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EVALUATING THE EFFECT OF THE *CYP1A2* rs762551 GENE POLYMORPHISM ON ARROWHEAD AGILITY DRILL TEST PERFORMANCE IN PHYSICALLY ACTIVE YOUNG MEN

Esra Yıldız[1], Mesut Cerit[1], Tolga Polat[2], Murat Anılır[1], Selin Yıldırım Tuncer[1*]
[1] Lokman Hekim University, Faculty of Spor Science, Ankara, TÜRKİYE
[2] Marmara University, Faculty of Dentistry, İstanbul, TÜRKİYE

Abstract: The purpose of this study is to determine the different results and genotype distributions associated with the effect of *CYP1A2* rs762551 gene polymorphisms on the development rates of arrowhead agility drill test performance after six weeks of training in active adult males. The research population comprised of 54 healthy young men aged 19 to 24 from the Faculty of Sports Sciences who freely participated. The arrowhead agility drill test was administered at the beginning and end of the 6-week trial to assess anaerobic performance. To evaluate within-group differences (pre- and post-test) for each genotype group, the Paired Samples T-test was applied. Additionally, between-group comparisons across genotypes (AA, AC, and CC) were conducted using one-way ANOVA. The genotype frequencies for the *CYP1A2* gene polymorphism are as follows: AA 29.78%, AC 63.82%, and CC 6.40%. No significant differences were found between pre- and post-test scores within or between genotype groups ($p > 0.05$). The CC group had a limited sample size ($n = 3$), limiting statistical power. The findings from this study indicate that the impact of caffeine on athletic performance differs among individuals, influenced by genetic composition, exercise type, dosage, and surrounding conditions. Our analysis reveals that the absence of a notable difference between *CYP1A2* (rs762551) genotypes and anaerobic agility performance indicates that caffeine's effects cannot be solely ascribed to genetic factors.

Key Words: *CYP1A2*, caffeine intake, physical activity

AKTİF YETİŞKİN ERKEKLERDE *CYP1A2* rs762551 GEN POLİMORFİZMİNİN ARROWHEAD ÇEVİKLİK YETENEK TEST PERFORMANSI ÜZERİNDEKİ ETKİLERİNİN İNCELENMESİ

Öz: Bu çalışma, aktif yetişkin erkeklerde altı haftalık antrenmanın ardından *CYP1A2* rs762551 gen polimorfizmlerinin arrowhead agility drill testi performans gelişim oranlarına etkilerinin açığa çıkardığı farklı sonuçlar ve genotip dağılımların belirlenmesi amaçlanmıştır. Araştırmanın evrenini Spor Bilimleri Fakültesi'nden gönüllü olarak katılan, yaşları 19-24 arasında değişen 54 sağlıklı genç erkek oluşturmuştur. Anaerobik performansı değerlendirmek amacıyla arrowhead çeviklik testi, 6 haftalık denemenin başında ve sonunda uygulanmıştır. Her bir genotip grubu (ön test ve son test) için grup içi farkları değerlendirmek amacıyla Eşleştirilmiş Örneklem T-testi kullanılmıştır. Ayrıca, genotipler (AA, AC ve CC) arasındaki grup farklarını karşılaştırmak için tek yönlü ANOVA testi uygulanmıştır. Ön test ve son test sonuçları arasında ya da genotip grupları arasında istatistiksel olarak anlamlı bir fark tespit edilmemiştir ($p > 0.05$). CC grubundaki düşük örneklem sayısı ($n=3$), istatistiksel gücü sınırlamaktadır. *CYP1A2* gen polimorfizmi için genotip frekansları şu şekildedir: AA %29,78, AC %63,82 ve CC %6,40. Bu çalışmanın bulguları, kafeinin sportif performans üzerindeki etkisinin bireyler arasında genetik yapı, egzersiz türü, dozaj ve çevresel koşullardan etkilendiğini göstermektedir. Yapılan analizler, *CYP1A2* (rs762551) genotipleri ile anaerobik çeviklik performansı arasında anlamlı bir farkın bulunmamasının, kafeinin etkilerinin yalnızca genetik faktörlere atfedilemeyeceğini ortaya koymaktadır.

Anahtar Kelimeler: *CYP1A2*, kafein alımı, fiziksel aktivite

[*] *Corresponding Author: Selin YILDIRIM TUNCER, Asst. Prof., selin.yildirim@lokmanhekim.edu.tr*

INTRODUCTION

Genetic research has contributed significantly to the understanding of the complex relationship between human biology, physiology, and disease. Furthermore, genomic data obtained through DNA sequencing has proven valuable in improving personalized performance training and adaptation (Denisov et al., 2022). Recent research has demonstrated that variations in DNA helices can influence responses to training loads, the efficacy of ergogenic supplements, recovery rates, caloric requirements, and injury susceptibility. Such findings aid in the formulation of individualized exercise regimens and activities tailored to specific loading thresholds, facilitating the development of personalized training programs (Baumert et al., 2016; Papadimitriou et al., 2016). In this context, talent identification and performance measurement and evaluation criteria are extremely important in order to reveal the current physiological and physical status, to monitor the effectiveness of the applied training programs, to predict maximum athletic performance and to reveal the strengths or weaknesses of the athlete in order to identify successful athletes and prepare personalized training programs (Ulucan et al., 2015).

According to the study's findings, which were based on the participants' VO2max values, the participants responded to the same training at varying levels, and the average increase in fitness level brought about by the exercise program was 33%, while the individual gains were roughly 88% and 5% in the other (Bouchard et al., 1999). In addition, in another study conducted to determine the average aerobic power ratio, it was stated that although all participants were included in the same exercise program (20-week mesocycle, 90-minute exercise session), they improved their cycling exercise performance at different rates (Bouchard & Rankinen, 2001). For this reason, it is foreseen that regulating the performance and training loads of elite and non-elite athletes and applying branch-specific performance tests, as well as genetic tests that reveal the relevant exercise models and personal status, can contribute to achieving a high-performance level as soon as possible (Bulgay et al., 2020; Yıldırım et al., 2022). In addition, this information can also guide coaches, enabling active athletes to overcome their physiological weaknesses in the best way and to design their personal training programs according to the physiological characteristics of the individual (Demirci et al., 2023).

There are about two hundred candidate genes that affect athletic performance. One of the candidate genes among these is Cytochrome P450 1A2 (*CYP1A2*). An enzyme called cytochrome P450 1A2 is encoded by the gene in question. It plays a crucial role in the metabolism of caffeine and other drugs. The *CYP1A2* gene sequence is located on chromosome 15. The gene in question consists of 7 exons and 6 intron regions with a length of approximately 7.8-kb. More than 40 single nucleotide polymorphisms (SNPs) have been identified in this gene region. *CYP1A2* gene variants determine the rate of metabolization of caffeine at different levels, leading to positive or negative effects on the performance levels of athletes during training and competitions. It is thought that these differences may be a reason for the different levels of absorption that caffeine use generates in the organism (Lovallo et al., 2006; Loy et al., 2015).

Caffeine largely facilitates the utilization of adipose reserves in the body as energy, enabling access to readily available energy sources. Numerous studies show that caffeine's ergogenic action directly affects fat reserves and enhances lipolysis by inducing cortisol and norepinephrine release, indicating that consuming it leads to improved lipid mobilization (Lovallo et al., 2006; Loy et al., 2015). The proposed hypothesis suggests that the enhancement of lipid breakdown postpones lactate accumulation during aerobic endurance exercise by

facilitating the conservation of glycogen reserves (Cornelis et al., 2016). According to Guest et al. (2018), C allele transporters metabolize caffeine more slowly, which probably results in prolonged vasoconstriction that affects performance during prolonged, low-intensity endurance exercises where it's essential for active muscles to receive oxygen and nutrients (Guest et al., 2018).

The cytochrome P450 1A 2 enzyme, which is associated with caffeine metabolism, is responsible for 95% of caffeine absorption. Polymorphisms in the *CYP1A2* gene can influence individual caffeine metabolism, resulting in variations in athletic performance (Grgic et al., 2020). Those with the AA genotype at rs762551, identified as "fast metabolizers" of caffeine, demonstrate different performance levels compared to individuals with AC/CC genotypes, who exhibit slower caffeine excretion rates. They are known as "slow metabolizers". The effects of the *CYP1A2* genotype on performance appear to be most pronounced during prolonged exercise or activities that cause fatigue to accumulate. Fast metabolizers (AA) are likely to metabolize caffeine quickly and reap the benefits of caffeine metabolites during exercise, while slow metabolizers (CC) are likely to feel the negative effects of limited blood flow and/or other effects of adenosine blockade during prolonged activities (Guest et al., 2019).

The mechanisms by which the ergogenic effects of caffeine can be modified remain little comprehended. Long-term caffeine consumption is anticipated to be influenced by epigenetic alterations in *CYP1A2* genes, resulting in enhanced caffeine clearance and potentially inhibiting genes that impact dopaminergic activity, thereby contributing to habituation via a reduction in the caffeine-induced excitation threshold (Hammons et al., 2001). The relationship between caffeine metabolism and *CYP1A2* gene polymorphisms, particularly regarding the effects of *CYP1A2* gene variants on athletes, remains contentious, and the existing scientific literature on this topic is notably inadequate. This study aims to ascertain the various results and genotype distributions associated with the influence of CYP1A2 rs762551 gene polymorphisms on the advancement of arrowhead agility drill test performance following 6 weeks of training in active adult males. This investigation of active adult males is expected to contribute to the existing knowledge and its results may guide similar studies.

MATERIAL AND METHOD

The research is categorized as case research, a type of analytical research. The study utilized the pretest-posttest analytical methodology.

Participants

The population of the study was formed based on volunteerism of healthy (n=54) male cadets between the ages of 19-24, consisting of students of the Faculty of Sports Sciences. In the study, the participants were informed verbally and in writing about the measurement procedure and the study one week in advance.

The study was approved by the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (decision number 2023-247/1), and it was carried out in compliance with the Declaration of Helsinki.

Research Design

The arrowhead agility drill test procedures were already known to all participants in this study from their exercise course instruction and performance evaluation methods. All groups participated in the study by providing mouth swab samples that were analyzed for *CYP1A2*

gene polymorphisms. Before the evaluations, all participants jogged for five minutes at a moderate pace and stretched their lower extremities dynamically for three minutes as part of a typical warm-up routine. The specified activities were done at a lower intensity than the later assessments. Before the testing, players were allowed three minutes to relax following the warm-up. The assessment was conducted twice, at the commencement and conclusion of the 6-week training session. Every participant had three sessions of 45-60 minutes of aerobic endurance training (circuit training) and anaerobic/aerobic threshold training (long-term tempo running) three times weekly for six weeks to improve their fitness. All individuals engaged in a training regimen six days per week, incorporating both aerobic and anaerobic exercises, with each session lasting between 45 and 60 minutes. The training regimen comprises 3 sessions each week. The program consists of one micro cycle weekly, incorporating three training sessions every micro cycle and one daily exercise session in the evening, amounting to around 180 minutes per week. Anaerobic and aerobic capacity, speed, plyometric training loads, inter- and intramuscular coordination, and other related metrics are the focus of the program's sessions.

Data Collection Tools

Arrowhead Agility Drill Test: The arrowhead agility test is used to assess agility, acceleration, and the ability to change direction. The participant starts behind the starting line, sprints forward to the center marker, turns left or right to a designated cone, then runs to the opposite cone before returning to the start point. The time taken to complete the course is recorded. The test is repeated for both left and right directions, and the best times are used for analysis (Rago et al., 2020).

***CYP1A2* rs762551 Polymorphism Analysis:** The KASP diagnostic approach was used to sequence the single-nucleotide variant (SNP) (LGC Genomics, Beverly, CA, USA). Two forward primers that are particular to each allele and one common reverse primer make up the three assay-specific, unlabeled nucleotides used in the KASP test. The rs762551 variation of the *CYP1A2* gene is the focus of the SNP analysis. Applied Biosystems' 7500 Real-time PCR System was used to perform a PCR reaction after SNP-specific KASP primers and the universal KASP Master mixture were added to the DNA samples. Afterwards, fluorescence measurements were taken, and the data was examined in conjunction with previous research (He et al., 2014).

Statistical Analysis

The investigation commenced with a screening of raw data to determine its suitability for statistical analysis and to verify the assumptions underlying parametric tests. As a result, seven (7) participants were excluded due to missing or incorrectly recorded data, and the analyses were conducted on the remaining 47 participants. Descriptive statistics including percentage, mean, and standard deviation were used to summarize the dataset. To assess the normality assumption, skewness and kurtosis values were examined. In accordance with the ±2 threshold suggested by George and Mallery (2019), the dataset was deemed to meet the assumption of normal distribution. To evaluate within-group differences (pre- and post-test) for each genotype group, the Paired Samples T-Test was applied. Additionally, between-group comparisons across genotypes (AA, AC, and CC) were conducted using one-way ANOVA. Due to the disparate group sizes, especially the limited sample size of the CC group (n = 3) which restricts statistical power, the Games–Howell post-hoc test was chosen to address potential variance heterogeneity. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY), with the significance level set at $\alpha = 0.05$ and 95% confidence intervals.

RESULTS

This section of the study presents the results obtained from the comparative analysis of agility drill test performance across CYP1A2 rs762551 genotypes. Table 1 illustrates that intra-group comparisons of pre-test and post-test values revealed no statistically significant differences for any genotype. For the right-foot agility drill test, the paired samples t-test yielded t=-0.823 (p>0.05) for the AA genotype, t=-0.884 (p>0.05) for the AC genotype, and t=1.708 (p>0.05) for the CC genotype. For the left-foot agility drill test, results were t=0.997 (p>0.05) for AA, t=-0.399 (p>0.05) for AC, and t=3.781 (p>0.05) for CC.

Between-group comparisons using one-way ANOVA also showed no statistically significant differences in agility test scores across the three genotype groups. The ANOVA results were as follows: pre-test (right foot): F(2, 44)=0.189, p=0.828; post-test (right foot): F(2, 44)=0.368, p=0.694; pre-test (left foot): F(2, 44)=0.335, p=0.717; post-test (left foot): F(2, 44)=0.133, p=0.876.

The genotype frequency distribution of the CYP1A2 rs762551 polymorphism among the participants was 29.78% AA, 63.82% AC, and 6.40% CC. The CC genotype group included only 3 participants; therefore, findings related to this group should be interpreted with caution due to limited statistical power.

Table 1. According to the *CYP1A2* gene polymorphism, the arrowhead agility drill test matched samples t-test results of the scores obtained from the right and left directions.

Variables	Genotype	n	Pre-test M±Ss	Post-test M±Ss	t	*p**
Agility drill	AA	14	9.72±.71	9.80±.66	-.823	.426
test	AC	30	9.59±.76	9.66±.73	-.884	.384
Right foot	CC	3	9.51±.09	9.45±.10	1.708	.230
p²			.828	.694		
Agility drill	AA	14	9.77±.70	9.66±.73	*.997*	.333
test	AC	30	9.58±,81	9.62±.76	-.399	.693
Left foot	CC	3	9.50±.15	9.42±.14	3.781	.063
p²			.717	.876		

Values are presented as mean ± standard deviation. The "t" and "p" columns reflect paired t-test results within each genotype group; "p2" indicates the one-way ANOVA p-value (p>0.05) comparing genotype groups for each test session (pre or post).*

DISCUSSION AND CONCLUSION

This study analyzed the influence of CYP1A2 (rs762551) genotypes on athletic performance, indicating that variations in genes may lead to various responses to caffeine consumption. The findings indicate that hereditary variables may significantly influence the ergogenic effects of caffeine. This aligns with other twin studies that highlighted the significance of genetic factors in caffeine metabolism (Carmelli et al., 1990; Laitala et al., 2008; Luciano et al., 2005; Swan et al., 1996; Vink et al., 2009).

The CYP1A2 gene is believed to be associated with persistent vasoconstriction, potentially hindering the delivery of nutrients and oxygen to muscles utilized in endurance sports. The rs762551 variant in this gene influences caffeine metabolism, leading to varying performance outcomes. Individuals possessing the AA genotype metabolize caffeine more rapidly, whereas those with the CC genotype metabolize it more slowly (Guest et al., 2018). In this context, AA carriers may gain advantages from brief, high-intensity activities, whereas the effects of caffeine may be prolonged and delayed in individuals with the CC genotype (Gonglach et al.,

2016; Guest et al., 2018). However, the literature presents conflicting conclusions. Womack et al. (2012) discovered that in their research on professional male cyclists, caffeine consumption led to a 4.9% enhancement in performance for fast metabolizers, whereas slow metabolizers experienced only a 1.8% improvement. Grgic and Mikulic (2021) suggested that AC and CC genotypes would be more advantageous than AA; nevertheless, Salinero et al. (2017) reported no differences associated to genotype. Consequently, there are conflicting results about the relationship between genotype and performance. Our analysis (Table 1) revealed no statistically significant differences in pre-test and post-test outcomes among genotypes. Furthermore, intra-group analyses employing One-way ANOVA indicated no statistically significant differences in agility test outcomes across the three genotype groups. Similar performances were observed among the AA and AC genotypes, which are considered to have high anaerobic capacity, and the CC variant (The limited sample size of the CC group (n = 3) constrains statistical power). This finding indicates that the ergogenic effects of caffeine are determined not only by genetic factors but also by training history, nutritional status, caffeine habituation, and exercise type (Timmons et al., 2010; Bouchard et al., 2011).

Numerous research have examined the influence of the CYP1A2 genotype on different forms of exercise. Grgic et al. (2020) found no significant differences in jump and sprint performance across CYP1A2 genotypes in strength training athletes. This indicates that genetic factors may exert a restricted influence in brief anaerobic assessments. Our data corroborates this concept, as there were no discrepancies among genotypes in the Arrowhead agility test results.

Multiple studies suggest that the immediate effects of caffeine consumption can improve performance regardless of genetic makeup. Salinero et al. (2017) found that caffeine consumption improved peak and average power in the Wingate test but did not affect genotype. Similarly, Salles Painelli et al. (2021) found that consistent caffeine uses improved strength, speed, and anaerobic capacity. The studies indicate that CYP1A2 expression may fluctuate with training, however the effects for individual and team sports are unclear.

Conclusion

The findings from this study indicate that the impact of caffeine on athletic performance differs among individuals, influenced by genetic composition, exercise type, dosage, and surrounding conditions. Our analysis reveals that the absence of a notable difference between CYP1A2 (rs762551) genotypes and anaerobic agility performance indicates that caffeine's effects cannot be solely ascribed to genetic factors.

This study exhibited specific limitations. The constrained sample size, uneven distribution of genotype groups, and limitation of evaluations to the Arrowhead test diminish the generalizability of the findings. Moreover, the varying levels of caffeine tolerance among the individuals may have affected the outcomes. Future research should be conducted with greater in size, genotype-balanced sample populations and should incorporate various exercise modalities. Furthermore, a comprehensive examination of gene-environmental interactions would enhance the predictability and validity of the anticipated results.

The association between CYP1A2 gene variants and caffeine metabolism remains under scientific investigation, with limited literature accessible. The results of this study are expected to offer guidance for subsequent research in the area of sports genomics.

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