Beneficial Effects of Cardiomyopathy-Associated Genetic Variants on Physical Performance: A Hypothesis-Generating Scoping Review

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Systematic review · Cardiogenetic · Cardiomyopathy · Physical performance

Abstract

\textbf{Background:} Genetic variants associated with cardiomyopathies (CMPs) are prevalent in the general population. In young athletes, CMPs account for roughly a quarter of sudden cardiac death, with further unexplained clustering in specific sports. Consequently, most CMPs form a contraindication for competitive sports. We hypothesized that genetic variants might (paradoxically) improve physical performance early in life while impairing cardiac function later in life.

\textbf{Methods:} Systematic PubMed search was done to investigate whether genetic variants in genes associated with CMPs could be related to beneficial performance phenotypes.

\textbf{Summary:} In a limited number of studies (n = 6), 2,860 individuals/subjects with genetic variants were able to outperform those without said variants, as measured by running speed (\(\sim 38\) m/min in heterozygous [HET] mice, \(n = 6\), vs. \(\sim 32\) m/min in wild type [WT] mice, \(n = 7\), \(p = 0.004\)) and distance (966 ± 169 km HET mice vs. 561 ± 144 km WT mice, \(p = 0.0035\), \(n = 10\)), elite athlete status in endurance athletes (\(n = 1,672\), \(p = 1.43 \times 10^{-8}\)), maximal oxygen uptake in elite athletes (absolute difference not provided, \(n = 32\), \(p = 0.005\)), maximal oxygen uptake in unrelated individuals (\(n = 473\), \(p = 0.0025\)), personal records in highly trained marathon runners \(2:26:28 \pm 0:06:23\) min HET, \(n = 32\), vs. \(2:28:53 \pm 0:05:50\) min without polymorphism, \(n = 108\), \(p = 0.020\)), and peripheral muscle force contraction in patients following a cardiac rehabilitation program (absolute values not provided, \(n = 260\)).

\textbf{Key Message:} Beneficial effects in genetic variants associated with CMPs could hypothetically play a role in the selection of young athletes, consequently explaining the prevalence of such genetic variants in athletes and the general population.

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Background

Genetic cardiomyopathies (CMPS) account for ∼25% of sudden cardiac death in young athletes and therefore form a contraindication for numerous competitive sports and intensive exercise [1]. Despite efforts to identify athletes at risk for sudden cardiac death through cardiovascular screening [2], the relatively high frequency of deaths due to CMPS in the athlete population is striking, with further clustering observed in sports such as basketball, soccer, and football [3]. These findings suggest that even after competitive selection and comprehensive screening, athletes with genetic variants that may eventually result in CMPS are still able to perform at elite levels. Furthermore, with prevalence of CMPS and genetic carriers in the general population as high as 1 in 200–500 [4, 5], it might be hypothesized that such variants might be or have been associated with evolutionary benefit, next to the clear negative effects on cardiac health general. To date, there is no adequate explanation for this high prevalence and the seemingly high number of cardiac events in athletes due to CMPS.

Genetic causes that underlie CMPS are continuously being extensively investigated and have been associated with hypertrophic-, dilated-, arrhythmogenic right ventricular-, restrictive-, and noncompaction CMPS. Current genetic panels for CMPS investigate about 54 genes [6] and include genes that encode for sarcomere, nuclear membrane, Z-disk, and desmosome.

Both the scientific and sporting communities acknowledge a clear genetic component for (athletic) performance. Maximal oxygen uptake (VO₂ max) [7], maximal force generation [8], sprint performance [9], and elite endurance performance [10] have all been shown to be (strongly) influenced by genetic traits. However, though a few genes have repeatedly been associated with elite athletic performance [11], genetic screening in athletes remains controversial, as no specific mutations have been reported to strongly predict athletic success [12].

Conversely, in the field of CMPS, negative effects on physical performance and prognosis have been extensively investigated and documented, and genetic testing has become the standard of care for the number of CMPS, with proven diagnostic value [13, 14]. In general, genetic screening in the absence of comprehensive clinical phenotyping is only advised in specific clinical situations, such as cascade screening [15], and clearly defined research settings.

While the heart of an athlete adapts to training stimuli [16], some hearts may have a predisposition to be better suited for physical exertion. We therefore hypothesized that genetic variants in genes associated with CMPS might (paradoxically) improve physical performance early in life and possibly impair cardiac function only later in life. This could explain why these variants are found relatively frequently in the general population and could, hypothetically, play a role in the selection of high-potential young athletes that train in a highly competitive environment. As the negative effects on physical performance of most CMPS have been extensively documented elsewhere [1], for this scoping review, we aimed to investigate whether genetic variants in CMP genes are associated with any beneficial performance phenotypes (Fig. 1).

Fig. 1. Illustration of study purpose: to investigate whether genetic variants associated with cardiomyopathies relate to any specific beneficial performance phenotypes.
Methods

We performed a scoping review according to the PRISMA-Scr statement [17]. Our systematic PubMed search through July 2021 consisted of Mesh-terms and text words in the title or abstract (Tiab) for known cardiomyopathy genes and performance outcomes, such as “Physical Endurance,” “Muscle Strength,” “Athletic Performance,” and “Physical Exertion.” In addition, we reviewed reference lists for relevant articles. Included genes for human and animal studies were based on typical, current genetic panels for CMPs and included ACTC1, ACTN2, ALPK3, ANKR1D, BAG3, CALR3, CAV3, CDH2, CRYAB, CSRP3, CTNNA3, DES, DSC2, DSG2, DSP, EMD, STA, FHL1, FHL2, FKRP, FLNC, GLA, HCN4, JPH2, JUP, LAMA4, LAMP2, LDB3, LMNA, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYLK3, MYL3, MYOZ2, MYPN, NEXN, PKP2, PLN, PPA2, PRDM16, PRKAG2, RBM20, SCN5A, TAZ, TCA, TME43, TNNC1, TNN3, TNN13K, TNN13, TNN2, TPM1, TTN, and VCL (for expansions of gene ab-

Fig. 2. Search of published research.

Table 1. Characteristics of included studies [19–24]

| First author       | Gene (variant) | Included population                                                                 | Intervention | Measurement                                                                 | Summary                                                                                     |
|--------------------|----------------|-------------------------------------------------------------------------------------|--------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Methawasin et al.  | RBM20, in-frame del. exons 6 and 7 | \( n = 13 \), 4-mo-old mice: \( n = 6 \) HET | –            | Maximal treadmill running speed                                             | Higher maximal running speed in HET mice                                                   |
| Najafi et al. [20] | MYBPC3, G>A exon 6 | \( n = 40 \), 3-wk-old mice: \( n = 5 \) in each group: genetic variant, sex, exercise | 8-week training program in exercised group | Treadmill running distance, cardiomyocyte force generation | In HET mice: further running distance + greater cardiomyocyte force generation |
| Al-Khelaifi et al. | MYBPC3, rs1052373 | \( n = 1,672 \): \( n = 796 \) European international-level athletes, \( n = 410 \) elite Russian athletes, \( n = 60 \) elite Japanese athletes, \( n = 406 \) controls | – | Elite endurance athlete status, \( VO_2 \) max in subgroup (\( n = 32 \)) | Higher representation of polymorphism in endurance athletes + higher \( VO_2 \) max in homozygous carriers |
| Stebbings et al.   | TTN, rs10497520 | \( n = 141 \) male marathon runners: \( n = 108 \) without genetic polymorphism       | –            | Personal record time for marathon running                                  | Faster personal best times in athletes with gene variant                                   |
| Timmons et al.     | TTN, rs10497520 | \( n = 473 \)                                                                               | 20-week training program | \( \Delta VO_2 \) max                                                                 | Greater increase in \( VO_2 \) max in polymorphism carriers                               |
| Thomaes et al.     | TTN, rs10497520 | Coronary artery patients: \( n = 260 \) at baseline, \( n = 204 \) after training        | 3-month training program | Quadriceps force generation at baseline and after training               | Greater force at baseline in TTN polymorphism carriers + greater force increases in TPM1 polymorphism carriers |
Beneficial Effects of CMP Mutations

Abbreviations, see online suppl. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520471). Exclusion criteria were (i) no comparison between individuals with and without (a) genetic variant(s) in the above-mentioned gene(s) and (ii) not reporting positive performance outcomes. We did not apply any language restrictions. All publications were independently screened and assessed by authors S.M.V. and H.T.J. Data extraction: for each study, the following data were extracted: first author, the studied gene(s) (variant[s] or polymorphism[s], as appropriate), included population, intervention (if applicable), performed measurements, and summary of positive results.

Statistical Methods

p values were calculated, if possible, by comparing means, standard deviations, and sample sizes of carriers of genetic variant(s) versus noncarriers, using MedCalc statistical software [18].

Results

After selection and review, we included 6 articles in the current analysis, comprising 2,724 humans and 136 mice (Fig. 2; Table 1). The included studies reported performance outcomes in 4 genes: RBM20, MYBPC3, TTN, and TPM1 (Fig. 3).

Methawasin et al. [19] engineered a mouse model that expresses giant titin proteins, allowing the group to study how titin compliance affects cardiac function in intact cardiomyocytes. In thirteen 4-month-old male mice, maximal treadmill running speed was measured using a rodent treadmill system following a progressively increasing speed protocol. Maximal speed was determined when the mouse left the treadmill and remained on a shock pad. Methawasin et al. [19] found that mice, with a heterozygous (HET) cardiac-specific in-frame deletion in exons 6 and 7 of the Rbm20 gene through homologous recombination, had a ≈18% higher maximum running speed compared with wild type (WT) mice (≈38 m/min HET, n = 6, vs. ≈32 m/min WT, n = 7, p = 0.004).

Najafi et al. [20] reported running distances in a targeted knock-in mouse model, carrying a heterozygous Mybpc3 point mutation (G>A transition on the last nucleotide of exon 6). Five-week-old mice were exposed to an 8-week voluntary wheel-running protocol, and running distances were recorded for each mouse. Voluntary running distances were ≈50% longer in HET female mice compared with WT female mice (966 ± 169 km HET vs. 561 ± 144 km WT, p = 0.0035, n = 10). Both sedentary and exercised female HET mice demonstrated a trend to-

Fig. 3. Overview of beneficial effects of cardiomyopathy-associated genetic variants on physical performance.
VO₂ max values were not reported [21].

The group of Al-Khelaifi et al. [21] aimed to investigate the association of multiple single-nucleotide polymorphisms (SNPs) identified using a genome-wide association study in European elite athletes, combined with a replication (of significant SNPs) study in Russian and Japanese elite athletes and Japanese controls (n = 796, n = 410, n = 60, and n = 406, respectively). Athletes were classified into different groups of sports following the Mitchell’s classification of sports [25]. Meta-analysis of all 4 cohorts confirmed overrepresentation of rs1052373 GG (MYBPC3) in high endurance (>70% of VO₂ max, according to the Mitchell’s classification) elite athletes (p = 1.43 × 10⁻⁸, indicating genome-wide association study and Bonferroni levels of significance). Furthermore, homozygous carriers of rs1052373 GG, in Russian elite athletes and Japanese controls (n = 80, n = 10; exercised: 23.1 ± 1.6 HET vs. 19.2 ± 2.3 WT, p = 0.0144, n = 10) [20].

Thomaes et al. [24] investigated a “genetic predisposition score,” based on earlier identified polymorphisms for different muscular phenotypes that could explain individual differences in muscular fitness and the response to training in patients with coronary artery disease. Patients were genotyped for the panel of earlier identified polymorphisms and followed a standard ambulatory supervised cardiac rehabilitation program for 3 months. TTN rs10497520 (n = 260 at baseline, 37 female and 223 male) and TPM1 rs707602 (n = 204 after training) were found to significantly contribute to genetic predisposition scores and were associated with greater quadriceps force generation at baseline and after 3 months of training, respectively (absolute values for isolated polymorphisms not reported) [24].

**Discussion**

With this first review on beneficial effects on physical performance of genetic variants found in genes involved in CMPs, we identified possible positive effects on different aspects related to performance. In mice models, our study identified associations between Rbm20 with increased running speed, and between Mybpc3 targeted knock-in with increased voluntary running distance and increased maximal cardiomyocyte force generation. In humans, we found MYBPC3 to be associated with an increased VO₂ max in elite-level endurance athletes and high endurance elite athlete status; TTN with faster marathon personal best times in highly trained marathon runners; TTN with a greater increase of VO₂ max after a training program in healthy participants; TTN in coronary artery patients with a greater quadriceps force generation at baseline; and TPM1 with a greater quadriceps force generation after 3 months of training.

Our findings of improvements in physical performance in individuals with genetic variants in CMP-associated genes constitute a different angle of investigations into the complex interplay between physical exercise and sports and genetic substrates. Hypothetically, an evolutionary benefit in the healthy/preclinical phase and only later deleterious effects on physical performance might be one of the explanations for the relatively high prevalence of CMPs in the general population. Similar to the protective effect of minor phenotypes of sickle cell and thalassemia anemia against malaria, such a beneficial effect might come at a price [26]. Subtle positive effects on physical performance could at first provide young athletes, who train in a highly competitive environment, with a
Beneficial Effects of CMP Mutations

slight advantage when competing against athletes without these genetic variant(s), but might later lead to a higher prevalence of CMPs and sudden cardiac death. Similarly, one could hypothesize on comparable effects in different ethnic groups. Athletes from African or Afro-Caribbean regions have a different cardiac physiology and pathophysiology compared with athletes from Asian and European regions. Currently, all but one of the men’s world records running (100-m sprint up until the full marathon) are held by athletes representing African or Afro-Caribbean countries, whereas the majority of competitive athletes who die from hypertrophic CMPs are found to be from identical regions [27, 28]. Additionally, in a retrospective study (1999–2014) of 508,108 athletes, Ethiopian and Kenyan athletes (both male and female) achieved the fastest half- and full-marathon times, despite accounting for <0.1% of participants [29]. Theoretically, a RBM20 haploinsufficiency could predispose an athlete to a cardiac phenotype with an increased TTN compliance and be able to run faster (beneficial effect) [19], while making some athletes susceptible to developing (arrhythmogenic) dilated cardiomyopathy later in life (deleterious effect) [30, 31]. However, the extent and the juncture in life of the beneficial effect, as well as the risk of developing pathology, remains highly unclear.

There is currently no unequivocal causal relationship between the identified genetic variants in our study and the clinical expression of CMPs. However, several mechanisms of pathogenic variants in genes associated with CMPs have been documented or suggested, including the genes described in this document: RMB20 (RNA Binding Motif protein 20), MYBPC3 (the gene encoding cardiac myosin-binding protein C), TTN (titin), and TPM1 (tropomyosin 1).

First, variants in RBM20, a heart- and skeletal muscle-enriched splicing factor controlling tissue-specific isoform expression, have been shown to result in an arrhythmogenic dilated CMP [32, 33]. Similar to the mouse model as investigated by Methawasin et al. [19], a genetic variant resulting in haploinsufficiency (i.e., partial inactivation) in RBM20 could present itself as a likely mechanism for dilated CMP in humans [30, 31]. Second, approximately 40% of identified hypertrophic CMP variants are found in the MYBPC3 gene, which encodes a thick filament-associated protein. The Mybpc3 mouse model as investigated by Najafi et al. [20] is highly similar to the proven pathogenic human genetic variant associated with a severe hypertrophic CMP phenotype with poor prognosis [34, 35]. Third, truncating variants in titin (TTN), the largest protein described to date and the “elastic” filament of the sarcomere, play important roles in the pathogenesis of CMPs and heart failure [36–38]. In humans, a TTN missense mutation, as investigated by Stebbings et al. [22], Timmons et al. [23], and Thomaes et al. [24], has been identified. Finally, TPM1 is a protein involved in calcium-activated muscle contraction. When calcium is absent, tropomyosin blocks the binding site on actin for myosin [39]. Pathogenic variants in TPM1 have been associated with hypertrophic and dilated CMP [40].

According to the Genome Aggregation Database, the SNPs rs10497520 (TTN), rs1052373 (MYBPC3), and rs707602 (TPM1) are currently considered benign variants. However, the relevance of polymorphisms/frequenty found genetic variants – such as the discussed rs10497520 missense mutation – in developing CMPs is still unclear, and although there is not enough data to conclude on a possible role of this variant in absence of a pathogenic effect, firm conclusions about a possible positive effect cannot be drawn either.

Strengths and Limitations

There are several strengths to our study. First, our review highlights a period in the athlete’s life radically different compared with more conventional studies, which are focused on the negative effects of genetic variants (Fig. 1). Second, we used a systematic and broad approach following the PRISMA-ScR statement to identify relevant articles. No filters were applied to increase the chances of finding articles of relevance. Third, the included studies provided detailed information on the investigated genetic variants, allowing for detailed replication in future research. Finally, our analysis included a large number of included individuals, both animals and humans.

A number of aspects of our review warrant consideration. First, the beneficial effects identified in our study were found in a limited number of studies of which most were not specifically designed to investigate positive (athletic) performance outcomes in individuals/subjects with CMP-related genetic variants, with the exemption of the studies of Al-Khelaifi et al. [21] and Stebbings et al. [22]. The limited number of found studies prevents drawing firm conclusions regarding possible beneficial effects of genetic variants in genes associated with CMPs. More importantly, this may be indicative of citation bias or selective reporting, as conventionally, positive performance outcomes in the preclinical phase of genetic CMPs are seldom to never rigorously investigated. In line with our study question, the search strategy and inclusion criteria were broad and exclusion criteria specific (excluding studies with negative outcome measures), in order to op-
timize identification of all possible studies reporting beneficial effects of cardiomyopathy-associated genetic variants and polymorphisms on physical performance. With this strategy, we aimed to investigate whether there is any evidence (at all) to support our hypothesis. Consequently, our study was limited to only positive effects (Fig. 1).

Second, the effects of exercise on developing pathology in individuals or subjects with cardiomyopathy-associated genetic variants (that display a beneficial effect on physical performance) are unclear. One could hypothesize that exercise is eventually harmful, which might explain the limited number of studies we identified. In line with this, physical exercise has been shown to contribute to the development of arrhythmogenic CMP phenotypes in individuals with variants in PKP2 or DSG2 [13, 41]. However, for subclinical or preclinical hypertrophic or dilated CMPs, such negative associations remain highly contested, and the current ESC guidelines recommend continued participation in exercise and sports in most main groups of preclinical CMPs [1]. Within our analysis, most (5 out of 6) reports were not designed to test such hypotheses. The studies of Al-Khelaifi et al. [21], Thomaes et al. [24], Timmons et al. [23], and Stebbings et al. [22] did not include the onset of any symptoms (including death). The mice of Najafi et al. [20] were euthanized, and Methawasin et al. [19] reported normal life spans in their mice. Therefore, based on the findings in these individuals/subjects, we cannot deduce the effects of exercise on the development of pathological phenotypes.

Third, the greater maximum cardiomyocyte force generation in mice found by Najafi et al. [20] was not found in male mice, suggesting a sexual dimorphic effect. The beneficial or negative effects may present themselves differently in female or male individuals/subjects. Unfortunately, most of the currently included small number of studies do not provide results with stratification based on sex and therefore do not allow for further analyses on sex differences in physical performance in the presence of CMP-associated genetic variant(s).

Finally, and possibly most importantly, the identified studies were highly heterogeneous. Two studies were performed in mice, while 4 studies were performed in heterogeneous groups of humans. The association of RBM20 and TPM1 with positive performance outcomes was also described in separate articles. Additionally, varying outcome measures were used, and the outcome measure that was used in multiple articles (VO2 max) was measured using different protocols. Finally, no association was replicated in a second study, limiting generalizability.

Conclusion

Genetic variants in RBM20, MYBPC3, TTN, and TPM1 are possibly associated with beneficial effects on physical performance, as shown in a limited number of heterogeneous studies. These findings should be interpreted with caution and warrant further investigation to elucidate the complex interplay between performance and (preclinical) CMPs. Future (basic) prospective research projects focused on pleiotropic effects of CMP-related polymorphisms, such as possible beneficial effects prior to pathogenic and negative effects, are necessary to further substantiate our hypothesis.

Conflict of Interest Statement

All authors report that they have no conflicts of interest to declare.

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Author Contributions

Sjoerd M. Verwijs is the main author. Yigal M. Pinto contributed to conception and design. Diederik W.D. Kuster contributed to acquisition and interpretation. Jolanda van der Velden contributed to acquisition and interpretation. Jacqueline Limpens contributed to design. Juliette C. van Hattum contributed to acquisition and interpretation. Saskia N. van der Crabben contributed to acquisition and interpretation. Ronald H. Lekanne Deprez contributed to acquisition and interpretation. Arthur A.M. Wilde contributed to conception and design. Harald T. Jørstad contributed to conception, design, acquisition, and interpretation.

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Beneficial Effects of CMP Mutations

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