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Genetic biomarkers of skiers from the Oğlağo Tribe in Muş Province, Turkey

An analysis of *ACTN3*, *VEGF-A*, and *GABPB1* polymorphisms

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Abstract

For many years, the relationship between genetic variants and athletic performance has been studied in terms of their effect on strength, power, endurance, muscle fiber type and other phenotypes. As a result of such research, many genes have been found to be associated with athletic performance. In this context, the success achieved by skiers from the same tribe living in Muş (Turkey) is thought to be due to a genetic predisposition. Therefore, this study examined the relationship between the α-actinin-3 (*ACTN3*) gene rs1815739, vascular endothelial growth factor A (*VEGF-A*) rs2010963, and GA Binding Protein Transcription Factor Subunit Beta1 (*GABPB1*) rs7181866 polymorphisms and the success achieved by skiers from the Oğlağo tribe. The study included 19 skiers and 130 sedentary individuals from the same tribe. The Chi-squared (χ^2) test and power analysis were used to analyze the genotype and allele distributions of *ACTN3*, *VEGF-A*, and *GABPB1* polymorphisms in the group of skiers and in the control group. As a result of the analysis, no statistically significant difference was found between the genotype and allele distributions of *ACTN3* and *VEGF-A* polymorphisms (P = .0659, .2018), while statistically significant differences were found across the groups in both the genotype and allele distributions of *GABPB1* polymorphism ($P < .001$). In addition, the genotype and allele percentages of the *ACTN3* (TT) and *VEGF-A* (CC) genotypes associated with endurance were found to be high. Summing up, the present study is the first to reveal the effect of genetics on skiing success in a genetically close cohort (Oğlağo tribe, Muş, Turkey). The results obtained were promising in terms of genetics and skiing success, but further studies are needed to deepen this relationship.

Abbreviations: *ACTN3* = alpha-actinin-3, EDTA = ethylene diamine tetra acetic acid, FIS = International Ski federation, *GABPB1* = GA binding protein, NRF2 = nuclear respiratory factor 2, PCR = polymerase chain reaction, TSF = Turkish Ski Federation, *VEGF-A* = vascular endothelial growth factor, $VO_{2\,max}$ = maximal oxygen uptake.

Keywords: *ACTN3*, cross-country skiing, *GABPB1*, genetic polymorphisms, Oğlağo tribe, *VEGF-A*

1. Introduction

In recent years, significant advances have been made in the field of genetic studies, owing largely to the knowledge gained through the Human Genome Project (1990–2003). Alongside this progress, notable findings have emerged regarding the relationship between sports and genetics, particularly concerning the role of genetic factors in determining sporting success.[1,2]

Evidence from multiple studies has shown that basic motor characteristics such as strength, endurance, power, etc are deeply rooted in genetic factors; besides, aerobic and anaerobic capacity also have a strong genetic basis, and both factors strongly influence sporting performance and are considered a determining factor in identifying talented athletes.[3–5] In addition, in the field of sports, genetic background has been shown to significantly influence strength, endurance, muscle mass, muscle fiber composition, and lung capacity.[6]

Research in the field of sports science and genetics has demonstrated a correlation between genetic factors and cardiopulmonary capacity, aerobic fitness, and skeletal muscle, all of which

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study protocol was approved by the Muş Alparslan University Ethics Committee (B.30.2.ATA.0.01.00/30.11.2017/27).

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are essential traits for endurance athletes.[7,8] Consequently, sports scientists and sports physicians have become increasingly interested in exploring the relationship between genetic factors and the sporting performance and success of athletes.

Performance is, by definition, the degree to which a person succeeds in carrying out a given task. Sports performance, in turn, is defined as the overall mental and physical output of an athlete during any sporting activity.[9,10] High-level sportive performance is the result of a combination of many factors such as training, genetics, epigenetics, nutrition, motivation, equipment, and other environmental factors and mental health variables.

Genetic characteristics are among the most significant factors influencing an athlete's career path. Research indicates that 66% of athletic performance is genetically determined, with the remaining 34% is influenced by training, nutrition, equipment, motivation, sleep, and nongenetic factors. Studies have demonstrated the contribution of genetic factors to both training and athletic performance development, which can be enhanced through regular training.[11,12]

The *ACTN3* rs1815739 polymorphism, resulting from a cytosine-to-thymine substitution in exon 16 of the *ACTN3* gene, is one of the most influential regions among the genes associated with athletic performance and has been extensively studied for its significant role in this field. This modification results in the formation of a stop codon (X) in the codon encoding amino acid at position 577 of the protein, replacing the codon encoding arginine (R). *ACTN3* rs1815739 is associated with human athletic fitness and muscle performance, and α-actinin-3 deficiency affects the function of fast twitch fibers and is known to activate aerobic pathways in muscle metabolism and increase endurance. Some studies have reported that strength and sprint athletes have a higher frequency of the CC (RR) genotype of the *ACTN3* gene compared to endurance athletes and the control group, while endurance athletes have a higher frequency of the TT (XX) genotype.[13,14]

VEGF-A genes play a significant role in angiogenesis and skeletal muscle adaptations. Angiogenesis, the process of new blood vessel formation, is crucial in endurance exercise because an increase in capillaries within the muscle directly improves gas exchange and migration[15] and, thus, increases $VO_{2\ max}$.[16] Oxygen-sensitive pathways, which are activated in response to acute changes in oxygen demand during exercise, have been shown to adapt by increasing capillary growth.[17]

Nuclear respiratory factor 2 (NRF2), also called GA binding protein (*GABP*) transcription factor, is a key transcriptional activator of many nuclear genes encoding a wide variety of mitochondrial enzymes. Variants of the *GABPB1* gene encoding the beta1 subunit of the NRF2 protein have been associated with physical performance, particularly with endurance.[18] NRF2 is a complex protein consisting of an alpha and beta subunit encoded by separate genes, *GABPA* and *GABPB1*, respectively.[19]

Many genes have been associated with endurance sports, but *VEGF-A* and *GABPB1* are the polymorphisms most associated with muscle type (white muscle) and $VO_{2\ max}$, both of which are considered among the most important markers of endurance capacity in sports.[20,21] The *ACTN3* genotype is a gene polymorphism associated with both endurance and speed.[22] The cross-country ski runners in the present study engage in 1500-meter sprints and long-distance races of 15 km or more. Therefore, the *ACTN3* gene polymorphism and the endurance and speed characteristics of the athletes will be better understood on the basis of these 2 types of races in mind. In addition, the 3 mentioned gene polymorphisms are significantly correlated, especially in high-level endurance athletes. Therefore, *ACTN3*, *VEGF-A*, and *GABPB1* polymorphisms were selected for this study.

Cross-country skiing has been included in the Olympic Games since the first Winter Games held in Chamonix (France) in 1924.[23] Since then, this sporting discipline has evolved to include different race styles and distances. Competitive cross-country skiing consists of 2 distinct categories. The first includes the Olympic disciplines, with competition formats ranging from short 1.5 km sprint events to 50 km races in hilly terrain using either the classical or skating styles. The second category is long-distance cross-country skiing, with races of between 40 and 90 km on more stable terrain and where the classic style predominates.[24,25]

A tribe living in a village in Muş province in eastern Turkey holds significant achievements in skiing. Nearly 40 members of the same tribe have been involved in skiing (cross-country skiing) and many of them have achieved significant success in international skiing competitions and national championships, the Balkan Cup, FIS (International Ski Federation) races, and World Cup. The tribe has also produced athletes who have participated in the Winter Olympic Games 4 times and in the Youth Winter Olympic Games many times.[26] The remarkable achievements of the members of this tribe have periodically attracted national attention, and this has led to questioning about the possible underlying genetic basis. The aim of this study was to explore the genetic factors underlying the remarkable skiing success of members of a tribe in Muş province, Turkey.

2. Materials and methods

2.1. Study group

The study included individuals of Turkish ethnic origin. Nineteen well-trained cross-country skiers from the same tribe living at an altitude of 1420 m in Muş, Turkey, along with 130 sedentary volunteers were involved in the investigation. To ensure the homogeneity of the experimental group, only athletes from the same tribe were included. The 130 sedentary participants were nonprofessional, non-licensed individuals with no history of competitive sports, who did not permanently reside at high altitudes. Only those who voluntarily agreed to participate and provided informed consent were included.

The exclusion criteria comprised individuals with cardiovascular diseases, metabolic syndromes, musculoskeletal disorders, genetic syndromes, or severe respiratory conditions. In the control group, those engaged in regular training as professional or amateur athletes, participating in endurance sports, or not matching the study sample in terms of age or sex were also excluded. Additionally, individuals who had lived at high altitudes for extended periods or whose DNA samples were inadequate for analysis were not included.

All participants signed an informed consent form, and the study was approved by the Ethics Committee of Muş Alparslan University (B.30.2.ATA.0.01.00/30.11.2017/27).

2.2. Blood sampling from the skier tribe members

Blood samples of 1 mL were taken by an experienced physician at the Muş Campus Tribes Health Center after the athletes had been resting in a sitting position. Then, they were transferred to EDTA tubes and sent to the Department of Basic Medical Sciences Laboratory of the Marmara University for genotyping.

2.3. DNA isolation and genotyping

The DNA isolation process was completed by using a PureLink DNA isolation kit (Invitrogen, Van Allen Way Carlsbad) from peripheral blood samples taken from individuals who voluntarily participated in the study. In addition to the 200 µL obtained, DNA isolation, 20 µL proteinase K, and 10 µLRNAase were added and vortexed. After waiting for 2 minutes at room temperature, 200 µL of binding buffer was added, mixed, and homogenized. After incubation in a 55 °C water bath for 10 minutes, 200 µL of ethanol was added. After the mixture was vortexed for 5 seconds, it was taken into a filtered tube and centrifuged at 13,000 rpm for 2 minutes. The supernatant was discarded and 500 µL of wash buffer was added to the pellet. After centrifuging at 13,000 rpm for 2 minutes, the supernatant was taken and 500 µL of the second wash buffer was added and centrifuged at maximum speed for 2 minutes. 125 µL of elution buffer was added and incubated. Pure DNA was obtained after centrifugation at maximum speed for 1 minute. An average of 20 ng of DNA was isolated from each sample and the isolated DNAs were evaluated according to the OD260/280 spectrophotometric ratio. The DNA samples obtained were stored at −20°C until the analysis of the relevant gene regions was completed.

Genotyping of the *ACTN3* rs1815739, *VEGF-A* rs2010963, and *GABPB1* rs7181866 polymorphisms was performed using Real-Time PCR on a StepOnePlus (Thermo Fisher Scientific, Inc.) device and Taqman single nucleotide polymorphisms Genotyping Assays genotyping kits according to the manufacturer's protocols (cat. no. 4362691, Thermo Fisher Scientific, Inc.). The C and T alleles for the *ACTN3* rs1815739 polymorphism were identified using the 6-carboxyrhodamine 6G (VIC) and 6-carboxy fluorescein (FAM) primers, respectively. The C and G alleles for the *VEGF-A* rs2010963 polymorphism were identified using the VIC and FAM primers, respectively. The A and G alleles for the *GABPB1* rs7181866 polymorphism were identified using the VIC and FAM primers, respectively. For a total volume of 10 µL reaction, 5 µL of Genotyping Master Mix (Applied Biosystems, Foster City), 3.5 µL of nuclease-free H_2O (Thermofisher, USA), 0.5 µL of genotyping test (Applied Biosystems), and 1 µL of DNA were used. The sequences of the TaqMan Probe used for genotyping are listed in Table 1.

2.4. Statistical analysis

In this study, the Chi-squared goodness-of-fit test was used to compare the distribution of genetic polymorphisms between athlete tribe members and the general population. Additionally, Fisher exact test was applied to assess associations in cases where sample sizes were small or when expected frequencies in certain cells were below 5. This allowed for a more accurate analysis of genotype and allele distributions across the studied groups.

To ensure the statistical validity and reliability of the data, a power analysis was conducted using G*Power 3.1.

The following key parameters were used in the power analysis:

- Effect size (Cohen w): 0.3 (medium effect size).
- Significance level (α err prob): .05, a commonly used standard value.
- Statistical power (Power, 1-β err prob): 0.80 (80%, considered adequate in scientific research).
- Degrees of freedom (Df): 1, as 2 categories were compared.

Table 1

Sequences of the TaqMan probe used for genotyping *ACTN3* rs1815739, *VEGF-A* rs2010963 and *GABPB1* rs77181866 polymorphisms.

SNP	qPCR	Sequence, 5'-3'
ACTN3 rs1815739	VIC/FAM	CAAGGCAACACTGCCCGAGGCTGAC**[T/C]**GAGAGCGAGGTGCCATCATGGGCAT
VEGF-A rs2010963	VIC/FAM	CGCGCGGGCGTGCGAGCAGCGAAAG**[C/G]**GACAGGGGCAAAGTGAGTGACCTGC
GABPB1 rs7181866	VIC/FAM	GATCCAACATAGAATAGGAGAGAGT**[A/G]**CCCAAAATGATGGTGAAGGGAGACC

FAM = 6-carboxy fluorescein, qPCR = quantitative polymerase chain reaction, SNP = single nucleotide polymorphisms, VIC = 6-carboxyrhodamine 6G.

Initially, the control group consisted of 50 individuals. However, preliminary analyses indicated that this sample size would not provide sufficient statistical power. The G*Power analysis revealed that a minimum of 88 individuals was required to achieve 80% statistical power.

Accordingly, the control group size for *VEGF-A* rs2010963 and *GABPB1* rs7181866 was increased to 130 individuals. The final analysis was conducted on 19 athletes and 130 control individuals. A subsequent power analysis estimated the statistical power at 92%.

These results confirm that the sample size in this study was statistically adequate, ensuring that the comparisons made yielded reliable conclusions.

3. Results

3.1. Identification of alleles and genotypes

Skiers from the Oğlağo Tribe have participated in many national and international competitions (Winter Olympic Games, Ski World Cup, FIS races, Balkan Cup, etc). As can be seen in Table 2, they have achieved significant success in these events (Table 2).[26]

In the analysis of *ACTN3* rs1815739 polymorphism, the TT genotype, which is associated with resistance, was observed in 7 individuals (36.8%). Additionally, the CT genotype was identified in 4 individuals (21.1%), while the CC genotype was detected in 8 individuals (42.1%). In relation to *VEGF-A* rs2010963 polymorphism, the most prevalent genotype was identified as GG (52.6%), followed by CG (31.6%) and CC (15.8%), respectively. Upon analysis of *GABPB1* rs7181866 polymorphism, it was observed that the AA genotype exhibited a dominant frequency (78.9%), while the AG genotype was present in 21.1% of the subjects and the GG genotype was not detected in any individual (Table 3).

A particularly noteworthy finding was that the number of individuals with *ACTN3* TT and *VEGF-A* CC genotypes together was 3 (15.8%). This genotype combination has been previously associated with endurance performance in the literature and may serve as an important marker for athletic success. Furthermore, 42.9% (3/7) of *GABPB1* rs7181866 AG genotype was associated with *ACTN3* TT genotype, suggesting that *GABPB1* AG genotype may also be associated with endurance sports.

3.2. ACTN3 rs1815739 polymorphism

The genotypic and allelic distributions of the *ACTN3* rs1815739 polymorphism in cross-country skiers (athlete group) were assessed and compared with the control group. The Chi-squared (χ^2) test showed no statistically significant difference in genotype distribution across the groups ($P = .0659$) (Table 4).

The TT genotype was the most common in the athlete group (42.1%), while the CT genotype was the most common in the control group (46.2%). No significant difference was found in the allelic distribution ($P = .3540$). However, the T allele was more frequent in the athlete group (52.6%), whereas the C allele was more common in the control group (55.0%). Given that the cohort of athletes was composed of tribe members, it is likely that their shared genetic background accounts for the observed disparities in allele frequencies when compared to the general population (Table 4).

3.3. VEGF-A rs2010963 polymorphism

The genotypic and allelic distributions of the *VEGF-A* rs2010963 polymorphism in cross-country skiers (athlete group) were assessed and compared with the control group.

Table 2

The success of Oğlağo tribe members in skiing.

STM	Olympiad championships	World championships	Balkan championships	Turkey championships	National state
STM1	Üniversiad 5. 4 times participated	11.	4 times 1. ve 2. 5 times 3.	16 times 1.	National
STM2	Üniversiad 41	27.	2.	1.	National
STM3	Üniversiad 39	21.	2.	1.	National
STM4		59		1.	National
STM5		82	13.	1.	National
STM6	Youth Games 80.	18	3 times 1. ve 2	1.	National
STM7		36		1	National
STM8		15		1.	National
STM9			6.	1.	National
STM10				1.	–
STM11		14		3.	–
STM12				1.	–
STM13				1.	–
STM14		29		1.	National
STM15			5.	1.	National
STM16				2.	–
STM17			3.	1.	National
STM18				1.	–
STM19			2.	2.	National

STM = Skier tribe members.

Table 3

Genotype distribution of *ACTN3* rs1815739, *VEGF-A* rs2010963 and *GABPB1 (NRF)* rs7181866 polymorphisms.

No	*ACTN3* rs1815739	*VEGF-A* rs2010963	*GABPB1 (NRF)* rs7181866
1	CC	GG	AA
2	CT	GG	AA
3	TT	CC	AG
4	CC	GG	AA
5	CT	GG	AA
6	TT	CG	AG
7	TT	GG	AA
8	TT	CG	AG
9	CT	GG	AA
10	CT	CG	AA
11	CC	CC	AA
12	CC	CG	AA
13	CC	CG	AA
14	CC	GG	AA
15	TT	CC	AG
16	TT	GG	AA
17	TT	CC	AA
18	CC	GG	AA
19	TT	CG	AA

The Chi-squared (χ^2) test showed no statistically significant difference in genotype distribution across the groups ($P = .2018$) (Table 5).

In the athlete group, the GG genotype was the most common (47.4%), followed by GC (31.6%) and CC (21.0%). Similarly, in the control group, the GG genotype (47.7%) was the most common, followed by GC (43.8%) and CC (8.5%). No significant difference was found in the allelic distribution ($P = .4222$). The G allele was more common in both groups, with a frequency of 63.2% in athletes and 69.6% in the control group. The C allele was found in 36.8% of athletes and in 30.4% of controls (Table 5).

3.4. GABPB1 rs7181866 polymorphism

The genotypic and allelic distributions of the *GABPB1* rs7181866 polymorphism in cross-country skiers (athlete group) and the control group were analyzed. The Chi-squared (χ^2) test revealed statistically significant differences in both genotypic and allelic distributions across the groups ($P < .001$) (Table 6).

Regarding genotype distribution, the AA genotype was the most common in both groups, though its frequency varied; it was observed in 79.0% of the athlete group and 97.0% of the control group. The AG genotype was found in 21.0% of the athletes, compared to 10.0% of the control group, while the GG genotype was absent in both groups (0.0%). The *P*-value ($P < .001$) confirmed a statistically significant difference in genotype distribution across the groups (Table 6).

Similarly, the allelic distribution showed a statistically significant difference ($P < .001$). The A allele was predominant in both groups, with a frequency of 89.5% in athletes and 95.0% in the control group. In contrast, the G allele was more frequent in athletes (10.5%) than in the control group (5.0%). This higher prevalence of the G allele in athletes may indicate a genetic factor influencing endurance performance (Table 6).

4. Discussion

In recent years, research has focused on gaining insight into the potential influence that genetic variants may have on athletic performance. This has led to the identification of promising candidate genes that may contribute to the distinction between elite and non-elite athletes. Although a limited number of candidate genes had been initially investigated, the present review demonstrates that at least 251 genetic variants have been reported to be linked to sport-related traits. However, only 128 (51%) of these variants (41 endurance-related, 42 strength-related, and 45 power-related) have been specifically associated with athletic performance.[27] Besides, the impact of genetic studies on athletic performance is complex due to multiple factors such as ethnicity, environment, the quality and size of the study group, the individual's training status, muscle composition, and muscle fiber type.[6,28] Working with homogeneous groups is considered the most effective way to reduce such complexity. Yet, in the literature, homogeneous studies in sports genetics seem to be limited. In this context, this study aimed to determine the association between *ACTN3*, *VEGF-A*, and *GABP1* polymorphisms and endurance in skiers from the same tribe.

The *ACTN3* rs1815739 polymorphism exerts a significant influence on physical and sports performance in both elite athletes and the general population.[29] The *ACTN3* gene has 2 alleles, "C" and "T," forming 3 possible genotypes: "CC," "CT," and "TT."[22] Research suggests that the ACTN3 CC genotype is associated with vigorous and rapid muscle contractions, thereby contributing to agility and power, while the TT genotype is associated with aerobic metabolism and increased endurance.[11,30]

In this study, no significant difference was observed between the athlete and control groups for the *ACTN3* rs1815739 polymorphism, similar to findings reported by Peplonska et al.[27] Likewise, studies conducted by Akazawa et al[31] in Japan and Döring et al[32] with Caucasian elite endurance athletes found no association between the X (T) allele and endurance performance. However, the TT genotype and T allele (TT: 42.1%, T: 52.6%), which are associated with endurance, were more frequent in the athlete group than in the control group (TT: 21.5%, T: 45%), consistent with the published literature.[33–35]

Yang et al[36] reported that the T allele frequency was at 46% in endurance athletes and 44% in the control group. Similarly, Yang et al[33] found that, in Chinese elite athletes, the TT (XX) genotype was present in 69.2% of endurance athletes and 74.0% of the control group, while the CT (RX) genotype was observed in 36.4% of endurance athletes and 40.0% of controls. In Estonian male skiers, the CC (RR) genotype was significantly more frequent, whereas the CT (RX) genotype was less common.[37] In the same study, the *ACTN3* TT genotype was found in 5.1% of sprinters and strength athletes, 31.8% of endurance athletes, and 34.0% of the control group. A large cohort study on Japanese endurance athletes reported *ACTN3* genotype distributions as RR: 24%, RX: 44%, and XX: 33% at the regional level; RR: 22%, RX: 50%, and XX: 28% at the national level; and RR: 23%, RX: 56%, and XX: 20% at the international level. The study observed that as athletes reached higher competitive levels, the percentage of the XX (TT) genotype decreased.[38]

On the other hand, some studies have reported no association between the *ACTN3* TT genotype and $VO_{2\,max}$ in well-trained winter sports athletes.[39] Similarly, a multiple-cohort quantitative analysis on 698 marathon runners suggested that the *ACTN3* TT genotype was unlikely to provide an advantage in endurance running performance.[40] Besides, Goleva-Fjellet et al[35] noted that the T allele frequency of the *ACTN3* gene was lower in individuals reporting high levels of physical activity.

Few studies have examined the relationship between these polymorphisms and cross-country skiing performance. Magi et al[37] found that male skiers had a higher frequency of the *ACTN3* CC genotype compared to controls. In the same study, male skiers with the *ACTN3* TT genotype showed a greater increase in peak $VO_{2\,max}$ over 5 years. However, Ahmetov et al[41] reported that the TT genotype was significantly underrepresented in Russian endurance athletes compared to controls. This study suggested that success in endurance sports involved not only endurance capacity, but also strength and power. In the present study, many athletes who excelled in the 1500-m cross-country skiing stage had high CC (RR) and TT (XX) genotypes, supporting Ahmetov et al findings.[41]

Table 4

***ACTN3* rs1815739 polymorphism genotype and allelic distributions.**

	Genotype				Allelic distributions		
	CC	**CT**	**TT**	***P*-value**	**C**	**T**	***P*-value**
Athlete (19)	7	4	8	.0659	18	20	.3540
Percentage	36.8%	21.1%	42.1%		47.4%	52.6%	
Control (130)	42	60	28		144	116	
Percentage	32.3%	46.2%	21.5%		55.0%	45.0%	

Significance was assessed at least at the $P < .05$ level. Comparison with the control group was made using the $\chi2$ test.

Table 5

***VEGFA* rs2010963 polymorphism genotype and allelic distributions.**

	Genotype				Allelic distributions		
	GG	**GC**	**CC**	***P*-value**	**G**	**C**	***P*-value**
Athlete (19)	9	6	4	.2018	24	14	.4222
Percentage	47.4%	31.6%	21.0%		63.2%	36.8%	
Control (130)	62	57	11		181	79	
Percentage	47.7	43.8	8.5		69.6	30.4	

Significance was assessed at least at the $P < .05$ level. Comparison with the control group was made using the $\chi2$ test.

Table 6

The *GABPB1* rs7181866 polymorphism genotype and allelic distributions.

	Genotype				Allelic distributions		
	AA	**AG**	**GG**	***P*-value**	**A**	**G**	***P*-value**
Athlete (19)	15	4	0	<.001	34	4	<.001
Percentage	79.0%	21.0%	%0.0		89.5%	10.5%	
Control (130)	127	3	0		257	3	
Percentage	97.0%	10.0%	%0.0		95.0%	5.0%	

Significance was assessed at least at the $P < .05$ level. Comparison with the control group was made using the χ^2 test.

Despite conflicting results in the literature, it is generally accepted that the *ACTN3* TT genotype contributes positively to athletic performance in endurance sports.[30,41] According to the present study and to the literature findings, although the *ACTN3* TT genotype and T allele percentages were higher in elite endurance athletes than in the control group, they were lower than the CC genotype and C allele percentages. Besides, sports disciplines such as skiing, athletics, or swimming may involve the development of both endurance and speed/strength simultaneously as a result of the application of appropriate training methods for both skills.[42] The fact that percentages in the athlete group were higher than in the control group in the present study supports the prediction made by Ahmetov et al[41]: "As the elite level of athletes increases, the percentages of genotypes are seen to approach each other." Cross-country skiing has traditionally been characterized by its high endurance requirements; however, there has been a notable increase in the strength and power demands of the sport in recent years.[43] Indeed, Sunde et al[44] demonstrated that maximal upper-body strength is a determining factor in double poling performance. Consequently, the aerobic capacity of cross-country skiers is of great importance, including maximal oxygen uptake ($VO_{2\ max}$) and peak oxygen uptake ($VO_{2\ peak}$).[45] Therefore, this research demonstrates that skiers who possess multiple attributes (power, strength, and endurance) are at a significant advantage when it comes to reaching the elite level.

The vascular endothelial growth factor-A (*VEGF-A*) plays an important role in angiogenesis and skeletal muscle adaptations. Angiogenesis, the process of new blood vessel formation, is very important in sports requiring endurance because an increase in capillaries within the muscle directly influences by regulating gas exchange and thus increasing $VO_{2\ max}$ capacity.[46]

The C allele of the *VEGF-A* has been associated with endurance athlete status[47] and higher $VO_{2\ max}$ values after 24 weeks of aerobic exercise training.[48] Moreover, the C allele of the G634C variant has been associated with higher $VO_{2\ max}$.[47,49] At the same time, Li et al[50] revealed that *VEGF-A* rs2010963 was significantly associated with tendon and ligament injury, that negatively affects athletic performance; individuals with the *VEGF-A* C allele and the CC genotype were at a higher risk in this respect.

In the present study, when *VEGF-A* genotype and allele distributions in the group of athletes were compared with the control group, although no significant differences were detected, the frequency of CC genotypes and C alleles was found to be higher in the athlete group compared to the control group. These findings are in line with the study conducted by Ahmetov et al,[49] where no significant difference was reported despite the large sample size. In the study, *VEGF-A* genotype and allele distribution in endurance sports disciplines were CC at 12.5% and C at 29.4% in biathlon, CC at 13.63% and C at 34.1% in track cycling, CC at 9.85% and C at 31 % in cross-country skiing, CC at 20% and C at 60% in marathon, CC at 9.52% and C at 26.2% in swimming, CC at 16.66% and C at 35.4% in race walking, and CC at 3.44% and C at 20.7% in triathlon. In the group of endurance athletes, the distribution of the *VEGF-A* C allele was significantly higher than in the control group. Moreover, for endurance athletes, the genotype and allele distributions were at 10.88% for CC and at 31.5% for C.[49] These authors suggested that the prevalence of the *VEGF-A* CC genotype and C allele increased with higher levels of athletic performance.

Although not directly contradicting previous findings, the study by Boidin et al[8] demonstrated that the G allele was associated with better strength adaptations, as compared with peak $VO_{2\ max}$ improvements, in 28 untrained men after 12 sessions of resistance training. A randomized, balanced cross-over design was employed, where the subjects engaged in 12 sessions of resistance training or endurance training over 4 weeks. GG homozygotes showed greater strength gains compared with peak $VO_{2\ max}$ improvements, possibly owing to lower circulating *VEGF-A* levels, whereas C-allele carriers may have impaired adaptation to resistance training due to a compromised extracellular matrix.

Since the athlete group in the present study consisted of members of the same tribe that had achieved remarkable success in cross-country skiing, their genetic composition might not be representative of the general population of endurance athletes. While the CC genotype has been associated with lower *VEGF-A* expression, its relatively higher frequency in the athlete group could suggest a potential genetic adaptation specific to this tribe. However, given the small sample size obtained, further studies with larger and more diverse athlete cohorts would be necessary to determine the reliability of this trend.

Although the CC genotype of *VEGF-A* was more common in the athlete group than in the control group, the overall distribution did not show statistical significance, probably due to the small sample size in the athlete group. However, the distribution trends also showed that although the frequency of the C allele was higher in athletes compared to controls, no statistical differences were detected. The high expression of the *VEGF-A* C allele suggests a greater adaptive growth of capillaries in response to aerobic physical exercise. Consequently, carriers of the *VEGF-A* C allele may have many advantages in increasing endurance performance, which has been revealed in this study and in previous ones.[51,52] This assumption is supported by the higher frequency of the *VEGF-A* C allele in the group of sports requiring high endurance compared to the control.[53]

These results provide significant insights into the role of the *GABPB1* in endurance sports. *GABPB1* has been associated with an increased $VO_{2\ max}$ in response to physical exercise.[20] NRF-2 protein is thought to increase cellular respiratory capacity and the ATP production rate during exercise.[54] When the studies in which the A/G polymorphism in intron 3 of the *GABPB1* gene (rs7181866) polymorphism was associated with athletic performance, it was found that it was related to higher oxygen uptake values in response to training,[55] and significant differences were observed in endurance athletes compared to sedentary individuals.[56] In another study, it was reported that the AG genotype of *GABPB1* could cause a significant increase in gene transcription and increased mRNA expression of the protein, and that it was most common in endurance athletes, especially in the elite group.[57] Therefore, variations in this gene could influence muscle function and energy production, both of which are key for endurance performance.

GABP1 genotype and allele frequencies in the present study were found to be higher as compared to the literature findings. However, in a study with similar results to the present one on Polish rowers and controls, the genotypes of the rowers were at 89.09% for AA and at 10.01% for AG, and GG genotypes were not found, while these figures were n = 127 AA and n = 3 AG, with GG genotypes not being found in the control group. Allele distributions were n = 104 in the case of A and n = 6 in the case of G alleles in the rowers, while these were at 97.69% for A and at 2.31% for G alleles in the control group. The rowers were divided into 2 groups: elite rowers and non-elite rowers. The genotypes of the elite rowers were at 90% for AA and at 10% for AG, and GG genotypes were not found, respectively, while these figures were 22 for AA and 3 for AG, with GG genotypes not being found in the non-elite group. About allelic distributions, 57 A and 3 G alleles were found in elite rowers and 47 A and 3 G alleles were found in non-elite rowers.[18] In *GABPB1* rs7181866 polymorphism, the AA genotype was found to be higher in percentage than the AG genotype; the GG genotype was not found in the study group. In line with a previous study, the higher rate of the A allele in sports requiring endurance was interpreted as predisposing to endurance.[58]

Given that the athlete group consisted of members of a highly successful tribe in cross-country skiing, it is important to consider whether these genetic variants represent an individual adaptation or a tribe-wide genetic advantage. The higher frequency of the G allele in the athlete group suggests that this genetic variant may contribute to sports performance. The higher frequency of the AG genotype in the athlete group suggests the presence of a distinct genetic profile among endurance athletes. This *GABP1* AG genotype frequency suggests that the polymorphism may affect endurance performance.[59] However, further functional studies are necessary to determine how these genetic differences impact athletic performance.[60]

In the present study, when the genotype and allele percentage distributions of the 3 polymorphisms were compared across groups (athlete and control), it was observed that the athlete group was at a higher level in this respect. Notably, the *ACTN3* TT and *VEGF-A* CC genotypes were observed together in 3 individuals (15.8%), suggesting a potential link to endurance performance. Additionally, the *GABPB1* AG genotype was found in 3 out of 7 individuals (42.9%) carrying the *ACTN3* TT genotype, indicating a possible association with endurance-related traits, though further studies with larger sample sizes are required to confirm these findings. Considering that the individuals in this study belonged to the same tribe, the potential influence of genetic similarity within this population group should be acknowledged. To investigate whether the co-occurrence of *ACTN3* TT and *VEGF-A* CC genotypes was significantly higher than expected, Fisher Exact Test and Chi-squared test were performed. The results showed that the association was not statistically significant (Fisher Exact Test $P = .269$, Chi-squared test $P = .269$), suggesting that the observed co-occurrence may be due to random distribution rather than a strong genetic linkage. However, given the family genetic background of the participants, these results might be influenced by inherited genetic patterns rather than independent genetic variations.

Further studies with larger and more diverse populations, including non-endurance athletes, would be necessary to determine whether these genotype combinations play a significant role in endurance performance beyond family inheritance. Additionally, to determine whether the co-occurrence of *ACTN3* TT and *VEGF-A* CC genotypes was statistically significant, Fisher Exact Test and Chi-squared test were performed, incorporating data from the control group. The results showed no statistically significant association (Fisher Exact Test $P = .730$, Chi-squared test $P = 1.000$), indicating that the observed co-occurrence in the athlete group does not significantly deviate from what would be expected to be found by chance. These findings suggest that, while certain genotype combinations, such as *ACTN3* TT + *VEGF-A* CC, and *ACTN3* TT + *GABPB1* AG, may indicate a potential endurance-related genetic pattern, they do not statistically differ from expected random distributions.

4.1. Novelty and contribution of the study

In sports science, many studies have examined the relationship between sports and genetics. However, contradictory findings arise in scientific evidence due to many variables such as altitude, environment, race, nutrition, climate, training, and sports discipline. In this context, the present study has revealed, for the first time in the literature, whether a specific skiing tribe that has attracted attention with its success at the international level has a genetic predisposition. The findings obtained from the study group, where the variables had almost no effect, are both unique and valuable in terms of their contribution to the field.

4.2. Limitations of the study

Since the athlete group in the present study consisted of members of the same tribe of skiers, this fact limits the applicability of the research. However, 19 elite skiers from the same tribe in the cohort of athletes arguably represents a significant number compared to the total population of elite skiers as a whole. Furthermore, although there are approximately 100 polymorphisms related to endurance, due to the limitations of this research (low budget, costly genetic analysis, etc), only the 3 gene polymorphisms were examined in this study. Therefore, this aspect also constitutes one of the limitations of the study.

5. Conclusion

The study concludes that genetic factors may play a significant role in the success of skiers from the Oğlağo tribe in Muş, Turkey. The research analyzed 3 genetic polymorphisms – *ACTN3* rs1815739, *VEGF-A* rs2010963, and *GABPB1* rs7181866 – in elite skiers and a control group. While no significant differences were found for *ACTN3* and *VEGF-A* polymorphisms, the *GABPB1* polymorphism showed a statistically significant association with endurance performance. The findings suggest that a combination of genetic factors, particularly the *ACTN3* TT and *VEGF*-A CC genotypes, along with the *GABPB1* AG genotype, could be linked to endurance sports success. However, due to the small sample size and the influence of environmental and training factors, further studies are required to confirm these results and better understand the genetic basis of skiing performance.

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