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Posted Date: 22 May 2026

doi: 10.20944/preprints202605.1489.v1

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Article

CPNE5 rs3213537 Polymorphism and Playing Position in Professional Football Players

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Abstract

The *CPNE5* rs3213537 polymorphism is a candidate genetic marker for sprint and power phenotypes, yet its distribution across football playing positions remains unclear. This study aimed to determine the genotype and allele frequencies of *CPNE5* rs3213537 in professional male football players and examine potential differences by playing position. Ninety-five professional male football players from Balkan leagues participated. Genomic DNA was extracted from buccal swabs, and genotyping was performed using a TaqMan allelic discrimination assay. Genotype distribution across positions (goalkeeper, defense, midfield, and forward) was evaluated using Monte Carlo-simulated chi-square and Fisher's exact tests. Exploratory analyses of physical performance (sprint, jump, Yo-Yo IRT2) were conducted in a sub-cohort. Observed genotypes were CC (71.6%) and CT (28.4%); we detected no TT genotype. Allele frequencies were C=0.858 and T=0.142, consistent with Hardy-Weinberg equilibrium. No significant associations were observed between *CPNE5* rs3213537 genotype and position. Similarly, sub-cohort analyses showed no significant genotype-related differences in sprint performance, jump height, aerobic capacity, or body fat percentage after adjusting for anthropometric variables and position. *CPNE5* rs3213537 genotype distribution does not differ by playing position in professional male football players. Furthermore, no association was found between this polymorphism and physical performance traits. These results suggest that the influence of *CPNE5* rs3213537 on football-specific performance may be limited or masked by the multifactorial nature of team sports.

Keywords: *CPNE5*; rs3213537; football; sports genetics; playing position

1. Introduction

In individual and team-based sports, factors such as physiological capacity, mechanical efficiency, sprint ability, and strength performance are important elements supporting success. Strength and speed components are considered among the primary determinants of sprint performance because, during acceleration phases, they reflect the interaction between maximal force production and speed output. Elite athletes in both individual and team sports—where speed and explosive strength are dominant—demonstrate superior neuromuscular efficiency during intermittent and repeated acceleration phases in competition [1]. Twin and family studies provide important evidence for heritability in sprint- and power-related phenotypes. It has been reported that traits such as maximal movement speed and explosive strength show moderate-to-high heritability, and that heritability estimates for explosive power may reach up to 70% [2]. Overall, these findings indicate that observed differences in physical performance between individuals are strongly influenced by genetic background.

Sprint ability is a polygenic trait regulated by the combined and interactive effects of multiple loci and allelic variants. To date, studies in sprint- and power-focused sports have highlighted several candidate genes that may contribute genetically to sprint and power phenotypes, including

polymorphisms in the vitamin D receptor gene, *IGF-1*, *PPARA*, *ADRB2*, and *AMPD1* [3–5]. In addition, previous research has reported that *ACTN3* and *ACE* gene polymorphisms are among the biomarkers most directly influencing sprint performance. Research in the field of sports genetics shows that athletic performance depends not only on environmental factors but also on specific genetic polymorphisms unique to individuals. In this context, studies conducted on Turkish elite athletes have revealed that the distribution of *ACTN3* rs1815739 and *ACE* I/D polymorphisms may play a decisive role in determining sport-specific success, particularly in strength and speed disciplines. These genetic markers are considered critical for optimizing training responses and physical capacities [6,7]. Another prominent candidate marker associated with speed performance is the *CPNE5* (Copine 5) gene [8]. *CPNE5* belongs to the copine family and encodes a calcium-dependent phospholipid-binding protein (C2) that binds to the cell membrane in a calcium-sensitive manner. This protein is involved in the regulation of membrane signaling, vesicle trafficking, and intercellular interactions [9,10]. The *CPNE5* protein contains two C2 domains (calcium-binding regions) and an “A domain”-like region [11]. In the presence of calcium, this structure binds to membrane lipids and contributes to intracellular signal transduction and synaptic plasticity [9,10]. Therefore, *CPNE5* may play an indirect role in both neuromuscular junction formation and rapid force production in muscle [12–14].

The rs3213537 polymorphism in the *CPNE5* gene is an intronic single-nucleotide variant [15]. Although intronic variants do not directly alter the structure of the encoded protein, they may indirectly regulate protein abundance and function by influencing gene expression, alternative exon usage, or RNA stability [16]. Findings from recent studies have suggested that the rs3213537 polymorphism is associated with physical performance. Research in elite athletes has shown that the C allele occurs at a higher frequency in athletes engaged in high-intensity (speed, strength, power) and short-duration anaerobic activities (sprint), whereas the T allele is more frequent in those involved in lower-intensity, long-duration aerobic endurance sports; the variant has also been reported to be significantly associated with fast-twitch muscle fibers (type IIa and IIb) [15,17]. Evidence to date supports this pattern, and the CC genotype has been reported to increase the likelihood of being a sprinter [18]. These findings indicate that *CPNE5* is a noteworthy candidate gene in relation to sprint performance. Although the biological functions of *CPNE5* have not yet been fully clarified, its links to central nervous system development, synaptic plasticity, and calcium-mediated intracellular signaling processes suggest that it may be related to both motor control via the nervous system and muscle performance via muscle cells [18]. Moreover, it has been proposed that clarifying the independent effects of *CPNE5* variants on sprint phenotypes may be important for verifying potential interactions with other candidate genes associated with performance. Accordingly, the present study aimed to investigate whether *CPNE5* rs3213537 genotype distribution differs across roster-defined playing positions in professional male football players, and to provide descriptive genotype/allele frequency data for this cohort.

2. Results

2.1. Genotype Distributions and Allele Frequencies

A total of 95 athletes were successfully genotyped for the *CPNE5* polymorphism. The distribution of genotypes was CC (n=68; 71.6%) and CT (n=27; 28.4%). The TT genotype was not observed in this cohort. The corresponding allele frequencies were C=0.858 and T=0.142 (Table 1). The genotype distribution did not deviate from Hardy–Weinberg equilibrium ($p>0.05$).

Table 1. Genotype and allele frequencies of the *CPNE5* polymorphism in the study sample (n=95).

Genotype	n	%
CC	68	71.6
CT	27	28.4
Allele	n	Frequency

C	163	0.858
T	27	0.142

n: number of observations; %: percentage of genotype; Hardy–Weinberg equilibrium: $p > 0.05$ (exact test or chi-square, as applicable).

2.2. Genotype Distribution by Playing Position

Genotype counts for the *CPNE5* polymorphism across playing positions are presented in Table 2. The chi-square test showed no evidence of an association between genotype and playing position ($\chi^2(3)=2.26$, $p=0.521$). This result was consistent when using sparse-cell robust procedures (Monte Carlo–simulated chi-square $p=0.538$; Fisher’s exact $p=0.554$). The magnitude of association was small (Cramér’s $V=0.154$).

Table 2. Genotype distribution of the *CPNE5* polymorphism across playing positions.

Position	CC (n)	CT (n)	Total
Goalkeeper	11	2	13
Defense	21	7	28
Midfield	19	11	30
Forward	17	7	24

n: number of observations; Chi-square test: $\chi^2(3) = 2.26$, $p = 0.52$.

2.3. Exploratory Performance Analysis in the FC Hebar Sub-Cohort

Performance testing data were available for an FC Hebar sub-cohort ($n=23$). Genotype distribution in this sub-cohort was CC ($n=16$) and CT ($n=7$). Descriptive results for jump performance, sprint times, Yo-Yo IRT2 distance, and body fat percentage by genotype are shown in Table 3.

Table 3. Multivariable linear regression for 30-m sprint time (s) in the FC Hebar sub-cohort ($n = 23$).

Predictor	β (estimate)	p value
Genotype (CT vs CC)	0.025	0.814
Height (cm)	0.041	0.035
Weight (kg)	−0.025	0.080
Position: GK (ref = ATT)	0.310	0.184
Position: DEF (ref = ATT)	0.060	0.773
Position: MID (ref = ATT)	0.047	0.815

Note: β coefficients are unstandardized and represent change in 30-m sprint time (s) per unit change in predictor. Genotype reference = CC; position reference = ATT. Significance set at $p < 0.05$.

Including position group (GK/DEF/MID/ATT) significantly improved the 30 m sprint model compared with the base model including genotype, height, and body mass (nested-model ANOVA $p = 0.046$).

Table 4. Physical performance outcomes by *CPNE5* genotype in the FC Hebar sub-cohort.

Outcome	CC (n=16)	CT (n=7)
SJ (cm)	35.1±4.4	37.1±2.6
CMJ (cm)	36.8±4.5	36.7±2.6
DJ (cm)	35.6±4.4	36.2±3.6
5m Sprint (s)	0.92±0.17	0.92±0.18
30m Sprint (s)	3.94±0.25	3.90±0.36
Yo-Yo IRT2 (m)	1028±158	1011±202
Body Fat (%)	7.99±1.78	9.08±2.58

Abbreviations: SJ, squat jump; CMJ, countermovement jump; DJ, drop jump; Yo-Yo IRT2, Yo-Yo Intermittent Recovery Test Level 2 distance covered in meters; cm: centimeters; s: seconds; m: meters.

Between-genotype comparisons were further examined using multivariable linear regression models adjusted for height, body mass, and position group (GK/DEF/MID/ATT). In adjusted models, *CPNE5* genotype (CT vs CC) was not associated with SJ, CMJ, DJ, 5 m sprint, 30 m sprint, body fat percentage, or Yo-Yo IRT2 distance (all $p > 0.05$; Table 4). In the Yo-Yo IRT2 model, body mass showed a negative association with distance, whereas genotype remained non-significant.

3. Discussion

CPNE5 (Copine-5) is a member of the copine protein family that regulates membrane interactions in a calcium-dependent manner [12]. Its high expression in neural tissue suggests a potential role in neuromuscular control [13,14]. Because copines participate in synaptic plasticity and calcium-dependent intracellular signaling processes, *CPNE5* may influence neuromuscular coordination and rapid force production mechanisms that are relevant for sprint and power performance in athletes.

In the present study, the genotype distribution of the *CPNE5* rs3213537 polymorphism was investigated in professional male football players, with a particular focus on whether genotype frequencies differed across playing positions. The main finding of the study was that no statistically significant association was observed between *CPNE5* genotype and roster-defined playing position.

Football is characterized by intermittent high-intensity activity involving sprinting, rapid accelerations, changes of direction, and jumping actions, which collectively require a combination of aerobic capacity and explosive neuromuscular performance [20,21]. Previous studies have examined the influence of genetic variants on traits that are advantageous for football performance, including speed, explosive power, and endurance [22–24]. Within this context, several candidate genes have been investigated in relation to sprint performance and muscle fiber composition.

Previous research has suggested that the *CPNE5* rs3213537 polymorphism may be associated with sprint performance and muscle fiber characteristics. For example, Pickering et al. (2019) reported that the C allele was associated with improved short-distance sprint performance in young football players [15]. Similarly, Guilherme et al. (2021) observed that the C allele occurred more frequently in elite sprinters compared with endurance athletes [17]. These findings have led to the suggestion that *CPNE5* may represent a potential candidate gene involved in explosive athletic performance.

Despite these observations, the present study did not detect differences in genotype distribution across football playing positions. This finding suggests that the contribution of the *CPNE5* rs3213537 polymorphism to positional specialization in football may be relatively modest. In team sports such as football, performance characteristics are influenced by multiple physiological and biomechanical factors that may reduce the observable effect of a single genetic variant.

Although this study did not find a significant relationship between the *CPNE5* genotype and player positions, the literature maintains that genetic profiling remains important. As Ulucan emphasizes, it is difficult for a single gene polymorphism to fully explain performance; instead, the athlete's genetic makeup should be evaluated as a whole. In multifaceted sports such as soccer, using genetic data for 'personalized training planning' and 'injury risk analysis' rather than player selection is considered a more efficient approach. This supports the view that the effect of genetic variation exhibits a multifactorial nature on the field [25,26].

Another important methodological consideration relates to the statistical power of the present study. Genetic association studies investigating single nucleotide polymorphisms often require relatively large sample sizes to reliably detect small genetic effects. Although the current sample size ($N = 95$) is comparable to several previous studies conducted in elite athlete populations, it may still be insufficient to detect modest genotype–phenotype associations. In particular, the absence of the TT genotype further reduces genotype variability and may limit the ability to identify small genetic effects.

The exploratory performance analyses conducted in the FC Hebar sub-cohort also did not demonstrate significant genotype-related differences in sprint performance, jump height, Yo-Yo IRT2 distance, or body fat percentage. However, these analyses should be interpreted with caution due to the small sample size of the sub-cohort and the limited statistical power associated with exploratory analyses.

It is also important to consider that athletic performance is a highly polygenic trait influenced by the combined effects of multiple genetic variants. Rather than being determined by a single polymorphism, performance phenotypes such as sprint speed, muscular power, and endurance capacity arise from the interaction of numerous genes involved in neuromuscular function, energy metabolism, and muscle fiber composition. Therefore, the absence of a detectable association between *CPNE5* rs3213537 and playing position in the present study does not exclude the possibility that this variant may contribute to performance within a broader polygenic framework.

Interestingly, significant differences in 30-m sprint performance were observed in relation to playing position and body height. These findings are consistent with previous studies suggesting that anthropometric characteristics may influence sprint mechanics and acceleration ability in football players [27].

From a practical perspective, understanding the potential contribution of genetic variation to athletic performance may help improve talent identification and individualized training strategies in the future. However, genetic information should not be used in isolation when evaluating athletes, as environmental factors, training history, and psychological characteristics also play essential roles in performance development.

Future studies should aim to investigate *CPNE5* polymorphisms in larger and more diverse cohorts of football players while incorporating standardized performance testing protocols. In addition, genome-wide approaches and polygenic score analyses may provide deeper insights into the complex genetic architecture underlying football performance.

4. Materials and Methods

4.1. Study Population and Sample Collection

A total of 95 professional male football players competing in professional leagues in the Balkan region (North Macedonia, Bulgaria, and Serbia) were recruited on a voluntary basis. The primary cohort comprised players with available *CPNE5* rs3213537 genotype data and roster-based playing position information, which were used for genotype/allele frequency and genotype–position analyses. Playing position was determined from official club roster records and classified into four categories (goalkeeper, defense, midfield, forward). When players had multiple listed positions, the primary position was defined as the position most frequently reported in the roster and confirmed by team staff where available. Physical performance test data were available only for a sub-cohort from FC Hebar (n=23, depending on completeness per variable). Therefore, analyses involving physical performance outcomes were conducted as an exploratory sub-cohort analysis and were not pooled with the full genetic cohort. Physical performance testing was conducted only in the FC Hebar subgroup because we collected these measurements directly and had permission to use them; comparable performance-test data were not available for the other clubs. Therefore, performance analyses were restricted to the FC Hebar sub-cohort and treated as exploratory.

All participants received written and verbal information about the study and provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (Decision No: 2025-110).

3.2. Genetic Analysis

Buccal swabs were collected using sterile cotton swabs and stored in phosphate-buffered saline (PBS) until processing. Genomic DNA isolation was performed using a commercial kit (PureLink™

Genomic DNA Mini Kit, Thermo Fisher Scientific, USA) according to the manufacturer's instructions. The concentration of the obtained DNA samples was accurately measured via fluorescence-based quantification using a Qubit 4 Fluorometer (Thermo Fisher Scientific, USA) with the appropriate assay kit. The isolated DNA samples were stored at -20 °C for subsequent analyses. Genotyping for *CPNE5* rs3213537 polymorphism was performed using the StepOnePlus Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific, Foster City, CA, USA) with TaqMan SNP Genotyping Assays (Catalog No: 4351379, Thermo Fisher Scientific, Inc.) in accordance with the manufacturer's protocols. Reactions were prepared in a total volume of 10 µL containing 5 µL master mix, 3.5 µL nuclease-free distilled water (H₂O), 0.5 µL TaqMan SNP genotyping assay (Assay IDs: C__3211614_10), and 1 µL DNA sample (10 ng). The target sequence and probe information for the analyzed *CPNE5* rs3213537 variants are presented in Table 5. Genotypes were called using the manufacturer's software with automatic clustering, followed by manual review of ambiguous clusters.

Table 5. Sequence of the TaqMan probe used in genotyping the *CPNE5* rs3213537 polymorphism.

DNA sequence (5'→3')	
VIC/FAM	GGCCAGAGAGTATGAGGGTCATGGT[C/T]CCAGCCAGGGCCAGA TGCCACAGCC

3.3. Physical Performance Assessments

Vertical jump performance was assessed using a photoelectric contact platform system (OptoJump, Microgate, Italy). Squat jump (SJ) and countermovement jump (CMJ) were used to evaluate vertical jumping ability. For SJ, participants adopted a standardized squat position (~90° knee flexion) and held the position for ~2 s before initiating the jump. For CMJ, participants performed a self-selected countermovement followed immediately by maximal extension of the lower limbs. All jumps were performed with hands on hips. Participants completed multiple trials with standardized rest intervals, and the best trial (highest jump height, cm) was retained for analysis.

Drop jump (DJ) was used to assess reactive explosive performance. Participants stepped forward from a platform, landed, and immediately performed a maximal vertical jump with minimal ground contact time, with hands on hips throughout. Because device-exported summaries may combine "best" values from different trials across variables, analyses were based on DJ jump height (cm) only; derived indices (e.g., RSI, contact time) were not included to avoid potential trial-mismatch bias.

Sprint performance was assessed using photocell timing gates (Witty Speed, Microgate Equipment, Italy) on an indoor track to minimize environmental variability. Timing gates were set to record sprint times over 5m and 30m. Participants started from a standing position ~0.5 m behind the start line and initiated the sprint when ready, completing the distance at maximal speed. Two trials were performed, separated by at least 5 min of rest, and the fastest time (s) was retained for analysis [19].

3.4. Yo-Yo Intermittent Recovery Test Level 2

The Yo-Yo Intermittent Recovery Test Level 2 (Yo-Yo IRT2) is a field-based assessment of an athlete's ability to perform and recover from intermittent high-intensity running. The test consists of repeated 2 × 20 m shuttle runs at progressively increasing speeds, interspersed with 10 s of active recovery between bouts. Participants followed standardized audio signals; the test was terminated when the participant failed to reach the line on time on two consecutive occasions. Total distance covered (m) was recorded as the outcome. The Yo-Yo IRT2 does not directly measure VO₂max; however, distance covered is strongly associated with VO₂max and is widely used as an indirect indicator of intermittent endurance performance.

3.5. Statistical Analyses

All statistical analyses were performed in R (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria). Genotype frequencies were obtained by direct counting, and allele frequencies were calculated using the gene-counting method. Hardy–Weinberg equilibrium was assessed using an exact test or a chi-square test when expected genotype counts were adequate. The association between genotype (CC vs CT) and playing position (GK/DEF/MID/ATT) was examined using a sparse-cell robust contingency-table approach (Fisher’s exact test or Monte Carlo–simulated chi-square p-values). Statistical significance was set at $p < 0.05$. Genotypes were called using the manufacturer’s software with automatic clustering, followed by manual review of ambiguous clusters. Standard quality control procedures were applied, including inspection of allelic discrimination plots and exclusion of ambiguous calls.

Because physical performance tests were available only for the FC Hebar sub-cohort, these analyses were conducted as exploratory sub-cohort analyses. Genotype group comparisons for performance outcomes were examined using Welch’s t-tests and multiple linear regression models adjusting for height, weight, and position. To address potential sparse-cell issues in the genotype–position contingency table, p-values were confirmed using a Monte Carlo–simulated chi-square test ($B = 100,000$) and Fisher’s exact test. Effect size for the association was quantified using Cramér’s V.

5. Conclusions

In professional male football players ($N = 95$), *CPNE5* rs3213537 genotype distribution did not differ across playing positions. In an exploratory sub-cohort with available performance testing (FC Hebar, $n = 23$), genotype was not associated with jump height, sprint performance, body fat percentage, or Yo–Yo IRT2 distance after adjustment for anthropometrics and position. These findings provide descriptive data for *CPNE5* genotype distribution in professional football and underscore the need for larger, multi-club studies with standardized performance testing to clarify any potential contribution of *CPNE5* to sprint- and power-related traits.

Limitations: Collecting genetic samples and conducting physical performance tests in professional athletes is challenging due to constraints imposed by coaching staff, training programs, and the competitive calendar. In the present study, although DNA samples were obtained from a larger group of athletes, performance testing was feasible only in a subset during the winter training camp, resulting in complete usable performance data for 23 players. Therefore, the performance analyses should be interpreted as exploratory and may be underpowered to detect small genotype effects.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, M.C., K.U. and M.D.; methodology, M.C., Ö.Ö.Y., T.G., and B.T.A.; validation, Ö.Ö.Y., T.G., and K.U.; formal analysis, A.Ş.Ö.; investigation, M.C., and A.Ş.Ö.; resources, M.C., A.Ş.Ö., and K.U.; data curation, Ö.Ö.Y., T.G., and B.T.A.; writing—original draft preparation, M.C., A.Ş.Ö.; writing—review and editing, M.C., K.U., and M.D.; visualization, Ö.Ö.Y.; supervision, M.D.; project administration, M.C., and K.U.; funding acquisition, M.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Marmara University Scientific Research Projects Commission, grant number TSA-2025-11799.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (protocol code 2025-110 and date of approval).

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

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments: The authors would like to thank all participants involved in this study. No additional support was received.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CPNE5	Copine 5
SNP	Single Nucleotide Polymorphism
DNA	Deoxyribonucleic Acid
PCR	Polymerase Chain Reaction
PBS	Phosphate Buffered Saline
HWE	Hardy–Weinberg Equilibrium
SJ	Squat Jump
CMJ	Countermovement Jump
DJ	Drop Jump
IRT2	Intermittent Recovery Test Level 2
GK	Goalkeeper
DEF	Defense
MID	Midfield
ATT	Forward (Attacker)
ANOVA	Analysis of Variance
SD	Standard Deviation
β	Beta coefficient
VO _{2max}	Maximal oxygen uptake
cm	Centimeter
m	Meter
s	Second
kg	Kilogram

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