Familial Aggregation and Heritability of Electrocardiographic Intervals and Heart Rate in a Rural Chinese Population

Jianping Li, M.D., Ph.D.,* Yong Huo, M.D., Ph.D.,* Yan Zhang, M.D., Ph.D.,* Zhian Fang, M.D.,† Jianhua Yang, M.D.,† Tonghua Zang, Ph.D.,‡ Xiping Xu, M.D., Ph.D., M.S.,‡ and Xin Xu, Ph.D.§

*From the *Peking University First Hospital, Department of Cardiology, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing, China; †Anqing Preventive Medicine Association, Anqing, China; ‡Anhui Medical University Biomedical Institute, Hefei, China; and §Harvard School of Public Health, Department of Environmental Health, Boston, MA*

Background: Estimates of the genetic influences on electrocardiographic (ECG) parameters are inconsistent in previous reports, and no such studies have been performed in China. So we estimated genetic contributions to PR and QRS intervals and the rate-adjusted QT interval (Bazett's QTc) in a Chinese rural population.

Methods: A total of 2909 subjects from 847 families were enrolled in the current study. Genetic contributions to ECG parameters were estimated in two ways: correlation coefficients among family members (father-mother, parent-offspring, first sibling-other sibling) and the heritability of each of the ECG parameters.

Results: Our results showed significant correlations among family members on theses parameters: the correlation coefficients for PR interval, QRS duration, QTc interval, and HR, between parent-sibling, and sibling-sibling were 0.17 and 0.13, 0.18 and 0.23, 0.22 and 0.28, 0.19 and 0.18, respectively. The heritability for PR interval, QRS duration, QTc interval, and HR were estimated as 0.34, 0.43, 0.40, and 0.34, respectively.

Conclusion: Genetic factors, together with the environmental and other cofactors contribute no more than 60% to the variance of the ECG intervals, supporting the concept that multiple factors, including gene-gene and gene-environment interactions could influence ECG interval phenotypes, and genetic factors play a major role.

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electrocardiogram (ECG); PR interval; QRS duration; QTc interval; heart rate; heritability

In spite of significant advances in modern diagnostic facilities, the standard 12-lead electrocardiogram (ECG) remains the most readily available, noninvasive, and highly cost-efficient test for detection of cardiac diseases. ECG not only provides direct diagnostic evidence for arrhythmia and myocardial ischemia, but also helps to monitor the cardiac response to drugs. Moreover, ECG measurements are effective markers for predicting the outcomes of patients with heart disease,[1–8] as well as for predicting cardiovascular mortality in healthy subjects.[9] ECG measurements are thought to be complex traits with possibly multiple genetic and environmental determinants. Genetic contributions to PR interval, QT interval, QRS duration, and RR interval (or ventricular heart rate, HR) have been investigated in both twin studies[10–16] and segregation analyses.[17,18] However, results from the previous studies are inconsistent, for example, Havlik et al. did not find a significant genetic component in QT interval,[13] while all other studies estimated a high degree of genetic contribution.[12,15–18] Similarly, a significant genetic contribution to QRS duration was found in Mathers et al.[12] and

Address for correspondence: Jianping Li, M.D., Ph.D., Peking University First Hospital, Department of Cardiology, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, 8 Xishiku St, Xicheng District, Beijing 100034. Fax: 861066137748; E-mail: lijianping@medmail.com.cn

Hanson et al.,[15] but not in Havlik et al.[13] and Russell et al.[16] The heritability of PR interval was estimated to be 0.78 in Moller et al.,[14] but 0.34 in Havlik, et al.[13] The heritability of HR was estimated to be 0.21 in the Framingham heart study,[19] but 0.77 in Russell et al.[16] Moreover, several known environmental factors, including obesity and cigarette smoking, have shown to have significant effects on ECG measurements.[20–22] So far, very few studies have explored the effect sizes of these factors simultaneously with the genetic heritability.

In this report, we studied correlations of four ECG measurements—PR interval, QRS duration, QTc interval, and the HR among family members in a rural Chinese community, and estimated the heritabilities and the contributions of various environmental factors using variance component analysis.

METHODS

Study Subjects

Families in this study were part of a large community-based genetic epidemiologic study, previously conducted in Anqing, China, on chronic diseases including cardiovascular disease, respiratory disease, and osteoporosis. Families were included for this report using the following criteria: (1) at least two members in a given nuclear family, (2) a standard 12-lead ECG was available for each of the family member, and (3) ECG showed a sinus rhythm. Subjects with any kind of arrhythmia were excluded. This report included a total of 2909 subjects from 847 families: 1354 males and 1555 females, aged 5 to 77 years. This study has been approved by the Human Subject Committee at the Anhui Medical University. Informed consent has been obtained from each participant.

Measures

ECG Measurements

Standard 12-lead electrocardiograms were recorded at a standard setting: 25 mm/s and 1 mV/cm, on a supine position after 10 minutes of resting. ECG intervals were measured manually by a group of trained readers using the Minnesota Code methodology.[23] Single PR interval and QT interval was measured on limb lead II. Three RR intervals were measured on limb lead II, and the average was used in the subsequent analyses. Ventricular HR was calculated as 60/average RR interval. From time to time the start and the end of a QRS complex is not obvious in a particular lead, so QRS duration was measured on precordial lead V_1, V_3, and V_5, separately. The average of the three QRS durations was used in the subsequent analyses. Heart rate corrected QT interval (QTc) was calculated using the Bazett's formula: QTc = QT/average RR interval$^{0.5}$.[24] To assess interreader repeatability, 150 randomly selected ECGs were re-read by independent readers, and the interreader correlation coefficients for PR interval, QRS duration, QTc interval, and HR were 0.92, 0.82, 0.88, and 0.94, respectively. Of note, we did not examine biological/technical variability by repeating ECGs on the same individuals.

Height and Weight

Subjects first removed their shoes and outerwear. Height was measured to the nearest 0.1 cm using a portable stadiometer. Weight was measured to the nearest 0.1 kg with the subject standing motionless on the scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Blood Pressure

Blood pressure was measured by a nurse according to standard procedure.[25] Briefly, the right arm was used for all blood pressure measurements, with the cubital fossa supported at heart level after the subject had voided, rested, and been seated comfortably for 10 minutes. A standard clinical sphygmomanometer was used, with the bell of the stethoscope placed over the brachial artery pulse, proximal and medial to the cubital fossa and below the bottom edge of the cuff. Systolic blood pressure was defined as Korotkoff phase I (appearance of sound), and diastolic blood pressure was defined as Korotkoff phase V (disappearance of sound). Three measurements were taken for each subject, with at least 30 seconds between readings. The mean of the three values was used in subsequent analyses.

Questionnaire

A questionnaire was administered to each enrolled subject, collecting information on demographic characters, including status of cigarette

Table 1. Epidemiological and Clinical Characteristics of the Study Subjects, Anqing 1994–1997

	Father (n = 611)	Mother (n = 668)	Siblings (n = 1630)
Age	47.5 (11.5)	44.6 (11.6)	21.5 (10.2)
BMI	20.8 (2.2)	21.1 (2.5)	19.2 (3.3)
SBP	121.4 (21.1)	120.1 (21.0)	107.4 (12.6)
DBP	72.9 (11.9)	70.8 (11.5)	64.0 (9.3)
PR (s)	0.14 (0.02)	0.14 (0.02)	0.13 (0.02)
QRS duration (s)	0.09 (0.01)	0.09 (0.01)	0.09 (0.02)
QTc (s)	0.39 (0.03)	0.41 (0.03)	0.41 (0.03)
HR (bpm)	69.8 (11.1)	76.3 (11.7)	82.5 (14.9)
Sex			
Male	611		743 (45.6)
Female		668	887 (54.4)
Smoking status			
Never	111 (18.2)	643 (96.3)	1360 (83.4)
Ever	500 (81.8)	25 (3.7)	270 (16.6)
Alcohol drinking			
Never	394 (64.5)	663 (99.3)	1540 (94.5)
Ever	217 (35.5)	5 (0.7)	90 (5.5)
Education			
Elementary	227 (37.2)	530 (79.3)	966 (59.6)
Junior and senior	346 (56.7)	133 (19.9)	592 (36.5)
College	37 (6.1)	5 (0.8)	63 (3.9)
Occupation			
Farmer	471 (77.1)	491 (73.5)	1211 (74.3)
Other	140 (22.9)	177 (26.5)	419 (25.7)

Continuous variables are expressed as mean ± SD, categorical variables are expressed as N (%). BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; QTc = corrected QT interval; SBP = systolic blood pressure.

smoking, alcohol consumption, education level, and occupation.

STATISTICAL METHOD

Two analyses were performed to estimate the genetic contributions to the PR interval, the QRS duration, the QTc interval, and the HR. First, the correlation coefficients of the four ECG measurements among family members were calculated. Three kinds of correlation coefficients were calculated for each ECG measurement using the unadjusted values, sex- and age-adjusted values, and ECG values adjusted for all potential covariates, including age, sex, mean blood pressure (mBP), cigarette smoking, alcohol consumption, education, occupation, and HR (for the PR interval and the QRS only). Then, the heritabilities of the four ECG measurements and the contributions of other covariates were estimated with a variance component method implemented in the software SOLAR (Southwest Foundation for Biomedical Research, San Antonio, TX, USA).[26] This method, essentially a mixed effect model that incorporates fixed effects for known covariates and variance components for genetic effects, partitions the total variation in the ECG measurements into additive genetic and individual environmental components.[27] In order to estimate the proportion of variation explained by known important covariates, age and sex were first put in the model and the effect of age and sex was estimated, then all the covariates, including BMI, mBP, cigarette smoking, alcohol consumption, and HR (for PR interval and QRS duration only), were added into the model to evaluate the proportion of variation explained by all of these covariates.

RESULTS

This study consists of 2909 subjects from 847 families, including 611 fathers, 668 mothers, 799 first siblings (the oldest offspring in a family), and 831 other siblings (offspring other than the oldest offspring). Epidemiological and phenotypic characterization of the study subjects is presented in Table 1. Of note, this is a predominantly farming population, with a high prevalence of

Table 2. Correlation Coefficients of PR Interval, QRS duration, QTc Interval, and HR among Family Members

	Father-Mother (n = 470)	Parent-Sibling (n = 1662)	First Sibling-Other Sibling (n = 831)
PR			
Unadjusted	0.12†	0.18†	0.23†
Age and sex adjusted	0.13†	0.17†	0.14†
Fully adjusted	0.11*	0.17†	0.13†
QRS			
Unadjusted	0.18†	0.19†	0.25†
Age and sex adjusted	0.18†	0.19†	0.24†
Fully adjusted	0.18†	0.18†	0.23†
QTc			
Unadjusted	0.22†	0.20†	0.28†
Age and sex adjusted	0.20†	0.23†	0.28†
Fully adjusted	0.18†	0.22†	0.28†
HR			
Unadjusted	0.03	0.17†	0.34†
Age and sex adjusted	0.03	0.18†	0.18†
Fully adjusted	0.03	0.19†	0.18†

Full covariate adjustment including age, sex, BMI, mean blood pressure (mBP), cigarette smoking (ever vs never), alcohol consumption (ever vs never), education, and occupation. HR = heart rate; QTc = corrected QT interval.
*$P < 0.05$; †$P < 0.01$.

smoking (81.8%) and alcohol drinking (35.5%) among fathers.

The crude and adjusted correlation coefficients of the PR interval, the QRS duration, the QTc interval, and HR among family members are presented in Table 2. Fathers and mothers were significantly correlated for PR interval, QRS duration, and QTc interval ($P < 0.05$ for PR interval, $P < 0.01$ for QRS duration and QTc interval), but not for HR. The four ECG measurements were highly correlated between parents and offspring and between first siblings and other siblings, and were comparable in magnitude. Overall, the magnitude of correlation coefficients between parents and offspring and between first-sibling and other-siblings were higher than that between father and mother.

The familial correlations appeared to be fairly robust to the adjustment of age, gender, and other covariates (BMI, mBP, smoking, alcohol, education, and occupation).

Table 3. Estimated Heritabilities and Percent Variance Explained by the Covariates for PR, QRS, QTc, and HR

	N	Heritability	Percent Variance Explained by Covariates
PR			
Unadjusted	1815	0.29	N/A
Age and sex adjusted	1815	0.30	0.08
Fully adjusted	1796	0.34	0.12
QRS			
Unadjusted	1773	0.39	N/A
Age and sex adjusted	1773	0.42	0.05
Fully adjusted	1754	0.43	0.06
QTc			
Unadjusted	1815	0.37	N/A
Age and sex adjusted	1815	0.36	0.06
Fully adjusted	1796	0.40	0.10
HR			
Unadjusted	1815	0.18	N/A
Age and sex adjusted	1815	0.21	0.18
Fully adjusted	1796	0.34	0.26

HR = heart rate; QTc = corrected QT interval.

We also examine the question if there is gender difference in familial correlation of ECG intervals (PR, QRS, QTc, and RR) in father-son, father-daughter, mother-son, and mother-daughter. We found that the correlations for the ECG intervals were not significantly different between father-son and father-daughter, and between mother-son and mother-daughter.

The overall contribution of genetic factors and covariates to the ECG measurements are summarized in Table 3. The estimated heritabilities were 0.34 for the PR interval, 0.43 for the QRS duration, 0.40 for the QTc interval, and 0.34 for the HR. These estimations were fairly robust to the adjustment of age, gender, and other listed covariates. In comparison, percent variances explained by the listed covariates were modest: 0.12 for the PR interval, 0.06 for the QRS duration, 0.10 for the QTc interval, and 0.26 for the HR.

DISCUSSION

ECG intervals are generally believed to be complex traits, that is, determined by multiple

environmental and genetic factors, instead of by a single major gene. Both twin study and family study design can be used for estimating relative role of genes versus environment. Twin study estimates genetic contribution to a trait by comparing the correlation for MZ twins with the correlation for DZ twins. If genetic variation exists for the trait under study, the correlation for MZ twins will be larger than for the DZ twins, since MZ twins share 100% of their genes and DZ twins share only an average of 50% of their genes. Familial aggregation analysis, on the other hand, compares correlation among family members, for example, between parents (spouses), siblings, and parents and offspring. If genetic variation exists for the trait under study, the correlation for the sib-sib and parent-offspring is expected to be greater than for the father-mother, since parent-offspring and siblings share 50% of their genes on average. In contrast, spouses share only familial environmental effects (we do not believe that consanguinity was an issue in this population).

One would expect that these two different types of studies would lead to similar conclusion if they are conducted in the same population in the same environment using the same phenotypic assessment and analytical approach. However, discrepancies between different studies may occur due to various reasons, including differences in study sampling frame, sample size, phenotype definition, analytical methods, environmental or confounding factors, and gene-environment interactions.

This familial aggregation analysis in a large rural Chinese population demonstrated a high degree of correlations in PR interval, QRS duration, QTc interval, and HR among family members, that is, between fathers and mothers, parents and offspring, and siblings. In general, we noted a higher correlation between siblings and between parents and offspring than correlation between spouses. This finding suggests a genetic contribution to these ECG measurements.

Our study also showed that the correlation coefficients for PR interval, QRS duration, and QTc between spouses are significantly larger than zero. Such correlation cannot be explained by the sample selection. All the study families were randomly selected. While many social and personal factors may contribute to the marriage of the couples, it is unlikely that ECG profile played a role in marriage. We speculate that the significant correlations between the spouses were likely due to shared environmental factors, such as diet and life styles.

Our estimates of heritabilities using the variance component method are generally consistent with previous reports: the estimate of 0.40 for the heritability of QTc in our study is in agreement with the estimate of 0.34 in Framingham Heart Study,[11] 0.36 in NHLBI twin study,[16] 0.40 in 80 Israeli families,[17] and 0.34 in NHLBI Family Heart Study.[18] The estimate of 0.34 for the heritability of HR agrees well with the estimate of 0.33 in the Canada Fitness Survey,[28] 0.34 in the HERITAGE study,[29] and 0.21 in the Framingham study.[19] The estimate of 0.34 for the heritability of PR interval is consistent with the estimate of 0.34 in Havlik et al.'s[13] and in NHLBI twin study.[16] Last, the estimate of 0.43 for the heritability of QRS duration is consistent with Hanson et al.'s estimate of 0.30–0.51 in their twins reared apart.[15] Our data along with previous publications did not support a single-gene effect.

Our studies, in combination with the previous, provide the basis for future studies exploring genetic variants responsible for the variance of the ECG parameters in general population. Using a genome screening approach, Kreutz et al. identified a genetic locus (HR-SP1) on rat chromosome 3 that regulates HR in stroke-prone spontaneously hypertensive rat ($SHRSP_{HD}$).[30] Busjahn et al. found significant linkage of QTc interval to LQT1 on chromosome 11 in patients with congenital long QT syndrome, and to LQT4 on chromosome 4 in general population.[31] Recently, the K897T polymorphism of HERG gene, which codes for the rapidly activating delayed rectifier K+ channel, has been shown to be significantly associated with the maximum QT interval in the middle-aged Finnish females.[32] The rapid advancement in genetic technologies and methodologies offers unprecedented opportunities to identify gene/loci that may have a significant role in determining ECG phenotypes.

In summary, our data indicate that both genetic factors and shared family environment factors play a role in determining the variation in PR interval, QRS duration, QTc interval, and HR. Furthermore, since our results showed that genetic factors and the adjusted covariates contribute no more than 60% to the variance of the ECG parameters, other environmental factors, gene-gene interactions, gene-environment interactions could also influence these phenotypes and remain to be identified.

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