Canadian Journal of Cardiology 41 (2025) 364–374

Review

Genetics, Fitness, and Left Ventricular Remodelling: The Current State of Play

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ABSTRACT

Cardiorespiratory fitness (CRF) exists on a spectrum and is driven by a constellation of factors, including genetic and environmental differences. This results in wide interindividual variation in baseline CRF and the ability to improve CRF with regular endurance exercise training. As opposed to monogenic conditions, CRF is described as a complex genetic trait as it is believed to be influenced by multiple common genetic variants in addition to exogenous factors. Importantly, CRF is an independent predictor of morbidity and mortality, and so understanding the impact of genetic variation on CRF may provide insights into both human athletic performance and personalized risk assessment and prevention. Despite rapidly advancing technology, progress in this field has been restricted by small sample sizes and the limited number of genetic studies using the "gold standard" objective measure of peak oxygen consumption (VO_2peak) for CRF assessment. In recent years, there has been increasing interest in the heritability of numerous parameters of cardiac structure and function and how this may relate to both normal cardiac physiology and disease pathology. Regular endurance training can result in exercise-induced cardiac remodelling, which manifests as balanced dilation of cardiac chambers and is associated with superior CRF. This results in a complex relationship between CRF, cardiac size, and exercise, and whether shared genetic pathways may influence this remains unknown. In this

RÉSUMÉ

La capacité cardiorespiratoire présente une grande variabilité qui découle d'un ensemble de facteurs, tant génétiques qu'environnementaux. Il existe donc, d'une personne à l'autre, de grandes différences quant à la capacité cardiorespiratoire de base et aux gains obtenus par un entraînement physique en endurance sur une base régulière. Contrairement aux maladies monogéniques, la capacité cardiorespiratoire est décrite comme un trait génétique complexe, puisqu'elle semble influencée par de multiples variants génétiques fréquents en plus de facteurs exogènes. Surtout, la capacité cardiorespiratoire est un facteur prédictif indépendant de la morbidité et de la mortalité, de sorte qu'une compréhension de l'effet des variations génétiques peut renseigner tant sur les performances athlétiques que sur les mesures personnalisées permettant d'évaluer et de prévenir les risques. Malgré la rapidité des progrès technologiques, les avancées dans ce domaine sont limitées par la petite taille des échantillons et le petit nombre d'études génétiques utilisant la mesure objective « étalon » de la consommation maximale d'oxygène (VO_2 max) pour évaluer la capacité cardiorespiratoire. Depuis quelques années, l'intérêt est de plus en plus porté sur l'héritabilité de nombreux paramètres de la structure et de la fonction cardiaques et sur la façon dont ils peuvent être liés à la physiologie cardiaque normale et à diverses maladies. L'entraînement physique en endurance sur une base

Received for publication October 17, 2024. Accepted December 11, 2024.

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Cardiorespiratory fitness (CRF) is a continuum influenced by genetic variation, environmental and behavioural differences (such as exercise training), and the integration of multiple body systems. Peak oxygen consumption (VO_2peak) quantifies CRF and is most accurately determined by cardiopulmonary exercise testing (CPET).[1] Although CRF may be seen

https://doi.org/10.1016/j.cjca.2024.12.017

review we highlight recent and relevant studies into the genomic predictors of CRF with a unique emphasis on how this may relate to cardiac remodelling and human adaptation to endurance exercise.

régulière peut mener à un remodelage cardiaque qui se manifeste par une dilatation équilibrée des cavités cardiaques et qui est associé à une amélioration de la capacité cardiorespiratoire. Ce phénomène traduit une relation complexe entre la capacité cardiorespiratoire, le volume du cœur et l'exercice, mais on connaît mal le rôle que pourraient jouer les voies génétiques communes. Dans cette analyse, nous traitons d'études récentes et pertinentes portant sur les facteurs prédictifs génomiques de la capacité cardiorespiratoire en mettant l'accent sur le lien avec le remodelage cardiaque et l'adaptation humaine à l'exercice en endurance.

as a marker of human athletic performance, it is often overlooked as an invaluable predictor of premature loss of functional independence, morbidity, and mortality.[2-5] As a result, the genetic contribution to baseline CRF and training response has been of increasing interest over the past 4 decades; however, few genetic studies incorporating objective assessments with VO_2peak have been performed.

There is a curvilinear dose-response relationship between CRF and mortality, meaning that even the smallest improvement in exercise capacity for an unfit individual can have a prognostic impact.[1,6,7] However, exercise training studies have consistently shown that there is significant variability in VO_2peak improvement with exercise training—promoting the concept of possible "super-responders" and "nonresponders" to exercise (Fig. 1).[8-11] Much of the human individual variation can be explained by complex traits, like CRF, which demonstrate large interindividual differences. Although the heritability of CRF is estimated at ~ 50%,[12] the genetic determinants of CRF are incompletely understood. Understanding the role of DNA sequence variation in defining individual CRF phenotypes will not only provide insight into the physiologic mechanisms of adaptation to exercise and human performance, but, more importantly, will allow for personalized risk prediction and exercise therapy.

CRF reflects the integration of multiple body systems to allow for adequate oxygen transport to skeletal muscle where extraction and use of oxygen occurs. Each body system and step in the oxygen pathway has the potential to be influenced by genetic and/or epigenetic differences (Fig. 2). As both central and peripheral factors contribute to CRF, there is interindividual variability in the mechanisms that may drive exercise limitation.[13,14] Oxygen delivery is determined by cardiac output (CO), in conjunction with noncardiac parameters such as alveolar ventilation-perfusion matching and capillary density, and it is often considered the main limiting factor to VO_2peak.[15-18] As such, the ability to augment CO with exercise is a critical determinant of CRF. Regular exercise training can lead to exercise-induced cardiac remodelling with balanced dilation of all 4 cardiac chambers, resulting in increased stroke volume and CO reserve.[19,20] Consequently, there is a strong positive association between exercise, cardiac size, and CRF, which has been outlined by the authors previously.[21-24] Left ventricular (LV) volume is the strongest independent cardiac imaging predictor of CRF[5] and there is accumulating evidence of genetic heritability of a range of LV structural traits, including LV volumetric measures, and how these relate to clinical outcomes, such as cardiomyopathy and heart failure. As such, shared genetics between cardiac structure and CRF may be a key mechanism by which the genetic basis for CRF is mediated, but this is yet to be investigated. In this review we explore the current knowledge of genomic predictors of CRF with a novel focus on cardiac structure, remodelling, and adaptation to exercise. Through summarizing relevant studies and highlighting key research involving hypothesis-free testing, we draw attention to the heritability of both heart size and fitness.

DNA and the Basics of Human Variation

Genetics and genomics

Pioneered by Mendel in the 19th century, the study of genes and gene expression has evolved considerably over time in the setting of rapid technological advances. The genetic code, or "blueprint," of an individual is underpinned by the DNA sequence of 23 pairs of chromosomes (22 autosomal pairs and 2 sex chromosomes). This genetic material is found in every nucleated cell, with additional genes encoded in mitochondrial DNA. A single chromosome is composed of 2 complementary strands of DNA made from 4 DNA bases (adenine [A], thymine [T], cytosine [C], guanine [G]). A gene is determined by the order and number of DNA bases along an interval of DNA that is then transcribed into RNA. Although "genetics" often focusses on the function and inheritance of genes, "genomics" encompasses the entirety of an individual's genes and their combined interaction with the environment to influence complex traits and development.[25]

The human genome comprises > 3 billion base pairs, with only 2% estimated to encode the ~ 20,000 known protein-coding genes.[26,27] A single gene is composed of coding regions (exons), noncoding regions (introns), and regulatory sequences. Importantly, each gene can encode more than 1 protein through mechanisms such as alternative splicing, and noncoding sequences act as major regulators of gene expression. Epigenetic modifications also impact gene expression without changing the DNA sequence. Each chromosome is packaged very tightly as nucleosomes around histone proteins with modifications to the conformation of this unit resulting in altered transcription.[28] Modifications, such as DNA methylation, can be reversible, and are affected by genetic and environmental factors, including physical activity and exercise training.[29,30]

Fitness as a complex trait

Monogenic diseases are typically characterized by Mendelian inheritance patterns, and result from single rare genetic

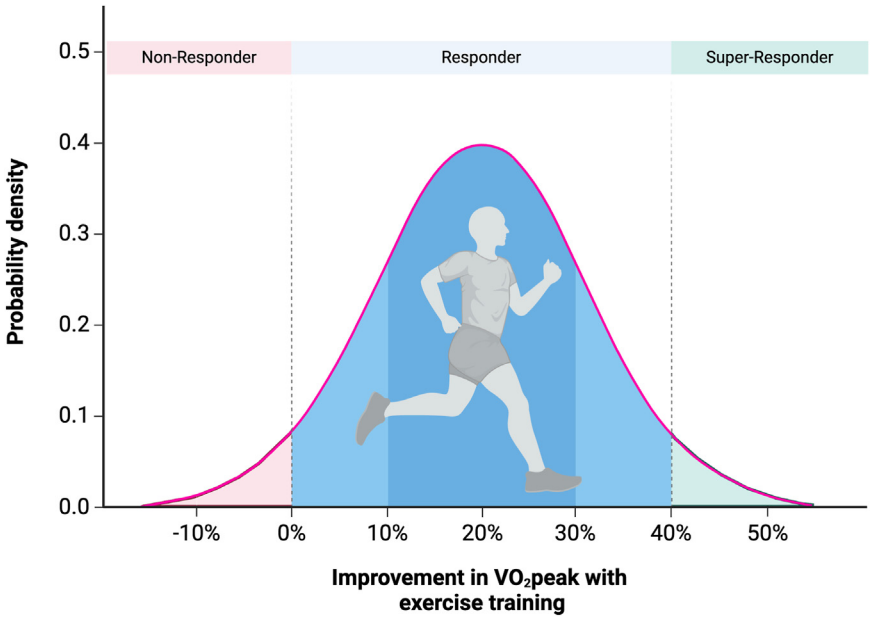

Figure 1. Variation in VO_2peak response to exercise training. Studies of exercise training demonstrate significant interindividual and familial variability in VO_2peak improvement. The majority of individuals appear to have some level of improvement in VO_2peak with endurance training whereas a smaller proportion may have no improvement (nonresponders) or a much greater improvement (super-responder). Created with BioRender.com.

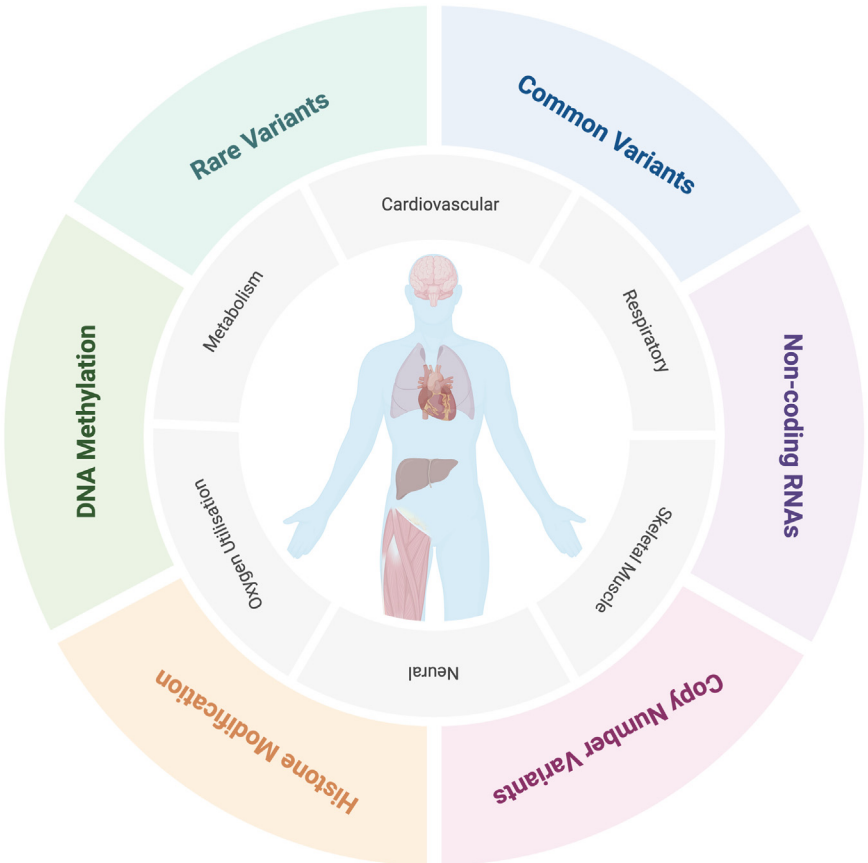

Figure 2. Genetic regulation of cardiorespiratory fitness (CRF). A summary of genetic and epigenetic mechanisms that may influence systems in the human body required for CRF and athletic performance. Created with BioRender.com.

variants that are sufficient to cause disease. In contrast, complex (or quantitative) genetic traits result from different combinations of common genetic variants that affect disease susceptibility, host factors such as age and sex, and acquired factors.[31]

Early attempts to understand the genetics of CRF used knowledge of exercise biology and pathways to select candidate genes for rare and common variant analyses. Genes with evidence of association with fitness phenotypes are synthesized in Bray et al.'s work on human gene mapping and fitness phenotypes, but are not within the scope of this review.[32] Over 200 candidate genes and markers have been identified. However, an association between these gene "discoveries" and CRF has not been replicated, although studies have been consistently underpowered.[32] Even the most frequently reported genes associated with fitness phenotypes, such as the ACE gene and its polymorphisms, have conflicting evidence and draw attention to our incomplete understanding of the complexity of fitness traits.[32]

Single-nucleotide polymorphisms (SNPs) reflect germline substitution at a single DNA base. Each individual's genome is thought to contain approximately 5 million SNPs compared with the human reference genome.[33] Any one variant may only confer a small effect, but the cumulative effect of multiple genetic variants may result in a large effect on the trait. Recent technological advancement has led to the increased accessibility and use of genome-wide association studies (GWASs), which now allow for hundreds of thousands of defined variants to be screened for and analyzed in an unbiased manner to find genetic associations with a trait.[34] GWASs use microarray technology to hybridize an individual's DNA against an array of short DNA sequences and are commonly used to compare cases and controls using hundreds of thousands or millions of SNPs. As a result of the volume of SNPs assessed, quality control is critical, with strict significance criteria (threshold for genome-wide significance of $P \leq 5 \times 10^{-8}$) underpinning this.[35]

The discriminative ability of any single significant GWAS locus is limited, however, due to a large overlap between cases and controls. To address this issue, GWAS data have more recently been refined by the derivation of polygenic risk scores, which take multiple GWAS loci into account. Currently, close to 4000 polygenic scores have been established for 619 traits from over 500 publications.[36] Polygenic risk scores (PRSs) have the potential to improve cardiovascular disease or trait risk prediction, but their clinical utility for individual patient management has yet to be proven.[37,38] Despite the high heritability of VO_2peak, recent GWAS results have yielded inconsistent results. The key association studies analyzing CRF and cardiac remodelling are discussed in detail in this review; however, there has yet to be successful construction of a PRS that predicts CRF and there have been a limited number of studies that detected SNPs reaching genome-wide significance (Table 1). With the clinical importance of CRF increasingly recognized, this topic requires greater attention in future research.

Estimating heritability

Heritability measures the proportion of phenotypic variation explained by genetic variation.[39] Traditionally, family, twin, and adoption studies have been used to quantify the genetic contribution to a trait.[40] In the current era, studies involving large cohorts of unrelated genotyped individuals predominate. Different statistical methods and software have been developed to provide accurate estimation in this context and these are reviewed in detail elsewhere.[39,41] For GWASs, SNP heritability refers to the proportion of phenotypic variation attributed to the measured SNPs. As an example, the heritability of left ventricular end-diastolic volume (LVEDV) from recent GWASs has been estimated at ~ 40%.[42,43] This means that the genotyped SNPs explained almost half of the variance in LVEDV in the studies.

Genetic Variation and CRF: Genes, Environment, or Both?

The untrained individual: Genes associated with baseline VO_2peak

Early animal and family studies undertaken close to 25 years ago provide the foundation for our knowledge of how our underlying genetic signature may impact baseline fitness. Selective breeding for exercise endurance in rats initially estimated that genetic factors may account for 39% of the variation in endurance performance.[44] After 15 generations of breeding of low- and high-capacity rats, the high-capacity rats had a 50% greater VO_2peak than the low-capacity rats[45]—this was attributed to a ~ 48% increase in stroke volume and enhanced oxygen delivery (Fig. 3). Similarly, the heritability estimate of CRF in the sedentary human has been established from family and twin studies. This is best characterized by the comprehensive **He**alth, **Ri**sk Factors, Exercise **T**raining **a**nd **Ge**netics (HERITAGE) Family Study,[12] in which 86 families (429 individuals) underwent cycle ergometer VO_2peak tests. After adjusting for age, sex, and body mass, the variance in VO_2peak was significantly greater between families than within families. The maximal heritability was at least 50%; however, a small but significant spousal correlation demonstrated that environment also influenced this result (ie, family members shared acquired behavioural traits associated with exercise training). These early results are supported by a recent meta-analysis of 15 studies providing heritability estimates of VO_2peak indicating that genetic variation accounted for 44% to 68% of VO_2peak variability.[46]

There have been few large genomic studies focussing on baseline VO_2peak, despite the strong evidence outlined in animal and family studies. Small sample sizes have impaired the ability to detect statistically significant genetic variants given the stringent P value required for GWASs, and few have directly assessed VO_2peak with CPET. Using data from the Nord-Trøndelag Health (HUNT) study, Bye et al. performed the most comprehensive study involving close to 3470 individuals with CPET, and > 120,000 SNPs.[47] They identified 41 SNPs associated with VO_2peak at a moderate significance level ($P < 5 \times 10^{-4}$), with only 6 SNPs replicated in a validation cohort. A genetic score was created and individuals were graded from 1 to 7, with higher values representing more favourable SNPs for higher VO_2peak. Those with the lowest genetic score had VO_2peak measures estimated at 22.3 mL/kg/min as compared with 32.7 mL/kg/min for participants with a score of 7. Furthermore, higher scores

Table 1. Overview of studies discussed in this review identifying GWAS-significant SNP associations ($P < 5 \times 10^{-8}$) relating to CMR-derived left ventricular volumes and CRF

Lead author and year	Population	Trait	Associated genes
Aung et al., 2019	UKBB	LVEDV	TTN, BAG3, SH2B3
Aung et al., 2019	UKBB	LVESV	TTN, MTSS1, BAG3
Pirruccello et al., 2020	UKBB	LVEDV	PLEKHM2, AKR1A1, ZNF638, SP3, TTN, TMEM43, MECOM, HLA-B, HLA-DQA2, VEGFA, PLN, NOS3, MTSS1, BAG3, LLPH, SH2B3, PTPN11, ALPK3, PKD1, MYO1C, ATP5SL, RSPH6A
Pirruccello et al., 2020	UKBB	LVESV	RPL22, PLEKHM2, AKR1A1, TTN, TMEM43, EPHB1, FNDC3B, HLA-DQB1, CDKN1A, PLN, FLNC, MTSS1, AGO2, BAG3, RRAS2, CSRP3, SSPN, SH2B3, PTPN11, PXN, ALPK3, LMF1, PKD1, MYO1C, MAPT, HLF, PRKCA, NEDD4L, ILF3, ATP5SL, RSPH6A, DERL3
Hanscombe et al., 2021	UKBB	CRF	LOC643355, CCDC141, SCN10A ERBB2IP, PAX2, NUP93, MGC32805, GJA1, LOC644172, KIAA1755 Male: SCN10A, PAX2, AK7, MGC32805
Klevjer et al., 2022	HUNT3 Fitness Study	VO_2peak	CDYL, LOC105371536 Male: DNAH14, LOC105375599 Female: TOE1, GCFC2, ACOXL, LRRC31, PCDH7, CFAP299, GPAT3, CDYL, CLDN3, EXOSC4, GPAA1, MAF1, APBA1, TRPM3, KLF9-DT, MTND2P8, LOC105376097, LOC101927450, LINC01507, LOC105376103, LOC107987084, ENSG00000226798, LOC107987085, LOC107987084, RASEF, UBE2V1P10, COL4A2, MYH10, ONECUT3, IPCEF1

CMR, cardiac magnetic resonance; CRF, cardiorespiratory fitness; GWAS, genome-wide association study; HUNT, Nord-Trøndelag Health Study; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SNP, single-nucleotide polymorphism; UKBB, UK Biobank.

were linked with lower prevalence of cardiovascular risk factors. *In silico* analyses and genotype-phenotype databases were used to explore the possible function of the identified SNPs and indicated that 2 SNPs may have a physiologic effect on features of cardiac structure or remodelling, including cardiac growth factors and cardiac mass (rs3803357 located in the *BAHD1* gene, and rs3757354 located near MYLIP [sex-specific]).

Two further studies identified genetic variants associated with baseline CRF; however, both used indirect measures of VO_2peak derived from a submaximal bicycle test completed in UK Biobank.[48,49] Klevjer et al. completed an association study with a larger cohort of the HUNT study (4525 participants), 14 million SNPs, and the UK Biobank as the validation cohort.[48] Of the SNPs identified in the HUNT study, 2 were replicated in the UK Biobank, and both were in the female population only. Interestingly, one of these SNPs (rs551942830) was located in a region encoding a regulatory subunit of PI3Ky, which has been implicated in cardiac remodelling and response to biomechanical stress in animal models.[50,51] Hanscombe et al.[49] found 12 significant SNPs for the derived VO_2peak measure ($P < 5 \times 10^{-8}$), with significant correlations shown between genetic variation of CRF and additional traits, such as physical activity and body mass index. The identification of SNPs with potential physiologic roles relating to cardiac growth and development provides a plausible connection between the genetic variation of CRF and cardiac remodelling. To support this emerging concept, larger studies with genetic data, cardiac imaging, as well as "gold standard" VO_2peak assessment are a necessity.

The athlete: Genes associated with athletic endurance performance

The elite endurance athlete may be a valuable prototype for examining gene-environment relationships, because, it may be argued, they have trained intensively, thereby exposing their genetic potential. In comparison, a sedentary individual may have the "genetics" of an Olympic athlete, but if they never start exercising their genetic potential will remain unknown. In the last decade, multiple GWASs for elite athletic performance have been undertaken with varied and inconsistent results.[52-55] These predominantly focussed on sport-specific phenotypes, with very few assessing associations with VO_2peak. Ahmetov et al.[52] performed a GWAS of VO_2peak using $>$ 1 million SNPs in 80 international-level endurance athletes and validated the results in a case-control manner. Three SNPs showed associations with VO_2peak and were associated with endurance athlete status. In combination, these 3 SNPs explained 24.6% and 48.8% of the variation in VO_2peak of male and female endurance athletes, respectively. Even more so than in nonathlete research, small sample sizes are commonly seen in athletic cohorts, particularly with regard to female athletes, thus limiting the ability to reach genome-wide significance. In addition, there are study cohorts currently investigating exercise genomics. However, to truly understand the physiology and adaptations seen in elite endurance athletes, comprehensive phenotyping is required.

Do "Nonresponders" to Exercise Exist?

The concept of possible "nonresponders" to exercise stems from the variable increase in VO_2peak seen in structured exercise training studies of nonathletes, ranging from 0% improvement up to almost 60% with the same dose of exercise (Fig. 1).[8] Part of this variation can be attributed to the need for adequate training stimulus for each individual, but emerging evidence continues to support the idea of a genetic contribution.[56] After adjusting for age and sex, the heritability of VO_2peak response to training is thought to be close to 50% in sedentary individuals.[10] Intriguingly, baseline VO_2peak has not been identified as a significant predictor of VO_2peak trainability. This is a critically important point in the derivation of genetic predictors because it implies that different

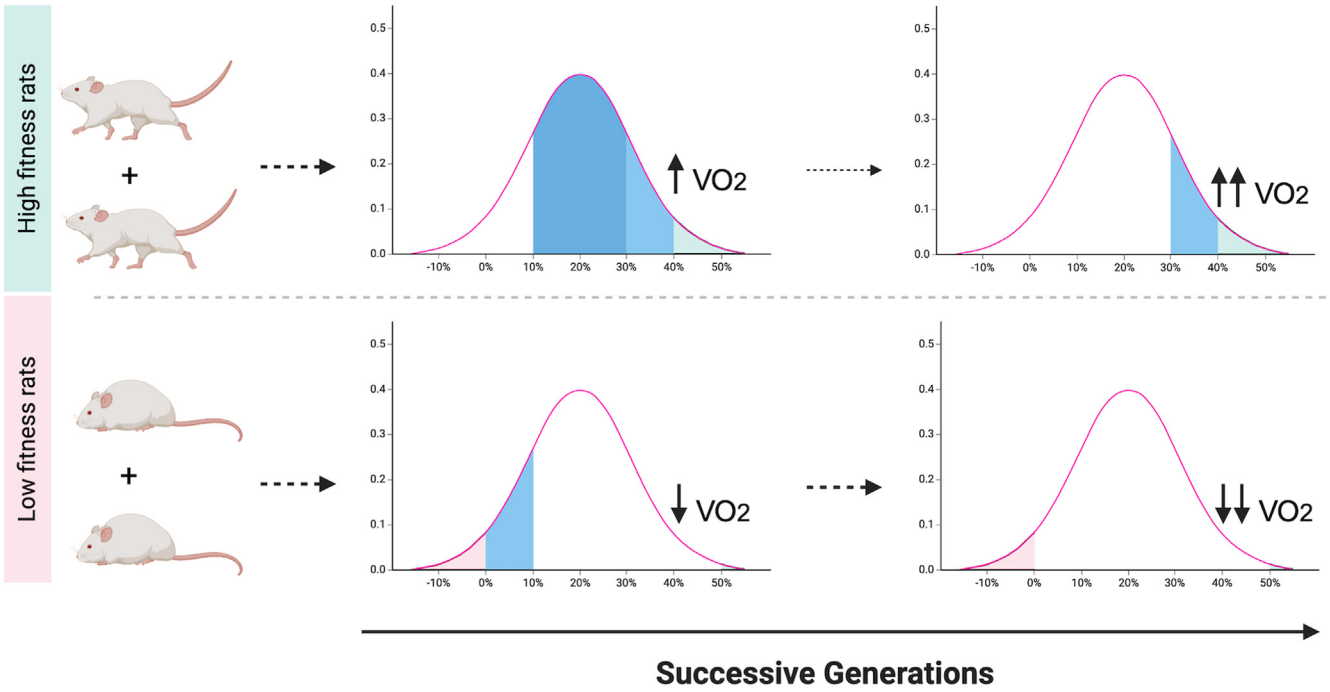

Figure 3. Change in fitness with selective breeding based on endurance performance. Animal studies suggest that over successive generations of selective breeding in rats with different levels of running capacity, the family lines diverge and result in higher levels of fitness in some, and lower levels in others. Created with BioRender.com.

genetic profiles may be associated with VO_2peak in the untrained and trained state.

Fitness trainability has arguably greater clinical value than baseline CRF in this current era of personalized medicine and the increasing application of exercise prescription in health care. It is important to identify whether an individual has low CRF, but predicting whether this is likely to improve with a certain dose of exercise may prove beneficial for risk stratification and primary prevention. From close to 100 genes identified as possibly influencing VO_2peak trainability, only 2 genetic variants have been replicated in 2 or more studies, and studies have failed to identify variants that reach the stringent cutoff for genome-wide significance.[57] Despite this, genetic prediction scores have been generated and indicate that different exercise "responder" levels do exist in the general population. In the first association study of exercising training response, 473 sedentary adults from the HERITAGE study completed a 20-week exercise program (customized for each participant based on baseline heart rate and VO_2peak assessments). Bouchard et al. identified 21 SNPs associated with improvements in VO_2peak with a significance of $P < 1.5 \times 10^{-4}$, but sufficient to generate a prediction score for high and low responders to exercise training.[58] The strongest association was with the SNP located in the *ACSL1* gene (rs655282) involved in lipid metabolism, as well as possible involvement in myocardial adaptation to chronic pathologic pressure overload.[59] Overall, participants with higher prediction scores had a 2.7-fold greater VO_2peak training response than those with lower prediction scores.

In recent years, SNPs related to high-intensity interval training have been investigated as differences in response to continuous training and interval training have been emphasized. Yoo et al. studied 79 healthy participants who completed a 9-week high-intensity interval training program, with approximately 25% of subjects showing zero improvement in VO_2peak.[9] Seven SNPs were selected, which accounted for 26% of the variance in VO_2peak response, and were able to differentiate participants into subgroups of nonresponders and medium or high responders with a prediction accuracy of 86%. As a result of improved and more accessible technology, we are accumulating increasing evidence that irrespective of an adequate training dose, there is interindividual variability in VO_2peak improvement and this may be genetically driven. Although the use of moderate significance cutoffs in genetic research has allowed the creation of prediction scores, identifying a statistically robust PRS to predict such measures will be key to incorporating this knowledge into clinical practice in the form of personalized exercise prescription. To our knowledge, there has yet to be a PRS shown to predict CRF. As such, examining the genetics of cardiac remodelling may provide insight into the genetic basis of CRF.

Genetics of Cardiac Structure and Exercise-induced Cardiac Remodelling

Exercise-induced cardiac remodelling is a form of physiologic remodelling resulting in predictable changes in cardiac structure, often referred to as the "athlete's heart." Characterized by a proportional increase in cardiac mass, wall thickness, and chamber size in the setting of normal or superior cardiac function with exercise, it represents a dynamic reversible state influenced by exercise training.[19,20] Much like CRF, there is a spectrum of cardiac remodelling. In the elite

endurance athlete, regular endurance training is associated with chamber dilation, with resultant implications for improved LV compliance and, consequently, increased stroke volume (SV) and CO to meet the demands of exercise.[21] In contrast, significant reductions in VO_2peak, LV mass, and chamber size consistent with cardiac "atrophy" have been observed with as little as 2-3 weeks of strict bedrest.[60,61] These findings suggest that sedentary behaviour could be related to cardiac atrophy, or a lack of cardiac remodelling normally seen with regular exercise. Recently, sedentary behaviour has been linked with small LV chamber size, increased LV stiffness, reduced cardiac reserve, and low CRF, suggesting significant clinical implications.[21,62-64]

Contemporary studies have indicated that cardiac structure and function are heritable.[42,65-67] Similarly, maximal heritability of SV and CO are estimated at 40% during submaximal exercise, with training response heritability estimates of approximately 30%.[68] However, there are limited human studies integrating cardiac physiology and cardiac imaging, but this knowledge will be crucial to understanding how CRF is genetically influenced.

Genetic variation and LV structure

Initial GWASs of cardiac structure and function incorporated linear measures of LV chamber size obtained with transthoracic echocardiography.[65,66,69] However, with improving technology and accuracy, volumetric analysis with cardiac magnetic resonance (CMR) imaging is currently considered the gold standard.[70,71] Recently, Aung et al. undertook the largest and most comprehensive study with CMR, providing unique insights into the genetics of LV structural traits.[42] Genome-wide studies for multiple LV traits were conducted with 16,923 UK Biobank participants who had no known history of heart failure or cardiomyopathy. The highest SNP heritability was observed for LV volumetric measures (LVEDV and left ventricular end-systolic volume [LVESV]), with both measures estimated to have a heritability estimate of 39%. Fourteen genomic loci were identified, including 3 loci for LVEDV, LVESV, and LV mass-to-volume ratio. The *TTN* (titin) gene was identified as a strong candidate gene given its association with dilated cardiomyopathy (DCM) and its proximity to loci associated with 4 LV structural traits (LVEDV, LVESV, LV ejection fraction [LVEF], and LV mass).

Rare genetic variants are strongly associated with cardiomyopathy phenotypes; however, common variants associated with LV structural traits are now being investigated with a particular interest in their role in penetrance for dilated and hypertrophic cardiomyopathy phenotypes.[43,72] Pirruccello et al. evaluated over 36,000 UK Biobank participants to assess the genetic association between CMR imaging phenotypes and the risk of DCM.[43] Similar to Aung et al., the estimated heritability for LVEDV and LVESV was $\sim$ 40%. After identifying 22 loci associated with LVEDV, 14 with LVEDV indexed to body surface area (LVESVi), and 32 loci for LVESV (with a genome-wide significance threshold of $P < 5 \times 10^{-8}$), PRSs were generated and tested. The variants occurred more commonly at loci near known cardiomyopathy-causing genes than expected, and resultant PRSs were significantly associated with incident DCM after adjusting for age and sex, with higher LVESVi PRS corresponding with higher DCM risk. Although these studies concentrated on the use of LV structural trait PRS in the context of cardiomyopathy, the value of these scores for predicting other clinical or physiologic phenotypes has only recently been revealed.

Genetic predisposition and athletic cardiac remodelling

The overlap between DCM and the "athlete's heart" poses significant challenges for the clinician and has prompted recent investigation into the genetic contribution to the extreme changes of athletic cardiac remodelling and how this may overlap with DCM. The concept of athletic remodelling emphasizes the need to assess LV structure in the context of cardiac function and CRF. In heart failure with reduced EF, LV dilation is considered a predictor of hospitalization and mortality.[73,74] In contrast, larger LV volume in the setting of normal (or low normal) LVEF is a hallmark of the elite endurance athlete and associated with greater CRF and subsequent survival advantage.[1,5,75,76] Recently, Claessen et al. combined comprehensive imaging and genomic analysis to investigate differences between elite endurance athletes with preserved or reduced LVEF in a cohort of 281 athletes without a history of cardiomyopathy or heart failure. For the first time, they were able to demonstrate that the phenotypic changes of exercise-induced cardiac remodelling in the athlete are not explained purely by the effect of exercise alone.[77] By applying the validated PRS for LVESVi associated with DCM from Pirruccello et al.,[43] they identified that athletes with LVESVi PRS in the top decile had an 11-fold increased likelihood of reduced EF (LVEF $<$ 50% or right ventricular EF $<$ 45%, or both) compared with those in the lowest decile.[77] Furthermore, athletes with reduced EF had a similar mean LVESVi PRS when compared with patients with familial DCM, suggesting a similar background genetic predisposition. This indicates a complex gene-exercise interaction and may be an important step in confirming a link between cardiac structure, function, exercise, and genetics. The question of how these genetic pathways involved in LV structural traits relate to VO_2peak has yet to be investigated; however, further studies extending this concept of PRS for cardiac structure may provide novel insights into the genetic determinants of both low and high CRF and their clinical implications.

Genes and epigenetics associated with physical activity

Although CRF is a stronger and more reliable predictor of mortality, physical activity (PA) remains an important metric of health outcomes.[78-80] Genetic factors contribute to the variation in PA; however, there is significant heterogeneity in the results, likely related to methods of data collection.[81] The heritability of PA is estimated at 20%, and up to 18% for sedentary behaviours.[82] Attempts have been made to investigate and identify the shared genetic contribution with PA and fitness, but these have been impacted by a lack of objectively measured exercise capacity, such as VO_2peak.[49] Importantly, there is growing evidence to suggest that PA induces epigenetic alterations that are associated with cardioprotective effects and cardiac remodelling. The complexities and impact of exercise and epigenetic modifications relating to cardiovascular

health and the noncardiac adaptations to exercise have been reviewed in detail elsewhere, and are not within the scope of this review.[28,83] However, high levels of PA and exercise training are associated with increased global DNA methylation in humans[29,30] and altered expression of noncoding microRNAs in animals, resulting in possible modifications of pathways associated with LV hypertrophy and remodelling.[30,84] The effect of CRF on epigenetic modifications and alterations is less well understood and further human mechanistic studies are required to understand the interplay between the epigenome, cardiac remodelling, and exercise.

Beyond the Cardiovascular System

In this review, we have summarized literature with a unique focus on the interplay between genetics, LV structure, and CRF. However, exercise genomics encompasses multiple body systems that may be influenced by genetic factors and contribute to CRF (Fig. 2). In addition to genetic variants hypothesized to be involved in cardiac remodelling, genetic factors have been identified relating to other phenotypes such as lipid metabolism and skeletal muscle growth and oxygen use.[57,85] Benegiamo et al. found that genetic variation that increases *COX7A2L* expression in skeletal muscle is associated with improved CRF, likely through its influence on mitochondrial function.[86] The favourable impact of genetic variation on iron homeostasis vital for oxygen-carrying capacity and mitochondrial function has also been investigated in a study of 170 elite athletes in France. Hermine et al. identified that 80% of the athletes who won international competitions possessed mutations in 1 *HFE* allele, with the frequency of these variants twice as high in elite athletes compared with controls.[87] Further functional studies are required to ascertain the mechanisms and pathways by which such variants influence CRF. In the future an integrated approach will be needed to understand the heterogeneity and complexity of CRF.

Limitations and future directions

Technological advances have led to increased accessibility to genetic testing and association studies, yet there are still many barriers to incorporating this knowledge into clinical practice. A core concern is the universal applicability of PRS to diverse ancestry groups, given the White populations from which these scores have traditionally been derived. As with other genomic research, larger sample sizes are required to identify novel variants and replicate results, and the incorporation of functional studies can assist in the interpretation of the biological role of genetic variants. Specifically, for exercise genomics, objective measures of VO_2peak must be incorporated and effort needs to be given to recruitment and inclusion of female participants and athletes.[88,89] Last, this review has focussed on the LV, but even less is known about the interplay between the right ventricle, genetics, and exercise. More research is needed to define how, and to what degree, genetics relating to the right ventricle contributes to CRF and arrhythmogenic cardiomyopathy.

Conclusions

Cardiorespiratory fitness is a complex trait that exists on a spectrum driven by genetic, behavioural, and environmental influences. The genetic contribution to fitness and response to exercise training is significant, and increasingly investigated with rapidly improving technology. Cardiac structure and function are also genetically influenced. In recent years, there has been much emphasis placed on the genetics of human athletic performance. However, recognition of the interplay between genetics and exercise is arguably most important and clinically relevant in the sedentary population, given that low CRF is an independent predictor of poor health outcomes and is increasingly prevalent in society. In view of the strong association between cardiac chamber size and CRF, understanding the genetic basis for cardiac remodelling could provide novel insights into the genomics of CRF, and may contribute to risk stratification and prevention strategies in vulnerable populations.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable as this is a review article.

Funding Sources

Dr Rowe is supported by a National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a Heart Foundation PhD Scholarship, and a University of Melbourne Elizabeth and Vernon Puzey Scholarship. Dr Bekhuis is supported through the Flanders Research Foundation (FWO-T004420N). Dr Janssens is supported through an Australian Government Research Training Program Scholarship. Dr Paratz is supported by the Wilma Beswick Senior Research Fellowship, the Department of Medicine at St Vincent's Hospital Melbourne, the University of Melbourne, a Heart Foundation Vanguard Grant, a Sylvia & Charles Viertel Foundation Clinical Investigator Grant, and a Mamoma Foundation Fellowship. Dr Fatkin is supported by NSW Health, the Heart Foundation, and the Medical Research Future Fund. Dr La Gerche is supported by an NHMRC Investigator Grant.

Disclosures

The authors have no conflicts of interest to disclose.

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