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# A meta-analysis of the association of CKM gene rs8111989 polymorphism with sport performance

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**ABSTRACT:** The muscle-specific creatine kinase (*CKM*) A/G variants (rs8111989) have been associated with skeletal muscle performance in humans; they are correlated with physical performance and contribute to differences in the maximum oxygen uptake ($VO_2$max) responses during power or endurance training. However, there is not enough definitive evidence to demonstrate whether the A and G allelic variants of the *CKM* gene rs8111989 are indeed genetic factors that can influence human physical performance. In our study, we identified 9 articles on *CKM* in a literature search, and conducted two meta-analyses on the *CKM* rs8111989 A/G allele or genotype differences between power or endurance athletes and general controls. We found that the power athletes had a significantly higher frequency of the G allele (OR, 1.14; 95% CI, 1.02-1.28, P=0.03) and GG genotype (OR, 1.54; 95% CI, 1.24-1.91, P<0.0001) compared to controls, but there was no significant difference for the endurance athletes (G allele, OR, 0.95, 95%CI, 0.85-1.06, P=0.34; GG genotype, OR, 1.00, 95%CI, 0.78-1.27, P=1.00). The results provide additional evidence to support the notion that human physical performance might be influenced by genetic profiles, especially in power sports.

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## INTRODUCTION

Human physical performance depends on genetics and its interaction with environmental factors such as physical training, nutrition, and technological support. Approximately 66% of the variance in athletic status can be explained by additive genetic factors [9]. As of 2016, more than 350 genetic variants have been associated with physical performance [1, 7, 33]. However, only about 155 of these genetic variants have been specifically identified in athletes [1, 13]. Furthermore, for most of these genes and variants, replication studies have failed to confirm an association with physical performance, partly due to the small sample size of the studies [4]. As the effects of genetic polymorphisms tend to be small, large sample sizes are needed to reliably detect such effects. Meta-analyses overcome the limitation of small sample size by pooling results from a number of individual studies to generate a single best estimation [23].

Among the many specific genes and sequence variants (polymorphisms) within genes that have been associated with performance, the muscle-specific creatine kinase (*CKM*) gene is an important candidate gene due to its role in energy homeostasis in muscle cells [16]. Specifically, a genetic predisposition for low *CKM* activity could be an advantage for endurance performance [10, 30]. The interest in *CKM* as a candidate gene for exercise-related traits is not new, as it was investigated more than 20 years ago by analysing electrophoretic variants of the protein [5].

The *CKM* gene is located on chromosome 19 (19q13.2-13.3) and has more than 260 polymorphisms [27]. The most frequently analysed genetic variant of this gene is a polymorphism located in the 3′-untranslated region (UTR) (rs8111989). There is evidence that this gene is involved in skeletal muscle performance in humans, especially during endurance training, as it has been shown to correlate with physical performance and contribute to differences in the maximal oxygen uptake ($VO_2$max) responses during endurance training [3, 29, 36]. Moreover, the GG genotype of *CKM* gene rs8111989 has a higher frequency in power athletes [19]. Several studies have shown a positive association of rs8111989 A/G variations with endurance athlete status or power capacity [15, 19, 32], whereas others have failed to show any significant association [12, 17, 19, 26, 30]. This discrepancy raises the question of whether the A and G allelic variants of the *CKM* gene rs8111989 are indeed genetic factors that can influence the physical performance.

The aim of this study is to summarize the association of *CKM* polymorphisms with success in power or endurance sports by conducting a systematic review and meta-analysis, which potentially can provide more definitive evidence compared with individual reports.

## MATERIALS AND METHODS

### *Literature Search*

Combinations of the key words "*CKM or CKMM* or muscle-specific creatine kinase or muscle creatine kinase" and "athletes or sports or sport or exercise or endurance or strength" and "polymorphism or gene or genotype" were used to screen for potentially relevant studies focused on *CKM* among all articles in the PubMed database or in the title or abstract of articles in the Web of Science database and Google Scholar. We finally found 63 unique articles published up to December 2, 2016, in these databases.

### *Inclusion and Exclusion Criteria*

Among 63 unique citations from the PubMed database and the Web of Science database and Google Scholar, 39 were excluded after the first screening based on their title relevance to our study, for example, those that involved experiments on animals, or the target population was not athletes. Nine were excluded after the second screening based on the abstract, such as reviews, comparisons only between athletes, or due to not being relevant to our analysis. After full-text reviews of 15 papers, 3 studies were excluded because the raw data were unavailable, and 1 study was excluded because the genotype distribution deviated from Hardy-Weinberg equilibrium. An additional 2 studies in which the data were not detailed or not relevant were also excluded. Finally, 9 studies [12, 14, 15, 17, 19, 26, 30, 32, 35] were included in our meta-analysis. A flow chart showing the study selection process is presented in Fig. 1.

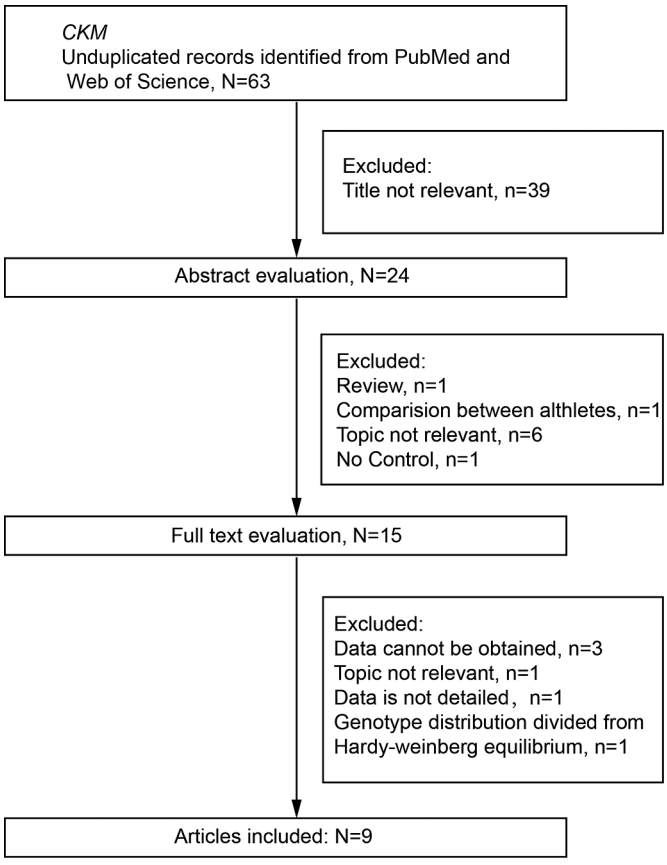


**FIG. 1.** Flow diagram of study selection.

### *Data Extraction*

We extracted the following data from the original publications of the included studies: first author and year of publication, distribution of *CKM* genotypes and allele numbers among athletes and controls, characteristics of the study design, and the study population. Then we separated all the athletes into two groups: endurance athletes and power athletes.

### *Statistical Analysis*

Hardy-Weinberg equilibrium was examined for each study using Pearson's chi-square test with the R package "genetics." We used Cochrane Review Manager (RevMan) version 5.3 to perform the meta-analysis (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) [8]. Random effects models were used for the meta-analysis, and the degree of heterogeneity between the study results was assessed with the $I^2$ statistic [21]. The association between polymorphisms and sport performance was estimated by odd ratios (OR) and 95% confidence intervals (CI), comparing athletes to controls. RevMan was also used to construct funnel plots to examine publication bias [11]. Two meta-analyses were performed with the endurance group and power group.

## RESULTS

After excluding the overlapping results of literature searches using the PubMed and the Web of Science databases, 63 articles focused on *CKM* were identified. For the literature searches, different combinations of key words were used, such as *CKM* OR *CKMM* OR "muscle-specific creatine kinase" OR "muscle creatine kinase" AND (athletes OR sports OR sport OR exercise OR endurance OR strength) AND (polymorphism OR gene OR genotype).

We designed the screening and inclusion criteria to consist of three steps for the selection process, as shown in Fig. 1. After the first step, in which papers whose titles were not relevant were excluded, 24 abstracts were retrieved for the second step. After evaluating the abstracts, 15 potentially relevant articles were reviewed in a more detailed full text evaluation. Finally, we included 9 articles in our quantitative analysis.

The identified 9 studies included a total of 1,559 athletes and 5,923 controls. The sports in the included studies were rowing, biathlon, skating (5-10 km), cross-country skiing (5-15 km), weightlifting, soccer, and cycling, among others. All the athletes were

separated into two groups (see Table 1, Table 2 and Table 3). We considered rowing as both an endurance and a power sport, while soccer was neither of them because it is much more complicated. The genotypic frequencies for both the cases and the controls in all studies were in Hardy-Weinberg equilibrium.

Fig. 2 and Fig. 3 present the OR and P values for the pooled analyses. Power athletes had a higher frequency of the G allele and GG genotype compared to controls ($P < 0.05$). The pooled OR of the G allele compared to the A allele was 1.14 (95% CI 1.02-1.28). The pooled OR for the GG genotype compared to the AA + AG genotype was 1.54 (95% CI 1.24-1.91). The heterogeneity among all studies was small ($I^2=0$), but there was no significance for endurance athletes (95% CI <= 1, $P > 0.1$). There was no publication bias (not shown).

**TABLE 1.** Overview of 9 case-control studies of G/A alleles and GG/AA+AG genotypes.

| Study | Group | n | AA | AG | GG | A | G | $\chi^2$ P Value |
|---|---|---|---|---|---|---|---|---|
| **Rivera 1997** | EEA (E) | 124 | 61 | 47 | 16 | 169 | 79 | 0.283 |
| | Controls | 115 | 63 | 42 | 10 | 168 | 62 | |
| **Muniesa 2008** | Rowers (E+P) | 39 | 15 | 18 | 6 | 48 | 30 | 0.208 |
| | Cyclists (E) | 50 | 23 | 23 | 4 | 69 | 31 | |
| | Runners (E) | 52 | 22 | 28 | 2 | 72 | 32 | |
| | Controls | 123 | 43 | 65 | 15 | 151 | 95 | |
| **Ruiz 2009** | EEA (E) | 46 | 21 | 20 | 5 | 62 | 30 | 0.372 |
| | Controls | 123 | 43 | 65 | 15 | 151 | 95 | |
| **Fedotovskaya 2012** | Boat racing (E+P) | 95 | 43 | 34 | 18 | 120 | 70 | 0.661 |
| | Biathlon (E) | 51 | 26 | 21 | 4 | 73 | 29 | |
| | Skating_5-10 km (E) | 13 | 10 | 3 | 0 | 23 | 3 | |
| | Jumping race (P) | 68 | 42 | 20 | 6 | 104 | 32 | |
| | Cross-country skiing_5-15 km (E) | 44 | 27 | 15 | 2 | 69 | 19 | |
| | Weightlifting (P) | 74 | 29 | 22 | 23 | 80 | 68 | |
| | Soccer | 39 | 19 | 16 | 4 | 54 | 24 | |
| | Controls | 1116 | 493 | 473 | 150 | 1459 | 773 | |
| **Fedotovskaya 2013** | Judo (P) | 29 | 10 | 11 | 8 | 31 | 27 | 0.055 |
| | Wrestling (P) | 79 | 29 | 35 | 15 | 93 | 65 | |
| | Boxing (P) | 51 | 19 | 25 | 7 | 63 | 39 | |
| | Controls | 1512 | 637 | 674 | 201 | 1948 | 1076 | |
| **Eider 2015** | Rowers (E+P) | 220 | 97 | 93 | 30 | 287 | 153 | 0.364 |
| | Controls | 1854 | 845 | 813 | 196 | 2503 | 1205 | |
| **Grealy 2015** | EET (E) | 196 | 93 | 83 | 20 | 269 | 123 | 0.290 |
| | Controls | 113 | 58 | 49 | 6 | 165 | 61 | |
| **He 2016** | Endurance (E) | 35 | 20 | 14 | 1 | 54 | 16 | 0.681 |
| | Speed Power (P) | 43 | 19 | 13 | 11 | 51 | 35 | |
| | Uyghur Soccer | 36 | 17 | 13 | 6 | 47 | 25 | |
| | Controls | 441 | 214 | 175 | 52 | 603 | 279 | |
| **Yvert 2016** | Runners (E) | 175 | 126 | 49 | 0 | 301 | 49 | 0.523 |
| | Controls | 649 | 465 | 166 | 18 | 1096 | 202 | |

2 test is performed between all athletes and controls for allele G and A.
EEA is short for Elite Endurance Athlete.
E is short for Endurance Sport.
P is short for Power Sport.

**TABLE 2.** Overview of power sports.

| Study | Group | n | AA | AG | GG | A | G | $\chi^2$ P Value |
|---|---|---|---|---|---|---|---|---|
| **Muniesa 2008** | Rowers (E+P) | 39 | 15 | 18 | 6 | 48 | 30 | 1 |
| | Controls | 123 | 43 | 65 | 15 | 151 | 95 | |
| **Fedotovskaya 2012** | Boat racing (E+P) | 95 | 43 | 34 | 18 | 120 | 70 | 0.079 |
| | Jumping race (P) | 68 | 42 | 20 | 6 | 104 | 32 | |
| | Weightlifting (P) | 74 | 29 | 22 | 23 | 80 | 68 | |
| | Controls | 1116 | 493 | 473 | 150 | 1459 | 773 | |
| **Fedotovskaya 2013** | Judo (P) | 29 | 10 | 11 | 8 | 31 | 27 | 0.055 |
| | Wrestling (P) | 79 | 29 | 35 | 15 | 93 | 65 | |
| | Boxing (P) | 51 | 19 | 25 | 7 | 63 | 39 | |
| | Controls | 1512 | 637 | 674 | 201 | 1948 | 1076 | |
| **Eider 2015** | Rowers (E+P) | 220 | 97 | 93 | 30 | 287 | 153 | 0.364 |
| | Controls | 1854 | 845 | 813 | 196 | 2503 | 1205 | |
| **He 2016** | Speed Power (P) | 43 | 19 | 13 | 11 | 51 | 35 | 0.111 |
| | Controls | 441 | 214 | 175 | 52 | 603 | 279 | |

$\chi$2 test is performed between all athletes and controls for allele G and A.
EEA is short for Elite Endurance Athlete.
E is short for Endurance Sport.
P is short for Power Sport.

**TABLE 3.** Overview of endurance sports.

| Study | Group | n | AA | AG | GG | A | G | $\chi^2$ P Value |
|---|---|---|---|---|---|---|---|---|
| **Rivera 1997** | EEA (E) | 124 | 61 | 47 | 16 | 169 | 79 | 0.283 |
| | Controls | 115 | 63 | 42 | 10 | 168 | 62 | |
| **Muniesa 2008** | Rowers (E+P) | 39 | 15 | 18 | 6 | 48 | 30 | 0.208 |
| | Cyclists (E) | 50 | 23 | 23 | 4 | 69 | 31 | |
| | Runners (E) | 52 | 22 | 28 | 2 | 72 | 32 | |
| | Controls | 123 | 43 | 65 | 15 | 151 | 95 | |
| **Ruiz 2009** | EEA (E) | 46 | 21 | 20 | 5 | 62 | 30 | 0.372 |
| | Controls | 123 | 43 | 65 | 15 | 151 | 95 | |
| **Fedotovskaya 2012** | Boat racing (E+P) | 95 | 43 | 34 | 18 | 120 | 70 | 0.067 |
| | Biathlon (E) | 51 | 26 | 21 | 4 | 73 | 29 | |
| | Skating_5-10 km (E) | 13 | 10 | 3 | 0 | 23 | 3 | |
| | Cross-country skiing_5-15 km (E) | 44 | 27 | 15 | 2 | 69 | 19 | |
| | Controls | 1116 | 493 | 473 | 150 | 1459 | 773 | |
| **Eider 2015** | Rowers (E+P) | 220 | 97 | 93 | 30 | 287 | 153 | 0.364 |
| | Controls | 1854 | 845 | 813 | 196 | 2503 | 1205 | |
| **Grealy 2015** | EET (E) | 196 | 93 | 83 | 20 | 269 | 123 | 0.290 |
| | Controls | 113 | 58 | 49 | 6 | 165 | 61 | |
| **He 2016** | Endurance (E) | 35 | 20 | 14 | 1 | 54 | 16 | 0.163 |
| | Controls | 441 | 214 | 175 | 52 | 603 | 279 | |
| **Yvert 2016** | Runners (E) | 175 | 126 | 49 | 0 | 301 | 49 | 0.523 |
| | Controls | 649 | 465 | 166 | 18 | 1096 | 202 | |

2 test is performed between all athletes and controls for allele G and A.
EEA is short for Elite Endurance Athlete.
E is short for Endurance Sport.
P is short for Power Sport.

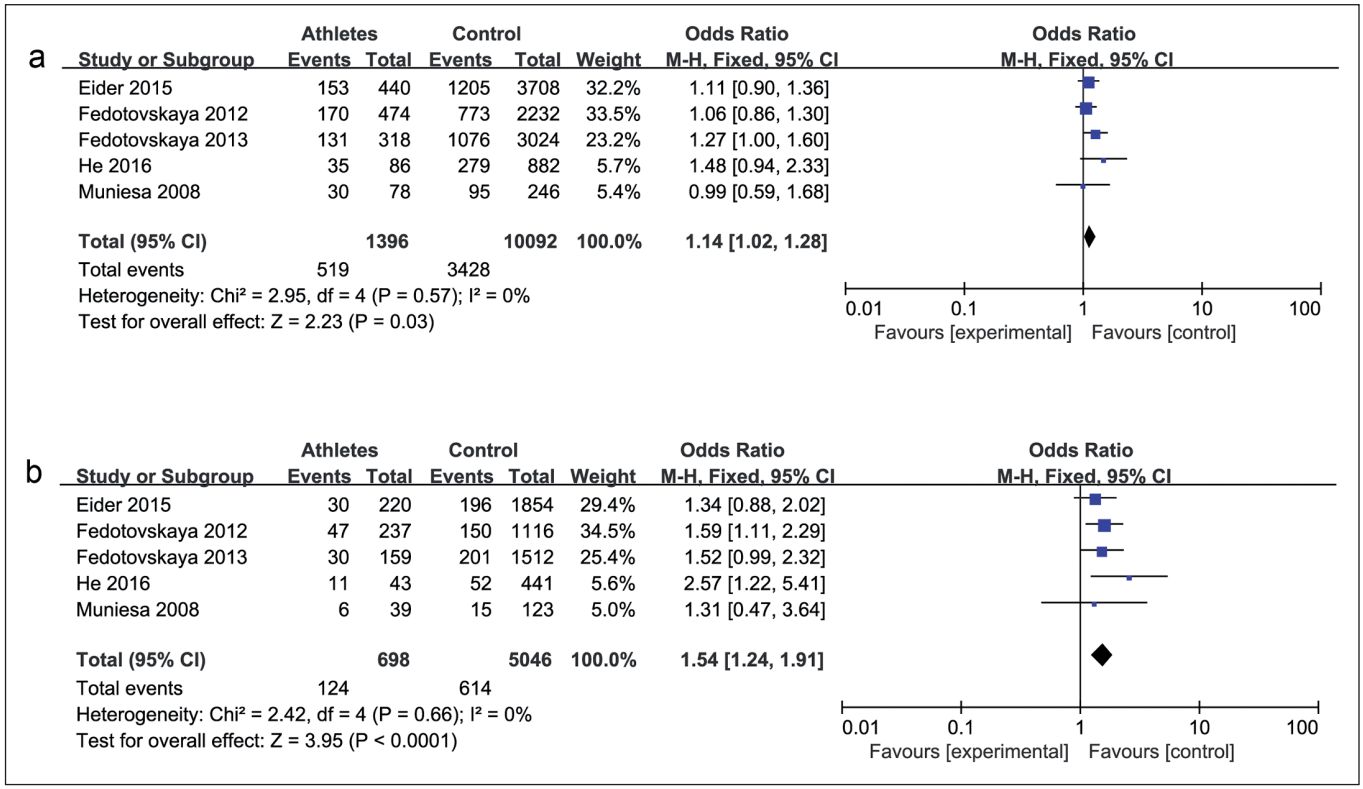


**FIG. 2.** Meta-analysis for association studies for *CKM* gene and power sports.
(a) Allele G vs A. (b) Homozygotes GG vs AA+AG. CI= confidence interval.

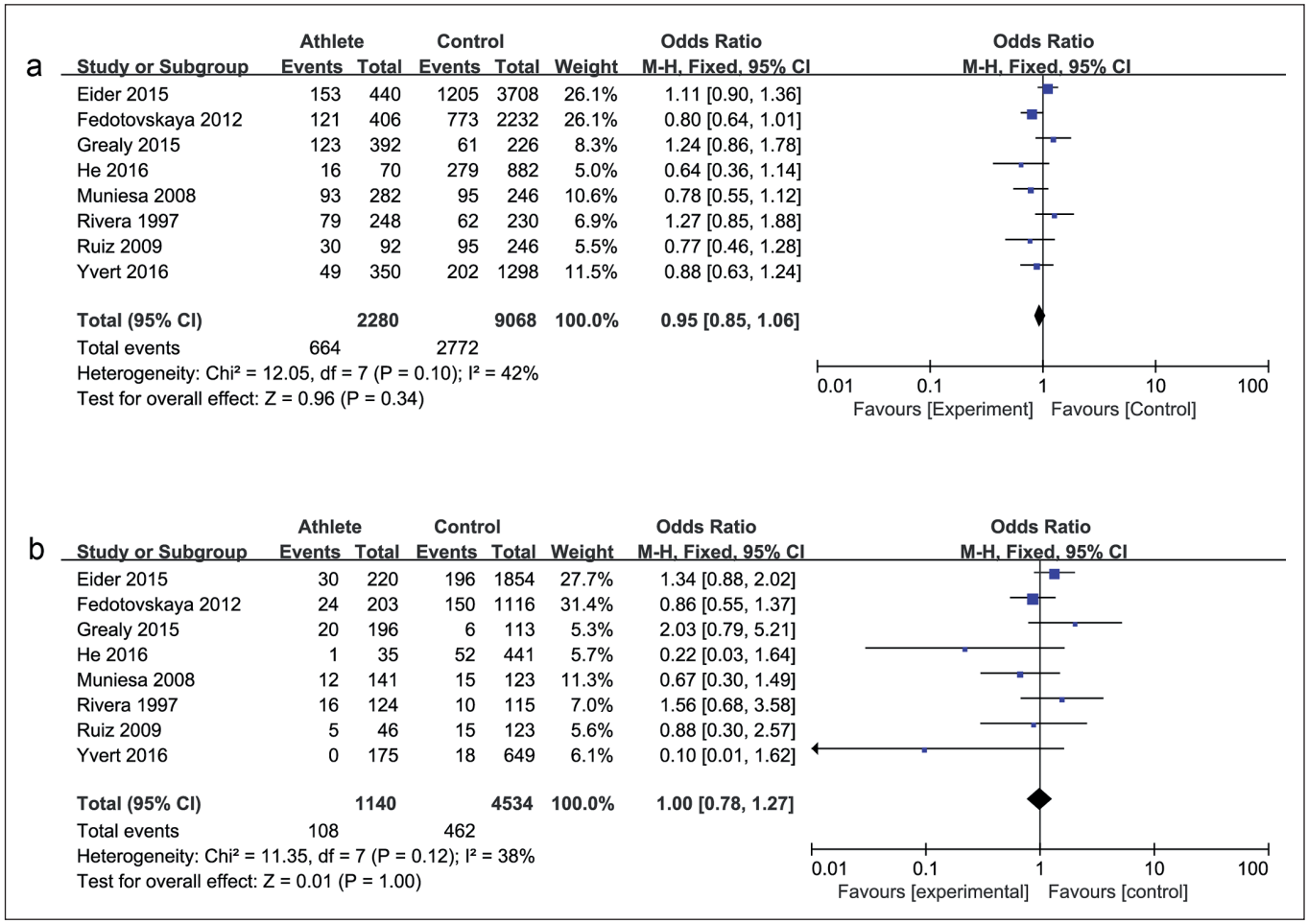


**FIG. 3.** Meta-analysis for association studies for *CKM* gene and endurance sports
(a) Allele G vs A. (b) Homozygotes GG vs AA+AG. CI= confidence interval.

## DISCUSSION

These meta-analyses were performed to estimate the association of human sport performance with *CKM* A/G variants (rs8111989). The analyses involved 1,559 athletes (power and endurance) and 5,923 controls from 9 studies (Table 1). Among these studies, we can find that it is a controversial issue whether the *CKM* A/G polymorphism is indeed a genetic factor that can influence physical performance. In terms of the two meta-analyses of power athletes and endurance athletes, our results indicate that power athletes have a higher frequency of the G allele (OR, 1.14; 95% CI, 1.02-1.28) and GG genotype (OR, 1.54; 95% CI, 1.24-1.91) compared to general controls, which provides significant evidence to answer this controversial question. Rankinen could not identify a panel of genomic variants common to elite endurance athlete groups even based on a total of 1520 endurance athletes and 2760 controls [28]. The result of our study suggested that there was not a significant difference of the G allele or GG genotype of *CKM* between endurance athletes and controls.

The *CKM* gene is a muscle-specific form of CK, which catalyses the conversion of hosphor-creatine (PCr) and ADP into creatine and ATP, as well as the reverse reaction [17]. It is also an important gene because of its role in energy homeostasis in muscle cells [12, 16]. A genetic predisposition for low *CKM* activity could be an advantage for endurance performance [10, 29].

Earlier studies have shown that a *CKM* single nucleotide polymorphism within the 3′-flanking gene region is associated with the change in $VO_2$max after endurance training [29, 31, 36]. Moreover, Fedotovskaya found that the *CKM* AA genotype was associated with high values of $VO_2$max [14]. In addition, a tendency for individuals with the GG and GA genotypes to reach higher $VO_2$max levels was reported [18].

The interdependence between the *CKM* A/G polymorphism (rs8111989) and individual differences in the expression of human physical performance has been shown in several studies [6, 10, 36]. The A/G variation located in the 3'-UTR of the *CKM* gene has been found to be the most relevant regarding genetic testing in sport performance [12]. It has been shown that athletes or individuals with the CKM-NcoI AA genotype have a six-fold higher likelihood of experiencing exertional muscle breakdown compared with the GG and AG genotypes. It has been hypothesized that the G allele is associated with a protective mechanism against exertional muscle breakdown [19].

Although the A/G polymorphism of the *CKM* gene rs8111989 is located in the 3′-UTR and thus does not result in a functional change in the *CKM* protein, deletion of the *CKM* 3′-UTR changes the mRNA cellular localization signal, which is important for correct CK/PCr shuttling [34] and may possibly result in altered expression levels of *CKM* due to mRNA instability [17, 20]. There are many genes associated with sport performance, such as angiotensin-converting enzyme (ACE), α-actinin-3 (ACTN3), and peroxisome proliferator activated receptor alpha (PPARA). Therefore, further studies are needed to determine whether these genes have any effects on endurance sport performance.

Case-control association studies have been widely used to identify susceptibility genes, and this study design remains the most common in sports genomics [1, 2]. The purpose of these studies is to determine whether one allele or one genotype of a polymorphism is more common in a group of elite athletes than in the general controls. However, the small sample size is one of the limitations of this type of study. A small sample size often results in statistical insignificance between athletes and controls, and controversial conclusions are often obtained in this kind of research. Yvert found that the total genotype score (TGS) based on some previously published endurance performance-associated polymorphisms does not influence endurance running performance in the Japanese population [35]. Thus, an important step in the investigation of previously inconsistent results is performing a meta-analysis [25]. Ioannidis and Lohmuller combined association studies with contradictory findings (IHD ACE (insertion/deletion)) and found that approximately 20-30% of genetic association studies were statistically significant [22, 24, 25]. In our study, this limitation can be overcome by performing a meta-analysis. Among the 9 studies considered separately, we cannot know whether the *CKM* gene rs8111989 A/G polymorphism is indeed a genetic factor that can influence physical performance. Our results indicate that power athletes have a higher frequency of the G allele and GG genotype compared to general controls, which provides significant evidence to answer this controversial question.

Although the number of samples in our study was substantial, the potential limitations of this study should be considered. First, all the identified studies focused on the effect of a single gene; therefore, the interaction of the *CKM* gene with other genes or with environment factors needs to be investigated in future studies. Second, most of the studies assessing the genetic factors of physical performance have focused on endurance and power; thus, future studies should focus on identifying genetic markers associated with other sport phenotypes such as stability, flexibility, and coordination. Finally, some family studies were excluded from our study, and an additional study may be needed to retrieve those data for the multi-analysis.

## CONCLUSIONS

In conclusion, the present study integrated and reanalysed data from 9 studies and provided additional evidence to support the findings regarding the differences in the frequency of the GG genotype and G allele of *CKM* between power athletes and general controls. We also performed another meta-analysis between endurance athletes and controls to demonstrate that there was no significance for endurance athletes. Although there were different results from our two meta-analyses, our findings strengthen the evidence that human physical performance might be influenced by genetic profiles.

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