Electrocardiographic Indices of Left Ventricular Hypertrophy and Repolarization Phase Share the Same Genetic Influences: A Twin Study

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Background: Both left ventricular hypertrophy (LVH) and repolarization phase (RP) are known to be attributable to genetic influences, but less is known whether they share same genetic influences. The aim of this study was to investigate to what extent individual differences in electrocardiographic (ECG) LVH and RP are explained by genetic and environmental influences and whether these influences are shared between these two traits.

Methods: Resting ECG recordings were obtained from 186 monozygotic and 203 dizygotic female twin individuals, aged 63 to 76 years. Latent factors, called LVH and RP, were formed to condense the information obtained from LVH indices (Cornell voltage and Cornell product) and T-wave amplitudes (leads V₅ and II), respectively. Multivariate quantitative genetic modeling was used both to decompose the phenotypic variances into additive genetic, common environmental, and unique environmental influences, and for the calculation of genetic and environmental correlations between LVH and RP.

Results: Additive genetic influences explained 16% of individual differences in LVH and 74% in RP. The remaining individual differences were explained by both common and unique environmental influences. The genetic correlation and unique environmental correlation between LVH and RP were -0.93 and -0.05 , respectively.

Conclusions: In older women without overt cardiac diseases, RP is under stronger genetic control than LVH. The majority of genetic influences are shared between LVH and RP whereas environmental influences are mainly specific to each.

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heritability; shared genetic influences; left ventricular hypertrophy; repolarization phase; aging

Left ventricular hypertrophy (LVH), most commonly resulting from chronic hypertension, obesity and/or increasing age,^{1,2} is a significant predictor of cardiovascular morbidity and mortality.³ The hypertrophied left ventricular wall finally causes detrimental changes in cardiac function, such as repolarization abnormalities,^{4–6} manifested by ST

segment depression and inverted T waves. T wave changes (both isolated and those related to LVH) are also associated with increased cardiovascular morbidity and mortality.^{7–10} The prevalence of both LVH and T-wave abnormalities strongly increase with age^{9,11} so that study of the underlying factors (either genetic or environmental) is

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important, especially in women due to their longer life expectancy.¹²

Previous studies have shown that left ventricular mass (LVM) and hypertrophy are affected by genetic factors in both men and women. Echocardiographic studies have reported varying estimates of the relative contribution of genetic influences to LVM, ranging from approximately 20–30%^{13–15} to 60–70%.^{16,17} The estimates for electrocardiographic (ECG) LVH indices are similar. For example, in a large family study Mayosi et al.¹⁴ reported that about 20–40% of interindividual differences in LVH indices (Sokolow-Lyon voltage, Cornell voltage, and Cornell product) were attributable to genetic influences whereas a previous twin study in older women showed slightly higher estimates for these indices (55–57%).¹⁸ T-wave characteristics also are strongly heritable traits. In older women, estimates of genetic influences have been reported to be about 50–70%.¹⁸ However, less is known whether these genetic influences are the same or distinct for LVM/LVH and T waves, that is, whether the same genetic (and/or environmental) factors explain the association between increased ventricular wall thickness/mass and subsequent repolarization abnormalities.

The aim of this study was to determine to what extent individual differences in ECG LVH and repolarization phase (RP) are explained by genetic and environmental influences and whether these influences are shared between these two traits in older female twins without overt cardiac diseases.

METHODS

Participants

The present study is part of the Finnish Twin Study on Aging (FITSA), a study of genetic and environmental influences on the disablement process in older women. The study sample was recruited from the nationwide Finnish Twin Cohort,¹⁹ which comprises all same-sex twins born in Finland before 1958 with both cotwins alive in 1975. On the basis of age and zygosity, an invitation to participate in FITSA was sent to 414 twin-sister pairs aged 63 to 76 years surviving in 2000. Details on recruitment have been described earlier²⁰ and are briefly summarized here. To be included, both twin pair members had to agree to participate. The reasons for nonparticipation were that one or both

sisters were unwilling to take part (106 pairs), had poor health status (85 pairs), or had died after vital status was last updated for all cohort members (6 pairs). As a result of the procedures, the study group consisted of 217 twin sister pairs, comprising 103 monozygotic (MZ) and 114 dizygotic (DZ) pairs. The zygosity of the participating pairs was determined using a battery of 10 highly polymorphic gene markers in DNA extracted from a venous blood sample.

Because specific conduction abnormalities make it impossible to interpret resting ECG features in a meaningful way, participants with left bundle branch block ($n = 16$), right bundle branch block ($n = 9$), and left anterior hemiblock ($n = 1$) were excluded from the statistical analyses. Myocardial infarction has an effect on resting ECG variables and thus participants with myocardial infarction ($n = 19$) were also excluded from the analyses. In addition, participants with pacemakers ($n = 4$) were excluded. After these exclusions, the number of participants included in the statistical analyses was 186 MZ and 203 DZ individuals (number of complete pairs was 86 MZ and 91 DZ pairs). Twin individuals without their cotwins can be included in the analyses since the statistical methodology used in the present analyses can also utilize data from unpaired twin individuals, enabling more accurate estimates of genetic and environmental influences than would be obtained if data from complete twin pairs alone are used.

The study was conducted according to the ethical standards stated in the Declaration of Helsinki. All the participants were informed about the study and they signed a written informed consent. The study was approved by the ethics committee of the Central Hospital of Central Finland.

ECG Measurements

Standard 12-lead resting ECG was recorded at 25 mm/s and 1 mV/cm standardization using a Nihon Kohden Cardiofax V Ecaps 12 (Nihon Kohden Corporation, Tokyo, Japan). The ECG variables used in the statistical analysis were predetermined and they were selected as follows. Cornell voltage ($RaVL + SV_3$)^{21,22} and Cornell product (Cornell voltage $\times$ QRS duration)²³ were used as indices of LVH, since these indices are among the most commonly used in clinical practice and have somewhat greater sensitivities and specificities in diagnosing of LVH compared to some other

widely used LVH indices.²⁴ T-wave amplitudes were measured from leads V₅ and II, which are among the T-wave variables most significantly associated with cardiovascular morbidity and mortality.^{7–9} T-wave amplitudes and the components of Cornell voltage were measured manually, and QRS duration was collected from the automatic listing of the ECG recorder. All ECG measurements were carried out blinded to zygosity and cotwin's data.

Clinical Examination

All participants were clinically examined by a physician. Self-reports of acute and chronic diseases and medication had been obtained earlier and were confirmed in the clinical examination. These included the history of myocardial infarction and the presence of a pacemaker (exclusion criteria), and the use of beta-blockers, which was taken into account in the statistical analyses as described below. Beta-blocker users numbered 47 MZ and 63 DZ individuals and nonusers 139 MZ and 140 DZ individuals.

Statistical Analysis

The sample description and data normality tests (Kolmogorov-Smirnov) were computed using SPSS 14.0 (SPSS Inc., Chicago, Illinois, USA). LVH indices and T-wave variables were normalized and then standardized by age and use of beta-blockers using the PROC RANK and PROC STANDARD procedures in SAS 8.2 (SAS Institute Inc., Cary, NC, USA). This transformation both reduces non-normality and standardizes the variables so that the means and variances are independent of age variability and use of beta-blockers in the sample. Thus, age and use of beta-blockers will not bias the parameter estimates in subsequent genetic analyses. The equality of the means of the participants' characteristics and studied ECG variables between the MZ and DZ twin individuals was analyzed with the adjusted Wald test and the equality of variances was tested with the variance ratio test, taking into account the dependence of observations between the cotwins (Stata 8.0, Stata Corp., College Station, TX, USA). Phenotypic correlations between the LVH indices and T-wave amplitudes in the whole sample were calculated with Mx software,²⁵ which also takes into account the dependence of observations between cotwins.

The relative contribution of genetic and environmental influences to each latent factor (see later)

or measured ECG variable was estimated using quantitative genetic modeling. The method is based on the fact that MZ cotwins share 100% of their genes whereas DZ cotwins share on average 50% of their segregating genes. Both types of twins are assumed to share to the same extent their environment relevant to the traits under study. Genetic influences cause greater similarity between MZ cotwins than DZ cotwins while shared environment leads to greater similarity between both MZ and DZ cotwins. Environmental influences not shared by the cotwins contribute to differences between them. Consequently, the total variance in a phenotype can be decomposed into additive genetic influences (A), dominance genetic influences (D), common environmental influences (C) and unique environmental influences (E). A refers to the sum of the effects of the individual alleles over the loci whereas D refers to interactions between alleles at the same or different loci. Hence, A + D is considered (broad sense) heritability or overall genetic influence on the trait under study. C includes factors that are shared by both cotwins, such as those related to their childhood environment, and E consists of exposures that are not shared by the cotwins, such as diseases that have affected only one sibling within a pair. E also includes measurement error as this is a random effect not correlated between twins.²⁶

To obtain preliminary information on the importance of the genetic contribution to LVH indices and T-wave amplitudes, intraclass correlation coefficients (ICC) were computed separately for the MZ and DZ pairs (SPSS 14.0, SPSS Inc.). The involvement of genetic influences is supported if the pair-wise correlation for a phenotype in MZ pairs is significantly higher than that in DZ pairs. Afterward, univariate genetic models were computed to estimate the relative contribution of genetic and environmental influences to each of the four phenotypes.

Multivariate quantitative genetic modeling was used for final analyses. As significant phenotypic correlations between the two LVH indices and between the two T-wave variables were observed, a common pathway model with two latent factors, called LVH and RP, were built and tested. The term "latent factor" means that the factor is not directly observable but it can be statistically estimated through the information available from the observed (measured) variables. In the present study, latent factors LVH and RP condensed the

information obtained from LVH indices and T-wave amplitudes, respectively.

The tested models (including all the possible combinations of A, C, and E; D was excluded since univariate analyses showed no dominance genetic influences on single ECG variables) were fitted to the raw data by Mx software²⁵ using maximum likelihood algorithms and treating unobserved data as missing-at-random. This enabled the estimation of both factor-specific (LVH or RP) and trait-specific (Cornell voltage, Cornell product, TV₅, TII) genetic and environmental influences. The latter describe the proportion of individual differences not explained by the genetic or environmental influences of a latent factor. Factor loadings from the latent factors to the observed data were also calculated to determine the degree of relationship between a latent factor and an observed variable.²⁶

The significance of the estimates for A, C, and E was tested by removing them sequentially in different submodels. The fit of the different models to the raw data were tested by analyzing standard likelihood-ratio tests and the Akaike's Information Criterion ($AIC = -2 \times \log\text{-likelihood} - 2 \times \text{degrees of freedom}$).²⁷ The AIC compares models on the basis of parsimony, taking into account the likelihood of every model and its degrees of freedom. Smaller AIC values indicate a better fit of the model. This sequential procedure eventually led to a model in which the pattern of variances and covariance was explained by as few influences as possible, provid-

ing an acceptable fit to the data. Final estimates of factor- and trait-specific genetic and environmental influences with 95% confidence intervals were obtained from the most parsimonious and theoretically acceptable multivariate model. To estimate the overlap between the sets of genes influencing the LVH and RP factors, the genetic correlation between the two sets was calculated. Correlations for common and unique environmental influences were calculated similarly.

RESULTS

The general characteristics, LVH indices and T-wave amplitudes of the MZ and DZ individuals are presented in Table 1. There were no statistically significant differences between the MZ and DZ individuals in means and variances, except for variance of age. Phenotypic correlations (for the whole sample) between the LVH indices and T-wave amplitudes ranged from -0.28 between Cornell product and TII to -0.31 between Cornell voltage and TV₅. The phenotypic correlation between TV₅ and TII was 0.78 and between Cornell voltage and Cornell product it was 0.98 .

The ICCs of the LVH indices and T-wave amplitudes were higher in the MZ than DZ pairs, suggesting the presence of genetic influences. The results of univariate genetic modeling were previously published as a part of another article,¹⁸ and are only briefly summarized here. All four

Table 1. Participant Characteristics, Electrocardiographic Left Ventricular Hypertrophy Indices and T-Wave Amplitudes by Zygosity

Characteristic	MZ Individuals (n = 186) Mean ± SD	DZ Individuals (n = 203) Mean ± SD	Total (n = 389) Mean ± SD	P*	P†
Age, years	68.1 ± 3.7	68.8 ± 3.1	68.5 ± 3.4	0.135	0.007
Height, cm	158.0 ± 6.4	159.1 ± 5.7	158.6 ± 6.0	0.191	0.097
Weight, kg	69.6 ± 12.0	70.6 ± 12.4	70.2 ± 12.2	0.517	0.628
Body mass index, kg/m ²	28.1 ± 4.9	28.0 ± 4.8	28.0 ± 4.8	0.866	0.767
Cornell voltage,‡ mV	1.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.5	0.724	0.119
Cornell product,§ mV × ms	98.9 ± 45.3	102.5 ± 48.8	100.8 ± 47.1	0.640	0.179
TV ₅ , mV	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.2	0.138	0.661
TII, mV	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.053	0.879

DZ = dizygotic; MZ = monozygotic; SD = standard deviation.

*For the equality of the means between the MZ and DZ individuals, based on adjusted Wald test. In four electrocardiographic variables, the equality of the means was analysed using variables standardized by age and use of beta-blockers;

†For the equality of the variances between the MZ and DZ individuals, based on the variance ratio test. In four electrocardiographic variables, the equality of the variances was analyzed using variables standardized by age and use of beta-blockers;

‡RaVL + SV₃.

§Cornell voltage (RaVL + SV₃) × QRS duration.

Figure 1. The best fitting common pathway model for the electrocardiographic (ECG) left ventricular hypertrophy (LVH) and repolarization phase (RP) factors, which combine the variance from the measured LVH indices and T-wave amplitudes. The percentages (95% confidence intervals) in the upper part of the figure are the proportions of the total variance of each latent factor explained by additive genetic (A), common environmental (C), or unique environmental (E) influences. The percentages (95% confidence intervals) in the lower part of the figure are the proportions of each measured ECG variable explained by trait-specific additive genetic (A_S) and unique environmental (E_S) influences. r_g and r_e refer to the correlation of additive genetic and unique environmental influences between the LVH and RP factors, respectively. The factor loadings of the LVH and RP factors on the measured ECG variables are shown with *. Cornell voltage = $RaVL + SV_3$; Cornell product = Cornell voltage $\times$ QRS duration.

variables were best explained by the models with additive genetic and unique environmental influences (AE). The estimates of additive genetic influences ranged from 55% for Cornell voltage to 72% for TV_5 . The best fitting common pathway model with two latent factors is shown in Figure 1 and the model-fitting statistics for all the submodels in Table 2. Additive genetic (16% for LVH and 74% for

RP) and unique environmental influences (49% for LVH and 26% for RP) explained individual differences in both the LVH and RP factors whereas common environmental influences (35%) were found only for LVH. Between the LVH and RP factors, the genetic correlation for additive genetic influences was -0.93 , while the correlation for unique environmental influences was -0.05 . The factor loadings of the LVH and RP factors on

Table 2. Multivariate Model-Fitting Statistics for all the Submodels

Influences on Latent Factors*			Trait-Specific Influences*				Fitting Statistics†				
LVH	RP	r	Cornell Voltage	Cornell Product	TV ₅	TII	–2LL	df	χ ² (Δdf)	P	AIC
ACE	ACE	r _g , r _c , r _e	A _s , C _s , E _s	A _s , C _s , E _s	A _s , C _s , E _s	A _s , C _s , E _s	2040.334	1528	–	–	–651.666
ACE	ACE	r _g , r _c , r _e	A _s , E _s	A _s , E _s	A _s , E _s	A _s , E _s	2405.370	1532	1.036 (4)	0.904	–658.630
ACE	ACE	r _g , r _c , r _e	C _s , E _s	C _s , E _s	C _s , E _s	C _s , E _s	2407.399	1532	3.065 (4)	0.547	–656.601
ACE	ACE	r _g , r _c , r _e	E _s	A _s , E _s	E _s	A _s , E _s	2045.370	1534	1.036 (6)	0.984	–662.630
ACE	ACE	r _g , r _c , r _e	E _s	E _s	E _s	E _s	2418.644	1536	14.310 (8)	0.074	–653.356
ACE	AE	r_g, r_e	E_s	A_s, E_s	E_s	A_s, E_s	2407.662	1536	3.328 (8)	0.853	–664.662
ACE	AE	r _e	E _s	A _s , E _s	E _s	A _s , E _s	2428.154	1536	24.623 (8)	0.002	–643.043
AE	AE	r _g , r _e	A _s , E _s	A _s , E _s	A _s , E _s	A _s , E _s	47059.141	1536	44654.807 (7)	<0.001	43989.141

AIC = Akaike's information criterion ($-2 \times \log$ -likelihood $-2 \times$ degrees of freedom); Cornell product = Cornell voltage $\times$ QRS duration; Cornell voltage = RaVL + SV₃; df = degrees of freedom; χ^2 (Δ df) = difference chi-square (and increment in degrees of freedom) with respect to the saturated (full) model (the submodel in the first row); LL = log-likelihood; LVH = electrocardiographic left ventricular hypertrophy; RP = repolarization phase.

*Each row represents one submodel, that is, a specific combination of genetic/environmental influences (on latent factors or measured electrocardiographic variables) and genetic/environmental correlations between latent factors. A, C, and E refer to additive genetic, common environmental, and unique environmental influences, respectively, which affect each latent factor, whereas A_s , C_s , and E_s are trait-specific additive genetic, common environmental, and unique environmental influences, respectively. r_g , r_c , and r_e represent genetic, common environmental, and unique environmental correlations, respectively.

†Fitting statistics describe how well a hypothetical submodel fits to the present data. The smaller the value of AIC, the better the fit of the model. For more details, see the Statistical Analysis section and reference no. 26.

The best fitting common pathway model is shown in bold.

the measured ECG variables ranged from 0.19 to 0.91.

Trait-specific additive genetic and unique environmental influences were also found for the measured LVH indices and T-wave amplitudes. Trait-specific additive genetic influences were found for Cornell product and TII, but they accounted for a small proportion of the overall variance (1% and 8%, respectively). Trait-specific unique environmental influences explained individual differences in each variable; these were 21% for TII and 1% for the other variables.

The data were also analysed using the Cholesky decomposition model and independent pathway model, but based on AIC, a common pathway model with two latent factors gave the most parsimonious explanation for the present data. The results of the Cholesky decomposition and independent pathway models are available from the first author.

DISCUSSION

Our study showed that ECG LVH and RP are affected by both genetic and environmental influences in older women. The contribution of additive genetic influences to individual differences in LVH was minor (16%), but for RP it was strong (74%). The remaining individual differences were explained by common and unique environmental influences in LVH and unique environmental influences in RP. The high correlation between additive genetic influences (-0.93) underlying LVH and RP suggest that to a large extent the same genes operate in both cases. On the other hand, the negligible correlation between unique environmental influences (-0.05) suggest that LVH and RP are mainly affected by distinct environmental factors.

The proportion of additive genetic influences in LVH (16%) was much less than might have been expected from our previous univariate results for single LVH indices (55% for Cornell voltage and 56% for Cornell product).¹⁸ However, in the present multivariate analysis we found common environmental influences (35%) for the LVH factor whereas in the univariate analyses they were not detected for single LVH indices. The discrepancies between the results of the multivariate and univariate analyses (concerning both the proportion of additive genetic influences and presence/absence of common environmental influences) might be explained by the higher statistical power of the mul-

tivariate analysis, which, because it takes into account all the available information, enables common environmental influences to be discriminated from additive genetic influences. For the RP factor, the estimate of additive genetic influences was nearly the same (74%) as for the single T-wave variables reported previously (72% for TV₅ and 61% for TII).¹⁸

The strong genetic correlation (-0.93) between additive genetic influences underlying the LVH and RP factors suggests that, to a large extent, the same genes that regulate LVH may also regulate RP. The negative correlation indicates that while these genes may increase the degree of LVH, they can lower T-wave amplitudes (i.e., lead to repolarization abnormalities). The negligible environmental correlation in turn indicates that the majority of the environmental factors affecting LVH and RP are distinct. Thus, these results suggest that the association between LVH and repolarization abnormalities mainly originates from genetic factors. These may include both genes that cause heritable hypertrophic disorders (e.g., hypertrophic cardiomyopathy) and genes that otherwise contribute to the development of LVH.

Searching for specific genes for electrocardiographic or echocardiographic LVH has been under intensive study during recent years. For example, variations in the angiotensin-converting-enzyme gene,²⁸ angiotensinogen gene,²⁹ insulin-like growth factor-I gene,³⁰ estrogen receptor β gene,³¹ and ghrelin receptor gene³² have been proposed to be associated with LVH. Based on our present results, it can be suggested that all these specific gene variations found for LVH might also be associated, at least to some extent, with T-wave characteristics and RP. Since minor trait-specific additive genetic influences were also found (1% for Cornell product and 8% for TII), it is possible that there might also exist some genes, which are specific only for LVH or RP.

An important consideration is that LVH does not necessarily always lead to repolarization changes. For example, Moore et al.⁶ reported that LVH associated with repolarization abnormalities in pathological LVH (resulting from hypertrophic cardiomyopathy, hypertension, aortic stenosis, or coarctation), but not in physiological LVH in high-trained athletes. Our data did not include many athletes, but is still in agreement that environmental factors may be more important in the etiology of LVH than in the etiology of repolarization

abnormalities. However, the common genetic component of LVH and abnormal repolarization is large, indicating that the same genes play a role in the etiology of pathologic LVH and repolarization abnormalities. In our data, among those who had a repolarization abnormality (negative T wave in lead V₅ and/or II), 20% had LVH, according to the Cornell voltage criterion (>2.0 mV),^{21,22} whereas among those who did not have a repolarization abnormality, only 4% had LVH.

Environmental influences accounted for individual differences in both LVH and RP. Given the absence of a significant unique environmental correlation, for these two traits the unique environmental influences seem mainly to be distinct. Also, trait-specific unique environmental influences were found for each LVH index and T-wave amplitude, but their role was small (1%), except for TII (21%). We are not able to specify what these unique environmental factors (or common environmental factors for LVH) are, but based on previous studies some suggestions can be made. Common environmental factors affecting LVH can include, for example, similar physical activity habits adopted in childhood and continued throughout adulthood. Alternatively, this can also be considered as a unique environmental factor since physical activity habits may not always be similar across the life span in twin pairs; studies in adults have not found evidence for shared environmental effects on physical activity.³³ Other unique environmental factors affecting LVH can be pressure overload^{1,2} or valvular disease. The respective factors for RP and T wave changes may be coronary artery disease-related ischemia³⁴ and medications. However, although the correlation for unique environmental influences between LVH and RP was negligible, it is nevertheless possible that unique environmental factors exist that are common to both LVH and RP.

One of the strengths of our study is that it was population based. However, since estimates of genetic influences are always population specific and likely to vary with age,³⁵ caution must be exercised when applying the results to populations other than Caucasian older women. Also, participants with significant cardiac diseases were excluded from the statistical analyses so that the results apply only to older women without overt cardiac diseases. However, our study sample is particularly important since older women are at increased risk for the development of LVH and T-wave abnormalities.^{9,11}

Although our study sample was population based, the inclusion criteria may have led to the exclusion of pairs with at least one sister in poor health. This may have reduced the variance in the LVH indices and T-wave amplitudes, increased the similarity within the pairs and thus affected the estimates of genetic influences. In addition, we determined LVH using ECG, which is also a limitation in our study, since ECG is not as sensitive in detecting LVH as echocardiography.

In conclusion, ECG LVH and RP are affected by both genetic and environmental influences in older women without overt cardiac diseases. RP seems to be a more heritable trait than LVH. Genetic influences underlying LVH and RP overlap to a large extent suggesting that the association between LVH and repolarization abnormalities mainly originates from genetic factors.

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