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

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Keywords

Systematic review · Cardiogenetic · Cardiomyopathy · Physical performance

Abstract

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. **Methods:** Systematic PubMed search was done to investigate whether genetic variants in genes associated with CMPs could be related to beneficial performance phenotypes. **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 (~ 38 m/min in heterozygous [HET] mice, $n = 6$, vs. ~ 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, $n = 260$). **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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Fig. 1. Illustration of study purpose: to investigate whether genetic variants associated with cardiomyopathies relate to any specific *beneficial* performance phenotypes.

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 CMP. 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 ($\text{VO}_2 \text{ max}$) [7], maxi-

mal 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. 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. [19]	<i>RBM20</i> , 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]	<i>MYBPC3</i> , 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. [21]	<i>MYBPC3</i> , 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
Stebbing et al. [22]	<i>TTN</i> , 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. [23]	<i>TTN</i> , rs10497520	$n = 473$	20-week training program	ΔVO_2 max	Greater increase in VO_2 max in polymorphism carriers
Thomaes et al. [24]	<i>TTN</i> , rs10497520 <i>TPM1</i> , rs707602	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 <i>TTN</i> polymorphism carriers + greater force increases in <i>TPM1</i> polymorphism carriers

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 hu-

man and animal studies were based on typical, current genetic panels for CMPs and included ACTC1, ACTN2, ALPK3, ANKRD1, 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, TCAP, TMEM43, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TTN, TTR, and VCL (for expansions of gene ab-

Fig. 3. Overview of beneficial effects of cardiomyopathy-associated genetic variants on physical performance.

breviations, 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-

wards higher maximal cardiomyocyte force generation (sedentary: 20.0 ± 2.2 kN/m² HET vs. 17.5 ± 1.4 kN/m² WT, $p = 0.0644$, $n = 10$; exercised: 23.1 ± 1.6 HET vs. 19.2 ± 2.3 WT, $p = 0.0144$, $n = 10$) [20].

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 ($p = 1.43 \times 10^{-8}$, indicating genome-wide association study and Bonferroni levels of significance). Furthermore, homozygous carriers of rs1052373 GG, in Russian elite athletes with available VO₂ max data ($n = 32$; 17 females), had a significantly greater VO₂ max than carriers of AG or AA ($p = 0.005$, adjusted for sex). The (difference in) VO₂ max values were not reported [21].

In 141 unrelated, Caucasian, highly trained (Olympic-, international-, and national-level) male marathon runners, personal record marathon times were recorded. Each participant was genotyped for the *TTN* rs10497520 C>T polymorphism, using real-time polymerase chain reaction. Independent samples *t* tests were conducted to identify any genotype differences in personal best times and demonstrated that marathon runners with the polymorphism were 2:02 min faster compared to individuals without the polymorphism ($2:26:28 \pm 0:06:23$ min HET polymorphism, $n = 32$, vs. $2:28:53 \pm 0:05:50$ min without polymorphism, $n = 108$, $p = 0.020$) [22].

Timmons et al. [23] aimed to investigate SNPs that could explain the heterogeneity in VO₂ max response in 473 apparently healthy Caucasian participants (243 female and 230 male) who completed a 20-week customized training program. Following 2 sequential, independent pilot studies (the second to validate the first) in 41 subjects that underwent a supervised customized endurance training program, a panel of 29 genes was tested. After adjusting the increase in VO₂ max for sex, age, baseline body weight, and baseline maximal oxygen consumption, a greater increase of VO₂ max after training was shown in carriers of the *TTN* rs10497520 C>T polymorphism (partial correlation coefficient 0.0204; stepwise regression model correlation coefficient 0.1146, $p = 0.0025$) [23].

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

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: *RBM20* (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 “elas-

tic” filament of the sarcomere, play important roles in the pathogenesis of CMPs and heart failure [36–38]. In humans, a *TTN* missense variant, 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/frequently 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 (VO_2 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 design and interpretation. Saskia N. van der Crabben contributed to acquisition and interpretation. Ronald H. Lekan 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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