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QT interval duration in the Jackson Heart Study: A segregation analysis

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Abstract

The aim of this study was to test for evidence of Mendelian segregation of a major gene in the Jackson Heart Study (JHS), a large African American cohort, and to develop models for future use in model-based linkage analysis. The QT interval, measured in electrocardiograms has been shown to be heritable, with an estimate of 41% in the Jackson Heart Study. Using data from the same cohort, a segregation analysis of the QT interval was conducted. A Box-Cox transformation was applied while simultaneously estimating the parameters of the model using the SEGREG program in the S.A.G.E 6.1.0 package. An environmental model with two means fitted the data better than an environmental model with one mean. The most parsimonious genetic model that best fitted the data was a codominant model with an allele frequency of 0.19, providing suggestive evidence of Mendelian segregation of a major gene underlying this trait. There was no significant residual spousal correlation in the environmental or genetic models. The models had significant and equal residual familial correlations of parent-offspring and sibs, which may be interpreted as a polygenic effect, or as a shared family environmental effect. Findings of polygenic effects (multiple loci with small effects) have previously been reported in genome wide association studies. The parameters estimated in the codominant genetic model described here will be applied in a model-based linkage analysis.

Introduction

Sudden cardiac death (SCD) is defined as a natural death resulting from an abrupt loss of heart function in which the victim was seen in a stable medical condition within a time period spanning 24 hours before the onset of symptoms. SCD and resuscitated SCD commonly caused by ventricular tachyarrhymias are responsible for over 300,000 deaths annually within the United States (American Heart Association, 2005. Several SCD risk factors, including coronary heart disease, age, hypertension, and left ventricular hypertrophy, have been identified in population-based studies. Identification of these risk factors allows us to identify high-risk groups, but the common occurrence of these risk factors unrelated to SCD in the general population makes them inadequate for the prediction of individual risk for SCD (Albert et al., 2003; Jouven et al., 1999; Schatzkin et al., 1984). Familial aggregation of SCD suggests that genetic components play a role in SCD (Albert et al., 2003; Dekker et al., 2004a; Friedlander et al., 1998; Jouven et al., 1999; Kaikkonen et al., 2006). Locating common genetic variants, such as single nucleotide polymorphisms (SNPs) contributing to arrhythmia risk could identify individuals at risk for SCD who could be targeted for preventive therapies. Unfortunately,

studying genetic influences on SCD is difficult because large population samples are required to detect common variants that typically have modest effects. Further, the collection of large SCD sample populations that would allow for detection of genetic variants influencing SCD at appropriately rigorous statistical thresholds is difficult because the presenting symptom is fatal.

Studies within the Framingham Heart Study (FHS) and Jackson Heart Study (JHS) found over a third — 35% in individuals of European descent (ED) and 40-41% in individuals of African descent (AD) — of the variation of QT interval duration to be attributable to additive heritable factors (Akylbekova et al., 2009; Newton-Cheh et al., 2005). Prolonged QTc intervals, i.e., heart rate adjusted QT, have been associated with a three-fold increased risk of sudden cardiac death (Straus et al., 2006). The widespread availability of noninvasive, inexpensive, quantitative ECG measurements in large sample populations combined with evidence of QT heritability makes QT a useful intermediate trait for the study of genetic factors influencing SCD. Additionally, identifying the genetic factors influencing QT is of interest because drug-induced prolongation of QT resulting in arrhythmias has been one of the leading factors in the restriction or recall of both cardiac and non-cardiac medications once they have already been marketed (Roden, 2004). Genetic markers, e.g., SNPs, influencing QT interval duration in AD individuals can be tested individually or in aggregate for their influence on SCD or drug-induced arrhythmias (Newton-Cheh & Shah, 2007). Recognition that a small percentage of individuals are genetically predisposed to drug-induced arrhythmias could protect individuals at-risk from toxic therapies while allowing beneficial medications to be given to the majority of the population who are at a reduced risk of arrhythmias.

Familial correlation and segregation analysis of QT in the NHLBI Family Heart Study attributed variation in QT interval duration to heritable factors and a major effect not attributable to a single gene (Hong et al., 2001). Genome-wide association studies (GWAS) have reported that variations within the nitric oxide synthase 1 adaptor protein (*NOS1AP*) explain approximately 1.5% of QT interval variation (Arking et al., 2006). These results were validated in three independent cohorts of European ancestry. Additionally, QTGEN, a recent research project consisting of a meta-analysis consortium of three cohorts (7650 FHS, 4606 Rotterdam and 853 Cardiovascular Health Study participants) identified, through genome-wide association, seven variants in five genes known to be involved in myocardial repolarization including *NOS1AP, KCNE1, SCN5A*, two independent signals in *KCNQ1*, and two independent signals in *KCNH2*. They also identified additional variants associated with QT interval duration at five novel loci: 16q21, 6q22, 1p36 and 16p13 and 17q12 explaining 5.4-6.5% of variation in QT interval duration in individuals of European Ancestry (EA) (Newton-Cheh et al., 2009). A genome-wide linkage analysis of QT in EA individuals from the FHS showed a genetic effect on chromosome 3 near *SCN5A* and other sodium and potassium channels [Newton-Cheh et al., 2005]. The S1102Y (S1103Y) variant of *SCN5A* has been found to be more common among African Americans (Splawski et al., 2002; Van Norstrand, Tester and Ackerman, 2008). This variant was associated with QT interval duration and showed evidence of linkage to QT prolongation in a linkage analysis of a single family (Splawski et al., 2002). While QT interval duration has been studied extensively in EA populations, less information is available in African American (AA) populations. Differences in QT have been documented in AA populations (Vitelli et al., 1998). SCD incidence rates are higher among African Americans compared to European Americans (Armstrong, Wing and Tyroler, 1996; Gillum, 1997; Traven et al., 1996).

A putative SCD risk factor Gln27Glu in the *ADRB2* gene in EA individuals is found more commonly in AA individuals but was not significantly associated with SCD (Liggett, 2006). This study aims to further describe the distribution and variance of QT in an African American cohort.

Methods

Study Sample

The Jackson Heart Study (JHS) cohort consists of 5,301 adult African Americans between the ages of 21 and 95 from the Jackson, Mississippi Metropolitan area including 1,601 participants from the Atherosclerosis Risk in Communities Study (ARIC). Pedigrees of 291 families were developed using Progeny as previously described in *Study design for genetic analysis in the Jackson Heart Study* (Wilson et al., 2005). Corrected pedigrees with 264 families were generated using 374 autosomal microsatellite markers from 1,499 participants typed by the Marshfield Mammalian Genotyping Service (MMGS) using marker set 16. Additionally, MID488 was used to detect gender errors because it has one allele on the X chromosome and a different allele on the Y chromosome.

Two programs, GRR (Graphical Relationship Representation) (Abecasis et al., 2001) and RELTEST (a program in the S.A.G.E. package (Statistical Analysis for Genetic Epidemiology), were used to test the relatedness between relative pairs. This was done in order to decrease the amount of error within the family pedigree structures. If RELTEST indicated that a putative parent-offspring relationship was not correct, we used the IBS (identity in state) and its standard error calculated using GRR to determine if the offspring was a first or second degree relative, and if he or she was more closely related to another person or persons within the pedigree.

Because the participants are all from the same metropolitan area, it seemed reasonable to expect to find relatedness across pedigrees, as well as within them. This was tested, and where clear cases of relatedness were found using microsatellite markers, pedigrees were merged. Where some links were still unclear, for example, in cousin pairs, we made use of markers on the sex chromosomes (Y only and/or X), and estimated haplotypes using MERLIN (Abecasis et al., 2001). Through the use of these programs, we have been able to minimize the number of putatively unrelated individuals who are actually close relatives. We began with 291 families and found that these relationships are better described by 264 pedigree structures.

In four families, there was a genotyped monozygotic twin pair. Each pair of monozygotic twins was treated as one individual in this analysis; in this way, the offspring of the MZ twins were treated as half-sibs rather than as cousins. There were no consanguineous mating pairs, but there were two pedigrees with known loops. The largest pedigree has 57 members, and the pedigrees have as many as four generations with both phenotype and genotype data.

Individuals without informed consent or electrocardiographic data and those taking digoxin were excluded. Digoxin use was an exclusion criterion because it shortens the QT interval. After these exclusions, our study sample consisted of 236 pedigrees of two or more individuals, plus 38 who were either known singletons (N=12) who had been genotyped by MMGS or were the only person in the family with non-missing data after exclusions were applied. This study sample comprised 1,396 individuals. Mean pedigree size, excluding the 38 singletons, was 5.94 with a standard deviation of 5.10 and a maximum size of 29 family

members, with an interquartile range of 2 to 7.75. There were two four-generation families. Pedigrees were constructed and drawn using (Progeny Desktop Version N/Progeny Enterprise Version 5/Progeny Lab Version 5) (Progeny Software LLC, South Bend, IN, www.progenygenetics.com).

Regression analysis using SAS version 9.2 showed that several covariates were significantly associated with QT. We adjusted for these covariates creating QT residuals by regression of QT duration on age, gender, BMI, CHD, diuretics, hypertension, potassium, RR, QRS, and Sokolow-Lyon Voltage. The residuals were adjusted to age 60, so that there were no negative values that would impede a subsequent Box-Cox power transformation, then used for analysis. PEDINFO in S.A.G.E. was used to estimate familial correlations.

Clinical characteristic ascertainment and ECG measurements

Data were collected from Jackson Heart Study participants through a home induction interview, three clinic examinations, and self-administered questionnaires (Taylor et al., 2005). Supine 12-lead digital electrocardiography was conducted using a Marquette MAC/PC electrocardiograph recorder. The University of Minnesota's Electrocardiograph Reading Center (ECGRC) interpreted the electrocardiographic reading using the Minnesota Code Modular ECG Analysis System (MC-MEANS) by methods previously described (Taylor et al., 2005). ECG measurements included QT interval, RR interval and diagnoses included left and right bundle branch block, atrial fibrillation or atrial flutter, other arrhythmias, or pacemaker use detected on the ECG (Taylor et al., 2005). Therapeutic Classification System was used to record any medications taken by the participants in the two weeks prior to their clinical examination.

Familial correlations

Familial correlations were determined using FCOR in the S.A.G.E v 6.1.0 package [S.A.G.E. 2009]. Heterogeneity tests were applied to test differences among subgroups.

Segregation Analysis

A segregation analysis was performed using SEGREG in the S.A.G.E v 6.1.0 package [S.A.G.E. 2009]. Working under the assumption of a single trait locus with two alleles, we estimated the segregation of these alleles through the JHS pedigrees by examining the distribution of QT interval duration. We allowed a set of parameters to depend on an unobserved qualitative factor characterized by the expected phenotypic distribution of individual of a particular type's offspring, where type is defined as u and u = AA, Aa or aa.

When the frequencies of the type variable are in Hardy-Weinberg equilibrium ($\psi_{AA} = q_A^2$; $\psi_{Aa} = 2q_A(1-q_A)$; $\psi_{aa} = (1-q_A)^2$) and we assume homogeneity of variance across generations, the probability of parent-offspring transmission of A is dependent on the frequency (q). The probability of person of type u transmitting the A allele to their offspring is defined as the transmission probability (τ). Under Mendelian inheritance, when u=AA, $\tau_{AA}= 1$, $\tau_{Aa} = .5$, $\tau_{aa} = 0$. Three other genetic models are allowed: (1) **General model**: $0\leq \tau_{AA}, \tau_{Aa}, \tau_{aa} \leq 1$ (2) **Homogenous general**: $\tau_{AA \text{ and } aa}$ are forced to be greater than or equal to zero and less than or equal to 1 while $\tau_{AB}=(q_A-q^2_A\tau_{AA}-(1-q_A)^2\tau_{aa})/[2q_A(1-q_A)]$; (3) **$\tau_{Aa}$ free:** τ_{AA} and τ_{Aa} are fixed to 1 and 0 respectively and τ for Aa is estimated. Under an environmental model, all three transmission probabilities are all equal to q. The transmission parameter is further classified by an estimated or fixed number of means, denoted (β). Three combinations of residual familial correlation are allowed in which the models could have either (1) sibling-sibling and parent-offspring correlations equal with no marital correlation, (2) equal mother-offspring and

father-offspring correlations with marital and sibling-sibling correlations functionally independent of the parent-offspring correlation, or (3) father-mother, mother-offspring, father-offspring, and sibling-sibling correlations functionally independent.

In our analyses, a standardized Box-Cox transformation was applied while simultaneously estimating the parameters of the model to ensure proper scaling of the data. $t = h(y^*_i) = ((y^*_i + \lambda_2)^{\lambda 1} - 1)/ \lambda_1 (y^*_{G1})^{(\lambda_1 - 1)}$ if $\lambda_1 \neq 0$; $y^*_{G1} \ln(y^*_i + \lambda_2)$ if $\lambda_1 = 0$ where t is the transform, y^*_i is the age adjusted QT residual of individual i and y^*_{G1} is the geometric mean of y^*_i. λ_1 was freely estimated while λ_2 was fixed to zero. The λ_1's for each model are listed in Table 2.

A relatively more complex model was compared to a nested simpler model which differed by one or two parameters to determine which model best fit the data. The parameter estimates from the best fitting model were then used in subsequent analyses. To select the best fitting model, a likelihood ratio statistical test (LRT) was used, where the test statistic is twice the difference between two log likelihoods and is distributed as chi-square with degrees of freedom equal to the difference (Δ) in the number of parameters between two nested models ($(\chi^2 \sim 2(\text{Log } L_2 - \text{Log } L_1))$, Δ df) . A chi-square test with an alpha level of 0.05 was used to determine statistical significance. If the models were nested, the most parsimonious model was selected. If the two models were not nested, the better fitting model was chosen as the model with the lower AIC score (Akaike's A information criterion) (Akaike, 1974).

Results

In a multivariate regression using data from the entire cohort, QT was significantly associated with age (beta= 0.25 [SE= 0.03], p< 0.0001), female gender (14.69 [0.66], p< 0.0001), BMI (0.26 [0.04], p< 0.0001), coronary heart disease (CHD) (4.8 [1.30], p=0.002), diuretics (2.2 [0.81], p=0.008), hypertension (3.1 [0.73], p<0.001), potassium (-5.1 [0.71], p<0.0001), RR (0.14 [0.001], p <0.0001), QRS (0.41 [0.03], p <0.0001) and Sokolow-Lyon Voltage (1.0 [0.37], p-value=0.01). Collectively, these covariates accounted for 59% of the variation seen in QT. The results were consistent with the findings reported by Akylbekova (2009) in the same cohort. After adjusting for theses covariates, Table 1 summarizes the familial pair correlations of QT-interval duration determined using FCOR.

The correlation estimate of QT within sib-sib pairs ($\rho = 0.22$) is higher than the parent-offspring correlations ($\rho = 0.13$). The sister-sister pair correlation ($\rho = 0.25$) is similar to that of the overall sib-sib correlation, but the brother-brother correlation ($\rho = 0.35$) is relatively high. Although the heterogeneity test for differences between these three subtypes is not significant, ($\chi_2^2 = 3.86$, p=0.145), a similar pattern is seen among the parent offspring correlations, where the same sex pairs have high correlations. The differences among the parent offspring pairs are significant, ($\chi_3^2 = 8.96$, p=0.03). These results, combined with increased correlation within sib-sib pairs compared to parent-offspring pairs suggest that having a sibling with prolonged QT-interval duration may be more predictive of one's risk of increased QT duration if both siblings are of the same sex, and the correlation is particularly high if they are both male. The QT correlation between grandparent and grandchild is not significantly different from zero, and may be reflective of changes in rate adjusted QT-interval duration with age (Buxbaum et al., 2009; Dekker et al., 2004b; Reardon & Malik, 1996).

Table 2 details the results for parameter estimates of the five best-fitting models for QT, and Table 3 summarizes the results of the LRT for nested models. Because QT interval duration is longer in women than men, we allowed for sex differences between the two-mean environmental model and the three-mean genetic model (Reardon & Malik, 2996). The sex-specific models labeled Model 2s and Model 4s are exactly the same as Model 2 and Model 4, respectively, except two distributions were assumed for each type, rather than one. Thus, we modeled up to six distributions in the three-mean genetic model. The sex specific models were then compared to the Model 2 and Model 4 and were not significantly different from Model 2 ($\chi^2 = 0.8$, $p = 0.37$) or Model4 ($\chi^2 = 1.4$, $p = 0.24$).

Table 1. Familial Pair correlations of QT residual

Relative Pair	Count	Pair Correlations (Standard error)	p-value	p-value for test of heterogeneity
Parent-offspring	609	0.13 (0.05)	0.003	0.006
Father-son	75	0.39 (0.11)	0.002	
Mother-son	155	0.008 (0.09)	0.927	
Father-daughter	96	-0.008 (0.11)	0.945	
Mother-daughter	283	0.18 (0.06)	0.005	
Sibling-Sibling	947	0.22 (0.05)	<0.0001	0.145
Sister-Sister	410	0.25 (0.06)	0.0002	
Brother-Brother	156	0.35 (0.09)	0.0006	
Brother-Sister	381	0.17 (0.07)	0.0378	
Half-Sibling	258	-0.06 (0.08)	0.4714	0.264
Grandparent-grandchild	85	-0.04 (0.11)	0.7622	
Avuncular	958	0.13 (0.04)	0.0018	0.097

Familial pair correlations of QT residuals, where QT-interval duration is adjusted for age, gender, BMI, CHD, diuretics, hypertension, potassium, RR, QRS, and Sokolow-Lyon Voltage and is adjusted to age 60.

Table 2. Maximum Likelihood Parameter Estimates for Segregation of QT- interval duration

Transmission	Number of Means	Mean Values (β_{AA}, β_{Aa} , β_{aa})	Residual Familial Correlation		Variance σ^2	Allele Frequency q_A	df	λ_1	AIC	-2 Log Likelihood
			$\rho_{PO} = \rho_{SS}$	ρ_M						
Environmental	One mean	59.564	0.19 (.03)	-0.16 (.1)	382.56	---	5	0.5883 (0.05)	12321.5	12311.5
Environmental	Two means	β_{AA}_β_{Aa}= 58.95, β_{aa} = 110.34	0.22 (.03)	-0.18 (.11)	382.77	---	7	0.8625 (0.07)	12296.4	12282.4
Homogeneous Mendelian Model	Two means	β_{AA}_β_{Aa}= 58.87, β_{aa} = 110.92	0.21 (.03)	-0.17 (.11)	320.92	.18	7	0.8537 (0.07)	12297.5	12283.5
Codominant (homogeneous Mendelian)	Three means	β_{AA}= 62.52, β_{Aa} =50.624, β_{aa} =109.03	0.23 (.03)	-0.18 (.12)	293.15	.19	8	0.82 (0.08)	12295.4	12279.4
Codominant (tau_{Aa}_free)	Three means	β_{AA}=62.69, β_{Aa} =50.13, β_{aa} =109.15	0.22 (.03)	-.20 (.13)	289.98	.23	9	0.8202 (0.03)	12295.2	12277.2

Table 3. Comparison of Nested Models for Segregation Analysis of QT-interval Duration

Models of Comparison	Best Fit Model	χ^2	Δ df	p-value
Model 4 vs. Model 5	Model 4	2.2	1	0.13
Model 2 vs. Model 2s	Model 2s	0.8	1	0.37
Model 4 vs. Model 4s	Model 4s	1.4	1	0.24

Δ df = the difference in degrees of freedom
Models 4s and 5s are Model 4 and Model 5, respectively, with sex-specific means.

In all models, the familial correlations were fixed so that parent-offspring correlations equaled sibling-sibling correlations, and spousal corrections were freely estimated. The Box-Cox transformation is applied to both the independent and the dependent sides of the model, thus, the estimates are on the untransformed scale. Familial sib-sib and parent-offspring correlations were close to 0.2 in all models, while the independently estimated spousal correlation showed a negative correlation within QT of approximately -0.2. The environmental two-mean model fit the data better than an environmental model with one mean with an AIC of 12296.4 and 12321.5, respectively. A two-mean model with homogenous Mendelian transmission probabilities was not significantly different from the two-mean environmental model.

The three-mean codominant Mendelian model was the most parsimonious genetic model and not significantly different from the tau Aa free mode of transmission ($p = 0.13$). The codominant model provided a slightly better fit to the data than the two-mean environmental model (AIC of 12295.4 and 12296.4, respectively). Because the two models were not nested, the AIC was used to select the best fitting model.

Discussion

All of the best fitting models had significant residual familial correlations that remain even after accounting for two or more underlying distributions with or without Mendelian transmission. This may indicate a shared familial environmental effect or it could be due to polygenic effects. Consistent with this study's evidence, though mild, for codominant Mendelian transmission, a model-free linkage analysis of the same dataset did find significant linkage (manuscript in preparation). Thus, the penetrance functions generated from the genetic models assessed here will be useful in future model-based linkage analysis of QT.

Additionally, the correlation of QT residuals estimated for half-sib pairs ($p = 0.05$) is less than what might be expected, given that the sib-sib correlation is 0.24. This result suggests that environmental factors play a role in QT interval duration, consistent with the finding in the segregation analysis that an environmental model best fits the data. Our findings are suggestive of a complex multifactorial trait with possible environmental findings that are similar to a segregation analysis preformed in Israeli families from the Kibbutz settlements (Aarnoudse et al., 2007). Their analysis found that the best fit model for QT is the result of many polygeneic effects, additive effect, and a major single genetic or environmental effect (Friedlander et al., 1999).

Although variation in QT interval duration has been extensively studied through GWAS in European ancestry populations, less information is available in the African ancestry populations. Even less information has been identified using family structure data. Given that multifactoral genetic traits can exhibit complex inheritance patterns or conceal monogenetic sub-entities which can only be identified through incorporation of family structure within genetics, the use of segregation analysis to identify the best fitting model for QT should increase our power in a future model-based linkage analysis (Clerget-Darpoux & Elston, 2007). Further, association analyses typically employ an additive model for analysis, including recent analyses of QT interval (Arking, Khera, Xing, Kao, Post, Boerwinkle, Chakravart, 2009; Lehtinen et al., 2008; Newton-Cheh et al., 2009; Post et al., 2007); however, our findings suggest that inclusion of a dominance factor in the model may provide a better fit to the data.

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