Review Article

Genetic approaches toward understanding the individual variation in cardiac structure, function and responses to exercise training

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Phenotype
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ABSTRACT Cardiovascular disease (CVD) accounts for approximately 30% of all deaths worldwide and its prevalence is constantly increasing despite advancements in medical treatments. Cardiac remodeling and dysfunction are independent risk factors for CVD. Recent studies have demonstrated that cardiac structure and function are genetically influenced, suggesting that understanding the genetic basis for cardiac structure and function could provide new insights into developing novel therapeutic targets for CVD. Regular exercise has long been considered a robust non-therapeutic method of treating or preventing CVD. However, recent studies also indicate that there is inter-individual variation in response to exercise. Nevertheless, the genetic basis for cardiac structure and function as well as their responses to exercise training have yet to be fully elucidated. Therefore, this review summarizes accumulated evidence supporting the genetic contribution to these traits, including findings from population-based studies and unbiased large genomic-scale studies in humans.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. According to the World Health Organization (WHO) fact sheets for CVD reported in 2017, approximately 17.3 million people died from CVDs in 2016, accounting for approximately 31% of all deaths globally. It has been proposed that, in conjunction with an increase in life expectancy, the medical cost of treating CVDs in the USA will have tripled by 2030 [2]. Accordingly, many medical trials are currently underway with the aim of preventing or treating CVDs, and several therapies, such as β-adrenergic receptor blockers, aldosterone antagonist, and angiotensin-converting enzyme inhibitors, appear to be effective in preventing morbidity and mortality in patients with CVD [3]. Nevertheless, cases of CVD are evidently increasing and this trend is no longer country-specific [4,5], suggesting the modest effects of current CVD therapies.

Many studies have shown that CVDs are heritable, meaning the genetic components contribute, at least in part, to CVDs. For example, parental CVDs can triple the likelihood of future offspring CVD events [6]. Therefore, efforts have been made in past decades to unveil the genetic basis of CVDs, such as hypertension [7], coronary artery disease [8], atherosclerosis [9], and heart failure [10].

Structural and functional changes in the heart are involved in CVDs. In the setting of disease, the heart, particularly the left ventricle (LV), manifests a structural plasticity called pathological remodeling, which refers to changes in the size, structure, and shape of the heart, ultimately contributing to decreased ejection fraction (EF) and stroke volume (SV) [11]. LV mass, hypertrophy, and wall thickness (WT) have been found to be independent CVD risk factors [12,13]. Accumulating data have provided evidence that the structure and function of the heart are heritable and multifactorial traits, hence, studies have been exerted to
identify the genetic determinants responsible for cardiac function and structure [14-21]. However, the majority of previous genetic studies (not limited for cardiac traits) were conducted for genotypic effects of a single or only few gene(s), thus were biased and unable to draw comprehensive genome system. Given the polygenic and multifactorial nature of the CV system, such as cardiac function and structure [22] and population-based biases [23], our understanding of the genetic basis for cardiac physiology remains largely unknown.

Twin and family studies have been used to explore the extent to which genetic factors contribute to the variation of a trait [24]. Assuming that monozygotic (MZ) twins share 100% of their genetic background and dizygotic (DZ) twins share an average of 50%, direct comparisons between MZ and DZ twins can reveal the magnitude of genetic variation in susceptibility to a phenotype [25]. If the phenotype is genetically influenced, a greater correlation is expected for MZ than DZ twins, and if it is 100% genetically determined (without environmental influence, albeit impossible), the correlation should be doubled in MZ compared to DZ twins, with a heritability ($h^2$) estimate of 100% [26]. In this context, twin studies have also been widely used to investigate the genotype × environment interaction since most traits or diseases are multifactorial. Along the same lines, family studies have long been used to effectively evaluate the genetic architecture of complex traits, such as CVDs [27,28]. Investigation of segregating patterns of a trait from parents to offspring enables the identification of responsible genes [29]. Detailed features of twin and family studies in genetics are reviewed elsewhere [26,28].

There are two general strategies used for discovering genes, more specifically genomic loci, for a certain trait. Linkage studies, which are used to identify the genomic loci responsible for a trait, even with moderate effects, via co-segregating with known genetic markers and estimating the recombination fraction, can only be performed using data collected from biologically related individuals; family members. Meanwhile, association studies assessing correlations between allelic and phenotypic variations can be executed in unrelated individuals from either random or case-control samples [28]. Advances in sequencing technologies have provided the foundation for the genome-wide association study (GWAS) [30], which is one of the most commonly used approaches for identifying genetic loci associated with a trait through the investigation of common genetic variation across the entire human genome in a large number of subjects [31]. Although single-nucleotide polymorphisms (SNPs) identified by a GWAS do not necessarily represent their causal effects, GWAS has been found to be a powerful tool, as it can be performed in unrelated subjects and is driven by unbiased hypothesis-free investigations. Through GWAS, candidate and/or putative SNPs associated with various types of CVDs have been identified [32], and some have been curated into the GWAS Catalog database (www.ebi.ac.uk/gwas/). According to the statistics from the GWAS Catalog database, as of July 2020, 125,244 SNP-trait associations have been reported from 4,582 publications. However, in general, the collective effect of loci identified via GWAS explains only a small portion of $h^2$; for instance, only ~3.5% of blood pressure (BP) $h^2$ was explained by loci found to be in statistically significant associations [30]. Therefore, further research in the field of CVD genomics is still required, as well as heterogeneous findings from different resources, such as different age, sex, race, and disease state, need to be reconstituted.

Regular exercise is a powerful method of managing CV health [33]. Previous studies have shown that regular exercise not only reduces the incidence and prevalence of CVDs [34], but also decreases all-cause mortality in patients as well as healthy individuals [35]. Strong evidence has demonstrated that regular exercise induces beneficial morphological and functional changes in the heart, including LV dilation and hypertrophy with enhanced contractile function, leading to increased SV or cardiac output (CO or Q) [36-38]. Combined with positive changes in the vascular system due to exercise training [39], exercise-induced morphological and functional alterations in the CV system improve the blood circulation throughout the body, resulting in improved CV health outcomes.

However, recently accumulating data indicate that not all individuals show positive changes following exercise training, and some even had negative outcomes [40-44]. Inter-individual differences in training responses have been highlighted elsewhere [45,46]. The previous studies demonstrate a variation in responses to exercise training among individuals, indicating the significant genetic contribution to training responses. This is also supported by previous twin studies showing that the responses of CV-related traits to regular exercise are more correlated in MZ twins compared to DZ twins with estimated $h^2$ of 0.22–0.57, depending on the nature of the response trait [24]. Further, a large consortium study, the HERITAGE Family Study, which examined CV responses to exercise training and investigated genetic influence on training adaptation in > 90 Caucasian and > 40 African American families [47], has provided strong evidence that exercise responses are heritable, multifactorial, and complex traits [48-53]. However, there have been few research trials to elucidate the genetic basis underlying responses, particularly in terms of cardiac structure and function, to exercise, suggesting that research in the field of exercise genetics is still in its infancy.

This review aims to summarize accumulated findings from population-based studies and unbiased large genomic scale studies emphasizing the structure and function of the heart. It is presented as a narrative review and detailed information for each single nucleotide polymorphism (allele, location, arbitrary genomic interval, and genes located in the interval) found to be associated with cardiac traits in the previous association/linkage studies is summarized in Tables 1–3. Since exercise genetics is in a state of constant flux with rapidly growing new information, we will also scrutinize the evidence collected from previous studies postulating the genetic contribution to cardiac responses to
### Table 1. Single nucleotide polymorphism (SNP) significantly associated with cardiac structure

<table>
<thead>
<tr>
<th>Trait</th>
<th>Race</th>
<th>Age (mean, y)</th>
<th>Marker</th>
<th>Alleles</th>
<th>Genomic location</th>
<th>Physical location (kb)</th>
<th>SNP type</th>
<th>QTL interval (kb)</th>
<th>Genes</th>
<th>Reference</th>
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</thead>
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<td>3,344–3,744</td>
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<td>NS (Dominicans) (n = 1,360)</td>
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<td>20q13.13</td>
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<td>Intergenic</td>
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<td>KCNB1, DOX27, PTG15, ZFAS1, ZNF5X1</td>
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<td>rs801633</td>
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<td>MEIS2, KCN9, KCNK17, KCNK16, KIF6</td>
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<td>COL17A1, CFAP43, GSTO1, GSTO2, SFR1, SLK, STN1</td>
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<td>216,314–216,743</td>
<td>SLC2A1, C1orf210, CFAP57, EBNA1BP2, FAM183A, TIE1, TMEM125</td>
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<td>TRIM38, HGC17, HCG18, HCG4B, HCG9, HLA-A, HLA-A1, HLA-L, PPP1R11, RNFS9, TRIM15, TRIM31, TRIM40, TRIM90, TRIM15, TRIM26, ZNRD1, ZNRDHAS</td>
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<td>SOX4, CASC15, PRL, NBT1</td>
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<tr>
<td>Trait</td>
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<td>Age (mean, y)</td>
<td>Marker</td>
<td>Alleles</td>
<td>Genomic location</td>
<td>Physical location (kb)</td>
<td>SNP type</td>
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<td>47,424–47,824</td>
<td>HTR2A</td>
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<td>rs4552931</td>
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<td>UBE2V2</td>
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<td>32,668–33,068</td>
<td>PKP2, DNM1L</td>
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<td>rs1035607</td>
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<td>Intronic</td>
<td>46,663–47,003</td>
<td>OR10AD1, ASK8, CCDC184, COL2A1, H1FNT, PKF, SENP1, ZNF641</td>
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<td>A/G</td>
<td>12q13.11</td>
<td>46,844</td>
<td>Exonic</td>
<td>46,644–48,044</td>
<td>SLC38A4</td>
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<td>46,844</td>
<td>Exonic</td>
<td>46,644–48,044</td>
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<td>Intronic</td>
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<td>8q24.13</td>
<td>124,844</td>
<td>Intergenic</td>
<td>124,644–125,044</td>
<td>MIR4662B, LINC00964, MTSS1, SQLE, WASHC5, ZNF572</td>
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<tr>
<td>NS (n = 44,203)</td>
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<td>rs3812625</td>
<td>A/G</td>
<td>10q22.2</td>
<td>73,997</td>
<td>Intergenic</td>
<td>73,797–74,197</td>
<td>VCL, ADK, AP3M1, C10orf55, CAMK2G, NDST2, PLAU, ZSWIM8</td>
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<tr>
<td>East Asian (n = 19,676)</td>
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<td>G/A</td>
<td>18q12.1</td>
<td>32,497</td>
<td>Intergenic</td>
<td>32,297–32,697</td>
<td>GAREM1, WBP11P1, KUHL14</td>
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<td>Intergenic</td>
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<td>32,297–32,697</td>
<td>GAREM1, WBP11P1, KUHL14</td>
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Each significant locus was re-evaluated by the authors using the latest version of UCSC Genome Browser (Human GRCh38/hg38). QTL interval was set at ±200 kb centered around each SNP and genes in the QTL interval were identified using the UCSC Genome Browser. The significant level for linkages or associations varies by studies and if not specified, a significant p-value of 1.00E-5 was used. LVM, left ventricular mass; LVDD, left ventricular diastolic dimension; LVWT, left ventricular wall thickness; IVWT, inter-ventricular septal wall thickness; LVEDV, LVED volume; LVESV, LVES volume; NS, non-specified. Bold font indicates genes reported in previous studies as the nearest genes. Plain text genes with no symbol are additionally identified in the QTL interval. *Genes newly identified as the nearest gene in the QTL interval.
## Table 2. Single nucleotide polymorphism (SNP) significantly associated with cardiac function

<table>
<thead>
<tr>
<th>Trait</th>
<th>Race</th>
<th>Age (mean, y)</th>
<th>Marker</th>
<th>Allele</th>
<th>Genomic location</th>
<th>Physical location (kb)</th>
<th>SNP type</th>
<th>QTL interval (kb)</th>
<th>Genes</th>
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<td>SV</td>
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<td>14q31.1</td>
<td>76,922</td>
<td>-</td>
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<td>ANGEL1, CIPC, IGF2BPL, LINC01629, LINC02288, LINC02289, LRRC74A, VASH1, VASH1-AS1</td>
<td>[77]</td>
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<tr>
<td>CO</td>
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<td>18q11.2</td>
<td>21,624</td>
<td>Intronic</td>
<td>21,424–21,824</td>
<td>ABHD3, ESCO1, GREB1L, MIB1, SNRPD1</td>
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<tr>
<td>EF</td>
<td>African Americans (n = 6,765)</td>
<td>51.3</td>
<td>rs9530176</td>
<td>T/A</td>
<td>13q22.1</td>
<td>73,244</td>
<td>Intergenic</td>
<td>73,044–73,444</td>
<td>KLF5, PIBF1, ABHD3, ESCO1, GREB1L, MIB1, SNRPD1</td>
<td>[19]</td>
</tr>
<tr>
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<td>East Asian (n = 19,676)</td>
<td>66.7</td>
<td>rs2404490</td>
<td>C/T</td>
<td>20p11.21</td>
<td>22,718</td>
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<td>22,518–22,918</td>
<td>CDF2, C20orf15, CABIN1, CHCHD10, DD1, DDTL, GSTT2, GSTT4, GSTT2B, CHGB, SHLD1*, CHGB, GPCR1, SLC2A1, VASH1, VASH1-AS1, LINC02245, RAB1A</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>East Asian (n = 19,676)</td>
<td>66.7</td>
<td>rs34866937</td>
<td>G/A</td>
<td>8q24.13</td>
<td>124,847</td>
<td>Intergenic</td>
<td>124,647–125,047</td>
<td>SLC1A4, CEP68, LINC01800, LINC02245, RAB1A</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>East Asian (n = 19,676)</td>
<td>66.7</td>
<td>rs5760061</td>
<td>G/A</td>
<td>22q11.23</td>
<td>23,835</td>
<td>Exonic</td>
<td>23,635–24,035</td>
<td>SLC1A4, CEP68, LINC01800, LINC02245, RAB1A</td>
<td>[16]</td>
</tr>
<tr>
<td>NS (European)</td>
<td>(n = 16,920)</td>
<td>62.5</td>
<td>rs945425</td>
<td>T/C/A</td>
<td>1p36.13</td>
<td>16,021</td>
<td>Intergenic</td>
<td>15,821–16,221</td>
<td>CLCNKA, ARHGEF19, CLCNKB, EPH2A, FAM131C, HSPB7, SPEN, ZBTB17</td>
<td>[15]</td>
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<tr>
<td></td>
<td>rs34866937</td>
<td>G/A</td>
<td>8q24.13</td>
<td>124,847</td>
<td>Intergenic</td>
<td>124,647–125,047</td>
<td>124,647–125,047</td>
<td>DERL3, C22orf15, CABIN1, CHCHD10, DD1, DDTL, GSTT2, GSTT4, GSTT2B, MIF, MIF-AS1, RGL4, SLC211, SLC221, SMARC1B, SLC23A1, VASH1, VASH1-AS1, LINC02245, RAB1A</td>
<td>[16]</td>
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<tr>
<td></td>
<td>rs72840788</td>
<td>G/A</td>
<td>10q26.11</td>
<td>119,655</td>
<td>Intronic</td>
<td>119,455–119,855</td>
<td>119,455–119,855</td>
<td>119,455–119,855</td>
<td>BAG3, GRK5, INPP5F5, MCMBP, TIAL1</td>
<td>[18]</td>
</tr>
<tr>
<td>FS</td>
<td>NS (n = 44,203)</td>
<td>62.7</td>
<td>rs9470361</td>
<td>G/A/T</td>
<td>6p21.2</td>
<td>36,655</td>
<td>Intergenic</td>
<td>36,455–36,855</td>
<td>SLC1A4, CEP68, LINC01800, LINC02245, RAB1A</td>
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</tr>
<tr>
<td></td>
<td>East Asian (n = 19,676)</td>
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<td>65,011</td>
<td>Intronic</td>
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<td>SLC1A4, CEP68, LINC01800, LINC02245, RAB1A</td>
<td>[16]</td>
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<td>8q24.13</td>
<td>124,847</td>
<td>Intergenic</td>
<td>124,647–125,047</td>
<td>SLC1A4, CEP68, LINC01800, LINC02245, RAB1A</td>
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<td>10q26.11</td>
<td>119,655</td>
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<td>119,455–119,855</td>
<td>119,455–119,855</td>
<td>BAG3, GRK5, INPP5F5, MCMBP, TIAL1</td>
<td>[18]</td>
</tr>
</tbody>
</table>

Each significant locus was re-evaluated by the authors using the latest version of UCSC Genome Browser (Human GRCh38/hg38). QTL interval was set at ±200 kb centered around each SNP. Genes in the QTL interval were identified using the UCSC Genome Browser. The significant level for linkages or associations varies by studies and if not specified, a significant p-value of 1.00E-5 was used. SV, stroke volume measured during exercising at 50W; CO, cardiac output measured during exercising at 50W; EF, ejection fraction; FS, fractional shortening; NS, non-specified. Bold font indicates genes reported in previous studies as the nearest genes. Plain text genes with no symbol are additionally identified in the QTL interval. *Genes newly identified as the nearest gene in the QTL interval.

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Kim M and Kim SK
exercise training. We believe that this is the first review of findings from previous genetic studies incorporating the baseline structure and function of the heart as well as its responsiveness to exercise training.

**GENETIC REGULATION OF CARDIAC STRUCTURE AND FUNCTION**

Cardiac structural and functional characteristics are important for CVD incidence and are significantly associated with CV morbidity and mortality [50,51,54-56]. Accumulated studies demonstrate that cardiac structural and functional traits are heritable [57], indicating the importance of elucidating the genetic basis of CV structure and function to understand CVDs. Here, we review results from previous twin and family studies and unbiased large genomic scale association/linkage studies in related and/or unrelated individuals for cardiac structure and function.

**Twin studies**

Previous twin studies have revealed the genetic predisposition to cardiac structure and function. In a teenager twin study published in 1991, correlation coefficients for left ventricular mass (LVM) in MZ twins were larger than those of DZ twins [13], indicating the significant role of inheritance in cardiac structural phenotypes. From several twin studies, the $h^2$ estimate, which is the proportion of phenotypic variation explained by a shared genome, has been reported for cardiac structural phenotypes. Swan et al. reported a $h^2$ of 0.69 for LVM in twins aged 30–85 years from the Western Europe population. Even after adjusting for age, sex, BP, and body weight, the $h^2$ estimate remained high (0.53) [13]. Busjahn et al. [58] also found $h^2$ estimates of SV, LV end-systolic (LVES), LV end-diastolic (LVED), and average LV mass of 0.77, 0.82, 0.83, and 0.84, respectively, in 13 MZ and 12 DZ twins with a higher $h^2$ in MZ than DZ twins for all measurements. In a larger study, the Georgia Cardiovascular Twin Study, which included more than 500 pairs of twins with approximately equal numbers of African Americans and European Americans aged between 14 and 18 years, body mass index-adjusted $h^2$ estimates for LV traits, such as WT, LVM, and LV inner diameter (LVID), ranged from 0.21 to 0.71 [59]. In this study, the $h^2$ of cardiac structure was substantial in both races. Few Asian twin studies exist to date. Noh et al. [60] investigated the genetic influences on cardiac structure and function in healthy Korean adults comprising 298 MZ twin pairs, 62 DZ twin pairs, 567 siblings, and 354 parents. They reported $h^2$ estimates of 0.44 for LVM, 0.47 for LVID, 0.27 for EF, and 0.44 for left atrial volume index adjusted for other confounding factors. Combined, these results from previous twin studies clearly indicate that the cardiac structure and function are genetically influenced, and the extent of the genetic contribution differs depending on race, sex, and age, suggesting that cardiac structure and function are multifactorial traits.

In contrast, several twin studies have suggested no significant influence of inheritance on cardiac structure and function. Fagard et al. [61] found no significant hereditary effects on LVM, LVID, and fractional shortening (FS) in 12 young MZ and 12 DZ twins. Additionally, Bielen et al. [62] found no significant influence of genetic endowment on LVID or WT in seven-year-old twin pairs, although adjusted LVM showed a significant genetic component. A year later, the same investigators reported that in differently aged groups of twins (18 to 31 years old), genetic contributions to LVID and LVM were not present [53]. However, this study found significant genetic contributions to WT, postulating that the extent to which the genetic predisposition explains variation in cardiac structure and function is trait-specific, or, as is common, the number of participants and sensitivity of measurement techniques may have contributed to such a discrepancy.

**Family studies**

Several familial studies have conferred familial resemblance in cardiac structure and function. A previous study from The Framingham Heart Study, which is committed to identifying the basis of CVDs, including the genetic factors in a large cohort recruited from 1948, showed an adjusted LVM $h^2$ of 0.32 in 6,218 subjects [52]. The authors also found significant intra-class correlations between first-degree (parent-child, siblings) and second-degree relatives compared to unrelated individuals, showing correlations of 0.15, 0.16, 0.06, and 0.05 between parent and child, siblings, second-degree relatives, and spouses, respectively. Another study from the Framingham Heart Study also found that adjusted LVM with other clinical factors, such as age, sex, and body size, showed familial concordance in 5,758 individuals from 1,093 nuclear families [64]. The most recent update from the Framingham Heart Study estimates a $h^2$ of 0.4 for LVM [50]. Additionally, 0.3 of the adjusted $h^2$ estimate was reported in 149 nuclear families [65]. A parent-offspring study conducted by Palatini et al. [65] claimed a LVM correlation between parent-child of 0.28, and the authors put forward that although the heredity effect on LVM seems small, the genetic contribution may differ by individual. In other words, the genetic contribution in some subjects may be large, while others may be small, indicating the inter-individual variation. A previous study from the HERITAGE Family Study also reported an adjusted $h^2$ of cardiac function measurements, such as SV and Q obtained during 50W exercise of 0.41 and 0.42, respectively, in 99 Caucasian families [49]. In another research network study, the Genetic Epidemiology Network of Arteriopathy (GENOA) study, which investigated a population consisting primarily of old and unhealthy individuals (mean age: 72.9 years, 13%; current smokers, 37%; diabetes or impaired fasting glucose, 70%; taking anti-hypertensive medications), African Americans presented a $h^2$ of 0.34 for LVM, 30% for interventricular septal WT (IVWT), 0.39 for LV diastolic diameter (LVDD), and 0.42 for
EF [54]. In 1,305 American Indians aged 45 to 74 involved in the
Strong Heart Study, the $h^2$ of LVM, LVID, and WT was 0.17, 0.33,
and 0.17, respectively [67]. Additionally, the Monitoring Trends
and Determinants in Cardiovascular Disease (MONICA) Project
by the WHO revealed a significant familial aggregation of LV
hypertrophy [68]. There are also ethnic differences in cardiac
structures according to the Hypertension Genetic Epidemiology
Network (HyperGEN) Study, which includes hypertensive sib-
lings who were diagnosed before reaching 60 years old. Correla-
tions for LVM between siblings were lower in Caucasians (0.22)
than African Americans (0.30), while Caucasians had stronger
sibling correlations (0.19 vs. 0.11) for WT [69]. In Asian cohorts,
the LVM $h^2$ was reported as 0.26 in 1,145 Chinese Taiwanese
subjects, and the authors presented distribution patterns of LVM,
highlighting inter-individual variation [70]. The genetic contribu-
tions to cardiac structure and function were further supported
by the findings of significant parent-child (0.32) and sibling-
sibling (0.29) correlations, but not in spouse pairs for WT in 181
nuclear family members with African ancestry [51]. A similar ap-
proach was used for Caribbean Hispanics (Dominicans) from the
Northern Manhattan Family (NOMAS) Study [71]. This study
presented an adjusted $h^2$ of LVM, WT, LVDD, LVSD, and Poste-
rrior WT to 0.49, 0.23, 0.23, 0.33, and 0.35, respectively. Combined,
these data from previous family studies demonstrate the genetic
predispension to cardiac traits, although $h^2$ varies depending on
trait and/or study population.

**Linkage/association studies**

Linkage and association approaches in related or unrelated in-
dividuals allow investigators to identify common genetic variants
associated with traits [72]. There have been several linkage
and association studies for cardiac structural and functional traits
in family members or unrelated individuals. Their findings are
summarized in Tables 1 and 2. Arnett et al. [72] first conducted
GWAS for LVM in the HyperGen study population consisting of
both Caucasians (n = 906) and African Americans (n = 1,467) and
identified novel SNPs for LVM on chromosome 5, 12, and 13 in
Caucasians and 5 in African Americans. Among SNPs, rs756529
is located in an intron of KCNB1, which was previously identi-
fied by the same research group as a novel candidate gene for LV
mass [73]. Two linkage studies for LVM were published from the
NOMAS Study. The first used 405 microsatellite quantitative trait
loci markers to map variants associated with LVM measured in
1,360 subjects [74]. The authors identified a statistically signifi-
cant marker (12S1042) associated with LVM on 12p11.23 (11th re-

gen, 2nd band and 3rd sub-band on the short arm [p] divided by
centromere of chromosome 12). A decade later, the same research
group conducted a deeper analysis for this region using denser
SNPs (n = 5,477), which was then replicated in an additional
618 unrelated Dominicans from the NOMAS and 12 Dominici-
an families. Nine SNPs were reached at the significance prob-
ability (rs1046116, rs1035607, rs1168459, rs2191162, rs731236,
rs74081827, rs35989439, rs1168985, rs7311790) [20]. They high-
lighted rs1046116 located in the exonic region of the PKP2 gene,
which was implicated in ventricular cardiomyopathy. In 2009,
a meta-analysis of GWAS was conducted in seven population-
based cohort studies, including the Cardiovascular Health Study
(European ancestry), Rotterdam Study (Rotterdam-population),
Multinational Monitoring of Trends and Determinants in Car-
diovascular Disease Study (Augsburg-population), Framingham
Heart Study (non-specified), Gutenberg Heart Study (Mainz and
Mainz-Bingen), Study of Health in Pomerania (West Pomerania),
and Austrian Stroke Prevention Study (Graz), and the last two
were used for replication [21]. Three loci for LVM on chromosome
2, 14, and 15, two loci for LVDD on chromosome 6, and three loci
for WT on chromosome 5, 10, and 16 were identified. However,
these loci only explained a small proportion (1%–3%) of individu-
als' variances in these structural phenotypes. An additional multi-
stage GWAS for cardiac structural traits was conducted in hyper-
tensive subjects from the HyperGEN and GENOA studies [14].

The authors first conducted GWAS in African Americans, and
then findings were replicated in Caucasians. Two loci for LVM on
chromosome 6 and 16, one locus for LVWT on chromosome 11,
and two loci for IVWVT on chromosome 2 and 8 were discovered.
One SNP, rs1436109, located in intron 1 of NCAM1, was success-
fully replicated, implying an important role of the NCAM1 gene
in cardiac structure. From the Old Order Amish Founder popu-
lation (n = 851), who immigrated to the USA, particularly Philadel-
phia, GWAS for LVM discovered 12 SNPS ($p < 10^{-8}$) [75]. None of
these significant SNPs were replicated, while one suggestive SNP,
rs2207418 (not listed in Table 1), which is located in the intergenic
area, was replicated in independent unrelated Caucasians. Us-

ing cardiac structure traits obtained from four population-based
cohorts of African Americans as a part of the CARe consortium,
Fox et al. [19] identified one SNP for LVM on chromosome 8,
two SNPs for LVDD on chromosome 7 and 17, and one SNP for
IVWVT on chromosome 10, although all four SNPs were not rep-
licated in other cohorts. The authors point out that the failure of
replication supports race-specific variants associated with cardiac
structural traits, indicating the need for additional studies. Re-
cently, the largest genetic association study to date was performed
for cardiac phenotypes collected from 46,533 subjects (primarily
European ancestry) from the EchoGen consortium comprising 30
studies, including most studies mentioned above [18]. The
authors first discovered SNPs via meta-analyses for data from
21 cohort populations (n = 30,201), and findings were replicated
in five independent population-based cohorts (n = 14,002) and
combined. As a result, one variant for LVM and three variants
for LVDD were discovered with regards to the baseline cardiac
structure and function. Another study by Aung et al. [15] using
data collected from 16,923 subjects of the European UK Biobank
also identified one locus for LVM on chromosome 2, three loci
for LVED volume (LVEDV) on chromosome 2, 10, and 12, and

https://doi.org/10.4196/kjpp.2021.25.1.1
three loci for LVES volume (LVESV) on chromosome 2, 8, and 10. Among them, two loci for LVESV and three loci for LVESV were further replicated, at least at the suggestive level, in an independent cohort from the Multi-Ethnic Study of Atherosclerosis [76]. There is a current GWAS incorporating Asian subjects [16]. In this study, three significant SNPs (rs34866937, rs3812625, and rs11874741) were identified for LVDD on chromosome 8, 10, and 11, respectively.

Several association studies have been conducted for functional phenotypes of the heart, such as SV, CO, EF, and FS [15,16,18,19,77], and the findings from these studies are summarized in Table 2. A research group previously found that baseline SV and Q obtained during exercise at 50W on a cycle ergometer are variable among individuals (n = 742) in the HERITAGE Family Study [77]. The authors conducted linkage analyses for the variation in baseline SV and Q using 509 genomic markers and found two significantly linked markers, D14S53 and D18S866, for SV in Caucasians and Q in African Americans, respectively. In an aforementioned study by Fox et al. [19], one marker, rs9530176, in chromosome 13 was reported as a significant SNP associated with EF in individuals from four population-based cohorts of African Americans. A large-scale study originating from the EchoGen consortium also discovered one locus (rs9470361), located in chromosome 6, to be significantly associated with FS [18]. Recently, using a dense marker (n > 6,108,953), four and three loci significantly associated with FS and EF, respectively, in an Asian population (162,255 Japanese participants) were reported [16]. Another study conducted by Aung et al. [15] found four SNPs for EF located in chromosome 1, 2, 8, and 10.

Together, the summarized data from previous twin, family, and linkage or association studies highlight evidence supporting the significant role of genetic components in cardiac phenotypes and offer insights into the genetic architecture of cardiac remodeling. However, none of the SNPs identified by previous linkage or association approaches overlap with each other, and most of the reported genetic variants have not yet had their effects confirmed per se by independent research experiments (i.e., candidate gene study, gene-editing study, etc.), meaning that the additional larger scale experimental studies are needed to provide unquestionable evidence for clinical applications. Ultimately, such data may reveal therapeutic targets for cardiac remodeling and dysfunction which are major causes of deaths in modern human life.

GENETIC REGULATION OF CARDIAC RESPONSES TO EXERCISE TRAINING

It is evident that exercise training induces positive changes in cardiac structure and function, such as physiological hypertrophy, wall thickening, and improved EF [56,78], thus, it has been used as a non-pharmacological means to prevent CVD and/or improve CV health, not only for patients but also for healthy individuals. However, recent studies indicate that responses to exercise training are variable across subjects, emphasizing the genetic contribution to training responses [45,46]. Therefore, elucidating the genetic basis for responses to exercise training is important in order to constitute the optimally individualized exercise training prescription. Previous studies have reported the significant roles of genetic factors on cardiac responses to exercise training [33,79]; however, the majority of the findings were from studies investigating genotypic effects of one or few candidate genes which were proposed by prior studies (reviewed in [80]), suggesting that the results were dependent on already known information and thus biased. In the sense of that most human traits are polygenic, including responses to exercise [81], unbiased population-based large genome scale studies can provide more information which enables to understand genetic architecture of physiological responses to exercise training comprehensively.

Nevertheless, population-based genetic studies exploring cardiac responses to exercise do not dominate literature as much as those for intrinsic or baseline cardiac features, demonstrating the infancy of the study field and necessity for future large population studies identifying genetic determinants responsible for cardiac adaptations to exercise. Although very limited, we here review the previous twin, family, and linkage/association studies addressing this topic.

Twin studies

Almost four decades ago, investigators examined cardiac responses to exercise in 65 pairs of twins [82]. The authors found that changes in cardiac frequency during submaximal exercise were genetically determined. Several years later (still three decades ago), a different research group assessed the changes in cardiac structural and functional indices during acute bicycle ergometer exercise in 33 healthy male pairs of twins aged from 18 to 31 years. They found different responses to exercise among subjects, indicating the inter-individual variation, and responses were more similar within rather than between twin pairs, supported by estimated h² of 0.24 and 47 for LV internal dimension and FS, respectively [63]. While in another twin study conducted by Adams et al. [48], changes in LVEDD after 14 weeks of exercise training in MZ twins were not different compared to age-matched DZ twins and siblings. Training-induced changes in LVEDD significantly differed from those of non-related individuals [48]. Although a handful of evidence exists, data from these previous twin studies demonstrate that morphological and functional cardiac responses to exercise training are affected, at least in part, by genetic factors. Meanwhile, a relatively recent study published in 2009 aimed to explore the effect of long-term exercise per se on LV mass excluding the genetic influence in twin pairs who were discordant for exercise level for 32 years [83]. In this study, long-term exercise increased LVM normalized to BW when genetic liability was controlled, meaning that cardiac...
responses to exercise training are multifactorial, interactively affected by both environmental and genetic factors.

**Family studies**

To our knowledge, there have been two family studies investigating the genetic influence on cardiac responses to exercise, and these are from the HERITAGE Family Study [47]. The first was published in 2000 [66], in which SV and CO were assessed in 99 Caucasian families who completed a 20-week standardized aerobic exercise program. The authors reported $h^2$ estimates of 0.41 and 0.42 for pre-training SV and CO measured in steady state during exercise at 50 watts on a cycle ergometer, respectively, and 0.29 and 0.38 for the respective changes after endurance exercise training. The $h^2$ estimates for the pre-training cardiac function were higher than that of responses to exercise training. The second study investigated the SV and CO changes in response to 20-week exercise training on cycle ergometers in 631 healthy individuals, including both Caucasians ($n = 414$) and African Americans ($n = 217$) aged between 17 and 65 years who had completed the HERITAGE Family Study protocol [84]. This study demonstrated race-dependent changes in SV and CO after exercise training. These indicate that cardiac responses to exercise training are genetically affected and provide justification to identify genetic determinants responsible for the genetic influence on cardiac function.

**Linkage/association studies**

Rankinen et al. [77], for the first time, conducted a genome-wide linkage scan for changes in SV and CO after standardized 20-week exercise training in 701 individuals consisting of 483 Caucasians and 259 African Americans from the HERITAGE Family Study. A total of 509 genomic markers was used to scan the genome in this study. For Caucasians, one marker, D10S1666, located on 10p11.2 (11th region and 2nd band on the short arm [p] divided by centromere of chromosome 10), was significantly ($p < 0.0023$) associated with changes in SV after exercise training, and several other markers were identified as suggestive SNPs associated with SV and CO responses to exercise training. In contrast, for African Americans, none of the markers were significantly associated with cardiac response traits to training, although several other markers were identified as suggestive SNPs associated with SV and CO responses to exercise training. These indicate that cardiac responses to exercise training are genetically affected and provide justification to identify genetic determinants responsible for the genetic influence on cardiac function.

| Table 3. Single nucleotide polymorphism (SNP) significantly associated with cardiac responses to exercise training |
|---|---|---|---|---|---|---|
| Trait | Race | Age (mean, y) | Marker Allele | Physical location (kb) | Genomic location (kb) | SNP type | Genes |
| ∆SV | Caucasian ($n = 475$) | 39.1 | D10S1666 - | 10p11.2 | 33,692 | Intergenic | LINC00838, RPL23P11 |
| | Caucasian ($n = 475$) | 39.1 | D2S324 - | 2q31.2 | 179,656 | Intergenic | TTN, ZNF365B |
| | African American ($n = 701$) | 38.5 | D2S353 - | 2q31.2 | 179,625 | Intergenic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | Caucasian ($n = 450$) | 39.1 | rs398686 - | 10p11.2 | 32,032 | Intergenic | TTN |
| | African American ($n = 701$) | 38.5 | rs172431 - | 10p11.2 | 31,837 | Intergenic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | Caucasian ($n = 450$) | 38.5 | rs172431 - | 10p11.2 | 31,837 | Intronic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | African American ($n = 701$) | 38.5 | rs211286 - | 10p11.2 | 31,846 | Intronic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | Caucasian ($n = 450$) | 38.5 | rs211302 - | 10p11.2 | 31,856 | Intergenic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| ∆CO | Caucasian ($n = 475$) | 39.1 | D2S148 - | 2q31.2 | 178,231 | Intronic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | African American ($n = 701$) | 38.5 | rs172431 - | 10p11.2 | 31,837 | Intergenic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | Caucasian ($n = 450$) | 38.5 | rs172431 - | 10p11.2 | 31,837 | Intronic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | African American ($n = 701$) | 38.5 | rs211286 - | 10p11.2 | 31,846 | Intronic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |
| | Caucasian ($n = 450$) | 38.5 | rs211302 - | 10p11.2 | 31,856 | Intergenic | CHROMR, OSBPL6, PDE11A, PRKRA, RBM45 |

Each significant locus was re-evaluated by the authors using the latest version of UCSC Genome Browser Human GRCh37/hg19, QTL interval was set as ±200 kb centered around each significant SNP, and genes in the QTL interval were identified using the UCSC Genome Browser. Bold font indicates genes reported in previous studies as the nearest genes. Plain text genes are additionally identified in the QTL interval.
a biological key player of the Frank-Starling mechanism in the heart; however, since this linkage was observed only in Caucasian, not in African American subjects, much more detailed DNA variants in this gene need to be sequenced further; however, no additional follow-up study has been conducted so far. Another focused on the genomic region 10p11 (11th region on the short arm [p] divided by centromere of chromosome 10), which was significantly associated with changes in SV after exercise training [85]. Through the deeper mapping using six microsatellite markers, they narrowed down the linkage region into a 7 Mb area, and an additional association analysis for this region was performed using 90 SNPs. Consequently, the authors found the KIF5B gene loci suggestively associated with SV responses to exercise training, which is known to have a biological role in mitochondrial localization and biogenesis. Particularly, the authors highlighted sequence variants in promoter region of KIF5B, implying that transcriptional regulation by enhancers, repressors or epigenetic regulators would be one of underlying mechanisms for interindividual differences in cardiac responses to exercise training.

Despite these previous data demonstrating the salient role of genetic components on cardiac response to exercise training, a handful of findings from previous studies have not been replicated and potential candidate genes have not been considered in any other independent studies. Moreover, any linkage/association studies for cardiac structural responses to exercise training have not yet been conducted, referring to the myriad research agenda left for this study field. Given the notion that responses to exercise training are polygenic and multifactorial and dramatic advancements in genome sequencing techniques, larger-scale future studies based on a large population are warranted to unveil the genetic basis of cardiac responses to exercise.

CONCLUSION

Here, we review previous findings highlighting the genetic contribution to cardiac phenotypes and responsiveness to exercise training. Accumulated results have shown that baseline cardiac structure and function are heritable and complex traits. Researchers have explored twin, family, and linkage/association studies to elucidate the genetic basis and many loci associated with LVM, LVDD, WT, LVEDV, and LVESV (Table 1), and SV, CO, EF, and FS (Table 2) have been reported. Meanwhile, it has been well-characterized that exercise training can improve cardiac health and prevent CVD; however, inter-individual variation in responses to exercise is currently highlighted, demonstrating that responses to exercise training are also genetically determined. A handful of evidence from the HERITAGE Family Study has provided several genetic variants modestly associated with cardiac responses to exercise training (Table 3). Nevertheless, the vast majority of mapped loci associated with the baseline structure and function of the heart as well as their responsiveness to exercise training are not in conjunction with one another across studies. This may be due to the heterogeneity in race, age, gender, environments and effect sizes. Therefore, collaboration and collection of larger cohorts with much denser genome sequencing are required to overcome these limitations. Additionally, translating genomic localization into the biological mechanisms remains a mystery. Considered with swift advances in genome editing techniques, future studies are warranted to further evaluate the biological functions of reported genetic variants and loci, which will serve as the basis for potential therapeutic targets and personalized risk stratification strategy for cardiac diseases in future.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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