

Heritability of QT Interval: How Much Is Explained by Genes for Resting Heart Rate?

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Heritability of QT Interval. *Introduction:* Objective of this study was to determine the optimal (most heritable) phenotype for gene finding studies of QT interval in the general population. We also studied the extent to which heritability of QT interval can be explained by genes that also influence resting heart rate.

Methods and Results: Subjects in this classic twin study were 105 monozygotic and 256 dizygotic female twin pairs (mean age: 49.9 ± 11.5). ECG parameters were measured electronically using the Cardiofax ECG-9020. Quantitative genetic modeling was performed with Mx software. Best-fitting univariate models showed significant heritabilities for resting heart rate (0.55, 95% CI: 0.44–0.65), uncorrected QT interval (0.60, 95% CI: 0.49–0.69), and the Framingham QTc interval (0.50, 95% CI: 0.39–0.60). Familial resemblance of Bazett's QTc was best explained by shared environmental factors (0.34, 95% CI: 0.24–0.43) rather than genes. Simultaneously modeling heart rate and the uncorrected QT interval confirmed considerable heritabilities of 56% and 60%, respectively. Forty-four percent of the variance in QT interval was due to genes in common with heart rate, whereas 16% was due to genes specific to QT interval. The heritability of QT interval after the removal of effects shared with heart rate within the bivariate model (cf. QTc) was 51%.

Conclusion: About a quarter of the QT interval heritability is due to genes specific for QT interval, while the majority is shared with genes for heart rate. Differences in QTc heritability estimates indicate that use of correction formulae is best avoided in gene finding studies to avoid erroneous results. (*J Cardiovasc Electrophysiol*, Vol. 19, pp. 386–391, April 2008)

QT interval, twin study, heritability, heart rate

Introduction

Elongation of cardiac repolarization, as measured by the QT interval, is associated with cardiac arrhythmias and sudden death in patients with cardiovascular disease¹ as well as

in healthy individuals.² Both cardiac and noncardiac drugs have been reported to prolong QT interval and induce arrhythmia in patients who have a QTc interval length within the reference range.³ This suggests that some individuals may have "normal" QT intervals but are more susceptible to these arrhythmias potentially caused by genetic factors that also underlie QT variability in the general population. Identification of such genes may thus be clinically relevant, and estimation of heritability of QT interval in family or twin studies is an important first step in this process.⁴

The QT interval is strongly dependent on heart rate (i.e., cardiac cycle length),^{5,6} and various formulae exist to correct for this influence.⁷ The most commonly used QT correction formula is the one proposed by Bazett in 1920 (QTc = QT/RR^{1/2}).⁸ However, the efficacy of Bazett's formula has been questioned. For example, Karjalainen *et al.*⁹ showed that Bazett's QTc overcorrects the measured QT interval at high heart rates and under-corrects it at low heart rates. Improved correction formulae have been suggested including one based on the Framingham data.¹⁰

The rate-corrected QT interval (QTc) is known to be influenced by genetic factors with heritability estimates between 25% and 52%.^{11–15} Furthermore, loci harboring known causative genes for long-QT syndrome (LQTS) were linked to the quantitative trait of QTc in a sample of healthy twins

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with P-values of <0.001 for the LQT1 (11p11.5) and LQT4 (4q25–27) loci.¹¹ Additionally, several studies have demonstrated that both resting heart rate^{16–18} and the uncorrected QT interval,^{14,17} which is highly correlated with heart rate, are also heritable with heritability estimates ranging from 36% to 77%.

The purpose of the present investigation was to determine the most suitable phenotype for gene-finding studies of QT interval in the general population. To this end, we conducted a classic twin study in which we estimated and compared the genetic and environmental influences on QT and QTc interval, based on different adjustment formulae. In addition, a more informative bivariate model including uncorrected QT interval and resting heart rate was then adopted to assess to what extent heritability of QT interval can be explained by genes that also influence heart rate.

Methods

Study Population

ECG data were available for 372 female Caucasian twin pairs for this study. Eleven twin pairs, in which at least one twin showed pathologic changes, such as left bundle branch block (QRS duration >120 ms), were excluded. The final analysis was performed on 361 twin pairs, comprising 105 monozygotic (MZ) and 256 dizygotic (DZ) twins. Zygosity was determined by questionnaire and confirmed by DNA fingerprinting. Informed written consent was provided by all participants. The local bioethical review board had given approval for the study.

Measures

Standard 12-lead electrocardiograms were recorded using a Cardiofax ECG-9020K (Nihon Kohden UK Ltd., Middlesex, UK), which produces automated measurements of the QT interval and other ECG parameters. QT interval was measured from the earliest onset of the QRS complex to the latest offset of the T wave. Test-retest reliability for the automated QT measurement was 0.71 for the uncorrected QT and 0.74 for the Framingham QTc. This was based on a sample of 76 subjects for whom ECGs were collected twice with an average intervening period of 3.78 ± 0.52 years (range: 2.0–4.4 years). We further conducted a validation study on a subsample of 45 subjects to manually confirm the automated measurement. Analysis was performed by one experienced cardiologist (IS) using a high-resolution digitizing board (GTCO CalComp Peripherals, Columbia MD, USA). The QT and preceding RR interval was measured in lead II in three consecutive sinus cycles and subsequently averaged. The two methods showed excellent agreement. Correlations between the two methods were 0.98 for heart rate and 0.80 for QT interval. Paired *t*-tests showed negligible and nonsignificant differences between the two methods for both heart rate (0.39 beats) and QT interval (1.46 ms).

We compared three methods for calculating QTc: (a) using the built-in correction formula from the Cardiofax ECG-9020K: $QTc(1) = QT + (1000 - RR)/7$ ¹⁹; (b) the Framingham Heart Study formula: $QTc(2) = QT + 0.154 * (1000 - RR)$ ¹⁰; and (c) the Bazett formula: $QTc(3) = QT/RR^{1/2}$.⁸ For QTc(1) and QTc(2), interbeat interval RR (60/heart rate) is

expressed in milliseconds. For QTc(3), RR is expressed in seconds.

Analytical Approach

Our statistical analysis consisted of three steps. First, we investigated the correlations of the different QT interval parameters amongst themselves and with age and heart rate. As recommended by Goldenberg *et al.*,⁷ we assessed the performance of the correction formulae by evaluating their correlation with heart rate, which is expected to be zero if correction is successful. We used Generalized Estimating Equations (GEE) to test for the significance of these associations. GEE accounts for the dependency between twins and yields unbiased standard errors and P-values.²⁰ Second, we used univariate quantitative genetic modeling to estimate the relative influence of genetic and environmental factors on resting heart rate, uncorrected QT and the three QTc measures. We performed the genetic model fitting of QTc after adjustment for age, because age significantly influenced QTc levels. We also explored the hypothesis that influence of genetic and environmental factors might be different between younger (<50 years) and older subjects (≥ 50 years) and tested whether parameter estimates of best-fitting models were significantly different between younger and older groups for heart rate, uncorrected QT, and the three QTc measures. Finally, we used bivariate genetic modeling to estimate to what extent heritability of uncorrected QT interval can be explained by genes that also influence heart rate and to what extent the uncorrected QT interval is influenced by genes specific to QT interval. This model also enabled us to estimate heritability for QT interval after the removal of all the genetic and environmental influences shared with heart rate.

Structural Equation Modeling

Model fitting is based on comparison of variance-covariance matrices in MZ and DZ twin pairs and allows separation of observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components.^{21,22} The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example, heritability (h^2). The significance of components A, C and D was assessed by testing deterioration in model fit after each component was dropped from the full model (ACE or ADE), leading to the most parsimonious model in which the variance/covariance patterns are explained by as few parameters as possible. Standard hierarchical chi-square tests were used to select the best-fitting model in combination with Akaike's Information Criterion ($AIC = \chi^2 - 2df$).²¹ The model with the lowest AIC reflects the best balance of goodness-of-fit and parsimony. Extension of univariate models to the bivariate case, including both QT and heart rate, additionally allows exploration of the question whether and to what extent the correlation between QT interval and heart rate can be explained by common genes (i.e., the genetic correlation [r_g]) or common environment (i.e., the environmental correlation [r_e]). In other words, this model enabled us to quantify which part of the (genetic or environmental) variance components was specific to QT and which part was due to the influence of heart rate.

TABLE 1

General Characteristics and ECG Parameters in MZ and DZ Twin Subjects

Variable	Overall	MZ	DZ
N (pairs)	361	105	256
Age (years)	49.9 ± 11.5	49.7 ± 12.4	50.0 ± 11.1
Heart rate (beats/min)	66.7 ± 10.3	66.6 ± 10.0	66.7 ± 10.5
PR (ms)	155.4 ± 21.4	154.5 ± 21.0	155.7 ± 21.6
QRS (ms)	86.0 ± 8.0	86.0 ± 7.9	86.0 ± 8.1
QT (ms)	399.7 ± 27.8	401.8 ± 27.5	398.8 ± 28.0
QTc(1) (ms)	411.7 ± 16.1	413.9 ± 16.6	410.8 ± 15.9
QTc(2) (ms)	411.8 ± 15.9	414.0 ± 16.3	411.0 ± 15.7
QTc(3) (ms)	418.3 ± 18.3	420.4 ± 18.5	417.4 ± 18.2

Values are mean (SD) unless stated otherwise.

PR = PR interval; QRS = QRS duration; QT = uncorrected QT interval.

QT intervals corrected for effects of RR interval [$= (60/\text{heart rate}) \times 1000$ (ms)]:

1) Using the built-in correction formula from the Cardiofax ECG-9320K:

$QTc(1) = QT + (1000 - RR)/7$.

2) Using the Framingham Heart Study formula: $QTc(2) = QT + 0.154 \times (1000 - RR)$.

3) Using Bazett's formula: $QTc(3) = QT / RR^{1/2}$.

Statistical Analysis and Software

Heart rate was logarithmically transformed prior to correlational analysis and model fitting to obtain a better approximation of the normal distribution. Data handling, preliminary analyses, and GEE were done with STATA (StataCorp, College Station, TX, USA). Structural equation modeling was carried out using Mx software.²³

Results

General Characteristics and ECG Parameters

Table 1 shows the general characteristics and ECG parameters in MZ and DZ twin subjects. No significant differences were found between MZ and DZ twins. The mean age of this sample is 49.9, with a range of 20.6–80.1 years. Table 2 shows the correlations amongst the different QT interval parameters and with age and log transformed heart rate (LogHR). Age showed a modest but significant positive correlation with QTc measures. LogHR showed a high inverse correlation with uncorrected QT ($r = -0.83$, $P < 0.001$). After correction for heart rate with the built-in correction formula from the Cardiofax ECG-9020K, QTc(1) still showed a significant negative correlation with LogHR ($r = -0.20$, $P < 0.001$). After correction with the Bazett's formula [QTc(3)] the correlation with LogHR was also significant, but became

TABLE 2

Correlations between Age, LogHR, Uncorrected QT, and the Three QTc Measures

	QT	QTc(1)	QTc(2)	QTc(3)
Age	0.03	0.13	0.14	0.16
LogHR	-0.83	-0.20	-0.06	0.44
QT	...	0.71	0.60	0.13
QTc(1)	0.99	0.78
QTc(2)	0.86

Significant correlations ($P < 0.05$) are in bold.

See Table 1 for QTc correction formulae.

TABLE 3

Twin Correlations of LogHR, Uncorrected QT and QTc Measures by Zygosity before and after Adjustment for Age

	Before Adjustment		After Adjustment	
	r_{mz}	r_{dz}	r_{mz}	r_{dz}
LogHR	0.50	0.33	0.50	0.32
QT	0.59	0.32	0.59	0.32
QTc(1)	0.50	0.34	0.50	0.32
QTc(2)	0.49	0.34	0.48	0.32
QTc(3)	0.39	0.34	0.38	0.32

See Table 1 for QTc correction formulae.

positive ($r = 0.44$, $P < 0.001$). Only after correction with the Framingham Heart Study formula [QTc(2)] was no significant residual correlation with LogHR detected ($r = -0.06$, $P = 0.12$). Log transformation of heart rate did not influence these correlations, i.e., they were virtually identical before log transformation of heart rate. QTc(1) and QTc(2) were highly correlated with the uncorrected QT interval with r 's of 0.71 and 0.60, respectively, whereas QTc(3) only showed a modest correlation of 0.13 with the uncorrected QT interval.

Twin Correlations

Table 3 shows the twin correlations of LogHR, QT, and QTc before and after the adjustment for age. All the MZ correlations except those of QTc(3) appeared noticeably higher than the DZ ones, indicating important genetic influences. For QTc(3), the MZ correlations were only slightly higher than the DZ correlations ($r_{MZ} = 0.39$ vs. $r_{DZ} = 0.34$ before age adjustment, and $r_{MZ} = 0.38$ vs. $r_{DZ} = 0.32$ after adjustment), suggesting common environmental effects on this QTc measure based on the Bazett's formula.

Univariate Genetic Model Fitting

To estimate the genetic and environmental influence on individual differences in LogHR, QT, and QTc, we performed univariate genetic modeling. QTc variables were adjusted for age. Parameter estimates of best-fitting models could be set equal across the younger (<50 years; 50 MZ and 113 DZ pairs) and older group (≥ 50 years; 55 MZ and 143 DZ pairs) for LogHR, QT, QTc(1), QTc(2), and QTc(3) without a significant loss of fit (P -values of 0.90, 0.08, 0.43, 0.41, and 0.64, respectively). This means that best-fitting models for the younger and older group are not significantly different from each other. For this reason, we only present results of analyses in which both groups were combined. The parameter estimates and 95% confidence intervals (CIs) for the best-fitting models are shown in Table 4. For LogHR and uncorrected QT interval, the models composed of common and unique environmental influences (CE model), which explain familial resemblance by shared environmental factors (C) instead of additive genetic effects (A), could be rejected significantly (i.e., ACE vs. CE: $P = 0.02$ and 0.001 , respectively). Thus, the best-fitting model (AE) revealed significant genetic influence with heritability estimates shown in Table 4. For QTc(1) and QTc(2), the CE model could not be entirely dismissed, but the AE model showed a better fit based on AIC. As for QTc(3), the CE model was significantly better

TABLE 4

Parameter Estimates and 95% CIs of Best-Fitting Univariate Models

Variable	h ² (95% CI)	c ² (95% CI)	e ² (95% CI)
LogHR	0.55 (0.44–0.65)		0.45 (0.35–0.56)
QT	0.60 (0.49–0.69)		0.40 (0.31–0.51)
QTc(1)	0.52 (0.40–0.61)		0.48 (0.39–0.60)
QTc(2)	0.50 (0.39–0.60)		0.50 (0.40–0.61)
QTc(3)		0.34 (0.24–0.43)	0.66 (0.57–0.76)

See Table 1 for QTc correction formulae. h² = heritability; c² = shared environmental variance component; e² = unique environmental variance component.

than the AE model, with shared environmental influences explaining 34% of individual differences. Dominant genetic influences were tested for all variables (ADE vs. AE) but never contributed significantly (data not shown).

Bivariate Genetic Model Fitting

The strong correlation between uncorrected QT interval and LogHR, as well as the significant genetic influences on both phenotypes revealed in univariate analysis, prompted us to perform bivariate genetic modeling of these two phenotypes. The model-fitting results are shown in Figure 1. The full models (ACE or ADE) and the rejected E model were not included to simplify the presentation. The AE model was the best-fitting model with the lowest AIC value of -0.16 (Fig. 1a). One of the submodels of AE (Fig. 1b) assumed that there was no genetic correlation (r_g = 0) between QT and heart rate, and hence all the phenotypic correlation was explained by unique environmental factors common to both traits. The other submodel of AE (Fig. 1c) assumed that the genetic influences on QT variation were entirely identical to those on LogHR (r_g = 1), i.e., no specific genetic influences on QT. Both submodels could be rejected, indicating significant genetic overlap between the two phenotypes and important specific genetic effects on uncorrected QT interval. The CE model could be dismissed because it showed a significant deterioration, compared with the full ACE model (P = .016, Fig. 1d).

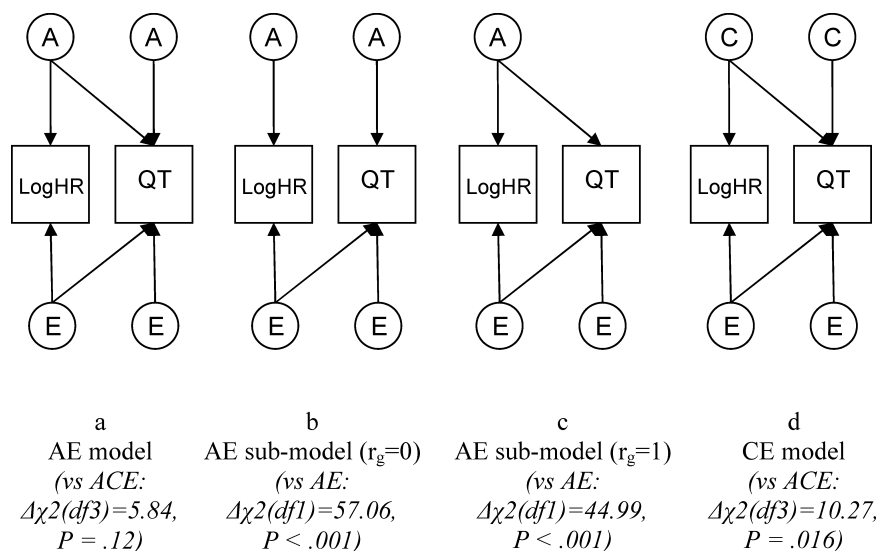
Figure 2 shows the parameter estimates of the bivariate model. The phenotypes of QT and LogHR were highly correlated genetically (r_g = -0.86, 95% CI: -0.90 to -0.80). The heritability estimates for uncorrected QT interval (0.60) and LogHR (0.56) were similar to those in the univariate modeling, as shown in Table 4. A breakdown of the genetic and environmental sources of variance for the uncorrected QT interval is presented in Figure 3. About 44% of the total variance of QT could be attributed to genetic effects that also influence LogHR, while 25% was due to unique environmental effects common to both traits. Genetic factors specific for uncorrected QT contributed 16% of the total variance. After the removal of all the genetic and environmental effects shared with LogHR, the adjusted heritability of QT was 0.51 (95% CI: 0.40–0.61), quite similar to the heritability estimates of corrected QT using linear regression formulae [QTc(1) and QTc(2), Table 4].

Discussion

The purpose of this classic twin study was to determine the optimal (i.e., most heritable) phenotype for gene finding studies of QT interval in the general population. To this end, we estimated and compared the genetic and environmental influences on QT and QTc interval, based on different adjustment formulae. In agreement with previous studies,^{11–18} best-fitting univariate models showed heritability estimates between 50% and 60% for heart rate (i.e., LogHR), uncorrected QT interval and the Framingham QTc interval. However, familial resemblance of Bazett’s QTc was best explained by shared environmental factors rather than genes.

Although Bazett’s formula is still commonly used by clinicians, recent studies suggest that use of Bazett’s formula is at best problematic and most certainly inaccurate.^{9,24,25} These conclusions are supported by our own results. We confirmed that Bazett’s formula insufficiently corrects for heart rate as indicated by a significant positive residual correlation of 0.44 between heart rate and Bazett’s QTc. More importantly, our results further indicate that correction with Bazett’s formula may lead to unacceptable bias in estimates of genetic and environmental variance components.

Figure 1. Models tested in bivariate analysis. Arrows indicate genetic or environmental loadings. A: additive genetic factor; C: common environmental factor; E: unique environmental factor. For clarity, only one twin is depicted. The full ACE and ADE models and the E submodel were also tested, but are not presented here for simplification. For each model it is indicated which model comparison is conducted. r_g = genetic correlation; Δχ² = chi-square value of the comparison between models; df = degrees of freedom of the chi-square test. Significant P-values indicate the model fits significantly worse than the model with which it is compared.



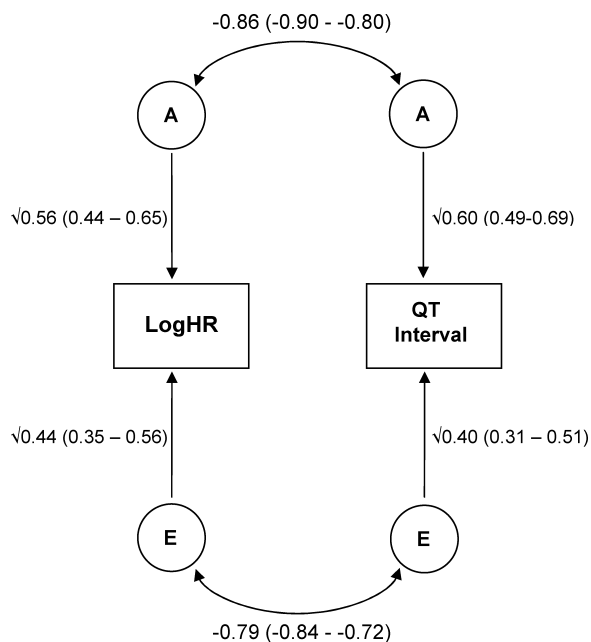


Figure 2. Genetic and environmental correlations and factor loadings of the best-fitting bivariate model for QT interval and LogHR. For clarity only one twin is depicted. Factor loadings (or path coefficients) are expressed as square roots to make clear that squaring those factor loadings yields estimates of genetic and environmental variance components, as shown in text. A: additive genetic factor; E: unique environmental factor.

Prompted by these results and the fact that heart rate itself has a significant genetic component,^{16-18,26} we decided to use a more informative bivariate genetic model including uncorrected QT interval and resting heart rate. This approach provided a number of important advantages. Rather than using a potentially biased QTc variable, it allowed us to correct QT for heart rate within the framework of the best-fitting model. Furthermore, we were able to assess to what extent uncorrected QT interval and resting heart rate are influenced

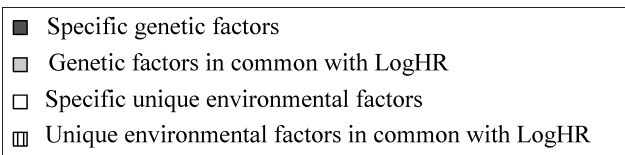


Figure 3. Sources of variance of QT interval based on the best-fitting bivariate model.

by the same genes. Both (logtransformed) heart rate ($h^2 = 56\%$) and QT interval ($h^2 = 60\%$) showed considerable heritabilities in the best-fitting bivariate model, with large overlap between the genes underlying both phenotypes. The heritability of QT interval after adjustment for heart rate within the bivariate model (cf. QTc) was 0.51. Of the total variance in QT interval, 44% was due to genes in common with heart rate, whereas 16% was due to genes specific to QT interval. A recent study by Martin *et al.*²⁷ offered support for the notion that heart rate and QT interval may be influenced by the same genes. This study found a significant linkage in a genome-wide scan for heart rate on Chromosome 4q in the same region as the AnkyrinB gene (LQT4), one of the genes underlying LQTS.

Until recently, all association studies of continuous QT interval duration had focused on candidate genes identified in studies of Mendelian LQTS. Genome-wide association studies can be used to systematically test common genetic variation, enabling the identification of previously unanticipated variants. Arking *et al.* demonstrated the involvement of an unsuspected gene influencing QT interval, the nitric oxide synthase 1 adaptor (*NOS1AP*) gene, which was found to explain approximately 1.5% of the QT variation in a large population-based cohort.²⁸

The current study has a number of strengths. An important improvement over some previous studies^{12,17} included the automated electronic measurement of QT interval instead of measuring QT intervals by hand, which is likely to reduce measurement error considerably. Moreover, this is the largest twin study (>350 pairs) of QT interval to date^{11,12,14,18} and the first to perform multivariate analyses modeling the association between QT interval and heart rate, further boosting the power of the study.²⁹ The reported results are likely to be representative of the general population because a wide range of disease related variables in the twins were similar to a population-based sample of singleton women participating in the Chingford cohort study in London.³⁰ On the other hand, the current study sample consisted of females only and results cannot necessarily be generalized to males.

In conclusion, our study shows that QTc heritability estimates depend on the specific correction formula applied. It confirms the inferior performance of Bazett's formula and extends it to gene-finding studies. Only about a quarter of the uncorrected QT interval heritability is due to genes specific to QT interval, while the remainder is shared with genes for heart rate. Recent developments in genotyping technology mean that detection of these genes no longer constitutes a distant goal. Genome-wide association studies of heart rate and QT interval likely will uncover which genes are specific to each trait and which genes are common to both heart rate and QT interval.

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