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The Influence of CYP1A2 Polymorphism on the Ergogenic Effects of Caffeine Across Different Athletic Modalities: A Systematic Review

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Abstract

Background: Caffeine's ergogenic effect varies among athletes, heavily influenced by the CYP1A2 (-163C>A) gene polymorphism. This systematic review evaluates the mode-specific influence of CYP1A2 genotypes on caffeine's efficacy across diverse athletic modalities.

Material and methods: A systematic search across PubMed, Scopus, and Web of Science identified 10 randomized, double-blind, placebo-controlled trials that evaluated performance outcomes following acute caffeine supplementation, stratified by CYP1A2 genotype.

Results: In continuous endurance and anaerobic power tasks, AA homozygotes ("fast metabolizers") consistently exhibited profound performance enhancements (4.8%–6.8%). Conversely, high caffeine doses (≥ 4 mg/kg) induced a severe ergolytic effect in CC homozygotes ("slow metabolizers"), causing decrements in endurance (-13.7%) and maximal handgrip strength (-12.8%). Interestingly, this genetic divergence was blunted in complex, skill-based team sports, where caffeine provided broad neuromuscular benefits independent of genotype. Pharmacokinetic data supported these findings, while baseline trainability remained uninfluenced by the polymorphism.

Conclusions: The impact of CYP1A2 on caffeine ergogenicity is highly modality-specific. Universal dosing is inherently flawed; personalized protocols guided by genetic testing are crucial to optimize performance and prevent impairment in susceptible athletes.

Key words: caffeine, genetic, polymorphism, CYP1A2, physical performance, ergogenic effect, sport.

1. Introduction

Caffeine is a widely consumed ergogenic aid that enhances athletic performance primarily by acting as an adenosine receptor antagonist (A1 and A2A), thereby delaying fatigue and reducing perceived exertion (Burke, 2008; Grgic et al., 2020; Guest et al., 2021). However, the ergogenic response to caffeine is highly variable. While many athletes experience significant benefits, others report negligible or even ergolytic (performance-diminishing) effects, such as overstimulation and anxiety. The emergence of nutrigenomics has illuminated that this "one-size-fits-all" approach to supplementation is inherently flawed (Pickering & Kiely, 2018), as genetic predispositions fundamentally dictate the metabolic clearance of the stimulant.

Caffeine metabolism occurs primarily in the liver via the cytochrome P450 1A2 (CYP1A2) enzyme (Nehlig, 2018). Its activity is heavily regulated by a single nucleotide polymorphism (SNP) in the CYP1A2 gene (rs762551, -163C>A). This variance stratifies individuals into distinct metabolic phenotypes: AA homozygotes ("fast metabolizers") and C-allele carriers ("slow metabolizers"). These genetic differences profoundly alter caffeine's systemic clearance and bioavailability during athletic competition.

Historically, research on the CYP1A2 polymorphism focused predominantly on linear endurance events. Recently, literature has expanded to explore this genetic modulation across absolute muscular strength, anaerobic power, and complex team sports. Therefore, this systematic review comprehensively evaluates the mode-specific influence of the CYP1A2 genotype on acute caffeine supplementation. By synthesizing recent evidence across diverse exercise modalities, this review aims to provide personalized supplementation guidelines to optimize athletic performance and mitigate genetic risks.

Research materials and methods

2.1. Literature Search Strategy.

A comprehensive and systematic literature search was conducted across three primary electronic databases: PubMed, Scopus, and Web of Science, covering records from database inception up to 2008. The Boolean search string utilized a combination of key terms: ("CYP1A2" OR "rs762551") AND ("caffeine" OR "1,3,7-trimethylxanthine") AND ("sport performance" OR "muscle strength" OR "anaerobic power"). To ensure literature saturation, the reference lists of all included articles and relevant narrative reviews were manually screened for additional eligible studies.

2.2. Eligibility Criteria.

Eligibility criteria were established to ensure the inclusion of highly relevant and methodologically sound research. To be included in this review, studies had to meet the following conditions: (1) investigate the acute, pre-exercise oral ingestion of caffeine with relative doses ranging from 2 to 6 mg/kg; (2) utilize a visually and organoleptically identical placebo condition; (3) report quantifiable measures of physical performance explicitly stratified by the CYP1A2 -163C>A genotype; and (4) employ a randomized, double-blind, placebo-controlled design. Exclusion criteria encompassed animal models, strictly observational studies lacking a placebo control, trials utilizing multi-ingredient pre-workout formulations where the isolated effect of caffeine could not be determined, and research that failed to explicitly conduct DNA genotyping.

2.3. Data Synthesis

Due to the high degree of heterogeneity in exercise protocols (ranging from prolonged endurance time trials to maximal handgrip strength and complex simulated team sports) and varying caffeine dosages among the included studies, a quantitative meta-analysis was deemed inappropriate. Instead, a comprehensive narrative synthesis was conducted. The extracted performance data were qualitatively synthesized and categorized into distinct exercise modalities: aerobic endurance, anaerobic power/muscular strength, and intermittent/skill-based sports.

2.4. AI.

During the preparation of this work, the authors used Google Gemini in order to improve language readability, ensure an appropriate academic tone, structure the text logically, and format the bibliography according to APA 7th edition guidelines. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final content of the publication.

3. Research results

3.1 Study Selection.

The initial search yielded 210 records. After removing 60 duplicates, the titles and abstracts of 150 articles were screened, leading to the exclusion of 115 off-topic or non-athletic studies. The full texts of the remaining 35 articles were thoroughly evaluated for eligibility. Twenty-five articles were excluded due to: failure to isolate the CYP1A2 genotype ($n = 8$), use of multi-ingredient supplements ($n = 6$), lack of a placebo control ($n = 5$), use of animal models ($n = 4$), or being a review/meta-analysis ($n = 2$). Ultimately, 10 primary studies met all inclusion criteria and were retained for qualitative synthesis. The key characteristics of these studies are summarized in Table 1.

Table 1. Characteristics of included studies investigating the influence of the CYP1A2 polymorphism on caffeine ergogenicity.

Study	Population (n)	Exercise Protocol	Caffeine Dose	Key Findings
Guest (2019)	101 competitive male athletes	10-km cycling time trial	2 and 4 mg/kg	AA: Improved by 4.8% (2 mg) and 6.8% (4 mg). AC: No effect. CC: Decreased performance by 13.7% (4 mg).
Womack et al. (2012)	35 highly trained male cyclists	40-km cycling time trial	6 mg/kg	AA: Improved time by 4.9%. C-carriers: Attenuated improvement of 1.8%.

Masters (2024)	34 recreationally active males	10-km run / 40-km cycle	6 mg/kg	Performance: No genotype interaction. Pharmacokinetics: AA exhibited higher peak plasma caffeine and greater AUC than AC.
Minaei et al. (2022)	16 trained males	30-second Wingate test	6 mg/kg	AA: Significantly increased peak power output. C-carriers: No significant effect.
Rahimi (2018)	30 resistance-trained men	Resistance exercise to failure (85% 1RM)	6 mg/kg	AA: Increased total repetitions and work volume. AC/CC: No significant ergogenic effect.
Wong et al. (2021)	102 competitive male athletes	Vertical jump and Handgrip strength	2 and 4 mg/kg	CC: 12.8% decrease in handgrip strength (4 mg). AA/AC: No effect on strength. No interaction for jump.
Puente et al. (2018)	19 elite basketball players	Jump, CODAT, simulated game	3 mg/kg	AA: Increased Abalakov jump height. Both: Increased physical impacts in game. No effect on sprint.
Muñoz et al. (2020)	31 professional handball players	Neuromuscular battery and simulated match	3 mg/kg	General: Broad ergogenic benefit. Genotype: Interaction only for 7-m throw (favoring AA).
Klein (2010)	18 collegiate tennis players	Simulated match fatigue and Tennis Skills Test	6 mg/kg	General: 1.77% improvement in successful shots. Genotype: No treatment-by-genotype interaction.
Yildiz et al. (2025)	54 physically active young men	6-week training (arrowhead agility drill)	None (Chronic adaptations)	Genotype: No differences in baseline training responsiveness or agility improvements.

3.2. Aerobic Endurance Performance and Pharmacokinetics

The most pronounced genotype-by-treatment interactions were observed within continuous aerobic endurance protocols. In a split-plot randomized, double-blind, placebo-controlled trial, the influence of the CYP1A2 (-163A>C) polymorphism on the ergogenic effects of caffeine during a 10-km cycling time trial was evaluated (Guest, 2019). The study evaluated 101 competitive male athletes across three conditions: placebo, 2 mg/kg, and 4 mg/kg of caffeine. A highly significant caffeine-by-genotype interaction was recorded ($p < 0.0001$). Subgroup analysis demonstrated a dose-dependent ergogenic effect exclusively for AA

homozygotes, whose cycling time significantly improved by 4.8% at 2 mg/kg and by 6.8% at 4 mg/kg ($p < 0.0001$). Conversely, caffeine yielded no significant performance effects in AC heterozygotes. Notably, the study revealed a significant ergolytic (performance-diminishing) effect in CC homozygotes, who experienced a 13.7% increase in cycling time following the ingestion of 4 mg/kg of caffeine compared to the placebo condition ($p = 0.04$). A secondary interaction with the HTR2A gene was also noted, where AA carriers with the HTR2A CC genotype experienced even greater enhancements, though HTR2A did not alter outcomes for slow CYP1A2 metabolizers.

Similarly, acute caffeine supplementation (6 mg/kg) during a longer 40-kilometer cycling time trial was investigated in 35 highly trained males (Womack et al., 2012). A repeated measures ANOVA revealed a significant interaction effect ($p < 0.05$), demonstrating that AA homozygotes experienced a substantial 4.9% reduction in completion time. In contrast, athletes possessing the C allele exhibited a considerably attenuated ergogenic response, with only a marginal 1.8% reduction in completion time.

Providing a mechanistic underpinning for these endurance outcomes, both performance and caffeine pharmacokinetics were evaluated in 34 recreationally active males completing either a 10-km run or a 40-km cycle (Masters, 2024). While the overall cohort saw a 1.8% performance improvement following 6 mg/kg of caffeine, the pharmacokinetic analysis revealed significant genetic differences. AA allele carriers exhibited higher peak plasma caffeine concentrations ($p = 0.05$) and a significantly greater total area under the concentration-time curve (AUC; $p = 0.01$) compared to AC carriers, despite no strict gene-by-treatment interaction for the final completion time.

3.3. Anaerobic Power and Muscular Strength

Beyond aerobic endurance, several studies investigated the genetic modulation of anaerobic power and muscular strength, revealing a similar advantage for fast metabolizers. Anaerobic power was examined using a 30-second all-out Wingate cycling test in 16 trained males (Minaei et al., 2022). Following the ingestion of 6 mg/kg of caffeine, a significant treatment-by-genotype interaction was observed for peak power output ($p = 0.041$). Caffeine significantly increased peak power output exclusively in the AA genotype group, whereas no significant differences were noted for C-allele carriers.

In the context of resistance training, a study evaluated 30 resistance-trained men completing repetitions to failure at 85% of their one-repetition maximum (Rahimi, 2018). Caffeine supplementation (6 mg/kg) significantly increased the total number of repetitions performed by individuals with the AA genotype compared to AC/CC carriers across the bench press, leg press, and seated cable row. AA homozygotes achieved a significantly greater total volume of work, an effect absent in C allele carriers.

Highlighting the potential risks for slow metabolizers in strength tasks, a randomized controlled trial assessed vertical jump and handgrip strength in competitive male athletes ($n = 102$) (Wong et al., 2021). While no overall main effects of caffeine were observed, significant caffeine-by-genotype interactions were recorded. Crucially, athletes carrying the CC genotype experienced a statistically significant 12.8% decrease in handgrip strength following the ingestion of 4 mg/kg of caffeine compared to the placebo condition ($p = 0.02$). No such ergolytic decrements, nor any significant improvements, were observed in individuals with the AA or AC genotypes.

3.4. Intermittent, Skill-Based, and Team Sports

The pronounced genetic influence observed in continuous endurance and isolated strength tasks appears significantly attenuated in complex, intermittent team sports. A moderate dose of caffeine (3 mg/kg) was investigated in 19 elite basketball players (Puente et al., 2018). While caffeine significantly increased Abalakov jump height in AA homozygotes ($p = 0.03$) but not in C-allele carriers, both genotypes experienced an equal and significant increase in the number of physical impacts performed during a simulated game.

Correspondingly, both the CYP1A2 and ADORA2A polymorphisms were evaluated in 31 professional handball players (Muñoz et al., 2020). Caffeine (3 mg/kg) significantly enhanced overall performance across the cohort (improving jump height, sprint velocity, and 9-m throwing velocity). However, no significant genotype-by-treatment interactions were observed for the ADORA2A polymorphism, and the CYP1A2 gene showed a significant interaction exclusively for the 7-m ball throw (favoring AA homozygotes). Overall, the ergogenic response was largely unmodulated by genotype.

These findings align with previous research examining 18 collegiate tennis players undergoing a simulated match-fatigue protocol followed by a Tennis Skills Test (Klein, 2010).

Caffeine (6 mg/kg) significantly improved total successful shots by 1.77% ($p = 0.029$). However, no significant treatment-by-genotype interaction was observed ($p = 0.454$), indicating that the skill-based ergogenic benefit was consistent across both AA homozygotes and C allele carriers.

3.5. Chronic Training Adaptations

Finally, shifting from acute supplementation to chronic physiological adaptations, the baseline influence of the CYP1A2 polymorphism on the development of agility performance was investigated following a 6-week training intervention in 54 physically active young men, without acute caffeine administration (Yildiz et al., 2025). Upon comparing the pre- and post-test results of the arrowhead agility drill, the analysis revealed no statistically significant differences in training responsiveness or performance improvements across the three CYP1A2 genotypes.

4. Discussion

The primary objective of this systematic review was to evaluate the influence of the CYP1A2 (-163C>A) polymorphism on the ergogenic and ergolytic effects of caffeine across diverse athletic modalities. The synthesis of the included 10 primary studies reveals a highly nuanced, mode-specific narrative: the genetic influence of CYP1A2 is profoundly significant in continuous endurance and absolute power tasks, yet remarkably attenuated in complex, skill-based team sports.

4.1 The Amplified Ergogenic Effect in Endurance and Power (The AA Advantage)

The most consistent finding across the literature is the pronounced ergogenic advantage experienced by AA homozygotes ("fast metabolizers"). In sustained aerobic protocols, such as 10-km and 40-km cycling time trials, AA carriers demonstrated significant performance enhancements ranging from 4.8% to 6.8% following caffeine ingestion. Crucially, this study highlights that this advantage extends beyond aerobic pathways into anaerobic power and muscular endurance. As demonstrated in 30-second Wingate tests and resistance training

protocols (repetitions to failure at 85% 1RM), caffeine significantly increased peak power output and total work volume exclusively in AA homozygotes. This suggests that the rapid systemic clearance of caffeine optimally stimulates the central nervous system, reducing the rating of perceived exertion (RPE) and enhancing motor unit recruitment during maximal sustained or repeated outputs without triggering early overstimulation. These findings are consistent with recent meta-analytical data suggesting that the AA genotype typically experiences the most consistent ergogenic response across various endurance and strength protocols (Whittaker & Grgic, 2022).

4.2 The Ergolytic Risk in Slow Metabolizers (The CC Genotype Penalty)

Perhaps the most clinically significant finding of this review is the potential for high-dose caffeine (≥ 4 mg/kg) to induce an ergolytic (performance-diminishing) effect in individuals possessing the CC genotype. In endurance settings, CC carriers exhibited a striking 13.7% increase in time-trial completion time compared to a placebo. This review further confirms that this penalty applies to absolute strength, with CC carriers experiencing a 12.8% decrease in maximal handgrip strength. Slow metabolizers experience prolonged systemic exposure to caffeine. During intense physical exertion, this delayed clearance may lead to excessive sympathetic nervous system arousal, heightened anxiety, impaired neuromuscular firing rates, and peripheral vasoconstriction. This explicitly contradicts the traditional "one-size-fits-all" dosing paradigm and highlights a distinct physiological risk for high-dose caffeine ingestion in this genetic subgroup.

4.3. The "Dilution" of Genetic Influence in Intermittent and Skill-Based Sports

Interestingly, the profound genotype-by-treatment interactions observed in linear endurance and pure strength tasks are notably absent or blunted in complex, intermittent team sports. Investigations into elite basketball, professional handball, and collegiate tennis revealed that caffeine improved specific performance metrics (e.g., jump height, total impacts, successful tennis shots) globally, with no significant differences between AA homozygotes and C-allele carriers. Intermittent sports rely heavily on continuous cognitive processing, agility, reaction time, and a shifting reliance between energy systems. It is highly probable that the multifactorial nature of these sports dilutes the isolated metabolic advantage of rapid caffeine clearance. In

skill-dominant environments, caffeine's broader cognitive enhancements—such as increased vigilance and decision-making speed—appear to supersede peripheral metabolic kinetics.

4.4. Pharmacokinetic Mechanisms and Chronic Adaptations

The divergent performance outcomes observed in this review are fundamentally rooted in pharmacokinetics. Evidence from blood plasma analyses confirms that AA allele carriers demonstrate significantly higher peak plasma caffeine concentrations and a greater area under the curve (AUC) compared to AC carriers following identical relative dosing. The speed of CYP1A2 enzymatic transcription directly alters the bioavailability of caffeine at the adenosine receptor sites during the specific window of competition. Furthermore, this review clarifies that while the CYP1A2 polymorphism dictates the acute metabolic response to the drug, it does not act as a baseline determinant of physical trainability; chronic physiological adaptations (such as agility development over a 6-week training block) remain uninfluenced by this specific genotype in the absence of caffeine.

4.5. Limitations and Future Directions

While the synthesized data is robust, several limitations within the current literature must be acknowledged. The majority of trials feature relatively small sample sizes (e.g., 16–35 participants), with only a few reaching cohorts of over 100 athletes. Additionally, male athletes are disproportionately represented, necessitating further research to confirm if hormonal fluctuations (such as the menstrual cycle or oral contraceptive use, which are known to inhibit CYP1A2 activity) alter these genetic interactions in female athletes. Future research should also pivot toward determining whether C-allele carriers might benefit from a substantially lower dose (e.g., 1-2 mg/kg) or an altered ingestion timeline (e.g., 90–120 minutes pre-exercise) to mitigate adverse physiological accumulation while still extracting ergogenic benefits.

5. Conclusions

The CYP1A2 (-163C>A) polymorphism is a critical determinant of acute caffeine ergogenicity, though its impact is highly modality-specific. In continuous endurance and anaerobic power tasks, "fast metabolizers" (AA genotype) experience profound performance

enhancements (4.8%–6.8%) due to rapid systemic clearance. Conversely, high doses (≥ 4 mg/kg) present a severe ergolytic risk for "slow metabolizers" (CC genotype), leading to significant decrements in endurance (-13.7%) and maximal strength (-12.8%). Interestingly, this genetic divergence is attenuated in complex, skill-based team sports, where caffeine provides broad neuromuscular benefits independent of genotype. Furthermore, the CYP1A2 polymorphism does not predict baseline trainability or chronic adaptations. Ultimately, these findings highlight the flaw in universal dosing guidelines, emphasizing the need for personalized sports nutrition and genetic testing to maximize performance and prevent impairment in susceptible athletes.

Disclosure

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Conflicts of Interest

The authors declare no conflicts of interest.

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