Genetic Influences on Resting Electrocardiographic Variables in Older Women: A Twin Study

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Background: Previous studies in young and middle-aged men and women have shown that resting electrocardiographic (ECG) variables are influenced by genetic factors. However, the extent to which resting ECG variables are influenced by genetic factors in older women is unknown. Thus, the aim of this study was to estimate the relative contribution of genetic and environmental influences to individual differences in resting ECG variables among older female twins without overt cardiac diseases.

Methods: Resting ECG recordings were obtained from 186 monozygotic and 203 dizygotic twin individuals, aged 63–76 years. Quantitative genetic modeling was used to decompose the phenotypic variance in each resting ECG variable into additive genetic, dominance genetic, shared environmental, and unique environmental influences.

Results: The results showed that individual differences in the majority of the resting ECG variables were moderately to highly explained by additive genetic influences, ranging from 32% for T axis to 72% for TV₅. The results also suggested dominance genetic influences on QRS duration, TV₁, and Sokolow–Lyon voltage (36%, 53%, and 57%, respectively). Unique environmental influences were important for each resting ECG variable, whereas shared environmental influences were detected only for QT interval and QTc.

Conclusion: In older women without overt cardiac diseases, genetic influences explain a moderate to high proportion of individual differences in the majority of the resting ECG variables. Genetic influences are especially strong for T-wave amplitudes, left ventricular mass, and hypertrophy indices, whereas other variables, including heart rate, intervals, and axes, are more affected by environmental influences.

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Cardiovascular diseases are one of the leading causes of death worldwide.¹ Alterations in resting electrocardiogram (ECG) have prognostic significance for future health since some resting ECG abnormalities, such as left ventricular hypertrophy

(LVH) and T-wave inversions, are associated with increased risk for cardiovascular disease morbidity and mortality.^{2–7}

Few twin and family studies have provided information about genetic influences on resting ECG

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variables.⁸⁻¹⁴ To our knowledge, at least three previous studies have used more sophisticated biometric methods to estimate genetic contribution to resting ECG variables. The results of Busjahn et al.¹¹ in young adult men and women (100 monozygotic (MZ) twin pairs and 66 dizygotic (DZ) twin pairs, mean age 34 years) showed that additive genetic influences explained 59% of individual differences in QRS axis, 52% in T axis and QTc, 46% in P duration, and 40% in QRS duration, while RR interval, PR interval, and P axis were influenced by environmental factors. Carter et al.¹² reported in women aged 18-71 years (103 MZ and 198 DZ twin pairs) that additive genetic influences explained 25% of the individual differences in QT interval. The study by Dalageorgou et al.¹⁴ showed that the proportions of additive genetic influences were 55% for resting heart rate, 60% for QT interval, and about 50% for QTc intervals in 21- to 80-year-old women (105 MZ and 256 DZ pairs).

Because both gender¹⁵ and age¹⁶ have effects on heart function characteristics, it is important to study genetic and environmental influences on resting ECG variables separately for men and women within a narrow age range. Until now, genetic influences on resting ECG variables in older women are unknown. Thus, the aim of this study was to estimate the relative contribution of genetic and environmental influences to individual differences in resting ECG variables among 63- to 76-year-old female twins without overt cardiac diseases.

METHODS

Study 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,¹⁷ which comprises all same-sex twins born in Finland before 1958 with both co-twins alive in 1975. On the basis of age and zygosity, an invitation to participate in FITSA was sent to 414 twin sister pairs aged 63-76 years surviving in 2000. Details on recruitment have been described earlier¹⁸ 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 the last update of vital status for all cohort members (6 pairs). As a result of the procedures, the study group consisted of 217 twin sister pairs, comprising 103 MZ and 114 DZ pairs. The zygosity of the participating pairs was initially determined through a validated questionnaire¹⁹ and was later confirmed 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 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. Conduction abnormalities were confirmed by a specialist in internal medicine (J. Karjalainen). 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 co-twins can be included in the analyses since the statistical methodology used in the analyses can also utilize data from pairless twin individuals, giving more accurate estimates of genetic and environmental influences than if using only data from complete twin pairs.

The study was conducted according to the ethical rules 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.

Electrocardiographic 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. The ECG variables measured are presented in Table 1. T-wave amplitudes in leads V_1 , V_5 , and II as well as R-wave amplitude in lead aVL and S-wave amplitude in lead V_3 for the calculation of Cornell voltage were measured manually, while the other variables were collected from the automatic listings of the ECG recorder. Heart rate-corrected QT interval was calculated by the equation: QT interval + (1000 - RR interval)/7. LVH indices

Table 1. Participant Characteristics and Resting Electrocardiographic Variables by Zygosity

Characteristic	Mean $\pm$ SD		
	MZ Individuals (n = 186)	DZ Individuals (n = 203)	Total (n = 389)
Age (years)	68.1 $\pm$ 3.7*	68.8 $\pm$ 3.1*	68.5 $\pm$ 3.4
Height (cm)	158.0 $\pm$ 6.4	159.1 $\pm$ 5.7	158.6 $\pm$ 6.0
Weight (kg)	69.6 $\pm$ 12.0	70.6 $\pm$ 12.4	70.2 $\pm$ 12.2
Body mass index (kg/m ²)	28.1 $\pm$ 4.9	28.0 $\pm$ 4.8	28.0 $\pm$ 4.8
Heart rate (beats/min)	69 $\pm$ 12	68 $\pm$ 10	69 $\pm$ 11
PR interval (ms)	164 $\pm$ 26	166 $\pm$ 26	165 $\pm$ 26
QRS duration (ms)	86 $\pm$ 8	87 $\pm$ 9	87 $\pm$ 9
QT interval (ms)	395 $\pm$ 31	399 $\pm$ 30	397 $\pm$ 30
QTc (ms)	411 $\pm$ 24	414 $\pm$ 22	413 $\pm$ 23
P axis (degree)	46 $\pm$ 20	48 $\pm$ 22	47 $\pm$ 21
QRS axis (degree)	28 $\pm$ 28	31 $\pm$ 26	29 $\pm$ 27
T axis (degree)	43 $\pm$ 35	46 $\pm$ 30	44 $\pm$ 33
Sokolow–Lyon voltage [†] (mV)	2.2 $\pm$ 0.7 [‡]	2.4 $\pm$ 0.7 [‡]	2.3 $\pm$ 0.7
Cornell voltage [§] (mV)	1.1 $\pm$ 0.5	1.2 $\pm$ 0.5	1.2 $\pm$ 0.5
Cornell product** (mV $\times$ ms)	98.9 $\pm$ 45.3	102.5 $\pm$ 48.8	100.8 $\pm$ 47.1
ECG left ventricular mass ^{††} (g)	114.2 $\pm$ 13.5	115.3 $\pm$ 14.0	114.8 $\pm$ 13.7
TV ₁ (mV)	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1
TV ₅ (mV)	0.2 $\pm$ 0.1	0.2 $\pm$ 0.2	0.2 $\pm$ 0.2
TII (mV)	0.2 $\pm$ 0.1	0.2 $\pm$ 0.1	0.2 $\pm$ 0.1

*Statistically significant difference in variances between the MZ and DZ individuals ($P < 0.05$), based on variance ratio test. The equality of the variances was analyzed using variables, which were standardized by age and use of beta-blockers.

[†]SV₁ + RV₅.

[‡]Statistically significant difference in means between the MZ and DZ individuals ($P < 0.05$), based on adjusted Wald test. The equality of the means was analyzed using variables, which were standardized by age and use of beta-blockers.

[§]RaVL + SV₃.

**Cornell voltage (RaVL + SV₃) $\times$ QRS duration.

^{††}Calculated by the formula: $0.02 \times (\text{RaVL} + \text{SV}_3) + 1.12 \times \text{body weight} + 36.2$.

DZ = dizygotic; ECG = electrocardiographic; MZ = monozygotic.

were calculated as follows: Sokolow–Lyon voltage (SV₁ + RV₅),²⁰ Cornell voltage (RaVL + SV₃),²¹ and Cornell product (Cornell voltage $\times$ QRS duration).²² Electrocardiographic left ventricular mass (LVM) was calculated using the following formula: $0.02 \times \text{Cornell voltage} + 1.12 \times \text{body weight} + 36.2$.²³ All ECG measurements were carried out blinded to zygosity and twin sister's data.

Clinical Examination

All participants underwent a 30-minute clinical examination 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, the presence of a pacemaker (exclusion criteria), and the use of beta-blockers, which were 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 tests for data normality (Kolmogorov–Smirnov) were computed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). The resting ECG 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 nonnormality and standardizes the resting ECG 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 the resting 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

co-twins (Stata 8.0, Stata Corp., College Station, TX, USA).

The within-pair resemblance in each resting ECG variable was estimated separately for the MZ and DZ groups using intraclass correlation coefficients (ICCs) (SPSS 14.0). Afterward, using biometric methods, univariate genetic analyses were carried out to estimate the relative contribution of genetic and environmental influences to each resting ECG variable. Quantitative genetic modeling is based on the fact that MZ co-twins share 100% of their genes, whereas DZ co-twins share on average 50% of their segregating genes. Both types of twins are assumed to share their environment to the same extent. Genetic influences make MZ co-twins more similar than DZ co-twins, while the shared environment leads both MZ and DZ co-twins to be more similar. The influence of the environment not shared by the co-twins contributes to differences between them. Consequently, the total variance in a phenotype can be decomposed into additive genetic influences (A), dominance genetic influences (D), shared environmental influences (C), and unique environmental influences (E). A refers to the sum of the effects of 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 co-twins, such as those related to their childhood environment, and E consists of exposures that are not shared by the co-twins, 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.²⁴

Genetic models were fitted to the raw data, using Mx software²⁵ with full information maximum likelihood methods. The possible hypothetical combinations of the different influences (ACE, AE, CE, ADE, DE, and E) were built and tested. As only data from two different groups of relatives are available (MZ and DZ twin sisters), all four possible influences (A, D, C, and E) cannot be modeled simultaneously. Consequently, not all the models are nested and the usual likelihood ratio test cannot be applied to compare all six biometric models. Instead, the Akaike's Information Criterion ($AIC = -2 \times \log\text{-likelihood} - 2 \times \text{degrees of freedom}$)²⁶ was calculated and used to obtain the resulting best-fitting model. The AIC compares models on the basis of parsimony, taking into account the like-

lihood of every model and its degrees of freedom. The AIC is smaller for better fitting models.

RESULTS

The general characteristics and resting ECG variables 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 the mean of Sokolow-Lyon voltage and variance of age.

Except for QTc, the ICCs were higher in MZ pairs than in DZ pairs (Table 2), suggesting the presence of genetic influences. In many resting ECG variables (e.g., QRS duration and TV_1) the ICCs of MZ twins were more than twice that of DZ pairs, suggesting the presence of dominance genetic influences in addition to additive genetic influences. Thus, the subsequent genetic modeling analyses also tested for dominance genetic influences.

The resulting best-fitting models (and their 95% confidence intervals) for the resting ECG variables are shown in Table 3. Details on the genetic modeling, including all the possible models, are available from the first author. Most of the resting ECG variables were best explained by the models with additive genetic and unique environmental influences (AE). Additive genetic influences were moderate to high, ranging from 32% for T axis to 72% for TV_5 . For QRS duration, TV_1 , and Sokolow-Lyon voltage, the best-fitting model included dominance genetic and unique environmental influences (DE). In these cases, dominance genetic influences were also moderate to high, being 36%, 53% and 57%, respectively. However, from the biological point of view and taking into account the results of genetic modeling, the most reasonable model for QRS duration and Sokolow-Lyon voltage is the model which includes both additive and dominance genetic influences, and unique environmental influences (ADE), since pure dominance genetic influences (interactions between certain alleles) are highly unlikely if additive genetic influences are not present. For QRS duration, the proportion of additive genetic influences was 12% and that of dominance genetic influences 23%. For Sokolow-Lyon voltage these estimates were 24% and 33%, respectively. In relatively small samples such as ours, the power to distinguish additive genetic influences from dominance genetic influences is limited, and hence for such models the

Table 2. Within-Pair Intraclass Correlation Coefficients for Resting Electrocardiographic Variables in Monozygotic and Dizygotic Twin Pairs

Resting ECG Variable	MZ Twin Pairs (n = 86)		DZ Twin Pairs (n = 91)	
	ICC	95% CI	ICC	95% CI
Heart rate (beats/min)	0.51	0.34–0.65	0.19	–0.01–0.38
PR interval (ms)	0.43	0.24–0.59	0.16	–0.05–0.36
QRS duration (ms)	0.35	0.15–0.53	0.11	–0.10–0.31
QT interval (ms)	0.21	0.00–0.40	0.15	–0.05–0.35
QTc (ms)	0.17	–0.04–0.37	0.19	–0.02–0.38
P axis (degree)	0.07	–0.15–0.28	0.05	–0.16–0.25
QRS axis (degree)	0.51	0.34–0.65	0.22	0.01–0.40
T axis (degree)	0.32	0.12–0.50	0.16	–0.05–0.35
Sokolow–Lyon voltage* (mV)	0.59	0.44–0.72	0.18	–0.03–0.37
Cornell voltage† (mV)	0.53	0.36–0.67	0.36	0.17–0.53
Cornell product‡ (mV × ms)	0.53	0.36–0.67	0.36	0.17–0.53
ECG left ventricular mass§ (g)	0.61	0.46–0.73	0.42	0.24–0.58
TV ₁ (mV)	0.54	0.37–0.67	0.08	–0.13–0.28
TV ₅ (mV)	0.70	0.57–0.80	0.29	0.09–0.47
TII (mV)	0.56	0.40–0.69	0.27	0.07–0.45

*SV₁ + RV₅.†RaVL + SV₃.‡Cornell voltage (RaVL + SV₃) × QRS duration.§Calculated by the formula: $0.02 \times (\text{RaVL} + \text{SV}_3) + 1.12 \times \text{body weight} + 36.2$.

DZ = dizygotic; ECG = electrocardiographic; ICC = intraclass correlation coefficient; MZ = monozygotic.

overall genetic influence (A + D) is the best estimate of genetic versus environmental influences. Thus, for TV₁, the overall genetic influence was 53%, but the true proportions of additive versus

dominance genetic influences could not be clearly established.

QT interval, QTc, and P axis were the only variables unaffected by either additive or dominance

Table 3. Standardized Estimates (and 95% Confidence Intervals) of Genetic and Environmental Influences on Resting Electrocardiographic Variables in Older Women, Based on Best-Fitting Quantitative Genetic Models

Resting ECG Variable	A	D	C	E
Heart rate (beats/min)	0.48 (0.32–0.60)	–	–	0.52 (0.40–0.68)
PR interval (ms)	0.40 (0.23–0.55)	–	–	0.60 (0.45–0.77)
QRS duration (ms)	–	0.36 (0.17–0.51)	–	0.64 (0.49–0.83)
QT interval (ms)	–	–	0.19 (0.04–0.33)	0.81 (0.67–0.96)
QTc (ms)	–	–	0.19 (0.03–0.33)	0.81 (0.67–0.97)
P axis (degree)	–	–	–	1.00 (1.00–1.00)
QRS axis (degree)	0.43 (0.27–0.56)	–	–	0.57 (0.44–0.73)
T axis (degree)	0.32 (0.14–0.48)	–	–	0.68 (0.52–0.86)
Sokolow–Lyon voltage* (mV)	–	0.57 (0.43–0.68)	–	0.43 (0.32–0.57)
Cornell voltage† (mV)	0.55 (0.40–0.67)	–	–	0.45 (0.33–0.60)
Cornell product‡ (mV × ms)	0.56 (0.41–0.67)	–	–	0.44 (0.33–0.59)
ECG left ventricular mass§ (g)	0.65 (0.52–0.74)	–	–	0.35 (0.26–0.48)
TV ₁ (mV)	–	0.53 (0.37–0.65)	–	0.47 (0.35–0.63)
TV ₅ (mV)	0.72 (0.61–0.80)	–	–	0.28 (0.20–0.39)
TII (mV)	0.61 (0.46–0.71)	–	–	0.39 (0.29–0.54)

*SV₁ + RV₅.†RaVL + SV₃.‡Cornell voltage (RaVL + SV₃) × QRS duration.§Calculated by the formula: $0.02 \times (\text{RaVL} + \text{SV}_3) + 1.12 \times \text{body weight} + 36.2$.

A = additive genetic influence; C = shared environmental influence; D = dominance genetic influence; E = unique environmental influence; ECG = electrocardiographic.

genetic influences. QT interval and QTc were best explained by the models with shared and unique environmental influences (CE), whereas P axis was best explained by the model with only unique environmental influences (E).

DISCUSSION

The results of our study provide new and valuable information about the genetic influences on resting ECG variables in older women. Resting ECG abnormalities strongly increase with age²⁷ so that understanding of the role of genetic influences on resting ECG variables in older age is important. Our study showed that a moderate to high proportion of the individual differences in resting ECG variables were explained by genetic influences. The proportions of additive genetic influences were 32–72% in the majority of the resting ECG variables and those of dominance genetic influences 36–57% in QRS duration, TV₁, and Sokolow–Lyon voltage.

Our study provides new information, especially about genetic influences on T wave amplitudes since, to the best of our knowledge, no previous studies have been conducted to quantify the genetic influences on these ECG variables. Understanding of the role of genetic influences on T waves is important because T-wave alterations (flattening and inversions) are known to be associated with increased risk for cardiovascular morbidity and mortality.^{2,6,7} We found that the proportion of the individual differences in T-wave amplitudes explained by both additive and dominance genetic influences was high, ranging from 53% to 72%. These findings suggest that in healthy older women variation exists in ventricular repolarization, which is largely due to genetic factors. This is important to take into account when interpreting T waves and their possible abnormalities.

Our study also showed rather strong genetic influences for LVH indices (55–57%). A previous family study (395 men and 473 women, mean age 52 years), which used different statistical methods, reported lower estimates for these same indices (19–41%).¹³ The estimate of genetic influences for electrocardiographic LVM was also high in our study (65%). This is in accordance with the results of a previous twin study (182 MZ and 194 DZ male and female twin pairs, aged 25–79 years) which reported that genetic influences amounted to 59% for echocardiographic LVM.²⁸ Our findings

of strong genetic influences on LVH indices in older women are important since LVH is one of the resting ECG abnormalities that increase with age^{6,27} and is of significant prognostic value for cardiovascular morbidity and mortality.⁵

We found similar results with the previous studies, especially with respect to frontal plane axes. In our study, additive genetic influences explained 43% and 32% of the individual differences in QRS axis and T axis, respectively, while Busjahn et al.¹¹ reported slightly larger estimates for young adult men and women (59% and 52%, respectively). Relatively high estimates of genetic influences on QRS axis were found in both studies. Our study showed strong genetic influences on LVH indices (about 60%), which may contribute to the estimate of genetic influences on QRS axis since the direction of QRS axis is partly influenced by the degree of LVH. P axis, in turn, seems to be unaffected by genetic factors. We found only unique environmental influences while Busjahn et al.¹¹ found both shared and unique environmental influences.

Interestingly, some of our results differ markedly from those obtained by Busjahn et al.,¹¹ Carter et al.,¹² and Dalageorgou et al.,¹⁴ who used the same biometric methods as we did. We found moderate additive genetic influences on PR interval (40%), whereas Busjahn et al.¹¹ found only environmental influences in young adult men and women. However, another twin study in middle-aged men, using different statistical methods, reported quite similar results to those of our study (34%).⁸ On the other hand, we found that QT interval and QTc were unaffected by genetic factors, whereas Carter et al.¹² and Dalageorgou et al.¹⁴ reported that the proportion of additive genetic influences in QT interval was 25% in 18- to 71-year-old women and 60% in 21- to 80-year-old women, respectively. A twin study using different statistical methods reported an estimate of genetic influences to be 36% for QT interval in middle-aged and older men.¹⁰ Genetic influences have also been reported for QTc in young adult men and women (52%)¹¹ and in 21- to 80-year-old women (50–52%, depending on the correction method used).¹⁴

Somewhat unexpectedly, we did not detect genetic influences on QT interval and QTc. On the basis of previous results, it seems that in younger women (and men) there are genetic influences on QT interval and QTc.^{10–12,14} However, because our selection criterion for the best-fitting model was purely statistical (AIC), it does not totally exclude

the possibility of the presence of genetic influences on QT interval and QTc also in older women. The model with additive genetic (23% for QT interval and 22% for QTc) and unique environmental influences fitted almost equally well as the model with shared and unique environmental influences, which was selected to the best-fitting model according to AIC. This almost equally well-fitting model (AE) would be in line with the previous studies. In addition, there can be other reasons why we did not detect genetic influences on these two variables. One reason may be the lack of statistical power to discriminate additive genetic influences from shared environmental influences. Also, heritable QT syndromes are different from normal variation and in our sample nobody had long QT syndrome. Normal variation in QT intervals can be more environmentally affected, for example by physical activity.

Comparing the present results with those of the previous studies, however, must be done cautiously. Different study designs (twin vs family study) and differences in the statistical methods used in some previous studies may lead to different estimates of genetic and environmental influences. These estimates are also population-specific and likely to change with aging.²⁹ In addition, the estimates from different studies have relatively wide confidence intervals, and hence some of the differences between studies may be due to sampling variation rather than true differences between populations due to gender, age, health status, or genetic makeup.

It should be remembered that finding genetic influences on resting ECG variables does not mean that environmental influences are unimportant. In our study, unique environmental influences explained varying proportion of the individual differences in each resting ECG variable (28–100%), which in large part is in agreement with other studies.^{11,12,14} We are not able to specify what the unique environmental factors (or shared environmental factors, as discussed below) are that influence the resting ECG variables. The literature suggests that among such factors are, for example, physical activity³⁰ and medications. Shared environmental influences were detected for only two variables and their role was rather small. One reason why shared environmental influences were not detected in other variables may be that moderately sized twin studies may not have the statistical power to do this. Shared environmental fac-

tors affecting resting ECG variables may include, for example, obesity,³¹ resulting from similar eating habits in a family. However, twin and family studies have generally not found any or at most a minor role for shared environmental factors in obesity.^{32,33}

Use of beta-blockers has influences on resting ECG variables, most commonly influencing heart rate and intervals. Beta-blocker medication is used in the treatment of cardiovascular abnormalities, which can originate from both genetic and environmental factors. The use of beta-blockers may not only increase the environmental component in the statistical analyses as could be expected, but it can also decrease it. We did the analyses also without beta-blocker adjustment. The results remained mainly unchanged, but there were five variables—PR interval, QT interval, QTc, Sokolow–Lyon voltage, and TV₅—that had different results without and with beta-blocker adjustment. In these cases (except for TV₅), unadjusted results showed smaller environmental components.

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 change with aging,²⁹ caution must be exercised when applying the results to other populations than to Caucasian older women. In addition, participants with significant cardiac diseases were excluded from the statistical analyses, which means that the results apply only to older women without overt cardiac diseases. Although our study sample was population-based, the inclusion criteria may have lead to the exclusion of pairs with at least one sister in poor health. This may have reduced the variance in the resting ECG phenotypes, increased the similarity within the pairs, and thus affected the estimates of genetic influences.

In conclusion, in older women without overt cardiac diseases, genetic influences explain a moderate to high proportion of the individual differences in the majority of the resting ECG variables. Genetic influences are especially strong for T-wave amplitudes, LVM, and hypertrophy indices, whereas other variables, including heart rate, intervals and frontal plane axes, are more affected by environmental influences.

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