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Comparison of HIF1 gene polymorphism (rs11549465) among elite and amateur karate-kas versus non-athletes

Mohammad Reza Batavani[1]✉, Sayyed Mohammad Marandi[2], Kamran Ghaedi[3], Mojtaba Babaei Khorzoghi[4], Neda Boroushak[5]

[1]Center of Physical Education, Isfahan University of Technology, Isfahan 84156-83111, Iran
[2]Department of Physiology, Faculty of Physical Education and Sport Sciences, University of Isfahan, Isfahan, Iran
[3]Department of Cell and Molecular Biology and Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Iran
[4]Health Research Group in Teaching and Workplace, Center of Physical Education, Isfahan University of Technology, 84156-83111, Isfahan, Iran
[5]Department of sports Biomechanics, Sport Sciences Research Institute, Tehran, Iran

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✉**Correspondence to:**
Mohammad Reza Batavani, Assistant Professor, Center of Physical Education, Isfahan University of Technology, Isfahan, Iran.
Postal Code:84156-83111
Tel: +98 9360286439
Fax: +983133912940-1
Email: batavani@iut.ac.ir

ABSTRACT

Introduction: One of the major energy systems for power performance in muscles is glycolysis that is regulated by the levels of Hypoxia-inducible factor-1α (HIF1), which acts as a transcription factor in response to hypoxia. The purpose of this study was to compare the HIF1 gene polymorphism (rs11549465) between elite and amateur power karate-kas versus non-athletes.

Materials and Methods: In this survey, the C/T polymorphism allelic and genotypic distribution of the "HIF1 rs11549465" gene was detected in 550 healthy Iranian persons who were divided into three groups: elite karate-kas (86 males and 86 females) and amateur karate-kas (100 males and 72 females) versus 206 non-athletes (100 males and 106 females). 5 cc blood was taken for DNA extraction and the HIF1 gene T/C polymorphism was determined by PCR from the extracted DNA. Also, RFLP analyses was exerted by electrophoresis separation. Statistical analyses included Chi-Square and multinomial regression tests and data with $P < 0.05$ were considered to be a significant amount.

Results: The distribution of HIF1 C/T genotype in the groups was significantly different in all of subjects (TC: 25.6%; TT: 11.4% and CC: 63%) ($\chi^2 = 99.889$, $P = 0.0001$), but it was not different between the groups significantly ($P > 0.05$). Furthermore, multiple regression analysis demonstrated that the genotype of HIF1 was not related to the karate-ka's athletic status.

Conclusion: In Iranian population, the HIF1 gene C/T polymorphism is not related to the karate-ka athletic status.

Keywords: HIF1 protein, Polymorphism, Karate, Elite

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Introduction

Approximately 66% of the variance in athletic status can be explained by additive genetic factors (1). Evidence has suggested that genetic markers may explain variation of physical performance specs in response to endurance or strength training (2). Until 2016, about 155 genetic variants have been associated with physical performance that some of these genetic variants have been specifically identified in athletes (3). Determining the relationship between gene variants and muscle injuries may help the coaches to prevent the probability of injury among their players, although it could provide a new way to succeed in the competition (4). It has been reported that the genetic potential is determining the heart size of endurance athletes; hence similar training habits develop the increased LV mass to different extents (5). Additional evidence is supported by the human physical performance, which might be influenced by genetic profiles; especially in Power Sports (6). Although it should be noted that due to the large number of Single nucleotide polymorphism (SNPs) related to sport performance and the high cost of reviewing them, we may not be able to test them all, therefore it needs to provide exact surveys to ensure the correct relation information about each polymorphism using any well-known sport. Exercise raises oxygen demand, which is necessary for muscular contraction (7). Glycolysis system is one of the most important energy supplies of skeletal muscles during highly intense exercise under anaerobic performance in sport. This imbalance condition between the amounts of oxygen demand and supply in the body is named hypoxia (7). The continuous exercise induced hypoxia, as a beneficial muscular adaptation, would result in inducing included increased expression of genes that codes glycolysis enzymes (8). Hypoxia via the expression of peroxisome proliferation activated receptor-gamma coactivator 1α (PGC-1α) regulates the Hypoxia-inducible factor-1 (HIF-1α) (9). Likely, HIF1α initiates the transcription of various hypoxia-adaptive genes like glycolysis, which improves glucose metabolism (10). The Pro582Ser polymorphism (rs11549465) was detected in the *HIF1A* gene, which codes α subunit of HIF-1 protein, resulting in the replacement of praline (Pro) with serine (Ser) at amino acid 582 (11). Pro582Ser is present in exon 12 (C/T at bp 85; rs11549465) and the T allele (Ser582) improves glucose metabolism (12). The HIF1A Ser allele can be associated with allele favoring the development of the speed/ power capacity; hence it was subdivided in power/strength-related genetic markers. It is reported that increased ratio of fast-twitch muscle fibers in the Vastus Lateralis was associated by 582Ser allele (13).

Karate is one of the most competitive sports that were at the 2020 Tokyo Olympics in 2021. According to the rules of the world karate federation, the first qualified punch or kick of a fighter receives a point, whereas his or her opponent's second punch or kick does not receive a point, even if it is correct. So, high speed of karate-ka among the other kind of fitness factors would be important for each elite karate-ka, and hence, this kind of sport would be appropriate in power/strength-related sport. So, there is a hypothesis that the incidence of the HIF1A Ser allele genotype polymorphism in power-orientated karate-kas is higher than sedentary controls. Until now, Ahmetov et al (2008) reported that the frequency of the HIF1A 582Ser allele in Russian weightlifters vs. controls was significantly higher and increase of its frequency was associated with their competitiveness levels (13). Cięszczyk et al (2011) also reported that the incidence of the HIF1A Ser allele genotype polymorphism was significantly higher in power-orientated runners, swimmers and weightlifters than in sedentary controls (14). These results were ingeminate by Gabbasov et al (2013) in Russian weightlifters and wrestlers and

Drozdovska (2013) in Ukrainian power-oriented athletes (15, 16). But Eynon et al (2011) did not get the same result in sprinters, while Mounier et al (2009) also found a significant decrease in HIF-1 mRNA after hypoxic training (17, 8).
Despite inconsistent findings in past studies, however, is there a linear relationship between genotype of the Hif1 gene polymorphism rs11549465 structures and power karate-kas?
Of course, in light of the physiological importance of the Hif1 gene polymorphism rs11549465, its larger quantity of expression in elite karate-kas, it would be a qualified nominee for gene talent and receipt of the Hif1 and success relationships in Iranian karate-kas. As a result, we compared the HIF1 gene polymorphism rs11549465 among Iranian elite/amateur power strength karate-kas vs. non-athletes to see if there was an association between genotype and karate-ka's athletic status or not?

Materials and Methods

Subjects

This survey was done on 550 Iranian subjects (age 27.2 ± 7.4 years) that were sub-divided into 172 elite (male: n=86 and female: n=86); 172 amateur (male: n=100 and female: n=72) compared with 206 non-athletes (male: n=100; and female n=106). Karate- kas had been trained in Kata = 17.3%; Kumite = 76.8% and Kata/Kumite = 5.9 % categories (Table 1).

Table 1. Some demographic characteristics of the different groups of subjects participated in the study.

Feature	Elite	Amateur	Non-athlete	Total
Frequency	172	172	206	550
Female/Male	86/86	72/100	106/100	264/286
Weight (kg)	64.31 ± 1.11	66.92 ± 2.21	67.59 ± 1.67	66.21 ± 1.01
Height (cm)	169.21 ± 4.23	171.31 ± 3.24	171.21 ± 3.17	170.61 ± 3.61

Data are shown as mean ± SD or number.

Elite karate-kas had experience of membership of national karate teams (from each age groups of Junior, youth or senior teams) that had taken the championship or good places in the world, Asian, international or national competitions in the last decade. 7 karate-kas were world or Asian championships; 50 karate-kas had international medal and 115 one of them had successfully in Iran karate championship as their athletic experience. Amateur karate-kas have upgraded their rankings to the black belt, but they hadn't got to the same places such as elite group. All elite and amateur karate-kas had 3 sessions (2 hours for every session) karate training in a week for at least 4 years. Subjects in the control group did not have any regular exercise experience in their life. This research was approved by the Physical Education Department of Isfahan University under the title of Doctoral Thesis. All subjects participated volunteer in this survey.

Sampling and DNA isolation

The methods of sampling were explained to the subjects, and they signed their written consent form to participate in the survey. Subjects with any existing medical condition or taking medication that could affect the results of the survey were excluded from the study. Besides, all people with familial relation were left out from survey; and bioethics items were considered relying on the standards described by advisory board of the faculty of sport sciences. In seated mode, at a given time and, in the laboratory, 5cc blood was taken and according to the alkali treatment protocol the total DNA was isolated (18). In this study, salting-out method was used for DNA extraction. All samples were kept at 4^{o}C. Then, the amount of 0.5 ml of blood sample with cell lysis buffer was added to

micro tube (1.5 ml), 15 minutes was incubated on ice that result to fragility on the membrane of red blood cells and centrifuged at 9000 rpm for 5 min, hence ⅔ of the supernatant discarded and cell lysis buffer was added. After 10 minutes of incubation, 5 minutes centrifuged at 9000 rpm 5 times until the time of observation of white pink pellet. The produced pellet by nuclease lysis buffer (to lysing the membrane of nucleus) was dissolved. Then NaCl and Chloroform was added then at 12000 rpm for 10 minutes centrifuged. Ethanol (96%) was added to the water phase of the tube that contained DNA, and then it was shacked again. By observing the DNA cluster, the tube at 12000 rpm was centrifuged for 10 minutes, and then Ethanol (70%) was added, again at 12000 rpm centrifuged for 10 minutes. After drying the tube at room temperature, sterile distilled water was added and extracted DNA was placed at -20 °C (19).
By the spectrophotometer and measuring via the ratio of DNA optical density (A260) and protein optical density (A280) the concentration and purity of the extracted DNA were analyzed. Also, for determining of DNA degradation, electrophoresis was performed on 1% agarose gel, either.

Analysis of DNA Amplification and Restriction Fragment Length Polymorphism (RFLP)

Via Polymerase Chain Reaction (PCR) Experiment using a specific primer pair (the forward primer, 5´AGGACACAGATTTAGACTTGG3´; the reverse primer, 5´GGAATACTGTAACTGCGCTTTG3) and the enzyme of Hph I, the HIF-1α gene T/C polymorphisms were determined. The PCR reaction was done at a volume of 25µl including 1µl extracted genome (100ng) as template and 0.2µM of each primer, 0.2mm each of deoxy nucleotide triphosphate (SinaGene Co.), 1.25U Smar taq DNA polymerase (SinaGene Co.), and 4mM Mg^{2+} (Sinagene Co.). PCR protocol was included of primary denaturation phase via 1 cycle for 5 min at 94°C, 35 repetitive amplification cycles including 30 Sec at 94°C, 45 Sec at 56°C and 30 Sec at 72°C as denaturation, annealing and extension phases; and final cycle for 10 min at 72°C as final extension phase. Amplicons, 150 bp in length, were treated via the restriction endonuclease Bsp/9I (SibEnzyme). A 150 bp fragment correspond to the Allele was able to cut producing100- and50-bp fragments. The length of fragment in 150 demonstrated as T/T genotype and the length of fragments in100 and 50 demonstrated as C/C genotype, and the length of fragments in 50, 100 and 150 demonstrated T/C genotype. In 1% Agarose gel, the RFLP were analyzed by electrophoresis separation followed by staining via ethidium bromide and visualization in transmitted ultraviolet light.

Statistical Analyses

Hardy-Weinberg equilibrium (HWE) of the HIF1 rs11549465 polymorphisms were tested using $\chi 2$ and multinomial regression tests. χ^2 test used for compare the genotype and allele prevalence between subgroups – non-athlete vs. athletes. Logistic regression analysis was applied to investigate the associations between HIF1optimal genotype contribution and competitive levels. Odds ratios (OR) and 95% confidence intervals (CI) were calculated under the dominant, recessive, and additive (allele counting) genetic models. Non–parametric tests were done throughout SPSS software (version 20). P value less than 0.05 was considered as a significant different.

Results

Qualitative analysis of 5 DNA samples (as typical) was performed on 1% agarose gel (Figure 1). The extracted DNA concentration was between 130 and 440 ng/µl

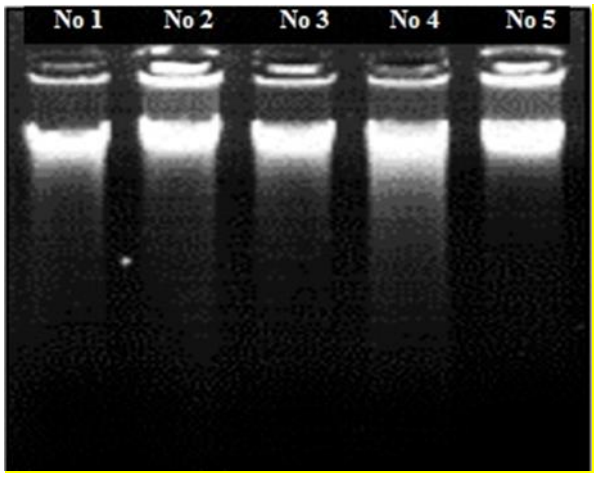

Figure 1. Qualitative analysis of DNA of 5 samples on 1% agarose gel.

PCR products were led to identification of the different types of the alleles (T/T: in length of 150 bp, C/C in length of 100 bp and 50 bp, and C/T in length of 100, 50 and 150 bp) and genotype of some subjects (Figure 2).

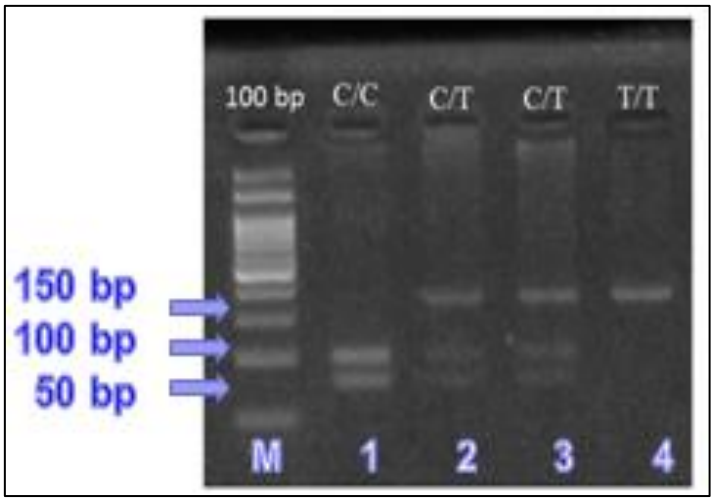

Figure 2. Representative of an agarose gel electrophoresis of PCR partial products of HIF1 gene. Lane 1; CC genotype (100 and 50 bp) and lanes 2, 3; CT genotype (50, 100 and 150 bp) and lane 4; TT genotype (150bp). Lane M is DNA 100 bp ladder.

Genotype and allelic frequencies analyses by the HIF1gene (T/C polymorphism) in all subjects (karate-kas + non-athletes) showed that the CC genotype (63%) had the most common incidence, while the TT genotype (11.4%) and TC genotype (25.6%) were less common. Chi-Square test demonstrated that there was a significant difference in frequencies of HIF1 gene allelic in all subjects, totally (χ^2= 99.889, P = 0.0001) (Table 2).

Table 2. Distribution of genotype frequencies by the HIF1gene (T/C polymorphism) in all subjects.

Genotype	Observed (%)	χ2 Statistical Expected (%)	Residual	Df	Chi-Square	P value
TT	11.4	33.3	-51.3			
TC	25.6	33.3	-18.3	2	99.889	P = 0.0001
CC	63	33.3	69.7			
Total	100	100				

Genotyping of T/C Polymorphism among and between Subgroups – Non-athletes vs. Athletes (elite and amateur)

The distribution of TC allele frequency of elite (C: 79.8% and T: 20.2 %); amateur (C: 76% and T: 24%) and non-athletes (C: 73.2% and T: 26.8%) were different significantly ($P < 0.05$). Also, the distribution of HIF1 T/C Genotype of elite (CC: 67.3%; TT: 7.7% and TC: 25 %) [χ^2= 41.830, P = 0.0001]; amateur (CC: 61.5%; TT: 9.6% and TC: 28.9%) [χ^2= 39.224, P = 0.0001] and non-athletes (CC: 61.6%; TT: 15.2% and TC: 23.2%) [χ^2= 53.128, P = 0.0001] were significantly different. The distribution of genotype and allele frequencies had the same pattern when it subdivided in elite and amateur karate-kas and non-athletes, either. Chi-Square test had shown that the T/C polymorphism distribution did not have any difference among elite, amateur and non-athlete groups, significantly (χ^2= 2.745, P > 0.05).

Genotyping of T/C Polymorphism between Genders

The distribution of genotype and allele frequencies of subjects had the same pattern when they were subdivided sexually, as well. The distribution of genotype and allele frequencies in female (CC: 59.9%; TT: 13.6% and TC: 26.5%) was significantly different (χ^2= 39.846, P = 0.0001). It was also different in male (CC: 66.1%; TT: 9.3% and TC: 24.6%) significantly (χ^2= 61.136, P = 0.0001). But the Mann-Whitney test showed that there was no significant difference in distribution of genotype of HIF1 between male and female (Mann-Whitney U=6.408E3, P = 0.0001).

Genotyping of T/C Polymorphism between Genders among Competitive Levels

The distribution of Hif1 (T/C) genotype in each competitive level included of non-athletes vs. athletes (elite and amateur karate-kas) had the same pattern when it was subdivided sexually, either. Analyses of data showed that the difference of groups (non-athletes, amateur and elite karate-kas) among gender was not significant (P > 0.05) (Figure 3).

Association of T/C Polymorphism among Karate-ka's athletic Status

Result showed HIF1 gene T/C polymorphism is not significantly associated with the karate-ka's athletic status in Iranian population. The frequency of T/T genotype vs. C/C genotype decrease in professional karate-kas and amateur karate-kas versus controlling non-athletes (odd ratio < 1), but it was not significant (P > 0.05).

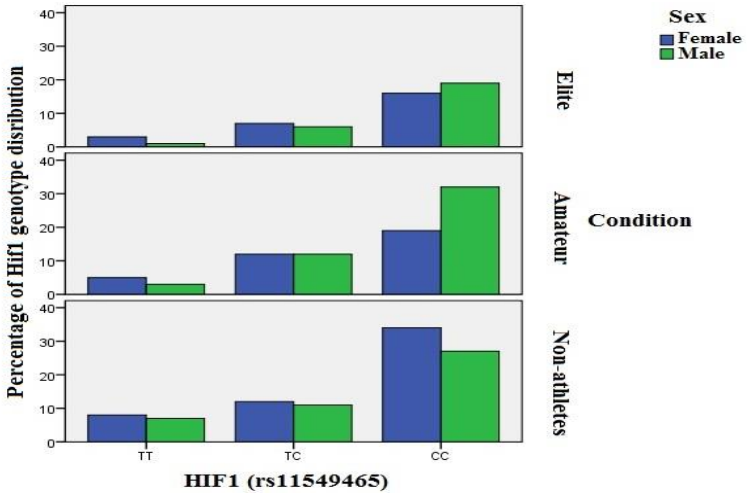

Figure 3. Simultaneous bar plot of female and male HIF1 allelic in different conditions: elite, amateur and non-athlete.

Also, the frequency of T/C genotype vs. C/C genotype increase in professional karate-kas and amateur karate-kas versus to control non-athletes (odd ratio > 1), and however it was not significant, too (P > 0.05). Odd ratio of T/T and T/C genotype compare to C/C in professional group versus control were 0.631 (CI: 0.262 - 1.516) and 1.363 (CI: 0.750 - 2.476) respectively. Odd ratio of T/T and T/C in amateur group versus control were 0.831 (CI: 0.417 - 1.656) and 1.198 (CI: 0.703 - 2.040), respectively (Table 3).

Table 3. Multinomial logistic regressions for HIF1 rs11549465 genotype distribution in professional, amateur karate-kas and non-athlete groups.

			95% Confidence interval for Exp(B)	
Condition[a]		Odd Ratio	Lower Bound	Upper Bound
Elite	HIF1 gene = T / T	0.631	.556	2.275
	HIF1 gene = T / C	1.363	.538	1.984
	HIF1 gene = C / C	1.000	.	.
Amateur	HIF1 gene = T / T	0.831	.535	1.876
	HIF1 gene = T / C	1.198	.715	2.205
	HIF1 gene = C / C	1.000	.	.

a. The reference group is non-athletes.

Discussion

This survey compared HIF1 gene polymorphism rs11549465 among elite/ amateur power athletes vs. non-athletes. Analyze have shown that the HIF1 gene TC genotype occurrence among all subjects (elite and amateur karate-kas and non-athletes, in both male and female) were significantly different between high incidence of CC, TC and TT; respectively. It is worth noting that HIF1 genotype frequency and T/C allele occurrence incidence between all groups (among elite, amateur and non-athlete) were not statistically different and not associated with the karate-ka's athletic status.

Our results were in confirm by the results that reported by Eynon et al. (2011) that did not find any significant differences in their survey in HIF1A genotype distribution and Ser582 allele frequency of endurance and sprinters athletes vs. controls (18). These results showed that HIF1A Ser allele carriers are not more predisposed to power-orientated karate-kas.

Our survey would not confirm previews studies by Ahmetov et al (2008) that reported an association between the HIF1A Pro582Ser polymorphism and increased levels of Russian sprint/strength weightlifters achievement and Zoll et al. (2006) that showed long exercise plan (i.e., 6 weeks) significantly increased hif-1 gene expression in Quadriceps muscle, too (13, 20).

Differences in the sports conditions, training design (frequency and duration), size of subjects, and experience and training sessions of subjects, etc. could explain these discrepancies, likely.

Differences in ethnicities of subjects (i.e. Russian [Ahmetov et al; 2008] and Polish [Cięszczyk; 2011] groups) and multiple sportive field of subjects (i. e. Runners/ Swimmers/ Weightlifters together in some mentioned surveys) are another possible explanation, as well (13, 14). In the studies by Khaledi et al (2014) on Iranian professional athletes (include of Olympic and world championship in variant branches) vs. non-athletes about ACTN3, PGC-1α, Angiotensin converting enzyme (ACE), Muscle-Specific Creatine Kinase (CKMM), PPARγ polymorphisms, and Salehi et al (2011) on 148 Iranian national teams (in different sports) vs. 175 non-athletes aboutACTN3, did not find significant differences, too (21).

Semenza (2010) narrated that HIF-1α protein stability is regulated by the mechanisms that are oxygen-independent (22). Cooper et al (2007) reported that acute exercise is attended by reduced partial

pressure of oxygen, too (23). Oxygen privation, among erythropoietin (EPO), VEGF and HIF-1α modulates several genes of oxygen homeostasis (24). Hypoxia condition product the ROS that likely reduce Fe^{2+} availability, which inhibits the activity of factor inhibiting HIF-1 (7).

In the state of hypoxia many factors such as the amount of ATP in muscles, high enzymatic performance for energy supply via glycolysis and phosphagen systems, creatine phosphate, glycogen, etc. Therefore, they effect the high anaerobic ability (13).

From the other hand, a complex interaction of psychological, sociocultural, etc. factors which result in variation of athletic performance (25). Mitchell et al (2005) reported that karate-Do is a low dynamic and high static sport; hence it needs to moderate the total cardiovascular demands, too (26). Aligned with that, Batavani et al (2017) has proposed to be the association between the CK-MM gene A/G genotype and brilliant karate-kas performance (21). Aerobics Energy supplies and the power ability of muscles during exercise are important, as well. Indeed, elite karate performance is a polygenic trait, with over one polymorphism like ACE and CKMM association (21). Also, elite status in karate seems to be depending on the simultaneous presence of multiple fitness factors such as skills, speed, etc. Indeed, it might recommend the fact that the HIF1A Pro582Ser polymorphism is not a very important factor in karate-kas status. Hence, for some branches of sport which are yielded by intensive training, the proper genetics are not enough to attach the optimal sport performances, basically. However, the effect of genes on adaptation and responding to exercise, is surely undeniable (27). Athletic performance that was predicted by genetic profiles examination alone, is not reliable (28). The most branches of sports need the combination of sprint or power-endurance demands together such as many other factors, including a broad variety of genetic, physical, environmental and psychological elements to reach the success, too (29). Specially, it is suggested that between the HIF1gene polymorphism and athletic status replicate additional large scale prospective studies among some worldwide branches of sports, separately. However, this conclusion needs to be supported by more experimental surveys related to HIF1A polymorphisms in professional athletes. Döring et al (2010) and Mason et al (2007) have written the articles about the role of the HIF1A gene as a genetic marker associated with endurance athlete performance. (30, 31).

Conclusion

Our study investigated the relationship among the *HIF1A* Pro582Ser polymorphism and karate-ka's athletic status. The investigated group included of elite and amateur karate-kas, and the results of our survey did not indicate the relation between HIF1A Ser 582 allele and the karate level of achievement. Indeed, the findings showed no association between *HIF1A* gene Pro582Ser polymorphism and Iranian karate-ka's athletic status. Therefore, it suggested that the *HIF1A* gene cannot be taken into consideration as a genetic marker in Iranian power-orientated karate-kas.

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Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. DeMoor MH, Spector TD, Cherkas LF, Falchi M, Hottenga JJ, Boomsma DI, et al. Genome-wide linkage scan for athlete status in 700 British female DZ twin pairs. TRHGs. 2007; 10(6): 812-820. doi: 10.1375/twin.10.6.812.
2. Bray MS, Hagberg JM, Pe´russe L, Rankinen T, Roth SM, Wolfarth B, Bouchard C. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update, Med Sci Sports Exerc. 2009; 41: 34–72. doi: 10.1249/MSS.0b013e3181844179.
3. Chen C, Sun Y, Liang H, Yu D, Hu S. A meta-analysis of the association of CKM gene rs8111989 polymorphism with sport performance. Biolsport, 2017; 34(4): 323- 330. doi:10.5114/biolsport.2017.69819.
4. Massidda M, Voisin S, Culigioni C, Piras F, Cugia P, Yan, et al. ACTN3 R577X polymorphism is associated with the incidence and severity of injuries in professional football players. Clin J Sport Med, 2019; 29(1): 57-61. doi: 10.1097/JSM.0000000000000487.
5. Karjalainen J, Kujala UM, Stolt A, Mäntysaari M, Viitasalo M, Kainulainen K, et al. Angiotensinogen gene M235T polymorphism predicts left ventricular hypertrophy in endurance athletes. JACC. 1999; 34(2): 494-499.
6. Batavani MR, Emadi S, Mousavi SR, Ashena H. Comparison of ACE gene single nucleotide polymorphism (rs4646994) profile in Iranian elite karate-kas and weightlifters. Yafte, 2022; 24 (2): 54-68. doi:10.32592/Yafteh.2022.24.2.5.
7. Sylviana N, Helja N, Qolbi HH, Goenawan H, Lesmana R, Rizky M, et al. Effect of Swimming Exercise to Cardiac PGC-1 and HIF-1 Gene Expression in Mice. Asian J Sports Med. 2018; 9(4): e65079 1-7. doi:10.5812/asjsm.65079.
8. Mounier R, Pialoux V, Roels B, Thomas C, Millet G, Mercier J, et al. Effect of intermittent hypoxic training on HIF gene expression in human skeletal muscle and leukocytes. Eur J Appl Physiol. 2009; 105(4): 515- 524. doi:10.1007/s00421-008-0928-y.
9. Jung S, Kim K. Exercise-induced PGC-1alpha transcriptional factors in skeletal muscle. Integr Med Res. 2014; 3(4): 155–60. doi:10.1016/j.imr.2014.09.004.
10. Ohno H, Shirato K, Sakurai T, Ogasawara J, Sumitani Y, Sato S, et al. Effect of exercise on HIF-1 and VEGF signaling. JPFSM. 2012; 1(1): 5-16.
11. Clifford SC, Astuti D, Hooper L, Maxwell PH, Ratcliffe PJ, Maher ER. The pVHL associated SCF ubiquitin ligase complex: molecular genetic analysis of elongin B and C, Rbx1 and HIF-1alpha in renal cell carcinoma. Oncogene. 2001; 20: 5067-5074. doi:10.1038/sj.onc.1204602.
12. Ahmetov II, Fedotovskaya ON. Current progress in sports genomics. Advances in clinical chemistry. 2015; 70: 247-314. doi: 10.1016/bs.acc.2015.03.003.
13. Ahmetov II, Hakimullina AM, Lyubaeva EV, Vinogradova OL, Rogozkin VA. Effect of HIF1A gene polymorphism on human muscle performance, Bull Exp Biol Med. 2008; 146: 351–353. doi:10.1007/s10517-008-0291-3.
14. Cieszczyk P, Sawczuk M, Maciejewska A, Ficek K, Eider J, Variation in peroxisome proliferator activated receptor α gene in elite combat athletes. Eur J Sport Sci. 2011; 11: 119–123. doi:10.1080/17461391.2010.487120.
15. Gabbasov RT, Arkhipova AA, Borisova AV, Hakimullina AM, Kuznetsova AV, Williams AG, et al. The HIF1A gene Pro582Ser polymorphism in Russian strength athletes. J Strength Cond Res. 2013; 27: 2055–2058. doi: 10.1519/JSC.0b013e31827f06ae.

16. Drozdovska SB, Dosenko VE, Ahmetov II, Ilyin V. The association of gene polymorphisms with athlete status in Ukrainians. Biolspor. 2013; 30(3): 163-167. doi: 10.5604/20831862.1059168.
17. Eynon N, Meckel Y, Alves AJ, Nemet D, Eliakim D. Is there an interaction between BDKRB2−9/+9 and GNB3 C825T polymorphisms and elite athletic performance? Scand J Med Sci Sports. 2011; 21 (6): 242-246. doi:10.1111/j.1600- 0838.2010.01261.x.
18. Martínez J, Khorsandi S, Sojo R, Martínez C, Martín JA, López-Taylor JR, etal. Lack of an association between CKMM genotype and endurance performance level in Hispanic marathon runners. MedicinaSportiva. 2009; 13(4): 219-223. doi:10.2478/v10036-009-0034-1.
19. Shokrzadeh M, Mohammadpour A. Evaluation of a modified salt-out method for DNA extraction from whole blood lymphocytes: A simple and economical method for gene polymorphism. PBR. 2018; 4(2): 28-32. doi: 10.18502/pbr.v4i2.218.
20. Zoll J, Ponsot E, Dufour S, Doutreleau S, Ventura-Clapier R, Vogt M, et al. Exercise training in normobaric hypoxia in endurance runners. III. Muscular adjustments of selected gene transcripts. J Appl Physiol. 2006; 100: 1258-1266. doi:10.1152/japplphysiol.00359.2005.
21. Batavani MR, Marandi SM, Ghaedi K, Esfarjani F. Comparison of muscle-specific creatine kinase (CK-MM) gene polymorphism (rs8111989) among professional, amateur athletes and non-athlete karatekas. Asian J Sports Med, 2017; 8(2). e43210, 1-5. doi: 10.5812/asjsm.43210.
22. Semenza GL. Oxygen homeostasis. Wiley Interdiscip Rev Syst Biol Med. 2010; 2: 336-361. doi:10.1056/NEJMra1011165.
23. Cooper DM, Radom-Aizik S, Schwindt C, Zaldivar F Jr. Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. J Appl Physiol. 2007;.103: 700-709. doi:10.1152/japplphysiol.00225.2007.
24. Lemus-Varela ML, Flores-Soto ME, Cervantes-Munguia R, Torres-Mendoza BM, Gudino- abrera G, Chaparro-Huerta V, et al. Expression of HIF-1 alpha, VEGF and EPO in peripheral blood from patients with two cardiac abnormalities associated with hypoxia. Clin Biochem. 2010; 43(3): 234–9. doi: 10.1016/j.clinbiochem.2009.09.022.
25. Brutsaert TD, Parra EJ. What makes a champion?: Explaining variation in human athletic performance. RESPNB. 2006; 151(2), 109-123. doi:10.1016/j.resp.2005.12.013.
26. Mitchell J, Haskell W, Snell P, Van Camp S. Classification of sports, J Am CollCardiol. 2005; 45(8): 1364-7. doi: 10.1016/j.jacc.2005.02.015.
27. Lippi G, Longo U, Maffulli N. Genomics and sports. Br Med Bull. 2010; 93: 27-47.
28. Guilherme JPLF, Tritto ACC, North KN, JUNIOR AHL, ARTIOLI GG. Genetics and sport performance: current challenges and directions to the future. Rev Bras Educ Fís Esporte. 2014; 28:177–93. doi:10.1590/S1807-55092014000100177.
29. Vlahovich N, Fricker PA, Brown MA, Hughes D. Ethics of genetic testing and research in sport: a position statement from the Australian Institute of Sport. BJSM. 2017; 51(1): 5-11. doi:10.1136/bjsports-2016-096661.
30. Döring F, Onur S, Fischer A, Boulay MR, Pérusse L, Rankinen T, et al. Common haplotype and the Pro582Ser polymorphism of the hypoxia-inducible factor-1α (HIF1A) gene in elite endurance athletes. J Appl Physiol, 2010; 108: 1497-1500. doi:10.1152/japplphysiol.01165.2009.
31. Mason SD, Rundqvist H, Papandreou I, Duh R, McNulty WJ, Howlett RA, et al.

HIF-1α in endurance training: suppression of oxidative metabolism. Am J Physiol. 2007; 293: 2059–2069. doi:10.1152/ajpregu.00335.2007.