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Genetic Influence on Left Ventricular Structure and Function: A Korean Twin and Family Study

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Genetic factors have been suggested to be one of the determinants of the variation of left ventricular (LV) structure and function. However, the heritability range of LV structure varies across studies and the influence of genetics on LV function is not well established, especially in Asian populations. Study subjects were 1,642 healthy Korean adults from 426 families, consisting of 298 pairs of monozygotic twins, 62 pairs of dizygotic twins, one set of triplets, 567 siblings, and 354 parents. LV structure and function were measured by M-mode and 2D echocardiography, and conventional and tissue Doppler imaging (TDI). Pairwise intra-class correlations for various familial relationships and heritability were estimated for LV structure and function. The heritability of LV mass, LV ejection fraction (LVEF), left atrial volume index, the ratio between early and late diastolic velocity of mitral inflow (E/A ratio), and the ratio between early diastolic velocity of mitral inflow and early diastolic mitral annular velocities (E/Ea ratio) was 0.44, 0.27, 0.44, 0.25, and 0.33, respectively. Bivariate genetic analysis showed that LV structural and functional traits had significant genetic correlations with cardiovascular risk factors. Additive genetic correlation (ρ_G) of LV mass with body mass index, systolic blood pressure, and high density lipoprotein cholesterol were 0.49, 0.42, and -0.15 respectively. LVEF ($\rho_G = 0.33$) and left atrial volume index ($\rho_G = 0.24$) also had a significant genetic correlation with systolic blood pressure. These findings support the theory that genetic factors have significant influence on these traits and necessitate further work to identify the specific genes involved.

■ **Keywords:** echocardiography, genetics, heart ventricles, Korean, twin study

Both LV mass and LV function are independent risk factors for morbidity and mortality from cardiovascular disease (Arnlov et al., 2005; Levy et al., 1990). LV mass varies markedly between individuals, and several factors, including age, ethnicity, sex, body size, blood pressure, and valvular heart disease are associated with LV mass (Devereux et al., 1997; Gardin et al., 1995; Levy et al., 1988; Lorber et al., 2003), explaining 50–60% of the variance of LV mass (Devereux et al., 1997; Jones et al., 1997). On the other hand, twin and family studies, including two Asian studies, have reported significant heritability in LV mass (Assimes et al., 2007; Busjahn et al., 2009; Chien et al., 2006), which suggests that genetic factors are involved in the interindividual variation of LV structure. However, the reported heritability of LV mass varied markedly, with a wide range of heritability (15–84%) and it is not clear whether the genetic influence on LV structure is greater than the environmental influence. Given that there were differences in study design (twin or family studies), the origin of study subjects (community-based or hospital-based), adjusted covariates, and ethnicity between the previous studies, a well-designed study is still needed.

LV function is also suggested to be influenced significantly by genetics (Bielen et al., 1991; Fox et al., 2010; Jin et al., 2011; Swan et al., 2003). The heritability of LVEF

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for Belgian (Jin et al., 2011) and hypertensive African American families (Fox et al., 2010) was 0.48 and 0.40 respectively. Among the echocardiographic measures reflecting LV diastolic function, the E peak was moderately heritable (0.37–0.49) in the Belgian twin study (Bielen et al., 1991), the Scottish twin study (Swan et al., 2003), and the hypertensive African American family study (Fox et al., 2010). In addition, the heritability of the A peak for Belgium and African American families was 0.26 and 0.45, respectively. However, the heritability of LV function has never been evaluated for Asian populations.

We conducted a Korean twin and family study in a community setting to evaluate the genetic influence on variation in LV structure and function while considering major cardiovascular risk factors. Using data from both twins and their family members provides a more accurate estimation of heritability because comparison of the phenotypic correlations between various family relationships that reflect different genetic correlations is possible. In addition, we sought to disentangle the genetic and environmental effects on LV structure and function by examining the change in estimated heritability with a stepwise adjustment for covariates and estimating additive genetic correlations between each echocardiographic measurement and each cardiovascular risk factor.

Methods

Subjects and Study Design

Study participants were twins and their siblings or parents who underwent echocardiography during a health examination for the Healthy Twin Study between March 2009 and February 2013. Details of the methodology of the Healthy Twin Study have been reported previously (Sung et al., 2006). In brief, the Healthy Twin Study is a nationwide cohort study recruiting Korean same-sex adult twins (≥ 30 years of age) and their first-degree adult family members from the general population. Among the initial 1,718 subjects, we excluded 76 subjects for the following reasons: insufficient echocardiogram quality ($n = 9$), previous history of ischemic heart disease ($n = 44$), congenital heart disease ($n = 8$), clinically significant heart disease such as moderate-to-severe valvular heart disease or a prosthetic valve ($n = 5$), and regional wall-motion abnormality ($n = 10$). Thus, 1,642 subjects from 426 families were included in the study, which was comprised of 298 pairs ($n = 596$) of monozygotic twins, 62 pairs ($n = 125$; including 1 set of triplets) of dizygotic twins, 567 siblings, and 354 parents. Written informed consent was obtained from all participants.

Measurement of Echocardiography and Covariates

A standard echocardiographic examination was performed according to the guidelines of the American Society of Echocardiography using echocardiography machines (Vivid 7 and Vivid E9, GE Medical System, Horten, Norway, and EKO 7, Medison, Seoul, Korea). All of the echocardiographers who were involved in the present study were registered diagnostic cardiac sonographers accredited by the American Registry for Diagnostic Medical Sonography. All members of the same family underwent echocardiographic measurements taken by a single sonographer with the same machine, while they were lying on their left side. Study participants refrained from smoking, heavy physical activity, and intake of caffeine containing drinks or alcohol for at least 3 hours prior to echocardiographic examination. The following components were measured by M-mode and 2-D echocardiography, and conventional and TDI: left ventricular internal diameter (LVID), interventricular septum (IVS), posterior wall thickness (PWT), left atrial diameter, aortic root diameter, mitral inflow velocities, and mitral annular velocities (Supplementary Table S1). LVID, IVS, and PWT were measured at the end of diastole and at the end of systole, according to the American Society of Echocardiography guidelines (Gottdiener et al., 2004). LVEF was calculated using the biplane Simpson's method. We computed LV mass in grams as $0.8 \times (1.04 \times [\{LVID + IVS + PWT\}^3 - LVID^3]) + 0.6$ (Gottdiener et al., 2004). Mitral inflow and annular velocities were measured using conventional Doppler and TDI techniques. Peak early diastolic velocities (E peak) and peak late diastolic velocities (A peak) of mitral inflow were measured using pulsed wave Doppler at the tip of the mitral valve leaflets. Peak early diastolic mitral annular velocities (Ea peak) and peak late diastolic mitral annular velocities (Aa peak) were acquired on TDI at the septum in apical four-chamber view.

We evaluated the reliability of echocardiographic measurements between different machines (GE and Medison) and between different echocardiographers. The inter-machine intra-class correlation coefficients were estimated in 21 randomly selected persons and were between 0.72–0.92 for LV structural and functional measurements, including ID, IVS, left atrial diameter, aortic root diameter, LVEF, LV mass, E peak, A peak, Ea peak, and Aa peak. The inter-observer intra-class correlation coefficients in 21 randomly selected subjects ranged between 0.64–0.99 for the same echocardiographic measurements (data shown in Supplementary Table S2).

Body weight and height for each participant was measured twice by trained research assistants according to the standardized protocol, and the average value of the repeated measurements was used for calculating body mass index (weight divided by height squared; kg/m^2). A trained research assistant measured blood pressure twice using a mercury sphygmomanometer, and the average value of the repeated measurements was used for analysis.

A blood sample was drawn after a 12-hour overnight fast on the same day that the echocardiographic measurement was taken. Serum concentrations of total cholesterol,

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high-density lipoprotein (HDL) cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol were enzymatically assayed in fresh sera using commercial kits in a designated central laboratory.

We collected information about pre-existing diseases (myocardial infarction, angina, hypertension, diabetes mellitus and dyslipidemia), current treatment for hypertension, diabetes mellitus, and dyslipidemia, smoking habits, alcohol consumption and physical exercise using a self-administered questionnaire. We categorized smoking habits into three groups: never smokers, former smokers, and current smokers. Alcohol consumption was categorized into two groups: ever drinkers and never drinkers. Physical exercise was defined as moderate or vigorous intensity of regular exercise activity and was categorized into three groups by the frequency of exercise per week.

The study protocol was approved by the Institutional Review Board of the Samsung Medical Center.

Statistical Analysis

We estimated the intra-class correlation coefficient for residual variances of echocardiographic measurements after adjusting for age and sex with respect to family relationship using the Statistical Analysis System (SAS Institute, Cary, NC, USA).

We estimated heritability using the Sequential Oligogenic Linkage Analysis Routines (SOLAR, Version 4.2.0; Southwest Foundation for Biomedical Research, San Antonio, TX, USA; Almasy & Blangero, 1998) with adjustment for age, sex, smoking habits, alcohol consumption, physical activity, height, body mass index, systolic blood pressure, fasting glucose, HDL-cholesterol, LDL-cholesterol, antihypertensive medication, diabetes medication and lipid-lowering medication as covariates. Total phenotypic variation (σp^2) in echocardiographic measurements after consideration of the measured covariates was partitioned into additive genetic variation (σa^2), a shared environmental component within a family (σc^2), and an individual specific unique environmental component (σe^2), according to the variance decomposition model. For the non-normally distributed variables, we performed normalization by inverse normal transformation. This model assumed that the effects of environmental factors are common to the members of a family, and that the three factors (σa^2, σc^2, and σe^2) have independent and additive effects on trait variance. The total residual variance is the sum of the additive and individual specific variance components ($\sigma p^2 = \sigma a^2 + \sigma c^2 + \sigma e^2$). The heritability ($h^2$) indicates the proportion of residual variance attributed to additive genetic factors. It was calculated as the ratio of the additive component and the total variance ($\sigma a^2/\sigma p^2$). In order to ascertain whether the echocardiographic measurement and cardiovascular risk factors are concurrently determined by shared genes and the environment, we also conducted bivariate variance-component-based genetic analysis that allows partitioning of phenotypic correlations into genetic (ρ_G) and environmental correlations (ρ_E).

Results

Characteristics and Echocardiographic Measurements of the Study Subjects

Table 1 shows demographic and clinical characteristics of the study subjects. The mean ages (*SD*) of monozygotic twins, dizygotic twins, siblings, and parents were 40.7 (8.1), 41.5 (7.6), 44.7 (9.5), and 65.7 (6.9) years, respectively. As compared with offspring, parents had higher levels of body mass index, systolic and diastolic blood pressure, fasting glucose and triglycerides. Parents were less likely to be current smokers or to drink alcohol. Table 2 shows the distribution of M-mode and Doppler echocardiographic measurements. Compared with offspring, parents had higher mean levels for LV mass, left atrial diameter, aortic diameter, left atrial volume index and E/Ea ratio, and lower mean levels for Ea peak and E/A ratio.

Intra-Class Correlations Between Intrafamilial Pairs and Heritability for Left Ventricular Structure and Function

Table 3 summarizes the intra-class correlations within each pair of diverse familial relationships and heritability for various measurements of LV structure and function. After considering age and sex, intra-class correlation coefficients were highest within monozygotic twin pairs for all echocardiographic measurements. The intra-class correlation coefficients were lowest within spouse pairs for LV mass, LV internal diameter, IVS, left atrial diameter, aortic root diameter, E/A ratio and Ea peak, while the intra-class correlation coefficients for ejection fraction (EF), left atrial volume index and E/Ea ratio were lowest within parent-child pairs. The age and sex-adjusted heritability for all LV structural and functional traits were low to moderate, ranging from 0.25 for IVS and E/A ratio to 0.58 for aortic root diameter. When we made further adjustments for other measured covariates, the level of heritability did not materially change. All measured covariates explained about 8.3% to 63.2% of the total variance for most LV structural and functional traits.

Additive Genetic Correlations Between Echocardiographic Measurements and Cardiovascular Risk Factors

Table 4 shows the additive genetic correlations between each echocardiographic measurement and each cardiovascular risk factor. Body mass index had a moderate-to-high level of genetic correlation with LV structural traits and diastolic functional traits. Systolic blood pressure had a significant correlation with most echocardiographic measurements except for aortic root diameter and E/A ratio. Glucose was genetically correlated with left atrial diameter and LV diastolic functional traits. LDL-cholesterol was genetically correlated with only Ea peak. HDL-cholesterol had a negative genetic

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TABLE 1

Characteristics of Study Subjects

	Monozygotic twins		Dizygotic twins		Siblings		Parents	
Number of subjects, pairs/persons	298 pairs		62 pairs		567 persons		354 persons	
Age (years)	40.7	(8.1)	41.5	(7.6)	44.7	(9.5)	65.7	(6.9)
Male (%)	34.6		41.6		42.9		37.6	
Body mass index (kg/m^2)	23.1	(2.9)	23	(2.8)	24.1	(3.2)	24.6	(3.2)
Height (cm)	161.6	(8.0)	163.1	(8.6)	163.6	(8.7)	158.5	(8.3)
Systolic blood pressure (mmHg)	107.0	(14.9)	110.7	(14.4)	111.5	(15.8)	119.9	(15.1)
Diastolic blood pressure (mmHg)	67.3	(10.5)	69.5	(10.6)	70.0	(10.9)	71.9	(8.9)
Smoking habit								
Ex-smoker (%)	11.2		13.6		14.3		18.1	
Current smoker (%)	19.6		19.2		22.8		9.3	
Ever drink alcohol (%)	84.4		88.0		80.8		57.1	
Physical exercise (%)								
1–2/week	16.3		10.4		11.6		7.6	
3–4/week	12.9		14.4		16.2		18.4	
≥ 5/week	8.1		10.4		9.5		16.9	
Fasting glucose (mmol/L)	5.2	(1.2)	5.0	(0.7)	5.2	(1.0)	5.6	(1.4)
Total cholesterol (mmol/L)	4.9	(0.9)	5.0	(0.9)	5.0	(0.9)	5.0	(0.9)
HDL-C (mmol/L)	1.3	(0.3)	1.2	(0.3)	1.3	(0.3)	1.2	(0.3)
LDL-C (mmol/L)	2.9	(0.9)	3.1	(0.8)	3.0	(0.8)	3.1	(0.9)
Triglycerides (mmol/L)	1.2	(1.0)	1.3	(0.7)	1.4	(1.0)	1.5	(1.0)
Diabetes medication (%)	2.3		0.8		2.1		8.2	
Anti-hypertensive medication (%)	5.7		11.2		6.9		24.6	
Lipid lowering medication (%)	3.4		1.6		2.8		9.3	

Note: Data are expressed as mean (standard deviation) or percentage; HDL-C = High density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol.

TABLE 2

Echocardiographic Measurements of Study Subjects

	Monozygotic twins		Dizygotic twins		Siblings		Parents	
	(298 pairs)		(62 pairs)		(567 persons)		(354 persons)	
M-mode/2D echocardiography								
LV mass (g)	113.2	(31.5)	115.9	(31.1)	123.1	(33.5)	129.4	(31.8)
LV internal diameter (mm)	48.3	(4.0)	48.4	(3.6)	48.8	(3.8)	48.2	(4.2)
Interventricular septum (mm)	7.2	(1.2)	7.4	(1.3)	7.7	(1.4)	8.1	(1.3)
Left atrial diameter (mm)	33.8	(4.4)	34.5	(4.6)	34.9	(4.4)	35.9	(5.0)
Aortic root diameter (mm)	28.7	(3.5)	28.7	(3.8)	30.0	(4.1)	32.3	(3.9)
Ejection fraction (%)	62.7	(5.4)	63.0	(6.0)	63.7	(5.7)	66.2	(5.9)
Left atrial volume index (ml/m^2)	26.3	(5.1)	27.3	(5.7)	26.9	(5.7)	29.8	(7.7)
Doppler echocardiography								
E/A ratio	1.52	(0.5)	1.52	(0.4)	1.38	(0.5)	0.83	(0.3)
Ea peak (cm/s)	11.0	(2.5)	10.9	(2.3)	10.0	(2.8)	6.8	(1.9)
E/Ea ratio	7.0	(1.7)	7.0	(1.7)	7.4	(2.2)	9.3	(3.1)

Note: Data are expressed as mean (standard deviation); LV = left ventricle; E peak = peak early diastolic velocity of mitral inflow; A peak = peak late diastolic velocity of mitral inflow; Ea peak = peak early diastolic mitral annular velocity.

correlation with most LV structural traits and a positive correlation with E/A ratio.

We also estimated the changes in heritability and variance of each echocardiographic measurement when each cardiovascular risk factor was additionally considered in the heritability estimation model. Among the cardiovascular risk factors, body mass index was found to explain more than 5% of the total variance of several LV structural traits (left atrial diameter, LV mass, and LV internal diameter) and LV functional traits (Ea peak and E/Ea ratio). Systolic blood pressure explained 5% and 5.1% of the total variance of LV mass and left atrial diameter, respectively. Glucose, LDL-cholesterol and HDL-cholesterol explained less than 3% of the total variance for all LV structural and functional traits.

Discussion

In this Korean study of twins and their families, we found that most LV structural and functional traits were under significant genetic influence, with moderate-to-low levels of heritability.

Among LV structural measurements, LV mass has been the most frequently studied in terms of the estimation of heritability. The level of heritability of LV mass in our twin and family study was similar to that estimated in previous family studies (Jin et al., 2011; Mayosi et al., 2002; Post et al., 1997; Vasan et al., 2007), while it was lower than that estimated in twin-only studies (Busjahn et al., 2009; Sharma et al., 2006; Swan et al., 2003). Twin pairs are more likely to share environmental factors with each other than

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TABLE 3

Intra-Class Correlations Between Diverse Intrafamilial Pairs and Estimated Heritability for Left Ventricular Structure and Function

	Age- and sex-adjusted intra-class correlation coefficient (95% confidence interval)								Model 1*		Model 2†		Model 3‡	
Echocardiographic measurements	Monozygotic twins (266 pairs)		Siblings and dizygotic twins (660 pairs)		Spouse (109 pairs)		Parents–child (1,112 pairs)		Heritability (SE)	Variance explained	Heritability (SE)	Variance explained	Heritability) (SE)	Variance explained
LV mass	0.56	(0.50, 0.61)	0.25	(0.17, 0.33)	−0.01	(−0.14, 0.13)	0.25	(0.19, 0.30)	0.55(0.04)	28.7%	0.55(0.04)	28.7%	0.44(0.04)	47.1%
LV internal diameter	0.57	(0.51, 0.62)	0.18	(0.10, 0.26)	−0.06	(−0.19, 0.07)	0.20	(0.15, 0.26)	0.51(0.04)	17.6%	0.51(0.04)	17.6%	0.47(0.04)	31.9%
Interventricular septum	0.34	(0.27, 0.41)	0.13	(0.05, 0.21)	0.08	(−0.06, 0.21)	0.16	(0.10, 0.21)	0.30(0.04)	16.7%	0.30(0.04)	17.0%	0.25(0.04)	24.9%
Left atrial diameter	0.52	(0.46, 0.58)	0.23	(0.15, 0.31)	−0.20	(−0.33, −0.07)	0.13	(0.07, 0.19)	0.48(0.04)	12.8%	0.48(0.04)	13.0%	0.38(0.05)	37.4%
Aortic root diameter	0.55	(0.49, 0.61)	0.35	(0.28, 0.42)	0.19	(0.06, 0.32)	0.22	(0.17, 0.28)	0.60(0.03)	42.0%	0.60(0.03)	42.1%	0.58(0.04)	47.3%
Ejection fraction	0.26	(0.18, 0.33)	0.15	(0.07, 0.23)	0.22	(0.09, 0.34)	0.13	(0.08, 0.19)	0.27(0.04)	8.0%	0.27(0.04)	8.0%	0.27(0.04)	8.3%
Left atrial volume index	0.39	(0.32, 0.46)	0.25	(0.17, 0.33)	0.25	(0.12, 0.37)	0.21	(0.15, 0.26)	0.43(0.04)	7.8%	0.43(0.04)	8.0%	0.44(0.04)	10.1%
E/A ratio	0.33	(0.26, 0.40)	0.20	(0.12, 0.28)	0.07	(−0.07, 0.20)	0.14	(0.08, 0.20)	0.27(0.04)	48.0%	0.27(0.04)	48.0%	0.25(0.04)	53.1%
Ea peak	0.48	(0.41, 0.54)	0.18	(0.10, 0.26)	0.05	(−0.08, 0.18)	0.21	(0.16, 0.27)	0.49(0.04)	53.9%	0.49(0.04)	53.9%	0.41(0.05)	63.2%
E/Ea ratio	0.37	(0.30, 0.44)	0.19	(0.11, 0.27)	0.18	(0.04, 0.30)	0.15	(0.09, 0.21)	0.39(0.05)	23.1%	0.39(0.05)	23.1%	0.33(0.05)	31.3%

Note: SE = standard error; LV = Left ventricle; E peak = peak early diastolic velocity of mitral inflow; A peak = peak late diastolic velocity of mitral inflow; Ea peak = peak early diastolic mitral annular velocity; Model 1* = adjusted for age and sex; Model 2† = adjusted for age, sex, smoking, alcohol and physical activity; Model 3‡ = adjusted for age, sex, smoking, alcohol, physical activity, height, body mass index, systolic blood pressure, antihypertensive medication, fasting glucose, diabetes medication, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and lipid lowering medication. All estimates were significant ($p < .05$) compared to 0.

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TABLE 4

Additive Genetic Correlation (ρ_G) Between Echocardiographic Measurement and Cardiovascular Risk Factors and the Influence of Additional Adjustment* for Cardiovascular Risk Factors on the Estimation of Heritability

	Height			Body mass index			Systolic blood pressure			Glucose†			LDL-cholesterol‡			HDL-cholesterol‡		
		Change			Change			Change			Change			Change			Change	
	ρ_G (SE)	VAR	h^2	ρ_G (SE)	VAR	h^2	ρ_G (SE)	VAR	h^2	ρ_G (SE)	VAR	h^2	ρ_G (SE)	VAR	h^2	ρ_G (SE)	VAR	h^2
LV mass	0.39(0.04)§	5.4%	−0.04	0.49(0.05)§	11.2%	−0.04	0.42(0.07)§	5.0%	−0.04	0.11(0.08)	0%	0	0.10(0.07)	0%	0	−0.15(0.06)§	0.9%	−0.01
LV internal diameter	0.36(0.04)§	5.3%	−0.03	0.39(0.06)§	8.2%	−0.02	0.21(0.08)§	1.2%	−0.01	0.11(0.08)	0.1%	0	0.01(0.07)	0%	0	−0.16(0.06)§	0.6%	−0.01
Interventricular septum	0.29(0.06)§	1.9%	−0.02	0.32(0.08)§	3.9%	−0.01	0.30(0.09)§	3.4%	−0.02	0.05(0.10)	0%	0	0.08(0.08)	0.5%	0.01	−0.10(0.07)	0.8%	−0.01
Left atrial diameter	0.15(0.05)§	1.3%	0	0.64(0.05)§	22.4%	−0.09	0.31(0.08)§	5.1%	−0.02	0.33(0.09)§	1.0%	−0.02	0.14(0.07)	1.1%	0	−0.19(0.06)§	2.2%	−0.01
Aortic root diameter	0.29(0.04)§	2.6%	−0.09	0.25(0.06)§	1.6%	−0.07	0.22(0.08)	0.7%	−0.05	0.11(0.08)	0.2%	−0.06	0.06(0.07)	0.1%	−0.06	−0.23(0.06)§	0%	−0.06
Ejection fraction	−0.07(0.06)	0%	0	0.07(0.09)	0.3%	0	0.33(0.10)§	0.5%	−0.01	0.003(0.10)	0%	0	0.10(0.09)	0%	0	0.11(0.08)	0%	0
Left atrial volume index	0.05(0.05)	0%	0	0.07(0.07)	0.2%	0	0.24(0.08)§	1.4%	−0.01	0.09(0.08)	0.3%	0.01	−0.03(0.07)	0.1%	0	0.05(0.06)	0%	0
E/A ratio	−0.02(0.06)	0%	0	−0.48(0.07)§	3.3%	−0.03	−0.15(0.09)	2.4%	0	−0.26(0.10)§	0.8%	−0.01	−0.13(0.08)	0.7%	0	0.20(0.07)§	0.4%	−0.01
Ea peak	0.05(0.05)	0.2%	−0.04	−0.54(0.06)§	6.2%	−0.11	−0.36(0.07)§	4.4%	−0.10	−0.18(0.09)§	1.4%	−0.04	−0.26(0.07)§	2.1%	−0.06	0.003(0.30)	0.3%	−0.04
E/Ea ratio	−0.03(0.05)	0.2%	0	0.38(0.08)§	5.5%	−0.04	0.41(0.09)§	4.1%	−0.04	0.22(0.09)§	1.2%	−0.02	0.13(0.08)	0.1%	0	−0.07(0.07)	0.3%	0

Note: SE = standard error; LV = Left ventricle; E peak = peak early diastolic velocity of mitral inflow; A peak = peak late diastolic velocity of mitral inflow; Ea peak = peak early diastolic mitral annular velocity; LDL = low density lipoprotein; HDL = high density lipoprotein; VAR = change in variance explained by covariates after the additional adjustment for each specific factor; h^2 = heritability change by the additional adjustment for each specific factor; *Adjusted for each selected variable in addition to age, sex, smoking, alcohol, and physical activity; †Fasting glucose and diabetic medication ‡lipid profile and lipid lowering medication; §$p < .05$.

the other pairs of non-twin family members, which makes it difficult to dissect environmental effects from genetic effects in twin-only studies unless sample sizes are very large. Thus, the estimation of heritability may be biased upwards in twin-only studies. Similarly, family-only studies that do not include twins also cannot separate genetic effects from common environmental effects. The combined twin and family design of our study could overcome the limitations of twin-only or family-only studies and provides a more accurate estimation of heritability by comparing the phenotypic correlations between diverse family relationships of different genetic correlations (Libhaber et al., 2009).

Among ethnic groups, the heritability of LV mass tends to be higher for African–Americans (0.34–0.72; Fox et al., 2010; Harshfield et al., 1990; Kotchen et al., 2000) and those of Caribbean Hispanic descent (0.49; Juo et al., 2005) than for Americans, Europeans (0.076–0.32; Devereux et al., 1997; Garner et al., 2000; Mayosi et al., 2002; Palatini et al., 2001; Post et al., 1997), or American Indians (0.17; Bella et al., 2004). There have been two studies of heritability of LV structure for Asian populations (Assimes et al., 2007; Chien et al., 2006). The heritability of LV mass was estimated to be 0.43 for Japanese hypertensive families and 0.61 for a population-based sample of families living in Hawaii (Assimes et al., 2007), whereas it was only 0.15 for Taiwanese families (Chien et al., 2006). In the present study of Korean twins and families, the magnitude of heritability of LV mass (0.44) was between that of Japanese families living in Hawaii (Assimes et al., 2007) and that of the Taiwanese family study (Chien et al., 2006). Given the data for LV mass heritability in Asians, including data from our study, the heritability of LV mass for the Asian population seems to be in between African–American and Caucasian descendants.

Estimated heritability of LVEF in the present study was 0.27, which suggests that environmental factors rather than genetic influence may make a greater contribution to determining LVEF for the Korean population. However, in our study, all of the measured covariates explained only 8% of the variance of LVEF, and none of the known cardiovascular risk factors was found to explain greater than 1% of the total variance. Thus, further study is needed to identify other candidate factors that may significantly explain the variance of LVEF. Compared with the Belgium family study (0.48; Jin et al., 2011) and hypertensive African American family study (0.40; Fox et al., 2010), the heritability of LVEF in our study was much lower. However, we could not determine the reason for the differences between studies.

We found that all LV diastolic functional measurements had significant low-to-moderate heritability (ranging from 0.25 for E/A ratio to 0.44 for left atrial volume index) in our Korean population. Similar to our estimates, the Belgium twin study (Bielen et al., 1991), the Scottish twin study (Swan et al., 2003) and the hypertensive African American family study (Fox et al., 2010) reported moderate heritability of the E peak (0.43, 0.49 and 0.37, respectively). In the Belgium twin study and African American family study, the heritability of the A peak was 0.26 and 0.45, respectively. However, the Scottish twin study reported that the estimated heritability of the A peak and E/A ratio was not significant, which is not compatible with the results of our study.

Interesting findings in the present study were that LV structural and diastolic functional traits had significant genetic correlations with several cardiovascular risk factors such as body size, systolic blood pressure, serum glucose, and cholesterol. This finding suggests the presence of cross-phenotype genetic association and seems to be compatible with previous findings from the HyperGEN study that reported a pleiotropic locus on chromosome 7 contributing to the variation of both LV wall thickness and BMI in the Caucasian population (Tang et al., 2009). However, considering that cardiovascular risk factors may cause change in LV structural and functional traits, the genetic correlations between these traits found in our study may indicate a mediated pleiotropic effect rather than a biological pleiotropic effect, and further study would be needed to characterize the underlying cause of the observed genetic correlation (Solovieff et al., 2013)

Our study had several strengths. First, we considered a wide range of covariates that may affect the heritability estimation of LV structure and function. This may have resulted in a more accurate estimation of genetic influence. Second, our study included both twins and their family members as study subjects, which could have provided a more accurate estimation of heritability (Libhaber et al., 2009). Third, we estimated the heritability of LV diastolic function by both conventional Doppler and TDI techniques. Compared with conventional Doppler assessments of diastolic function, TDI assessment is less load-dependent and is considered to be a good surrogate measure of LV relaxation. Fourth, we demonstrated the moderate heritability of the left atrial volume index, which reflected the diastolic burden and is a predictor of adverse cardiovascular outcomes such as atrial fibrillation, stroke and congestive heart failure (Abhayaratna et al., 2006).

Despite these strengths, there are several limitations to this study. First, this study addresses heritability in a narrow sense without considering dominance variance. Second, several echocardiographers and two different types of machines were involved in the measurement of LV structure and function, which could be a source of bias. We sought to minimize the bias by using echocardiographic measurements of participants from the same family, performed by the same operator on the same machine. In addition, we evaluated inter-observer repeatability and inter-machine repeatability by intra-class correlations, which were moderate-to-high levels. Despite these precautions, the possibility that inter-observer and inter-machine variability might have led to an underestimation of heritability cannot be entirely excluded. Third, the mean level of LVEF

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was unexpectedly higher for the parent group than for the other offspring groups in our study. Given that EF tends to decrease with aging, a higher LVEF in the parent group than in the offspring groups is an unusual finding. This may have been caused by the strict exclusion criteria (previous myocardial infarction and impaired systolic function such as regional wall-motion abnormality) of our study. Most subjects who were excluded from the study belonged to the parent group and, thus, a relatively greater proportion of echocardiographically healthy subjects from the parent group compared to the offspring group may have been included in the study. However, we could not estimate the impact of this situation on the estimation of heritability.

In conclusion, this Korean twin and family study found that both LV function and structure were moderately heritable and had significant genetic correlations with several cardiovascular risk factors. This finding supports a discernible role of genetic influence on the LV structure and function of the Korean population and necessitates further genetic studies to identify candidate genes.

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Supplementary Material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/thg.2015.18.

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