *et al.* A common nonsense mutation results in α-actinin-3 deficiency. Nature 1999;21(april):353-4.

[36] Yang N, MacArthur DG, Gulbin JP, *et al.* ACTN3 genotype is associated with human elite athletic performance. Am J Hum Genet 2003;73(3):627-31.

[37] Nance K (North). ACTN3 genotype screen for athletic performance - Patent # 7615342 - PatentGenius. 7615342 ACTN3 genotype screen for athletic performance 2009;

[38] Clarkson PM, Devaney JM, Gordish-Dressman H, *et al.* ACTN3 genotype is associated with increases in muscle strength in response to resistance training in women. J Appl Physiol 2005;99(1):154-63.

[39] Walsh S, Liu D, Metter EJ, *et al.* ACTN3 genotype is associated with muscle phenotypes in women across the adult age span. J Appl Physiol 2008;105(5):1486-91.

[40] Chiu L-L, Chen T-W, Hsieh SS, *et al.* ACE I/D, ACTN3 R577X, PPARD T294C and PPARGC1A Gly482Ser polymorphisms and physical fitness in Taiwanese late adolescent girls. J Physiol Sci 2012;62(2):115-21.

[41] Niemi A-K, Majamaa K. Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes. Eur J Hum Genet 2005;13(8):965-9.

[42] Roth SM, Walsh S, Liu D, *et al.* The ACTN3 R577X nonsense allele is under-represented in elite-level strength athletes. Eur J Hum Genet 2008;16(3):391-4.

[43] Druzhevskaya AM, Ahmetov II, Astratenkova IV, *et al.* Association of the ACTN3 R577X polymorphism with power athlete status in Russians. Eur J Appl Physiol 2008;103(6):631-4.

[44] Ahmetov II, Druzhevskaya a M, Astratenkova IV, *et al.* The ACTN3 R577X polymorphism in Russian endurance athletes. Br J Sports Med 2010;44(9):649-52.

[45] Papadimitriou ID, Papadopoulos C, Kouvatsi A, *et al.* The ACTN3 gene in elite Greek track and field athletes. Int J Sports Med 2008;29(4):352-5.

[46] Eynon N, Duarte JA, Oliveira J, *et al.* ACTN3 R577X polymorphism and Israeli top-level athletes. Int J Sports Med 2009;30(9):695-8.

[47] Massidda M, Vona G, Calò CM. Association between the ACTN3 R577X polymorphism and artistic gymnastic performance in Italy. Genet Test Mol Biomarkers 2009;13(3):377-80.

[48] Döring FE, Onur S, Geisen U, *et al.* ACTN3 R577X and other polymorphisms are not associated with elite endurance athlete status in the Genathlete study. J Sports Sci 2010;28(12):1355-9.

[49] Shang X, Huang C, Chang Q, *et al.* Association between the ACTN3 R577X polymorphism and female endurance athletes in China. Int J Sports Med 2010;31(12):913-6.

[50] Ruiz JR, Fernández del Valle M, Verde Z, *et al.* ACTN3 R577X polymorphism does not influence explosive leg muscle power in elite volleyball players. Scand J Med Sci Sports 2011;21(6):e34-41.

[51] Ahmetov II, Druzhevskaya AM, Lyubaeva EV, *et al.* The dependence of preferred competitive racing distance on muscle fibre type composition and ACTN3 genotype in speed skaters. Exp Physiol 2011;96(12):1302-10.

[52] Chiu L-L, Wu Y-F, Tang M-T, *et al.* ACTN3 genotype and swimming performance in Taiwan. Int J Sports Med 2011;32(6):476-80.

[53] Hand BD, McCole SD, Brown MD, *et al.* NOS3 gene polymorphisms and exercise hemodynamics in postmenopausal women. Int J Sports Med 2006;27(12):951-8.

[54] Rankinen T, Rice T, Perusse L, *et al.* NOS3 Glu298Asp Genotype and Blood Pressure Response to Endurance Training: The HERITAGE Family Study. Hypertension 2000;36(5):885-9.

[55] Saunders CJ, de Milander L, Hew-Butler T, *et al.* Dipsogenic genes associated with weight changes during Ironman Triathlons. Hum Mol Genet 2006;15(20):2980-7.

[56] Data SA, Roltsch MH, Hand B, *et al.* eNOS T-786C genotype, physical activity, and peak forearm blood flow in females. Med Sci Sports Exerc 2003;35(12):1991-7.

[57] Wolfarth B, Rankinen T, Mühlbauer S, *et al.* Endothelial nitric oxide synthase gene polymorphism and elite endurance athlete status: the Genathlete study. Scand J Med Sci Sports 2008;18(4):485-90.

[58] Buxens A, Ruiz JR, Arteta D, *et al.* Can we predict top-level sports performance in power vs endurance events? A genetic approach. Scand J Med Sci Sports 2011;21(4):570-9.

[59] Gómez-Gallego F, Ruiz JR, Buxens A, *et al.* The -786 T/C polymorphism of the NOS3 gene is associated with elite performance in power sports. Eur J Appl Physiol 2009;107(5):565-9.

[60] Eynon N, Ruiz JR, Yvert T, *et al.* The C Allele in NOS3 -786 T/C Polymorphism is Associated with Elite Soccer Player's Status. Int J Sports Med 2012;

[61] Ruiz JR, Arteta D, Buxens A, *et al.* Can we identify a power-oriented polygenic profile? J Appl Physiol 2010;108(3):561-6.

[62] Sessa F, Chetta M, Petito A, *et al.* Gene polymorphisms and sport attitude in Italian athletes. Genet Test Mol Biomarkers 2011;15(4):285-90.

[63] Maciejewska A, Sawczuk M, Cięszczyk P. Variation in the PPARα gene in Polish rowers. J Sci Med Sport 2011;14(1):58-64.

[64] Broos S, Windelinckx A, De Mars G, *et al.* Is PPARα intron 7 G/C polymorphism associated with muscle strength characteristics in nonathletic young men? Scand J Med Sci Sports 2011;1-7.

[65] Eynon N, Meckel Y, Sagiv M, *et al.* Do PPARGC1A and PPARalpha polymorphisms influence sprint or endurance phenotypes? Scand J Med Sci Sports 2010;20(1):e145-50.

[66] Ahmetov II, Mozhayskaya I a, Flavell DM, *et al.* PPARalpha gene variation and physical performance in Russian athletes. Eur J Appl Physiol 2006;97(1):103-8.

[67] Cieszczyk P, Sawczuk M, Maciejewska A, *et al.* Variation in peroxisome proliferator activated receptor α gene in elite combat athletes. Eur J Sport Sci 2011;11(2):119-23.

[68] Zempo H, Tanabe K, Murakami H, *et al.* ACTN3 polymorphism affects thigh muscle area. Int J Sports Med 2010;31(2):138-42.

[69] Novembre J, Johnson T, Bryc K, *et al.* Genes mirror geography within Europe. Nature 2008;456(7218):98-101.

[70] Chen J, Zheng H, Bei J-X, *et al.* Genetic structure of the Han Chinese population revealed by genome-wide SNP variation. Am J Hum Genet 2009;85(6):775-85.

PMID: 22789016