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The *AMPD1* Gene's rs17602729 Polymorphism and Athletic Performance in Track and Field Athletes

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Abstract: The aim of the current study was to determine whether the rs17602729 polymorphism in the Adenosine monophosphate deaminase-1 (*AMPD1*) gene is related to elite athlete performance. A total of 60 elite athletes, aged 18–35, who were split into two groups—31 sprinters/power athletes and 29 endurance athletes—as well as 20 control/sedentary individuals, willingly participated in the study. The performance levels of the athletes, based on their personal bests (PBs), were rated using the World Athletics (WA) score. Whole exome sequencing (WES) was performed on the genomic DNA that was extracted from the subjects' blood samples. Using linear regression models, the study sought to determine the relationship between the athletes' PB, sex, and sport type and the rs17602729 polymorphism both within and between the groups. The distribution of the GG, GA, and AA genotypes of the rs17602729 polymorphism differed significantly within and between the groups, according to the data ($p < 0.05$). Nonetheless, no statistically significant variations were observed in the correlation between the athletes' PBs and the rs17602729 polymorphism among the groups ($p > 0.05$). In conclusion, the G allele of the *ADMP1* rs17602729 polymorphism appears to provide a benefit to sprinters and power athletes. Nonetheless, to confirm this hypothesis, additional research with more participants and a multi-genetic analysis approach is required.

Keywords: *AMPD1*; athletics; endurance athletes; rs17602729; polymorphism; sprinters; power athletes; Turkish population

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1. Introduction

For many years, it has been commonly accepted that an athlete's success in a specific sport is influenced by a blend of various elements. These elements encompass the characteristics and roles of muscle fibers, the peak level of oxygen consumption (VO_2 max), and the effectiveness of their training regimens [1,2]. However, research conducted over the past two decades has revealed that, alongside these factors, genetics also plays a crucial role in determining athletic success. The inherent genetic makeup of an individual and the ways in which these genes are expressed and interact significantly contribute to improvement in athletic performance [3]. Genetic factors are increasingly becoming important in understanding and improving athletic performance [4]. According to findings from recent studies conducted in the field of sports genetics, the genetic background of an individual athlete has a substantial influence on their athletic performance [2]. These studies suggest

that the training and physiological fitness levels of athletes may be limited by their genetic capacities and that genetic factors must be considered to achieve the optimal performance levels [5]. For example, the genetic profile of athletes can be a key factor in defining their potential physiological abilities and how these abilities can be enhanced, the strategies they can employ to optimize their circulatory system using certain nutrients, and the approaches they can adopt to assess their non-impact injury risk [6].

Research in the field of sports genetics has revealed that over 200 genes have been linked to athletic performance [2]. Some of the crucial genes that have been identified include Alpha-actinin-3 (*ACTN3*), Angiotensin-I-converting enzyme (*ACE*), Bradykinin receptor B2 (*BDKRB2*), Endothelial nitric oxide synthase 3 (*NOS3*), Alpha-2A adrenergic receptor genes (*ADRA2A*, *ADRA2B*, and *ADRA2C*), Peroxisome proliferator-activated receptors (*PPAR*), Peroxisome proliferator-activated receptor gamma coactivator 1a (*PPARGC1A*), Vitamin D receptor (*VDR*), Erythropoietin (*EPO*), and C-Reactive protein (*CRP*) [7–10]. It has been reported that specific polymorphisms in these genes may be associated with the type of sport parameters affected and the performance of athletes. Similar association studies have been conducted and reported in different populations and for diverse genes and sports disciplines [1,11–14]. Considering this information, the impact of genetic factors on athletic performance holds significant importance in the development of training programs and in maximizing athletes' physical and physiological potential. This knowledge would enable athletes to understand their genetic backgrounds and use these findings to enhance their performances.

Adenosine monophosphate deaminase-1 (*AMPD1*) is another fundamental gene attracting the interest of sports scientists due to its association with athletic performance, opening up a new and exciting field for future research. The enzyme AMPD encoded by the *AMPD1* gene is crucial in the production of energy within the skeletal muscles. AMPD plays a pivotal role in regulating the energy metabolism of the skeletal muscles during physical activity. The enzyme AMPD facilitates the conversion of adenosine monophosphate (AMP) into inosine monophosphate (IMP). This process reduces the buildup of adenosine diphosphate (ADP) and shifts the myokinase reaction toward adenosine triphosphate (ATP) production [15–20]. AMPD is a key regulator in cellular energy metabolism during intense physical exercise. Nevertheless, single-nucleotide polymorphisms (SNPs) in this gene may result in altered muscle energy metabolism. For instance, in the case of the rs17602729 polymorphism (NM_000036.3:c.34C > T:p.Gln12Ter), in individuals with the TT genotype of the *AMPD1* gene, the AMPD activity in the skeletal muscles is considerably low. Conversely, those with the CT genotype exhibit moderate levels of AMPD activity, whereas individuals possessing the CC genotype have high levels of AMPD activity. This scenario illustrates the impact of *AMPD1* gene variations on AMPD activity in the skeletal muscles [21,22].

The 1000 Genomes project revealed that the *AMPD1* rs17602729 polymorphism occurs at varying frequencies across different populations: it was observed in European Caucasians at an overall rate of 11%, with specific occurrences of 11% in Finland, 14% in both England and Spain, and 8% in Italy. In contrast, this polymorphism was much less common in Africans, showing a frequency of just 1%. It was found in 8% of the American population surveyed. However, this genetic variation was not detected in any of the Asian groups studied (http://www.1000genomes.org/, accessed on 13 January 2024). When examining research related to the mentioned gene, studies have reported that individuals carrying the rs17602729 polymorphism T allele were susceptible to muscle cramps, pain, delayed recovery of muscle strength, and early fatigue during exercise [1,2,23–25]. Moreover, some studies associate this allele with power and sprint disciplines [16,18,26] while others link it to endurance activities [27,28]. The presence of both similar and differing studies across various populations makes this research area particularly intriguing [15,21,29].

Considering the aforementioned information, the main aim of this research was to analyze the differences in the genotype and allele frequencies of the *AMPD1* rs17602729 polymorphism between Turkish elite athletes specializing as sprinters/power athletes and

endurance athletes, including a control group for comparison. Additionally, the study aimed to explore the potential link between the rs17602729 polymorphism and competitive performance in elite endurance athletes and sprinters/power athletes. To the best of the authors' knowledge, this investigation is the first pivotal study to analyze the *AMPD1* rs17602729 polymorphism in elite Turkish track and field athletes.

2. Materials and Methods

2.1. Ethical Approval

The current investigation was carried out in strict accordance with the principles outlined in the Declaration of Helsinki. The Gazi University Non-Interventional Clinical Research Ethics Committee issued ethical clearance under approval number 09, dated 5 April 2021.

2.2. Participants

The study's participant pool comprised 60 elite athletes, divided into sprinters/power athletes (sprinters, throwers and jumpers) and endurance athletes (long-distance runners). The sprinter/power athlete group consisted of 11 female (35.5%) and 20 male athletes (64.5%) while the endurance athlete group included 10 female (34.5%) and 19 male athletes (65.5%), together with 20 control or sedentary individuals, aged 18–35 years, who voluntarily participated in this study. These athletes, who are all members of the Turkish Athletics Federation, possess licenses in various sports disciplines and follow a demanding training schedule, practicing a minimum of six days per week. All athletes and controls were of Caucasian descent. Table 1 provides comprehensive details regarding the participants.

Table 1. Demographic characteristics of the research disciplines.

Variables	Disciplines	n	$\overline{X}$	SD
Age (year)	Sprinters/power athletes	31	26.58	3.02
	Endurance athletes	29	27.51	4.19
	Controls	20	24.90	3.13
Height (cm)	Sprinters/power athletes	31	177.87	8.09
	Endurance athletes	29	170.58	7.44
	Controls	20	176.86	5.22
Body weight (kg)	Sprinters/power athletes	31	86.51	20.58
	Endurance athletes	29	54.44	6.60
	Controls	20	76.95	22.69
Sports experience (year)	Sprinters/power athletes	31	7.41	3.62
	Endurance athletes	29	11.51	5.06
	Controls	20	-	-
PB (sn or cm)	Sprinters/power athletes	31	990.19	104.72
	Endurance athletes	29	1022.13	80.87
	Controls	20	-	-

$\overline{X}$: mean; SD: standard deviation.

Athletes were categorized into two groups: sprinters/power or endurance athletes. This classification was determined by the specific characteristics, including the distance, length, and the energy system requirements, of their sports. Each athlete achieved a national ranking among the top 10 in their specific disciplines. The elite group comprised individuals who have taken part in prestigious international competitions including the Olympic Games, European Championships, and Balkan Championships. The sprinter/power group category includes events that mostly rely on anaerobic energy. In contrast, the category

of endurance athletes consisted of individuals participating in aerobic races such as the 3000 m, 5000 m, and 10,000 m runs and marathon.

2.3. Athletic Performance

Prior to conducting measurements, we gathered informed consent forms from both the athlete and control groups, as well as their demographic information. To analyze the performance levels of the athletes, their personal bests were evaluated using the scoring system devised by the International Association of Athletics Federations (IAAF; currently known as World Athletics) as explained by Spiriev, 2014 [30]. The IAAF scoring system offers a standardized way to evaluate and compare performances across various track and field events depending on the sex of the athletes. According to this evaluation system, for instance, a male athlete who completes a 100 m sprint in 9.58 s would earn a score of 1355 whereas a male marathon runner finishing in 2 h, 0 min, 34 s would receive a score of 1336. This comparison shows that according to the IAAF's metrics, the sprinter's achievement is considered slightly superior to that of the marathon runner. Essentially, the IAAF scoring system provides a uniform framework for assessing the accomplishments of athletes in different track and field disciplines.

2.4. Whole Exome Sequencing

The genomic DNA of the participants was extracted from their peripheral blood samples using the DNeasy Blood and Tissue Kit (QIAGEN, Hilden, Germany), adhering to the protocol provided by the manufacturer. To ensure the purity of the DNA obtained, 1% agarose gel electrophoresis was employed, and the concentration of DNA was measured using a NanoDrop 1000 Spectrophotometer (Thermo Scientific, Waltham, MA, USA).

Following the manufacturer's guidelines, the DNA specimens were prepared for whole exome sequencing (WES) utilizing the Twist Human Comprehensive Exome Panel from Twist Biosciences, South San Francisco, CA, USA. This process involved the enzymatic fragmentation of DNA, succeeded by size-based fragment selection. Hybridization was conducted using Twist hybridization probes in conjunction with Dynabeads™ MyOne™ Streptavidin T1 beads (Invitrogen, Waltham, MA, USA) and the library was subsequently enriched using a polymerase chain reaction (PCR). Prior to sequencing using the Illumina NextSeq 500 platform (Illumina Inc., San Diego, CA, USA), the libraries underwent quantification and purification, in accordance with the standard protocols provided by the manufacturer.

The initial sequencing data were analyzed utilizing the Genome Analysis Toolkit (GATK) as described by van der Auwera et al., 2013 [31]. Within this toolkit, the HaplotypeCaller function was employed to create Binary Alignment Map (BAM) files. These files were subsequently transformed into Variant Call Format (VCF) files, referencing the GRCh38/hg38 human genome. For variant annotation, the ANNOVAR tool https://wannovar.wglab.org/ accessed on 19 September 2023 [32] was used, and single-nucleotide polymorphisms (SNPs) underwent manual examination. The curated sequences have been made available to the public at https://figshare.com/s/07d47d0a0d89d7242d51 (accessed on 13 January 2024).

2.5. Statistical Analyses

In the present research, the G*Power 3.1 software was employed for power analysis to ascertain the required sample size. Based on Cohen's (1998) criteria [33], the size was categorized as 0.10 for small, 0.30 for medium, and 0.50 for large effects. The study aimed for a large effect size of 0.50. According to the contingency model's goodness-of-fit test, a minimum of 52 participants was necessary to achieve 90% power with an alpha of 0.05. The genotypic and allelic frequencies of the polymorphism were calculated and the Hardy–Weinberg equilibrium (HWE) was assessed using either chi-square (χ^2) or Fisher's exact test, based on the data's appropriateness. A one-way ANCOVA was utilized to investigate the correlation between the *AMPD1* rs17602729 polymorphism and personal

best (PB) performances, adjusting for variables like gender and years of sports experience. Linear regression models were also applied to determine the robustness and significance of these associations across various genetic models, including co-dominant, dominant, recessive, over-dominant, and additive. These analyses produced 95% confidence intervals (CI) for each association. Additionally, the SNPStats software [34] was used for supplementary validation of the findings, facilitating allele and genotype frequency analysis and association studies. This tool was particularly useful for linear regression analysis across multiple genetic inheritance models. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software version 29.0, tailored to Mac operating systems.

3. Results

The current study was conducted to explore the potential link between the *AMPD1* rs17602729 polymorphism and the personal best (PB) or competitive performance of elite athletes in the presence of a control group.

Initially, we assessed the genotype and allele frequencies of the polymorphism. The findings indicated a significant difference between the sprinters/power athletes and endurance athletes in their genotype frequencies ($p = 0.023$; Table 2). In terms of the allele frequencies, the G allele was more prevalent than the A allele (allele nomenclature differs from the database (C/T) owing to the selection of a complementary strand (G/A)); however, this difference was not statistically significant either within or between the groups ($p > 0.05$; Table 2).

Table 2. Genotype and allele frequencies of *AMPD1* rs17602729 polymorphism in elite athletes and controls.

	Genotype			*p*-Value	Allele		*p*-Value
	GG	GA	AA		G	A	
Sprinters/power athletes	22 (33.8%)	9 (75.0%)	---	0.023 *	53 (85.7%)	9 (14.3%)	0.435
Endurance athletes	27 (41.5%)	---	2 (66.7%)		54 (93.0%)	4 (7.0%)	
Controls	16 (24.6%)	3 (25.0%)	1 (33.3%)		35 (87.5%)	5 (12.5%)	

* Sprinters/power athletes–endurance athletes * $p = 0.023$.

Additionally, when we compared the genotype distribution of sex and sports experience, there were, again, no statistically significant results ($p > 0.05$).

Due to the complete absence of the rs17602729 AA genotype in the sprinters/power athletes, only the GG and GA genotypes were considered for further analysis. The PB average of individuals with the GG genotype was higher than those with the GA genotype (GG: 1003.18; GA: 958.44). Nevertheless, this difference was not statistically significant in the sprinters/power athletes. Due to the complete absence of the rs17602729 GA genotype in the endurance athletes, only the GG and AA genotypes were considered for further analysis. The PB average of the individuals with the AA genotype was higher than those with the GG genotype (AA: 1067.50; GG: 1018.77). However, this difference was also not statistically significant in the endurance athletes. Therefore, to enhance the robustness of the statistical results, we opted to aggregate the sample. After pooling the data, the association was analyzed using various genetic models, including codominant, dominant, recessive, and over-dominant models. The analysis revealed no significant associations between the rs17602729 polymorphism and the PBs of the athletes in any of the models tested ($p > 0.05$; Table 3).

Table 3. Association analysis of the *AMPD1* rs17602729 polymorphism with athletic performance.

Model	Genotype	n	(PB) Mean Score	Difference (95% CI)	*p*-Value
Co-dominant	GG	49	1009.73	0.00	0.18
	GA	9	958.44	−56.44 (−119.96 to 7.07)	
	AA	2	1067.50	37.82 (−87.20 to 162.85)	
Dominant	GG	49	1009.73	0.00	0.2
	GA-AA	11	978.27	−39.10 (−97.97 to 19.77)	
Recessive	GG-GA	58	1001.78	0.00	0.47
	AA	2	1067.50	47.04 (−79.79 to 173.88)	
Over-dominant	GG-AA	51	1012.0	0.00	0.07
	AG	9	958.44	−58.03 (−120.96 to 4.90)	

4. Discussion

The present study investigated the rs17602729 polymorphism among elite athletes registered with various clubs under the Turkish Athletic Federation, specifically examining sprinters/power athletes, endurance athletes, and a control group. The research also included an analysis of performance based on the genotype distributions. The results indicated that the AA genotype of the rs17602729 polymorphism was less prevalent across the groups and no notable differences were observed in the assessments of genotype and performance. Nevertheless, a statistically significant variation was detected in the frequency of genotypes between the sprinters/power athletes and endurance athletes ($p = 0.023$; Table 2).

In this recent study, it was found that the GG genotype of the rs17602729 polymorphism occurred in 40% of the subjects whereas the GA genotype occurred in 7.5% and the AA genotype in 3% of all groups. These data point out the diversity of the genotype distribution amongst the Turkish population. Accordingly, the 1000 Genomes Project, which aimed to chart human genetic variation, has shown that the rs17602729 polymorphism varied widely among various ethnic groups. For example, in European Caucasians, this polymorphism is found in 11–14% of the population, suggesting that the GG and GA genotypes might be more common in Europeans. On the other hand, this polymorphism is rarer in Africans, seen in only 1% of the population, and is almost non-existent in Asians. These findings highlight the extent to which genetic diversity and the distribution of genetic traits can differ from one population to another.

The *AMPD1* gene, which encodes the AMPD enzyme, plays a crucial role in regulating the energy metabolism in the skeletal muscles during exercise. It has been a prominent focus of research in the field of energy in sports. It is associated with both endurance and sprint/power disciplines. There is a consensus that genetic variations can influence the biomotor abilities of athletes whether they are at an elite level or not. Numerous studies have identified *AMPD1* as a critical candidate gene, with its product significantly impacting the athletic performance of both elite and sub-elite athletes [3,19,35–37].

Various studies have reported that the *AMPD1* rs17602729 polymorphism is one of the genetic variations that affects the performance of endurance athletes. For example, whereas the occurrence of the mutant T allele in the rs17602729 polymorphism is less common among Caucasian elite endurance athletes compared to controls, it does not have a substantial negative impact on the endurance performance of individuals already reaching an elite rank in their respective sports [38]. The genetic distribution of professional athletes, particularly in endurance sports like cycling and elite running, as well as in football, demonstrates a trend of genetic predisposition in these specific sporting fields [28,29]. Another study explored how different *AMPD1* gene variants were linked to cardiorespiratory fitness and endurance in cycling, both before and after training. The research predicted that indi-

viduals possessing the T allele in the rs17602729 polymorphism would initially have lower performance levels and showed less improvement with training [27]. A study on Polish male rowers indicated that the T allele was linked to their physical performance levels. Therefore, this allele has the potential to detrimentally impact athletic performance [18]. In the current study, we observed that the G allele, despite its higher frequency, was associated with lower mean PB scores.

Considering the importance of endurance traits to long-distance runners, the present research into the rs17602729 polymorphism reveals that athletes with the AA genotype are less common, and this genotype shows no significant correlation with performance, aligning with previous findings [39]. These findings elucidate the relative significance of hereditary and environmental influences in the genesis of athletic prowess. Genetically inherited traits play a significant role in athletic performance; nevertheless, athletic performance is determined not only by genes but also the exercises performed and the lifestyle that forms around them.

In the current study, while we found no significant difference in the PB performance values across different genotypes in sprinters/power athletes, it is noteworthy that several other studies have identified the rs17602729 polymorphism as a variant influencing sprinters' and power athletes' athletic performance. In a study carried out on Lithuanian sprinters/power athletes, it was indicated that the rs17602729 polymorphism C allele may assist athletes in achieving an elite status in sprint/power-oriented sports [34]. Among Polish power-oriented athletes, it is suggested that the C allele may contribute to athletes reaching an elite level in strength-focused sports [26]. In another study, it was reported that the rs17602729 polymorphism allele C may be regarded as indicative of a predisposition to high-speed and strength-based muscular activities [16]. In the present study, it was found that those with the GG genotype among sprinters/power athletes had the best PB averages. The advantageous impact of carrying the GG genotype on the athletic performance of elite sprinters/power athletes was further reinforced by observations that the athletes at the elite level with the GG genotype exhibited superior outcomes in PB. However, it is important to note that among these Turkish athletes, none of them possessed the AA genotype. In this context, it can be suggested that directing athletes with the G allele to sprint and power branches and tailoring their training programs based on these genetic findings could be more beneficial for the development of their performance.

There are some limitations in the present research. First, since the participants were elite athletes, we carefully limited the sample size to ensure a homogeneous sample. The second limitation is that the study focuses only on a single gene and polymorphism. Future research should include different performance tests and be conducted in a broader population with multi-genetic approaches. Finally, considering that an athlete's success is determined not only by genetic factors but also environmental ones, contradictory results may emerge in the studies. In this context, conducting a combination of multigenetic and epigenetic research could contribute to obtaining more reliable results.

5. Conclusions

In the current study, despite the lack of a significant relationship between genotype and PB values, the higher prevalence of the GG genotype and the elevated PB values in the sprinters and power athletes are noteworthy. Furthermore, considering the information available in the literature [16,18,19], the G allele of the *ADMP1* rs17602729 polymorphism appears to provide a benefit to sprinters and power athletes. Nonetheless, to confirm this hypothesis, additional research with more participants and a multi-genetic analysis approach is required.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are openly available in repositories: https://figshare.com/s/07d47d0a0d89d7242d51, https://doi.org/10.6084/m9.figshare.24496090.

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