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Differences in Muscle Strength Performance According to the Genotypes of the rs4646994 Polymorphism of the ACE Gene in a Sedentary Population

Diferencias en el Rendimiento de la Fuerza Muscular Según los Genotipos del Polimorfismo rs4646994 del Gen ACE en una Población Sedentaria

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SUMMARY: The angiotensin converting enzyme gene (ACE) has been associated with endurance and strength performance through its I/D polymorphism. Nevertheless, contradictory results exist between different populations. In this context, the purpose of this research was to determine the influence of the I/D polymorphism of the ACE gene on muscle strength in a sedentary Chilean sample. In this study 102 healthy male students (21.3 ± 2.2 years) completed the assessment. I/D genotyping, cardiovascular, anthropometric, grip strength and knee extensor peak strength were evaluated. The ACE polymorphism frequency was: II, 33.3 %; ID, 46.1 %; DD, 20.6 %. The results showed significant differences and large effect size in maximum ($p = 0.004$; $d = 0.85$) and relative handgrip strength ($p = 0.004$; $d = 0.9$) between genotype II vs DD. No difference was found for maximal or relative knee extensor strength between groups ($p = 0.74$), showing a low effect size ($d = 0.20$). In conclusion, this study provides insights into the role of the ACE gene in muscle strength and highlights the importance of investigating genetic variants in sedentary populations to better understand strength performance.

KEY WORDS: Angiotensin-converting enzyme gene; I/D polymorphism; Sedentary.

INTRODUCTION

Young people's physical traits are influenced by several factors, including age, sex, size, body composition, state of biological maturity, level of usual physical activity and muscle strength (Huang & Malina, 2007; Moliner-Urdiales *et al*., 2010). However, in recent years it has been recognized that the genetic influence on phenotype (that is, height, muscle mass, strength, etc.) has an important role and it is determined by small changes in the structure of DNA, which are called polymorphisms (Ahmetov & Fedotovskaya, 2015). The heritability of muscle strength and power has been shown to vary from approximately 30 % to 80 % in tests such as grip, isometric knee, and elbow flexion strength (Hughes *et al*., 2011). Therefore, several methodological approaches have been introduced to find associations between genetic polymorphisms and performance for different physical abilities in both elite athletes and sedentary subjects (Hughes *et al*., 2011). One candidate to partially explain differences in physical capacities such as power and endurance is the gene for angiotensin converting enzyme (ACE) (Weyerstraß *et al*., 2018). The ACE gene plays a key role in the regulation of the renin-angiotensin-aldosterone system (Masuyer *et al*., 2014). It is known that ACE primarily catalyzes the conversion of angiotensin-I to angiotensin-II and is relevant for electrolyte balance and systemic blood pressure regulation (Bernstein *et al*., 2012). In addition, Angiotensin-II is recognized as an important regulating factor for the hypertrophic response of skeletal muscle when subjected to overload, through both receptors, the angiotensin type 1 receptor (AT1), that favors differentiation of satellite cells, while the AT2 receptor participates in the regeneration of skeletal muscle (McBride, 2006).

The published data focuses on one specific polymorphism, which describes the presence (insertion, I allele) or absence (deletion, D allele) of a 287 bp sequence

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in intron 16, resulting in three genotypes: II and DD, homozygote's, and ID, heterozygous (Rigat *et al*., 1990). Therefore, carriers of the D allele would have higher circulating ACE activity than those who carry the I allele, while the I / D heterozygotes would be in between the aforementioned conditions (Montes-de-Oca-García *et al*., 2021).

The differences of ACE circulating levels on physiological responses to stress, due to ACE genotype polymorphism, have been studied mainly through exercise, and they have been associated with both cardiovascular and musculoskeletal systems (Rankinen *et al*., 2001). With regards to physical abilities, it has been proposed that those who present the I allele would have better performance in endurance efforts, while presence of the D allele would favor strength and power capacity (Montgomery & Dhamrait, 2002). However, the published data does not allow a clear association between the ACE gene polymorphism and physical qualities to be established, given that the studies have been carried out on very heterogeneous samples, differing in size, age, level of physical activity of the participants and ethnicity (Woods, 2009). Given the controversial results in this area of research, the purpose of this research was to determine the influence of the I/D polymorphism of the ACE gene on muscle strength in a sedentary Chilean sample.

MATERIAL AND METHOD

Subjects: The sample size was calculated using the Epi-Info 7 program (CDC, USA), considering a confidence interval of 95 %, a margin of error of 10 % and 50 % heterogeneity, which determined a sample of 96 individuals, as to obtain a representative sample of the local genotypic distribution. The participants were invited to participate through social networks, posters distributed in universities, and face-to-face invitation. Inclusion/exclusion criteria were Men between 18 and 30 years old, no diagnosis of hypertension, diabetes, metabolic, musculoskeletal or osteoarticular pathologies, drug users that could alter the parameters of interest, BMI> 30 Kg / m2, direct blood relationship with another participant, physically active subjects, or athletes, use of orthotics or prostheses. Sedentary according to assessment by the short version in Spanish of International Physical Activity Questionnaire (Serón *et al*., 2010). A total of 126 healthy male university students from the Maule Region agreed to participate in the evaluations. Only 102 (21.3 ± 2.2 years) completed the full set of tests. The Ethics Committee approved the study protocol.

Blood sampling and ACE genotyping: Genomic DNA was extracted from 5 cc of peripheral blood by NaI procedure optimized by Salazar *et al*. (2001). Genotyping of the ACE I/D (rs4646994) was performed using polymerase chain reaction, using forward 5'-CTGGAGAGCCACTCCC ATCCTTTCT-3' and reverse 5'-GACGTGGCCATCACATT CGTCAGAT-3' primers, designed with Primer3 v0.4.0 software which was available at http://frodo.wi.mit.edu/. The polymerase chain reaction (PCR) was performed in accordance with manufacturer protocol (GoTAQ Promega, USA) in a T100 Thermal cycler (Bio-Rad, USA) (Salazar *et al*., 2001). The thermal conditions were: one step of 95°C for 5 minutes, followed by 32 cycles of 30 seconds at 95°C, 60°C and 72°C, and one final step of 10 minutes at 72°C. Finally, the products were subjected to electrophoresis in a 2 % agarose gel and stained with GelRed© (Biotium, Hayward, USA.). The I allele was interpreted as one band of 479 bp and the D allele was a unique band of 192 bp. The heterozygous ID genotype corresponded to the presence of both 192 bp and 479 bp bands. PCR results were scored blinded by two independent observers. To confirm genotype assignment, the PCR procedure was performed on 50 % of samples on 2 separate occasions. Discordant results were resolved by repeated genotyping.

Physical Assessment

Cardiovascular Variables: Assessment was carried out before the execution of the physical tests following the recommendations of the seventh report of the joint national committee for the prevention, detection, evaluation, and treatment of arterial hypertension VII (JNCVII), used by the 2010 National Survey of Chilean Health (Ministerio de Salud, 2010), and included heart rate and blood pressure.

Anthropometric measurements. Body weight (in kilograms using a weight scale DETECTO®) and body height were measured using a portable stadiometer (Seca 213, Seca Corporation, Chino, California, USA). Both were used to calculate the body mass index (BMI) (kg/m2) according to the formula proposed by Keys *et al*. (1972).

Strength Variables. Grip strength of the dominant hand was measured using a Jamar ® Hydraulic Hand Dynamometer, Model J00105 (Sammons Preston, Bolingbrook, Illinois). The participants were tested in a standing position with their elbow at 90º, according to recommendations by the American Society for Hand Therapy (Mathiowetz *et al*., 1985). Three attempts were made with the dominant hand, using 60-second rest between them and the best effort was recorded in kilograms.

Knee extensor peak strength was evaluated by adapting the isometric protocol proposed by Hart *et al*. (2006) where the participant sits on a strength test chair, with the hips and knees at 90°. The custom-made adjustable bar on the back and the roller that contacted the ankle were moved to ensure that the tension towards the load cell was horizontal. A

strap maintained the participant's hip against the chair to avoid compensation. Participants performed three maximal isometric contractions for three seconds each, with a 60 second rest period between consecutive contractions. The maximum value of the dominant limb was used in the final analysis.

Statistical analysis: All statistical analyses were performed using GraphPad Prism 6.0 software (GraphPad Software, USA). All data was presented as mean ± standard deviation (SD). Student's t-test or one-way analysis of variance (ANOVA) was used to test differences in the mean between the groups. When significance was found, Tukey post hoc comparisons were performed. Cohen's effect size (d) was also calculated for comparisons between genotypes and difference was determined by ranking Cohen's effect size (small effect, 0.2; moderate effect, 0.5; large effect, 0.8) The genotype distribution, allele frequency, and Hardy–Weinberg equilibrium were tested by chi-square (χ^2) analysis. Statistical significance was set at $P<0.05$.

RESULTS

The genotype frequencies of the ACE polymorphism were: II, 33.3 % (n = 34); ID, 46.1 % (n = 47); DD, 20.6 % (n = 21) were in Hardy–Weinberg equilibrium (Table I).

Table I. Genotypes distribution and relative frequency of alleles for the Ins / Del polymorphism of the ACE gene for the sample analyzed.

	Frequency (102)	Hardy Weinberg's equilibrium
Genotype		
Ins/Ins	0.318 (34)	$X^2 = 0.4075989$
Ins/ Del	0.492 (47)	P= 0.523191
Del/Del	0.190 (21)	
Allele		
Ins	0.564	
Del	0.436	

Statistical test: Chi squared. 1 gl. Number of individuals in parentheses. P<0.05

The characteristics of the subjects are presented in Table II. No significant differences in mean age, heart rate, systolic and diastolic blood pressure, height, body weight, and body mass index (BMI) were observed among the three genotypes groups. In addition, there was no significant difference between the genotypes when they were grouped by I dominance model (II + ID vs DD) or D dominance (II vs ID + DD).

The results showed that there were significant differences and large effect size in maximum (p = 0.004; d = 0.85) and relative handgrip strength (p = 0.004; d = 0.9) between genotype II vs DD. Furthermore, the analysis revealed that there were significant differences in maximum and relative handgrip strength between genotypes II vs ID (difference of means 6.2 kg, p = 0.001), II vs DD (difference of means 4.2 kg, p = 0.015). There were no differences when comparing the ID vs DD groups (mean difference 2 kg, p = 0.09) (Figs. 1A and 1C).

The maximum handgrip strength presented significant differences when grouping the data of the D allele. The carriers of the II genotype presented an average of 5.8 kg more force than carriers of the D allele (p = 0.001) with moderate effect size (d = 0.70). Relative handgrip strength was higher for carriers of the II genotype, (p = 0.001) and moderate effect size was found (d = 0.70).

Figure 2A shows that there would be no difference in the comparison of maximal knee extensor strength between groups (p = 0.74), also showing a low effect size (d = 0.20). When the relative strength of the knee extensors is analyzed with respect to the BMI (Fig. 2C), no differences are observed between the groups (p = 0.47), with a low effect size (d = 0.35).

When comparing genotype II versus the pool of ID + DD genotypes, the data indicated no difference between groups in maximal knee extensor strength (Fig. 2B) (p = 0.46) even when normalized by the BMI (Fig. 2D) (p = 0.29), showing a low effect size (d = 0.16 and 0.23, respectively).

Table II. Baseline biometric characteristics by genotype and by Ins (Ins / Ins + Ins / Del vs Del / Del) and Del (Ins / Ins vs Ins / Del + Del / Del) dominance models

	Men (102)	Genotype *Ins/Ins* (34)	Genotype *Ins/Del* (47)	Genotype *Del/Del* (21)	P‡	Ins/Ins+Ins/ Del (81)	P†	Ins/Del+Del /Del (78)	P
Age. years	21.3±2.2	21.0±1.8	22.6±2.5	21.8±2.6	0.676 (a)	21.1±2.0	0.597 (c)	21.1±1.8	0.581 (c)
HR. bpm	78.2±13.2	77.5 ± 12.0	80.2 ± 14.0	78.3±12.0	0.511 (a)	81.1±12.1	0.759 (c)	81±12.2	0.814 (c)
SBP, mmHg	129.4±9.2	130.6±8.9	129.4±10.0	131.8±8.3	0.601 (a)	129.8±9.2	0.439 (c)	129.8±9.8	0.742 (c)
DBP, mmHg	74.9±8.1	74.0 ± 9.0	75.3±7.9	75.2±7.0	0.810 (a)	74.2±7.6	0.861 (c)	74.1±8.2	0.967 (c)
Weight, kg	70.1±9.6	70.4 ± 8.5	70.3±9.5	71.2±11	0.971 (a)	69.2±9.8	0.471 (c)	68.2±11.1	0.353 (c)
Height, cm	172.6 ± 6.03	173.5 ± 5.3	172.3± 6.8	171.6± 5.1	0.328 (a)	172.2±6.1	0.396 (c)	71.9±5.9	0.134 (c)
BMI, kg/m^2	23.5±2.8	23.5 ± 2.8	24.7±2.8	24.3±2.9	0.757 (a)	23.5±2.7	0.523 (c)	24.0±2.8	0.553 (c)

Average ± standard deviation. Number of individuals in parentheses. Bpm: Beats per minute. mmHg: millimeters of mercury. BMI: Body Mass Index. m^2: metres squared. Statistical test: (a) One-way ANOVA. Tukey's test of multiple comparisons; (c) Unpaired t-test. * P <0.05. ‡ Comparison between Genotypes; † Comparison Ins/Ins vs Ins/Del + Del/Del. ¤ Comparison Ins/Ins + Ins/Del vs Del/Del.

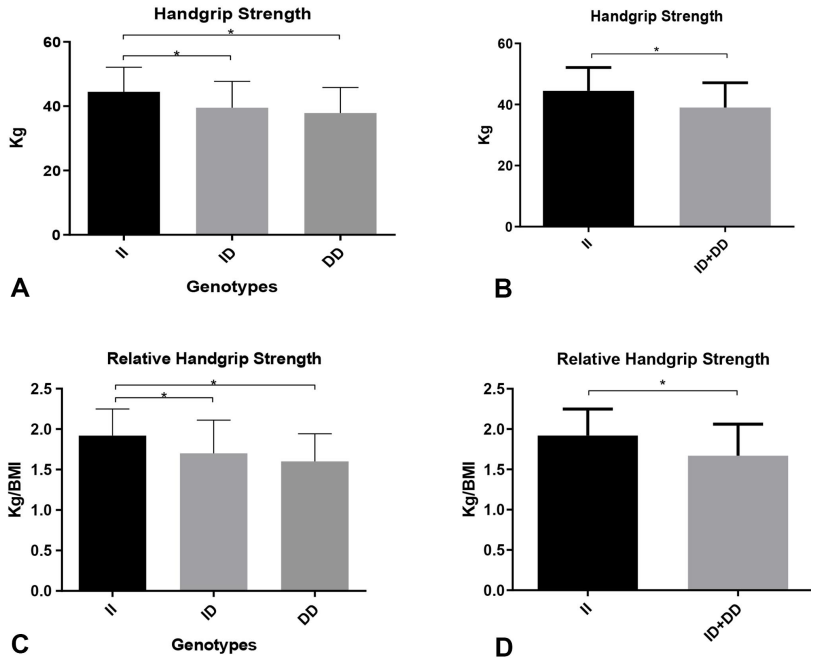

Fig. 1. Handgrip strength and relative handgrip strength by genotype and dominance models Del (Ins/Ins vs Ins/Del + Del/Del).

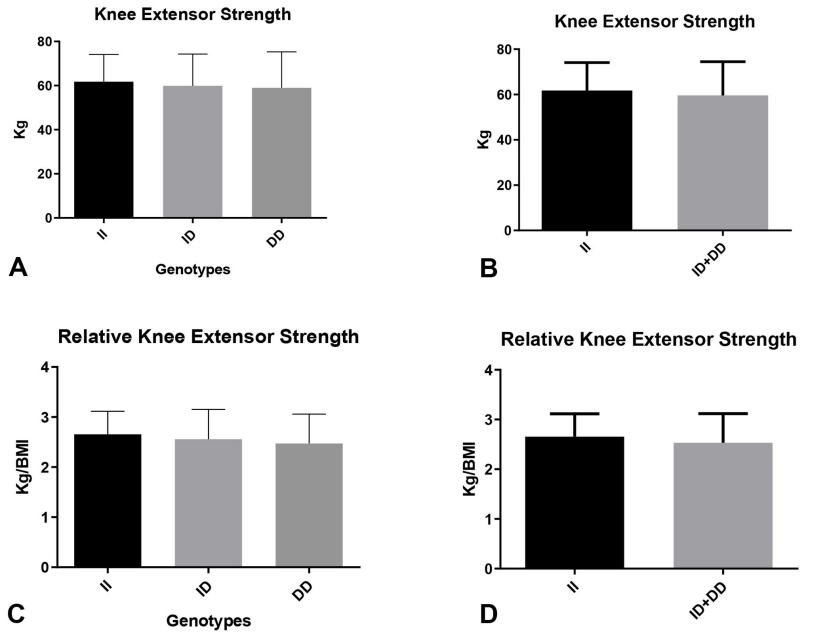

Fig. 2. Knee extensor strength and relative knee extensor strength by genotype and dominance models Del (Ins/Ins vs Ins/Del + Del/Del)

DISCUSSION

The objective of this study was to determine whether the ACE polymorphism influences the performance of maximum handgrip and knee extensor strength in sedentary male university students. Our results indicate that participants who carry the D allele have a significantly lower grip strength than those with genotype II, even when the strength data are relativized by BMI. Furthermore, it seems that the influence of the genotype on the expression of hand grip strength in sedentary subjects could be considerable, as the effect size analysis shows. Thus, II ACE genotype could be a protective factor against conditions known to diminish grip strength such as immobility or aging (Revelas *et al*., 2018). Interestingly, these differences were not found in maximal knee extensor strength. This is consistent with Moran *et al*. (2006) who studied the association of the ACE gene polymorphism in physically active Greek children aged 11 to 18 years. Their results indicate that women carrying genotypes DD and ID have worse results in grip strength and vertical jump compared to genotypes II. Furthermore, Gineviciene *et al* (2016), found that the most frequent genotype for Russian athletes is ACE II but ACE ID genotype for Lithuanian strength/power athletes. Garatachea *et al*. (2012) also found a lower grip strength in subjects with the D allele compared to genotype II carriers but in healthy Spanish older adults. Ahmetov *et al*. (2013) compared the results of various physical tests, including grip strength, on 457 physically active Russian children. He found that children carrying the D allele have better results in the long jump test, but not in handgrip strength. Yusof *et al*. (2019) studied the influence of the ACE polymorphism on cardiovascular and muscular adaptations in normotensive and untrained men. Their results indicate that there would be no differences in the initial assessment of hand grip strength, but there would be differences in cardiovascular variables. Finally, Bustamante-Ara *et al*. (2010) compared upper and lower limb muscle strength, in addition to performing a series of functional tests in 41 nonagenarian adults, finding that in the elderly, it seemed that there would be no influence of the ACE polymorphism on the handgrip strength when data are compared by genotype or by dominance pattern.

In summary, several published data support the findings of our study, that the presence of D allele is associated with lower grip strength when compared to II genotype, but interestingly no such difference is present when considering lower body strength. Of note is that this finding has been reported in samples of both sexes, in sedentary and athletic samples, and of different ages. Is relevant to note that Yusof *et al*. (2019) used an isometric protocol of training, which might have influenced his results of not finding association with grip strength (Gómez *et al*., 2020). Bustamante-Ara *et al*. (2010) whereas, trained a sample of elderly people that might have conditions very different to all of the aforementioned studies.

It is worth to note that studies that associate the ACE gene polymorphism with handgrip strength are scarce, so their results, individually and as a whole, must be considered with care, given their heterogeneity in population characteristics such as age (children, adults with altered metabolic conditions or the elderly), sex, ethnicity and training level. Nevertheless, the frequency of the ACE genotype in our sample conforms to the expectations of the Hardy-Weinberg equilibrium and corresponds to what has been previously reported in the Chilean population (Rosales *et al*., 2009; Muñoz Cofré *et al*., 2017), meaning that this distribution of ACE phenotype seems to be consistent and that may help for some degree of generalization for Chilean subjects, although with care.

It is important to consider that several other genetic variants have also been linked to the development of strength and power. Wagle *et al*. (2021) proposed that a combination of the genetic variants ACTN3 RR and ACE DD tends to result in enhanced strength performance. Both genes contribute to their expression through different pathways (Wagle *et al*., 2021).

The present study did not evaluate the potential mechanisms by which ACE I/D may modulate physical function responses to an acute force stimulus. However, it is possible that the interaction between the ACE I/D polymorphism and the effects of angiotensin-II varies according to the level of physical activity of the subjects (Garatachea *et al*., 2012), which would resemble in some way a prolonged stimulus such as it would be the presence of a cardiometabolic disease.

The levels of circulating ACE in each subject could influence the generation of muscle force. It is known that its plasma concentration can range from 18 % to 47 % (Inanir *et al*., 2014) and therefore, the same can be expected for angiotensin-II levels. Brink *et al*. (2001) demonstrated that Angiotensin-II led to weight loss and that this directly affected muscle mass. On the other hand, Rezk *et al*. (2012) described the effects of Angiotensin-II in the diaphragm of rats as an important factor in the pathophysiology of muscle atrophy and cachexia in conditions of congestive heart failure and chronic kidney disease. The mechanisms by which these phenomena occur are related to the role that angiotensin-II has over degradation of proteins, and the decrease in the levels and signaling of IGF-1, which is the main anabolic pathway in skeletal muscle (Cabello-Verrugio *et al*., 2012). Furthermore, it has been proposed that elevated serum angiotensin-II concentrations would have effects on protein degradation through the activation of the ubiquitin-proteasome pathway and would neutralize skeletal muscle regeneration by suppressing the function of satellite cells (Du Bois *et al*., 2015).

The study's results reveal that, even after adjusting for body mass index, sedentary adult males with the genotype II exhibit superior handgrip strength performance compared to D allele carriers, despite the absence of genotype differences in BMI. This suggests that the genotype associations cannot be attributed to BMI differences between the groups. In contrast, no differences in maximum isometric force of the knee extensor muscles were observed between the groups, whether analyzed as absolute or normalized results. Further randomized controlled studies are needed to determine the mechanistic explanations for these differences.

PRACTICAL APPLICATIONS. Given these findings, it is possible that the ACE polymorphism may be a protective or risk factor against immobility, bedridden or impairing movement conditions that lead to strength loss. If so, it is relevant to determine on the basis of existing data whether it is true for both upper and lower limbs or not. This research demonstrates that the ACE gene variant has a relationship that is significant and of moderate magnitude with handgrip strength in a male Chilean population. Future research should continue to explore the relationship between genetic variants and strength in a sedentary population, as well as the inclusion of other traits related to strength expression. This can be valuable in devising prevention, treatment and rehabilitation plans with greater precision, allowing for a greater chance of success.

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MOLINA-GUTIÉRREZ, N.; FLORES-QUEZADA, M.; CONTRERAS-MONTERO, C.; PACHECO VALLES, A. Diferencias en el rendimiento de la fuerza muscular según los genotipos del polimorfismo rs4646994 del gen ACE en una población sedentaria. *Int. J. Morphol., 42(2)*:227-233, 2024.

RESUMEN: El gen de la enzima convertidora de angiotensina (ACE) se ha asociado con el rendimiento de resistencia y fuerza a través de su polimorfismo I/D. Sin embargo, existen resultados contradictorios entre diferentes poblaciones. En este contexto, el propósito de esta investigación fue determinar la influencia del polimorfismo I/D del gen ACE sobre la fuerza muscular en una muestra chilena sedentaria. En este estudio, fueron evaluados 102 estudiantes varones sanos (21,3 ± 2,2 años). Se realizaron aplicaron las siguientes evaluaciones: genotipado del polimorfismo I/D, cardiovascular, antropométrica, fuerza de prensión y fuerza máxima de extensión de rodilla. La frecuencia del polimorfismo I/D de ACE fue: II, 33,3 %; DNI, 46,1 %; DD, 20,6 %. Los resultados mostraron diferencias significativas y un gran tamaño del efecto en la fuerza máxima (p = 0,004; d = 0,85) y relativa de prensión manual (p = 0,004; d = 0,9) entre el genotipo II y el DD. No se encontraron diferencias en la fuerza máxima o relativa de los extensores de rodilla entre los grupos (p = 0,74), lo que muestra un tamaño de efecto bajo (d = 0,20). En conclusión, este estudio proporciona información sobre el papel del gen ACE en la fuerza muscular y destaca la importancia de investigar variantes genéticas en poblaciones sedentarias para comprender mejor el rendimiento de la fuerza.

PALABRAS CLAVE: Gen de la enzima convertidora de angiotensina; Polimorfismo I/D; Sedentarismo.

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