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Original article

The relationship of polymorphism with explosive forces in ACTN3, ACE, and UCP3 genes in soccer players

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Summary. *Study Objectives:* The purpose of the study was to investigate the relationship of polymorphism with explosive forces in ACTN3, ACE, and UCP3 genes in soccer players. *Methods:* A total of 19 male soccer players and 9 sedentary voluntarily participated. Countermovement jump, squat jump, and standing long jump tests were applied to the subjects. On the same day, the subjects performed the jump tests twice again and the best score was recorded. Blood was drawn from subjects for Genomic DNA isolation. PCR products of ACTN3 and UCP3 genes Medical Genetics department genotypic differences between the groups were determined by analyzing with an automatic DNA sequencing system. Since taken non-parametric assumptions, it was analyzed by the Spearman test. *Results:* In subject group, a statistically significant relationship was found between all three jump performances in the subjects with ACTN3 RR and ACE ID genotype (p CMJ=0.04; SJ=0.04; SLJ=0.05) ($p<0.05$). In subject group, statistically significant correlation was found between countermovement jump and squat jump performances in subjects with ACTN3 XX and UCP3 -55C/T genotype (p CMJ=0.04; SJ= 0.04) ($p<0.05$), the same relationship was not found in the control group with the genotype ACTN3 XX and UCP3 -55C/T (p CMJ=0.1; SJ=0.11; SLJ=0.1) ($p>0.05$). A statistically significant relationship was found between all three jump performances in subjects with ACE ID and UCP3 -55C/C genotype (p CMJ=0.00; SJ=0.00; SLJ=0.00) ($p<0.05$). *Conclusion:* We found that, associations of explosive forces with polymorphisms. Although genotypes of athletes are similar to previous studies, stronger evidence is needed to establish a meaningful relationship between genotype and explosive power.

Key words: ACTN3, ACE, UCP3, Genotype, Polymorphism, Soccer

Introduction

Genetics plays an important role in understanding the athlete's capacity in performance. However, sports genetics has shown a rapid expansion in recent years, spreading by the sequencing of the human genome (1). Sports genetics focuses on genetic variants that affect individuals' athletic performance, disability risks, and nutrition. Identifying genetic variations that are thought to affect these characteristics will allow athletes to develop more efficient training programs (2). Therefore, the ability to maximize the performance of athletes in elite environments is among the leading research topics of sports science (3). Genetic factors have significant effects on sports performance. Components such as strength, strength, endurance, muscle fibril dimensions, muscle fibril structures, flexibility, nerve-muscle coordination, which are important for sportive performance, are directly related to genetics. Research shows that 66% of sports performance is genetically related. The rest is related to training, nutrition, equipment, motivation, sleep, and non-genetic factors (4, 5). An individual's physical capacity reflects a complex phenotype influenced by

genetic and environmental factors. How these polymorphisms and metabolic pathways affect individual performance is a point of current research and interest in sports genetics because it is important to identify genetic variants that make significant contributions to individual sport performance (6). Sports performance is not determined by a single gene but by the interaction of more genes. Although it is impossible to know the exact relationship between athletic nature and nutrition, a generally accepted sports science proposition is that genes represent approximately 50% of the athletic change in performance (1). The number of genes that affect sporting performance is increasing day by day. It is known that there are many different components of athletic performance and these components together create an athletic performance in athletes by affecting the physiological system (7). The relationship between genetic infrastructure, which is one of these components, and sports performance has gained more importance in recent years, especially after 2010. Yang et al. (8) reported that a structural mutation in the alpha-actin gene (ACTN3) caused the shorter than normal form of the protein to produce arginine instead of the stopping codon in amino acid 577 of the actin protein encoded by the gene. The effects of this change on athletic performance have been reported and an important contribution has been made to the field of sports genetics. Previously, Montgomery et al. (9), important studies in the field of sports genetics, Yang et al. (8) with the support of studies in this area has become even more important. Today, many centers all over the world are working in this field. In our country, studies are continuing in this field and the relationships between genetic parameters examined and susceptibility to sports performances are tried to be revealed. Approximately 250 genetic regions related to human performance have been found in scientific studies. Currently, it is estimated that 99.9% of the human DNA sequence is known to the entire world population. The remaining 0.1% shows all genetic differences between humans. The first stage of sports genetics studies consists of identifying candidate genes, genes that affect performance. The physiological and anatomical development of living things is determined by the interaction of genes and their environment. Genetic or gene fragments affecting athletic performance are identified by linkage assays that can be performed in single and double twins. In the next step, the genetic sites identified and proposed as candidates are analyzed in successful athletes and sedentary individuals. The data obtained from these analysis results are repeated in different populations and the effect of the related genetic variation on the examined performance is tried to be determined (10). The human genome responsible for sports success is estimated to have dozens of 10 million different single nucleotide polymorphisms (SNPs), depending on sports performance and sports success in various sport codes (11). Performance-enhancing polymorphisms are examples of natural genetic variations that affect the outcome of sporting challenges (1). Numerous studies of specific gene polymorphisms have revealed physical abilities in various sports fields and various relationships between different ethnicities and genders (12). Two genes that have been extensively studied related to sporting ability are angiotensin I-converting enzyme (ACE) and α-actinin-3 (ACTN3) (13). However, the uncoupling protein 3 (UCP3) gene is one of the genes included in the research. ACE I/D polymorphism is the first specific gene variant associated with human physical performance (9). ACTN3 is the first structural gene-specific to skeletal muscle that depends on athletic performance (13). Ahmetov et al. (14) showed that the ACE D allele is associated with a high percentage of strength and muscle volume with fast-twitch muscle fibers. In addition, it has been shown that the D allele is associated with the strength of elite athletes. It is generally accepted that muscle fiber composition may affect physical performance. The ACTN3 gene R577X polymorphism is thought to be one of the gene variations that contribute to the determination of muscle fiber type structure and athletic status (15). UCP3 is a highly expressed mitochondrial anion carrier protein in skeletal muscle (Fang et al., 2005). Concerning the relationship between UCP3 and sports performance, the literature data are conflicting. Echegaray et al. (16) -55 bp C / T polymorphism of the UCP3 gene is an indicator of elite endurance athlete status, whereas Fang et al. (17) and Schrauwen et al. (18) found that this polymorphism increased energy consumption during resting due to increased gene expression, high aerobic potential and reduced risk of obesity. Developments

in sports science, new and effective training methods, developing team or individual techniques, high advertisements in the sports sector, and high expectations of clubs made athletes train more frequently and more intensively. Accordingly, new technology and training methods are constantly being tested and developed to improve performance and raise athletes to the elite level (19). One of the branches where these technological methods are frequently used is football. Football is an intermittent team sport characterized by high intensity (20,21). In football, jumps, collective games, sprints, deceleration-accelerations, (20) and change of direction every 2-4 seconds are performed in a total of 1200–1400 times during a match (22). The effect of genetic and mental factors on both the formation and development of the athletic performance which can be improved by the regular training of football players has been demonstrated by the studies conducted to date (23). In this study, the relationship between polymorphism in ACTN3, ACE, and UCP3 genes and explosive force in soccer players will be examined. In scientific studies, the most important factor affecting sporting performance is genetic differences. The results of this study; which can be successful in the sport branches, or the most suitable sports branch can be determined in advance with genetic analysis can lead. The test results obtained; it is thought that it will contribute to the field in terms of directing the athlete to the branches and determining the ideal position and position-specific to that branch.

Materials and Methods

Subjects

19 healthy male soccer players (subjects) and 9 adults (control group) who do not actively play in the amateur football leagues in Denizli will voluntarily participate in this study. All participants will be informed that they should not exercise or rest until at least 48 hours before starting the exercise. Subjects with a disease and subjects reporting any lower limb disability prior to the trial will not be included in the study. The subjects were informed about the possible risks and benefits of the study and gave their informed consent to participate in this study, which was approved by the Clinical Research Ethical Committee of Pamukkale University.

Procedure and Measurements

Anthropometric Measurements

The height of the subjects was measured with a stadiometer (Seca, Germany) with a sensitivity of 1 mm and body weight measurements with a sensitivity of 0.1 kg. In the anatomical posture, the heels were combined, holding the breath, and the head was positioned in the frontal plane with the overhead table touching the vertex point and the measurement was recorded as 'cm' and 'kg'.

Jumping performance measurements

Countermovement jump, Squat jump, and Standing long jump tests measurement

To estimate the explosive power of the players, the countermovement (active) jump (CMJ) and squat jump (SJ) tests were conducted. Before the test, participants performed a 10-min warm-up involving 5 vertical jumps. The test comprised two maximal vertical jumps without an arm swing (SJ) and two with arm swings (CMJ). In the SJ, participants settled down in a full squatted posture with knees close together and maximally flexed. After that, the knees and hips were extended to jump vertically off the ground with arms resting on hips. A CMJ was performed from an upright standing position. The vertical jump was preceded by a downward movement (active phase) until a full squatted posture with arms swinging back. In a propulsive phase of the jump, the knees and hips were extended and arms swinging upward. The rest interval between jumps was one minute. The best (the highest) jump was used in subsequent analysis. In the standing long jump, the subject stands on hard ground and waits with his feet spreading over the shoulder. When ready, he takes both hands backward and bends his knees simultaneously. With the forward movement of the arms, it jumps and falls as far forward as possible on a soft

Figure 1. Countermovement (active) jump, Squat jump, and Standing long jump tests

surface. The last trace of his heels is measured. Two repetitions for each subject will be noted and the best rating will be noted.

The jump measurements of the athletes were simultaneously recorded with the iPhone 7S smartphone's 240 Hz high-speed video capture and analyzed with the MyJump2 smartphone app.

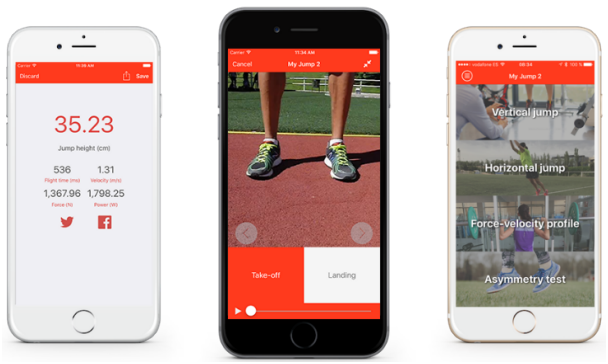


Figure 2. MyJump 2 Smartphone Application

Test Protocol

All subjects were informed that they should not exercise and rest until at least 48 hours before starting exercise. The subjects performed the countermovement jump, squat jump, and standing long jump test in 1 day. The best two replicates for each subject were recorded in cm. The jump test was performed between 09:00-12:00 am. Blood was taken from the subjects before the tests.

Collection of Biological Material

2 cc venous blood from the subjects and control groups were taken into EDTA (purple-top). Genomic DNA isolation was performed using the kit in accordance with the manufacturer's instructions. The purity and quantity of genomic DNA obtained was measured by the medical genetics department on a nanodrop spectrophotometer.

Genotyping

Deletion (D) and insertion (I) phenotypes can be detected by electrophoresis in the 16th exonic region of the ACE gene. PCR was performed using the following primer pair of exon 16 to determine the genotypes of interest. PCR products were run on agarose gel containing EtBr to determine genotypes of the samples:

F- 5´-CTGGATAGCCA GTCCCATCCTATCT-3´	R- 5´GTCGTGGGCATA ACATTCCTCAGAT-3´

In order to examine the differences in ACTN3 and UCP3 genes, the 16th exon of the ACTN3 gene including 577X polymorphism, which was previously associated with elite athletes, was amplified using the following primer pair:

F- 5_-CTGAAGCCTG TATTAAGTGGG-3	R- 5_-TAATCACAGTAT CTAGGTGGG-3

All exons of the UCP3 gene were amplified using the following primer pairs:

U1 F 5´-TATCGAAGAGGCCTTGACC-3´	U1 R 5´-CGGCTGGACTGAATCTCTATCA-3´
U2F 5´ TCTAAAGCCCCTCCTGGGTA-3´	U2 R 5´ GAAGGGTCCTAAGCAGTGGA3´
U3 F 5´ GTCCTCACGGTCCTGCTATTG3´	U3R 5´ AAGCTTTACTAAGACCGC3´
U4 F-5´ TCAGCCTCTCCAAATGAC3´	U4 R 5´ ACTCCACTTAGTTCTGGGTT3´
U5 F 5´ GTCTCTCACCTTCTCCGACT3´	U5 R 5´ GAGGAGTCCACCCCTTGTA3´
U6 F 5´ TCGCTGCCTAACACAGTAACC3´	U6R 5´ CGGGGATTCAGTCTCCAAC3´
U7F 5' GGTTGGAGACGTGTATCCCC3´	U7 R 5´ CCCTGACATGAGAAAGCCTGA3´

PCR products of ACTN3 and UCP3 genes were analyzed by ABI Prism 3.0 automated DNA sequencing system within the medical genetics department to determine genotypic differences between subjects and controls.

Statistical Analysis

Descriptive analyses of subjects' jump performances and gene analyses were calculated with mean and standard deviation values. Since taken non-parametric assumptions, it was analyzed by the Spearman test. The level of significance was taken as $p<0.05$ (Tables 1, 2).

Results

The performance test boxplot results for subjects with correlation ACE, ACTN3 and UCP3 genes version are presented in Figures 3 to 6. In subject group, a statistically significant relationship was found

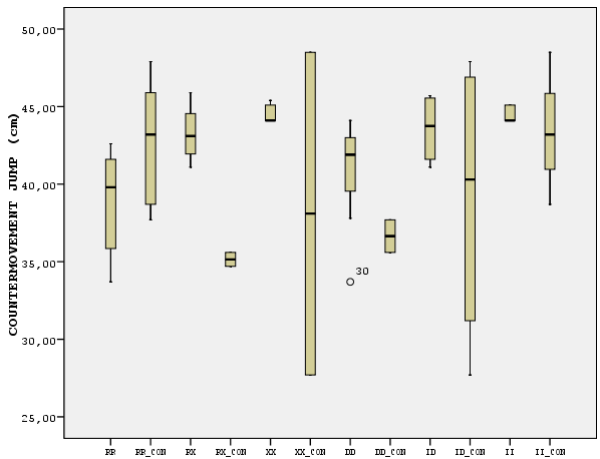
Table 1. Descriptive statistics of the subject group

	N	Min	Max	Mean	SD
Age (year)	19	19	25	20,94	1,87
Height (cm)	19	167	182	177,26	3,73
Body Mass (kg)	19	62	86	73,57	8,41
Countermovement Jump (CMJ)	19	33,7	45,9	41,73	3,88
Squat Jump (SJ)	19	30,2	39,5	34,05	2,73
Standing Long Jump (SLJ)	19	2,18	2,76	2,40	0,13

Table 2. Descriptive statistics of the control group

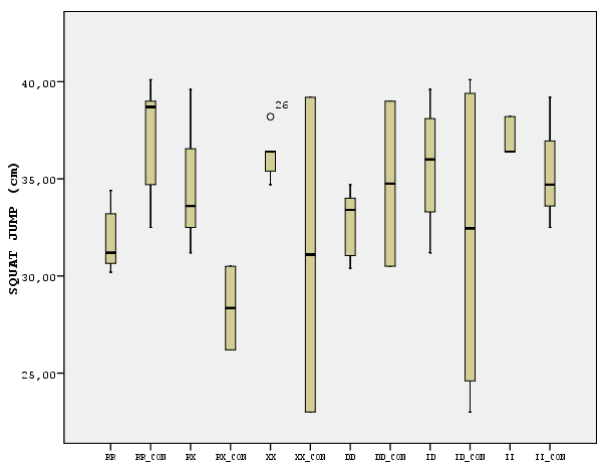
	N	Min	Max	Mean	SD
Age (year)	9	18	25	20,55	2,18
Height (cm)	9	168	185	175,77	5,19
Body Mass (kg)	9	60	77	69,22	6,35
Countermovement Jump (CMJ)	9	27,7	48,5	39,98	6,94
Squat Jump (SJ)	9	23	40,1	33,76	6,20
Standing Long Jump (SLJ)	9	2,1	2,55	2,332	0,14

between all three jump performances in subjects with ACTN3 RR and ACE ID genotype (CMJ p = 0.04; SJ p = 0.04; SLJ p = 0.05) (p<0.05). However, the same relationship was not found in the control group with ACTN3 and ACE genotype (CMJ p = 0.06; SJ p = 0.1; SLJ p = 0.07) (p>0.05). In subject group, statistically significant correlation was found between countermovement jump and squat jump performances in subjects with ACTN3 XX and UCP3 -55C / T genotype (CMJ p = 0.04; SJ p = 0.04) (p<0.05), but a significant relationship was not found in standing long jump performance (SLJ p = 0.06) (p>0.05). Similarly, the same relationship was not found in the control group with the genotype ACTN3 XX and UCP -55C / T (CMJ p = 0.1; SJ p = 0.11; SLJ p = 0.1) (p>0.05). A statistically significant relationship was found between all three jump performances in subjects with ACE ID and UCP3 -55C / C genotype (CMJ p = 0.00; SJ p = 0.00; SLJ p = 0.00) (p<0.05), but the same relationship was not found in the control group (CMJ p = 0.08; SJ p = 0.08; SLJ p = 0.4) (p>0.05).



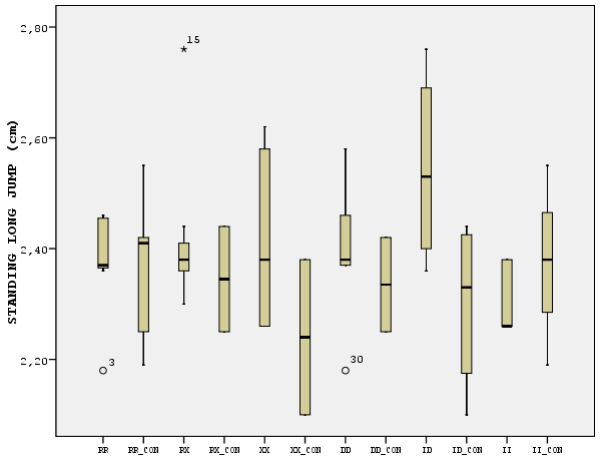
(CON= Control Group)

Figure 3. Boxplot: Results that subjects with different ACTN3 genotype (XX, RR, RX) and ACE genotype (DD, II, ID) achieved on the "Countermovement jump" test.



(CON= Control Group)

Figure 4. Boxplot: Results that subjects with different ACTN3 genotype (XX, RR, RX) and ACE genotype (DD, II, ID) achieved on the "Squat jump" test.



(CON= Control Group)

Figure 5. Boxplot: Results that subjects with different ACTN3 genotype (XX, RR, RX) and ACE genotype (DD, II, ID) achieved on the "Standing long jump" test.

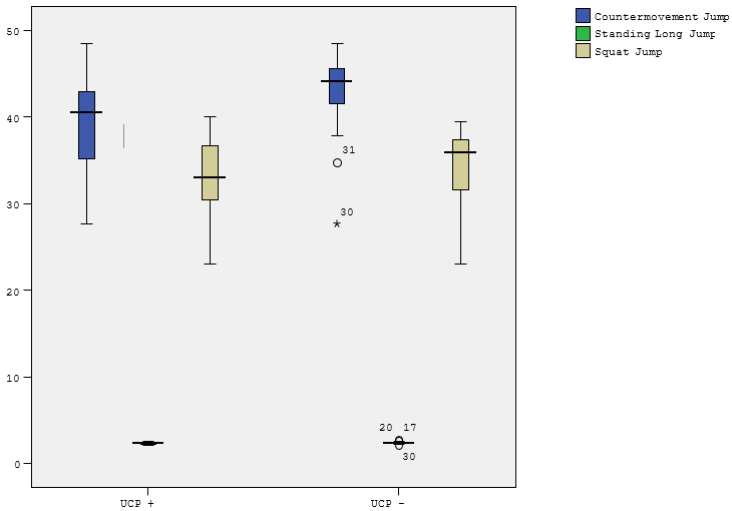


Figure 6. Boxplot: Results that subjects with different UCP3 genotype achieved on the "Countermovement jump, Standing long jump, and Squat jump" test.

Discussion and Conclusion

Recent studies have indicated that several genes are involved in determining the performance of the players, both physiologically and psychologically. 25 Genetic models could be developed and used to find the optimal genetic endowment of a player to help scientists establish which genetic polymorphisms are advantageous for proper performance in different sports types. Therefore, the creation of genomic databases will be very useful for sport scientists. In the present study, we observed, to our knowledge, for the first time, the increased expression levels of ACTN3, ACE, and UCP3 genes in the majority of the studied soccer players. Thus, it is difficult to discuss the obtained results due to the lack of other published studies focused on ACTN3, ACE, and UCP3 gene expression. In this study, we examined 19 soccer players and 9 sedentary of ACE, ACTN3, and UCP3 polymorphisms and aimed to associate these polymorphisms with the explosive

force. In our study both groups, the RR genotype for the ACTN3 genotype was higher than XX and RX. Egorova et al. (24) reported similar our results in Russian football players; they examined 240 football players, and 46.25% had the RR genotype. Santiago et al. (25) analyzed 60 Brazilian football players, and in their cohort, 48.3% of the players had RR genotype. Pimenta et al. (25) aimed to compare acute inflammatory responses, muscle damage, and hormonal variations with eccentric training in soccer athletes and examined 37 professional soccer players of which 40.5% were RR. The available data clearly show a significant association between ACTN3 genotype and performance in multiple cohorts of athletes (26, 27). This mechanism is strongly supported by mechanistic data from the ACTN3 knockout mouse model (28). It is not clear whether the observed changes in ACTN3 expression are a direct result or the cause of adaptation to physical activity. Ma et al.'s (29) study clearly documented the association between ACTN3 polymorphism (R allele) and power events. These findings suggest that polymorphic gene variants influence human physical performance. The first evidence of genetic polymorphisms influencing human physical performance is reported for the ACE gene. The ACE insertion/deletion (ACE I/D, rs1799752) polymorphism has been related to improvements in performance and exercise duration in a variety of populations. The I allele, which represents an insertion of 287 bp, is associated with lower serum and tissue ACE activity and improved performance in endurance sports. The deleted form of the variant (D allele) is associated with higher circulating and tissue ACE activity and enhanced performance at sports requiring sprinting or short bursts of power (17). In our study soccer player group, 44% of the players had ID genotype, 40% of the players had DD genotypes for ACE, and 84% of the players had at least one D allele. The allelic count revealed the D allele as 62% in players. Gineviciene et al. (30) examined 199 Lithuanian football players and reported similar results to ours. They showed that ID was the highest genotype (46.7%), and together with the DD genotype, the percentage of the players having at least one D allele was 76.3%. Juffer et al. (32) analyzed 54 male professional soccer players, and ID was the most detected genotype. Unlike our results, Egorova et al. (24) examined 213 Russian football players and found the frequency of ID and DD genotypes as 28.6% and 50.7%, respectively, giving both genotypes an overall frequency of 79.3%, which is similar to our results. Uncoupling protein 3 (UCP3) is a mitochondrial anion carrier protein that is highly expressed in skeletal muscle (17). It diminishes mitochondrial superoxide production and may protect against oxidative endothelial damage (17, 31). Uncoupling protein 3 is believed to be involved in total body energy expenditure, including the regulation of fat and glucose metabolism. However, available genetic association studies have been inconsistent. These inconsistencies may depend on healthy lifestyle patterns, such as physical activity, a factor that affects UCP3 expression. In middle-aged men, homozygosity for the 55 T allele in the promoter region of the UCP3 gene, which is likely associated with reduced gene expression, accelerates the onset of diabetes (18). Regarding the relationship between UCP3 and sports performance, literature data are conflicting. Echegaray et al. (16) have not found that the 55 bp C/T polymorphism of the UCP3 gene is a marker of elite endurance athlete status, whereas Fang et al. (17) and Schrauwen et al. (18) have found that this polymorphism increases energy expenditure at rest because of enhanced gene expression, high aerobic potential, and decreased risk of obesity. In our study, a significant relationship was found between specific genotypes and jump performance, especially in the subject group. This result supports the relationship between genotype and sporting performance suggested by previous studies. However, a statistically significant similar relationship was not found in the control group individuals with the same genotype. It is unclear whether this difference between the subject group and the control group is genotype or athletic performance. The present studies summarized the associations of explosive forces with ACE I/D, ACTN3 R577X, and UCP3 -55C/T polymorphisms. We found that certain ACTN3 and ACE genotypes had a statistically significant relationship in jump performance. Although genotypes of athletes are similar to previous studies, stronger evidence is needed to establish a meaningful relationship between genotype and explosive power. Soccer players may not give important information regarding their physical abilities, and thus their use as one of the factors for talent

identification is questionable. Although genetics may predispose a subject for some sport, it is the interaction of the phenotype with a genotype that makes the final result. Athletic performance is the result of many different factors, such as training characteristics, anthropometric and morphometric characteristics of the athlete, etc. These phenotypes are influenced by a variety of other processes and cellular pathways which are eventually influenced by a large number of individual and relevant genes.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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