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Review Article

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

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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

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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

Trait	Race	Age (mean, y)	Marker	Alleles	Genomic location	Physical location (kb)	SNP type	QTL interval (kb)	Genes	Reference
LVM	Caucasian (n = 906)	60.5	rs409045	C/T	5p13.2	34,628	Intergenic	34,428–34,828	**RA114**	[72]
			rs1833534	C/G/T	5q11.2	163,393	Intergenic	163,193–163,593	**CCNG1**, NUDCD2, HMMR, MAT2B	
			rs4129000	C/T	12q14.3	65,559	Intronic	65,359–65,759	**LOC729298**, MSRB3, RPSAP52	
			rs4129218	G/A	12q14.3	65,564	Intronic	65,364–65,764	**LOC729298**, MSRB3, RPSAP52	
			rs1155635	A/C/G	13q21.33	70,373	Intergenic	70,173–70,573	**KLHL1**	
	African Americans (n = 1,467)	50.8	rs238688	G/A	20p13	3,544	Intronic	3,344–3,744	**ATRN**, ADAM33, C20orf194, GFRA4, HSPA12B, SIGLEC1	
			rs756529	G/A	20q13.13	49,394	Intronic	49,194–49,594	**KCNB1**, DOX27, PTGIS, ZFAS1, ZNFX1	
	NS (Dominicans) (n = 1,360)	46.1	D12S1042	G/T	12p11.23	27,539	Intronic	27,338–27,738	SMCO2*, AARNTL2, PPFIBP1, MRPS35	[74]
	NS (n = 12,612)	62.0	rs17568359	G/C	14q12	26,168	Intergenic	25,968–26,368	**NOVA1**	[21]
			rs7565161	A/G	2p21	47,267	Intronic	47,067–47,467	**CALM2**, EPCAM-DT*, BCYRN1, C2orf61, EPCAM, MSH2, STPG4, TTC7A	
			rs8031633	T/C	15q14	37,247	Intergenic	37,047–37,447	**MEIS2**	
	African Americans (n = 1,258)	45.3	rs7774046	T/C	6p21.2	39,334	Exonic	39,134–39,534	**KCNK5**, **KCNK17**, **KCNK16**, **KIF6**	[14]
			rs7205297	G/A	16q22.2	71,991	Intronic	71,791–72,191	**AP1G1**, **DHODH**, **DHX38**, **HP**, **HPR**, **KIAA0174**, **PKD1L3**, **PMFBP1**, **TXNL4B**, ATXN1L, ZNF821, IST1, PKD1L3, HP	
	Caucasian (n = 851)	43.0	rs1320448	A/G	10q25.1	104,086	Intergenic	103,886–104,286	**COL17A1**, CFAP43, GSTO1, GSTO2, SFR1, SLK, STN1	[75]
			rs12757165	A/G	1q41	216,543	Intronic	216,334–216,743	**ESRRG**, USH2A	
			rs16830359	G/A/T	1p34.2	43,130	Intergenic	42,930–43,330	**SLC2A1**, C1orf210, CFAP57, EBNA1BP2, FAM183A, TIE1, TMEM125	
			rs10947055	T/C	6p22.1	30,125	Intergenic	29,915–30,315	**TRIM38**, HCG17, HCG18, HCG4B, HCG9, HLA-A, HLA-J, HLA-L PPP1R11, RNF39, TRIM15, TRIM31, TRIM40, TRIM10, TRIM15, TRIM26, ZNRD1, ZNRD1ASP	
			rs1916521	C/T	10q21.1	55,657	Intergenic	55,267–55,857	**ZWINT**	
			rs1484170	T/C	10q23.1	80,939	Intergenic	80,739–81,139	**NRG3**	
			rs6995588	C/T	8q12.1	60,091	Intergenic	59,891–60,291	**CA8**	
			rs4520040	G/A	6q16.3	103,984	Intergenic	103,784–104,184	**GRIK2**	
			rs769554	C/T	3q13.13	109,485	Intergenic	109,285–109,685	**DPPA4**, DPPA2, LINC01205	
			rs4236016	C/G/T	6p22.3	22,246	Intergenic	22,046–22,446	**SOX4**, CASC15, PRL, NBAT1	

Table 1. Continued

Trait	Race	Age (mean, y)	Marker	Alleles	Genomic location	Physical location (kb)	SNP type	QTL interval (kb)	Genes	Reference
			rs17636733	T/C	15q12	25,667	Intergenic	25,467–25,867	**UBE3A**, ATP10A, LINC02250	
			rs1575891	T/A/C	13q14.2	47,624	Intergenic	47,424–47,824	**HTR2A**	
	African Americans (n = 6,765)	51.3	rs4552931	A/G	8q11.21	48,258	Intergenic	48,058–48,458	**UBE2V2**	[19]
	NS (n = 44,203)	62.7	rs1454157	C/T	4q34.2	176,437	Intergenic	176,237–176,637	**SPCS**3, ASB5	[18]
	NS (Dominicans) (n = 180)	46.2	rs1046116	G/A	12p11.21	32,868	Exonic	32,668–33,068	**PKP2**, DNM1L	[20]
			rs1035607	A/C/T	12p11.22	29,356	Intronic	29,156–29,556	**ERGIC2**, FAR2, OVCHI-AS1, TMTC1	
			rs11168459	G/A	12q13.11	48,202	Exonic	48,002–48,402	**OR10AD1**, ASK8, CCDC184, COL2A1, H1FNT, PFKM, SENP1, ZNF641	
			rs2191162	A/G	12q13.11	46,803	Intronic	46,663–47,003	**SLC38A4**	
			rs731236	G/A	12q13.11	47,844	Exonic	47,644–48,044	**VDR**, COL2A1, ENDOU, HDAC7, RAPGEF3, RPAP3, SENP, SLC48A1, TMEM106C	
			rs74081827	A/G	12q12	45,439	Exonic	45,239–45,639	**ANO6**	
			rs35989439	T/A	12p11.21	30,992	Exonic	30,792–31,192	**TSPAN11**, DDX11, DDX11-AS1	
			rs11168985	A/C	12q12	38,652	Intergenic	38,452–38,852	**CPNE8**	
			rs7311790	A/G	12q13.11	47,667	Intronic	47,467–47,867	**RPAP3**, ENDOU, RAPGEF3, HDAC7, VDR	
	NS (European) (n = 16,920)	62.5	rs2255167	T/A	2q31.2	178,693	Intronic	178,493–178,893	TTN, CCDC141, TTN-AS1	[15]
LVDD	NS (n = 16,706)	61.0	rs89107	A/G	6q22.31	118,256	Intronic	118,056–118,456	SLC35F1	[21]
			rs11153768	C/T	6q22.31	118,666	Intronic	118,466–118,866	CEP85L, BRD7P3, MCM9, PLN, SELENOKP3	
	African Americans (n = 5,555)	51.3	rs2700294	G/A/C	7p15.3	21,318	Intergenic	21,118–21,518	DNAH11, SP4	[19]
			rs7213314	C/T	17q24.2	68,689	Intergenic	68,489–68,889	ABCA8, FAM20A, PRKAR1A, WIPI1, LINC01482	
	NS (n = 44,203)	62.7	rs11153730	C/T	6q22.31	118,346	Intergenic	118,146–118,546	SLC35F1, BRD7P3, CEP85L	[18]
			rs12541595	G/T	8q24.13	124,844	Intergenic	124,644–125,044	MTSS1, SQLE, WASHC5, ZNF572	
			rs10774625	A/G	12q24.12	111,472	Intronic	111,272–111,672	ATXN2, BRAP, CUX2, FAM109A, PHETA1, SH2B3	
	East Asian (n = 19,676)	66.7	rs34866937	G/A	8q24.13	124,847	Intergenic	124,647–125,047	MIR4662B, LINC00964, MTSS1, SQLE, WASHC5, ZNF572	[16]
			rs3812625	A/G	10q22.2	73,997	Intergenic	73,797–74,197	VCL, ADK, AP3M1, C10orf55, CAMK2G, NDST2, PLAU, ZSWIM8	
			rs11874741	G/A	18q12.1	32,497	Intergenic	32,297–32,697	GAREM1, WBP11P1, KLHL14	

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Table 1. Continued

Trait	Race	Age (mean, y)	Marker	Alleles	Genomic location	Physical location (kb)	SNP type	QTL interval (kb)	Genes	Reference
LVWT	Caucasian and African Americans (n = 3,611)	51.7	rs1436109	G/T	11q23.2	113,120	Intronic	112,920–113,320	NCAM1, TTC12	[14]
	NS (n = 16,706)	61.5	rs7910620	C/G/T	10q23.1	86,087	Intronic	85,887–86,287	GRID1	[21]
			rs2059238	A/C/T	16q23.1	78,224	Intronic	78,024–78,424	WWOX, CLEC3A	
			rs17132261	C/T	5q21.1	110,672	Intronic	110,472–110,872	TMEM232*, SLC25A46	
IVWT	African Americans (n = 1,258)	45.3	rs16855517	G/A	2q24.3	168,571	Intronic	168,371–168,771	CERS6*, LASS6	[14]
			rs7836010	G/C	8q24.11	117,849	Intronic	117,649–118,049	EXT1	
	African Americans (n = 5,555)	51.3	rs1571099	C/T	10q26.12	120,507	Intronic	120,307–120,707	PLPP4, RPL21	[19]
LVEDV	NS (European) (n = 16,920)	62.5	rs2042995	T/C	2q31.2	178,694	Exonic	178,494–178–894	KCNMB2*, TTN	[15]
			rs7071853	T/C	10q26.11	119,552	Intergenic	119,352–119,752	RGS10*, BAG3, TIAL1, INPP5F	
			rs7310615	C/G	12q24.12	111,427	Intronic	111,227–111,627	ATXN2*, SH2B3, PHETA1	
LVESV	NS (European) (n = 16,920)	62.5	rs2042995	T/C	2q31.2	178,694	Exonic	178,494–178,894	TTN, CCDC141	[15]
			rs200712209	A/T	8q24.13	124,846	Intronic	124,646–125,046	**MTSS1**, ZNF572, SQLE, WASHC5	
			rs72840788	G/A	10q26.11	119,656	Intronic	119,456–119,856	**BAG3**, TIAL1, RGS10, INPP5F, MCMBP, GRK5	

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

Trait	Race	Age (mean, y)	Marker	Allele	Genomic location	Physical location (kb)	SNP type	QTL interval (kb)	Genes	Reference
SV	Caucasian (n = 475)	39.1	D14S53	-	14q31.1	76,922	-	76,722–77,122	ANGEL1, CIPC, IRF2BPL, LINC01629, LINC02288, LINC02289, LRRC74A, VASH1, VASH1-AS1	[77]
CO	African American (n = 272)	37.9	D18S866	-	18q11.2	21,624	Intronic	21,424–21,824	ABHD3, ESCO1, GREB1L, MIB1, SNRPD1	
EF	African Americans (n = 6,765)	51.3	rs9530176	T/A	13q22.1	73,244	Intergenic	73,044–73,444	**KLF5**, **PIBF1**	[19]
			rs16991189	T/C/G	20p12.3	5,717	Intergenic	5,517–5,917	**C20orf196**, **CHGB**, SHLD1*, CHGB, GPCPD1	
			rs2404490	C/A/T	20p11.21	22,718	Intergenic	22,518–22,918	**FOXA2**, LINC01747*, LINC00261	
	East Asian (n = 19.676)	66.7	rs6546120	G/A/T	2p14	65,011	Intronic	64,811–65,211	**SLC1A4**, CEP68, LINC01800, LINC02245, RAB1A	[16]
			rs34866937	G/A	8q24.13	124,847	Intergenic	124,647–125,047	**MIR4662B**, **LINC00964**, MTSS1, SQLE, WASHC5, ZNF572	
			rs5760061	G/A	22q11.23	23,835	Exonic	23,635–24,035	**DERL3**, C22orf15, CABIN1, CHCD10, DDT, DDTL, GSTT2, GSTT4, GSTT2B, MIF, MIF-AS1, RGL4, SLC211, SMARCB1, VPREB3, ZNF70	
	NS (European) (n = 16,920)	62.5	rs945425	T/A/C	1p36.13	16,021	Intergenic	15,821–16,221	**CLCNKA**, ARHGEF19, CLCNKB, EPHA2, FAM131C, HSPB7, SPEN, ZBTB17	[15]
			rs2042995	T/C	2q31.2	178,693	Exonic	178,493–178,893	**TTN**, CCDC141, TTN-AS1	
			rs34866937	G/A	8q24.13	124,847	Intergenic	124,647–125,047	**MTSS1**, LINC00964*, MIR4662B, SQLE, WASHC5, ZNF572	
			rs72840788	G/A	10q26.11	119,655	Intronic	119,455–119,855	**BAG3**, GRK5, INPPF5F, MCMBP, TIAL1	
FS	NS (n = 44,203)	62.7	rs9470361	G/A/T	6p21.2	36,655	Intergenic	36,455–36,855	**CDKN1A**, DINOL*, CPNE5, KCTD20, SRSF3PPIL, STK38	[18]
	East Asian (n = 19,676)	66.7	rs6546120	G/A/T	2p14	65,011	Intronic	64,811–65,211	**SLC1A4**, CEP68, LINC01800, LINC02245, RAB1A	[16]
			rs34866937	G/A	8q24.13	124,847	Intergenic	124,647–125,047	**MIR4662B**, **LINC00964**, MTSS1, SQLE, WASHC5, ZNF572	
			rs11025521	T/G	11p15.1	20,348	Intergenic	20,138–20,548	**DBX1**, **HTATIP2**, PRMT3	
			rs5760054	C/T	22q11.23	23,819	Intronic	23,619–24,019	**SMARCB1**, C22orf15, CABIN1, CHCHD10, DDT, DDTL, DERL3, DRICH1, GSTT2, GSTT4, GUSBP11, MIF, MIF-AS1, RGL4, SLC2A11	

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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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 ethnical differences in cardiac structures according to the Hypertension Genetic Epidemiology Network (HyperGEN) Study, which includes hypertensive siblings who were diagnosed before reaching 60 years old. Correlations 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 contributions 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 approach 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 Posterior WT to 0.49, 0.23, 0.23, 0.33, and 0.35, respectively. Combined, these data from previous family studies demonstrate the genetic predisposition 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 individuals 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 identified 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 significant marker (12S1042) associated with LVM on 12p11.23 (11th region, 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 Dominican families. Nine SNPs were reached at the significance probability (rs1046116, rs1035607, rs11168459, rs2191162, rs731236, rs74081827, rs35989439, rs11168985, rs7311790) [20]. They highlighted 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 Cardiovascular Disease Study (Ausburg-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 individual variances in these structural phenotypes. An additional multistage GWAS for cardiac structural traits was conducted in hypertensive 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 IVWT on chromosome 2 and 8 were discovered. One SNP, rs1436109, located in intron 1 of NCAM1, was successfully replicated, implying an important role of the NCAM1 gene in cardiac structure. From the Old Order Amish Founder population (n = 851), who immigrated to the USA, particularly Philadelphia, GWAS for LVM discovered 12 SNPS ($p < 10^{-5}$) [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. Using 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 IVWT on chromosome 10, although all four SNPs were not replicated 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. Recently, 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

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 h^2 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

Table 3. Single nucleotide polymorphism (SNP) significantly associated with cardiac responses to exercise training

Trait	Race	Age (mean, y)	Marker	Allele	Genomic location	Physical location (kb)	SNP type	QTL interval (kb)	Genes	Reference
ΔSV	Caucasian (n = 475)	39.1	D10S1666	-	10p11.2	33,692	Intergenic	33,492–33,892	LINC00838, RPL23P11	[77]
	Caucasian and African American (n = 701)	38.5	D2S324	-	2q31.2	179,656	Intronic	179,456–180,056	**TTN**, ZNF365B	[86]
			D2S385	-	2q31.2	179,625	Intronic	179,425–180,025		
			D2S148	-	2q31.2	178,231	Intronic	178,031–178,431	CHROMR, OSBPL6, PDE11A, PRKRA, RBM45	
	Caucasian (n = 450)	39.1	rs398686	C/T	10p11.22	32,032	Intronic	31,832–32,232	**KIF5B**, ARHGAP12	[85]
			rs172431	G/A	10p11.22	32,037	Intronic	31,837–32,237		
			rs211286	G/A	10p11.22	32,046	Intronic	31,846–32,246		
			rs211302	C/G	10p11.22	32,056	Intergenic	31,856–32,226		
ΔCO	Caucasian and African American (n = 701)	38.5	D2S148	-	2q31.2	178,231	Intronic	178,031–178,431	CHROMR, OSBPL6, PDE11A, PRKRA, RBM45	[86]

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. ΔSV, changes in stroke volume by exercise training; ΔCO, changes in cardiac output by exercise training. Bold font indicates genes reported in previous studies as the nearest genes. Plain text genes are additionally identified in the QTL interval.

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 Q 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 Q 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 Q 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 Q 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 suggestive linkages ($0.01 > p > 0.0023$) were also identified (Table 3). Several potential candidate genes were identified near the significant and/or suggestive SNPs. Two follow-up studies were performed to scrutinize the results of the prior study [85,86]. One closely examined genomic region was 2q31 (31th region on the long arm [q] divided by centromere of chromosome 2), where a suggestive linkage was found for SV response to exercise training [86]. Using an additional 12 microsatellite markers, the linkage signal for this region was amplified with an average density of one marker per 2.3 Mb. The authors found the two strongest markers located in and near the *Titin* gene, which is known to be

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 collation of larger cohorts with much denser genome sequencing are required to overcome these limitaions. 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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