The narrow-sense and common single nucleotide polymorphism heritability of early repolarization

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ABSTRACT

Background: Early repolarization (ER) is a risk marker for sudden cardiac death. Higher risk is associated with horizontal/descending ST-segment ER in the inferior or inferolateral ECG leads. Studies in family cohorts have demonstrated substantial heritability for the ER pattern, but genome-wide association studies (GWAS) have failed to identify statistically significant and replicable genetic signals.

Methods and results: We assessed the narrow-sense and common single nucleotide polymorphism (SNP) heritability of ER and ER subtypes using ECG data from 5829 individuals (TwinsUK, BRIGHT and GRAPHIC cohorts). ER prevalence was 8.3%. In 455 monozygous vs 808 dizygous twin pairs, concordances and twin correlations for ER subtypes (except horizontal/descending ST-segment ER) were higher and familial resemblance (except notched ER) was significant. Narrow-sense heritability estimates derived from 1263 female twin pairs using the structural equation program Mx ranged from 0.00–0.47 and common SNP heritability estimates derived from 4009 unrelated individuals of both sexes using Genome-wide Restricted Maximum Likelihood (GREML) ranged from 0.00–0.36, but none were statistically significant.

Conclusion: From our data, ER shows limited genetic predisposition. There appears to be significant environmental influence and these modest narrow-sense and common SNP heritability estimates may explain why previous GWAS have been unsuccessful.

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1. Introduction

Early repolarization (ER), particularly in the inferior and inferolateral electrocardiogram (ECG) leads, has emerged as a risk marker for sudden cardiac death (SCD) [1,2]. The morphology of the ST-segment appears important in determining risk for arrhythmic events in the general population and survivors of idiopathic ventricular fibrillation (IVF) [3,4]. ER with a rapidly ascending ST-segment, consistent with historical descriptions of benign ER, is more prevalent in young, male, athletic individuals of Afro-Caribbean ethnicity [5]. It does not appear to confer risk of arrhythmic events, whereas ER with a horizontal/descending ST-segment does [3,4,6].

Pedigree analysis of the families of SCD victims has suggested that ER has autosomal dominant inheritance with incomplete penetrance [7]. Heritability studies conducted in family and community based cohorts
have demonstrated substantial heritabilities of 50–80% for the ER pattern and its associated morphologies [8,9]. At present, there are little data on the genetic basis of ER. Candidate gene studies have identified a limited number of rare variants in early repolarization syndrome probes, including a gain of function variant in KCNJ8, and presumed loss of function variants in CACNA1C, CACNB2, CACNA2D1 and SCN5A [10–12].

Although previous cohort studies have demonstrated substantial heritability for the ER pattern, genome-wide association studies (GWAS) have been unable to identify a statistically significant and replicable signal [13]. We sought to estimate the heritability of ER, with attention to ST-segment morphology, using twin analyses to determine narrow-sense heritability (the proportion of variance of a trait that is due to additive genetic factors). We then undertook common single nucleotide polymorphism (SNP) based heritability analyses using data from three large independent cohorts. This study therefore adds to prior literature by using both methods to measure heritability.

2. Methods

2.1. Populations

Study subjects were identified from the TwinsUK registry, the MRC British Genetics of Hypertension (BRIGHT) study, and the Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC) study. The TwinsUK cohort is a national register of monozygous (MZ) and dizygotic (DZ) adult Caucasian twins recruited as volunteers through a series of media campaigns and not selected for particular diseases or traits [14]. The BRIGHT study comprises over 2000 unrelated hypertensive cases and normotensive controls of white European ancestry recruited in the UK general population to investigate the genetic determinants of blood pressure and related cardiovascular traits. The studies have previously been given ethical approval and comply with the Declaration of Helsinki.

Subject age was defined at the time of the ECG. Individuals across all three cohorts with ECG data available were potential candidates for study inclusion. The study exclusion criteria were atrial fibrillation; complete heart block; right or left branch bundle block; a pacemaker; prior history of cardiac arrhythmia, Brugada syndrome, long or short QT syndromes; medical therapy with anti-arrhythmic drugs; or missing data on covariates. Following exclusion criteria, 3539 individuals from TwinsUK (504 MZ and 822 DZ twin pairs, 11 twin pairs with unknown zygosity, 35 twin-sib pairs, 163 other sibs, and 632 singletons), 1358 hypertensive cases from BRIGHT and 932 unrelated individuals from GRAPHIC.

2.2. Electrocardiogram analysis and early repolarization scoring

When more than one ECG was available [TwinsUK], the earliest was used, as prevalence of ER appears to decline with age [1]. TwinsUK and BRIGHT ECGs were evaluated at St George’s University of London. Each ECG was examined by two blinded individuals yielding 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described [9]. To determine interobserver variability between UK and German teams, a yield of 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described. When more than one ECG was available (TwinsUK), the earliest was used, as prevalence of ER appears to decline with age [1]. TwinsUK and BRIGHT ECGs were evaluated at St George’s University of London. Each ECG was examined by two blinded individuals yielding 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described [9]. To determine interobserver variability between UK and German teams, a yield of 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described. When more than one ECG was available (TwinsUK), the earliest was used, as prevalence of ER appears to decline with age [1]. TwinsUK and BRIGHT ECGs were evaluated at St George’s University of London. Each ECG was examined by two blinded individuals yielding 98% concordance. GRAPHIC ECGs were evaluated in Germany as previously described [9]. To determine interobserver variability between UK and German teams, a yield of 98% concordance.

The resulting data set for heritability estimation contained 532,301 SNPs. To determine whether the observed variability between UK and German teams, a yield of 98% concordance.

2.3. Genotyping and imputation

Subjects from the TwinsUK cohort were genotyped using the Illumina HumanOmniExpress-12v1.1 700k platform (Illumina, San Diego, USA).

Because the cohorts used different genotyping platforms, the genotype data set of each cohort was enlarged by imputation using the HapMap Phase 3 CEU set as a reference panel [18]. This reference set was chosen as it contains >1.5 × 107 independent SNPs and the imputed data sets can be used in GEMEL directly, without further pruning or clumping of SNPs. After imputation, data from the three cohorts were filtered on minor allele frequency >5% and imputation quality >0.5, converted to best-guess genotypes, where only genotypes with a probability of >0.9 were considered valid, and finally filtered on call rate >95%. These high-quality datasets were subsequently merged based on rs-id and filtered on SNPs that were present in all three cohorts. Finally, SNPs that differed significantly in allele frequencies between either pair of cohorts (p < 0.0001) were excluded. The resulting data set for heritability estimation contained 532,301 SNPs.

2.4. Heritability estimation

Classical twin modeling was undertaken in the TwinsUK cohort using the DZ and MZ female twin pairs. The narrow-sense heritability of ER and ER subtypes was estimated using the structural equation program Mx (version 1.3.65), meaning that only additive genetic effects were considered [19]. It is possible to quantify the genetic and environmental contribution to a dichotomous variable, such as the presence or absence of ER, by assuming that there is a continuous normally distributed underlying liability to disease and that a threshold of liability divides subjects into two categories: affected and unaffected [20]. MZ and DZ twin pair correlations of the underlying liability distribution were based on 2 × 2 contingency tables in which the cells contain the frequencies of pairs concordant and discordant for the presence or absence of disease in the MZ and DZ twins.

In the classical ACE twin model the correlations between MZ and DZ correlations were used to investigate the relative contribution of genetic and environmental influences to individual differences in a trait. The variance of the trait was split into independent components for additive genetic (A), common environmental factors (shared by twins within a twin pair) (C) and unique environmental factors (E). Twin modeling was conducted on raw ordinal previously [17]. Subjects from the GRAPHIC study were genotyped using the Illumina HumanOmniExpress-12v1.1 700k platform (Illumina, San Diego, USA).

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data using Mx, which can accommodate missing data, and differential resemblance by zygosity was compared [19]. Twin pairs with incomplete trait data were included in the analyses as they contributed information for estimation of liability thresholds. Given that prevalence rates of ER vary with age, estimated liability thresholds were adjusted according to age of the participant. The Mx model for thresholds included regression of threshold on observed age at screening, using the definition variable approach [19]. A total of 455 MZ and 808 DZ female twin pairs from the TwinsUK cohort were available for analysis using this approach. Male individuals were excluded due to low numbers, particularly of affected male twins.

Due to the predominant female gender of the TwinsUK cohort and the lower prevalence of ER in females, two well-characterized large mixed-sex cohorts of unrelated individuals were subsequently included. The common SNP heritability from the combined genome-wide SNP data of the three cohorts (including males and the other siblings and singletons from the TwinsUK cohort) was estimated using GREML analysis from the Genome-wide Complex Trait Analysis (GCTA) package [21–23]. GREML is an assumption free method that quantifies the percentage of phenotypic variance explained by genome-wide SNPs using estimates of identity-by-state (IBS) sharing of alleles between pairs of unrelated individuals. The common SNP heritability estimate is denoted by hSNP [23]. As the three cohorts were not enriched for ER cases, no correction was made for ascertainment bias (that is the prevalences were assumed to be equal to the proportions of cases observed in the sample), but a back-transformation from liability to case-control scale was applied [24]. The genetic relationship matrix was calculated between all pairs of individuals from all three cohorts and the set of individuals with a genetic relationship to a twin pair. The genetic relationship matrix was calculated between all pairs of individuals.

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find statistically significant genetic associations for ER or ER subtypes, and suggest larger studies will be required [13].

### 4.1. Comparison with other studies

Thus far heritability studies have been conducted in family and community-based cohorts [8,9]. Prior analysis of 505 Caucasian nuclear families from the GRAPHIC cohort estimated the narrow-sense heritability using variance component analyses adjusted for age and sex. The estimated overall heritability of ER was 0.49 ± 0.14 (p = 2.7 × 10−5), with higher estimates calculated for inferior and notched ER (0.61 ± 0.18 and 0.81 ± 0.19 respectively). When ER was present in the parents’ ECGs, a 2.5 fold increased risk of the offspring presenting with ER was reported [9]. Another community-based cohort showed that siblings of subjects with ER carry a two-fold increased risk of ER themselves, although this was no longer significant after adjustment for age and sex [8].

Our heritability estimates are lower and not statistically significant. The differences may partly reflect differences in the populations studied as our cohort included a larger proportion of middle-aged Caucasian women (from TwinsUK). Although our sample size was not much greater than other studies, our analyses used SNPs to estimate the genetic similarity between unrelated individuals and compare that to their trait similarity. Differences in methodology may therefore explain the differences in results from prior studies, particularly the GRAPHIC analysis which used only family based h² estimates, not hSNP estimation. A (additive genetic factors) and C (common environmental factors) are confounded in family studies, so the reported h² heritability estimates may have included a C component. Our findings imply that ER heritability is substantially lower than previously described.

### 4.2. ST-segment morphology

In our population, the ER ST-segment morphologies were found in similar proportions. Higher concordances and twin correlations in MZ compared with DZ twin pairs pointed to a genetic contribution for ER with a rapidly ascending ST-segment, but not ER with horizontal/descending ST-segment. ER with a rapidly ascending ST-segment also demonstrated greater heritability than ER with horizontal/descending ST-segment. This was not statistically significant, but large 95% confidence intervals suggest that this might be attributed to lack of power rather than non-existent genetic effects.

### Previous retrospective analysis of a community-based cohort also found greater heritability of the rapidly ascending ST-segment morphology [26]. As this pattern is more prevalent in young male athletes, heritability studies in a younger more active cohort may clarify this more accurately. ER subtype is considered benign and therefore the heritable component of ER does not appear to be associated with adverse outcomes. This is supported by findings that ER with horizontal/descending ST-segment has been associated with older age. ECG signs of coronary artery disease, and longer QRS duration, suggesting a more acquired phenotype [3]. Those with horizontal/descending ST-segments in our population were also older with longer QRS duration.

Previous work has shown that first-degree relatives of autopsy negative SCD victims have increased prevalence of ER with both rapidly ascending and horizontal/descending ST-segment morphologies, when compared to matched nuclear families [27]. A recent study demonstrated higher prevalence of ER in survivors of unexplained cardiac arrest (UCA) who had first-degree relatives with the ER pattern [28]. It therefore remains possible that ER is heritable when seen in the context of SCD and UCA and that ER with rapidly ascending ST-segment may not be completely ‘benign’ in this setting.

We also found that lateral and rapidly ascending ER subtypes were influenced by age. These subtypes are consistent with the historical description of ER [5]. The horizontal/descending subtype would only be considered ER according to more recent definitions, first described by Haissaguerre et al. [2] All ER is not necessarily the same and may explain why age influences lateral and rapidly ascending ER but not other subtypes [29].

Interestingly a recent GWAS of ST-segment and T wave voltage has identified SNP associations that might be relevant to ER-associated ST-segment morphology, but cannot yet be extrapolated directly to ER

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### Table 2

<table>
<thead>
<tr>
<th>ER subtypes</th>
<th>a²</th>
<th>c²</th>
<th>e²</th>
<th>Influence of age on threshold</th>
<th>A + C</th>
<th>p-Value test drop A + C</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ER</td>
<td>0.36</td>
<td>0.16</td>
<td>0.48</td>
<td>0.01 (-0.005 to 0.01)</td>
<td>0.52 (0.31 to 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ER by type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notched</td>
<td>0.19</td>
<td>0.11</td>
<td>0.69</td>
<td>0.008 (-0.01 to 0.0066)</td>
<td>0.31 (0.03 to 0.62)</td>
<td>0.16</td>
</tr>
<tr>
<td>Slurred</td>
<td>0.31</td>
<td>0.03</td>
<td>0.33</td>
<td>0.67 (0.46 to 0.83)</td>
<td>0.007 (n.a. to 0.007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ER by territory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.01 (-0.02 to -0.003)</td>
<td>0.51 (0.17 to 0.76)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.47</td>
<td>0.04</td>
<td>0.49</td>
<td>0.02 (-0.02 to -0.008)</td>
<td>0.62 (0.35 to 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.007 (-0.001 to 0.02)</td>
<td>0.49 (0.28 to 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ER by ST-segment morphology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>0.46</td>
<td>0.10</td>
<td>0.38</td>
<td>0.007 (-0.001 to 0.02)</td>
<td>0.49 (0.28 to 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HD</td>
<td>0</td>
<td>0.10</td>
<td>0.51</td>
<td>0.007 (-0.001 to 0.02)</td>
<td>0.49 (0.28 to 0.73)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* p-Value < 0.05; ER, early repolarization; RA, rapidly ascending ST-segment; HD, horizontal/descending ST-segment; CI, confidence interval; n.a. not applicable (no MZ cases concordant for the disease); a² = proportion of variance in disease liability explained by additive genetic factors (i.e. heritability); c² = proportion of variance in disease liability explained by common environment; e² = proportion of variance in disease liability explained by unique environment; drop A + C = test of the E model (familial resemblance).

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### Table 3

<table>
<thead>
<tr>
<th>ER subtypes</th>
<th>h²SNP (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ER</td>
<td>0.07 (-0.31 to 0.45)</td>
<td>0.72</td>
</tr>
<tr>
<td>ER by type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notched</td>
<td>0.00 (-0.59 to 0.59)</td>
<td>1.00</td>
</tr>
<tr>
<td>Slurred</td>
<td>0.14 (-0.33 to 0.62)</td>
<td>0.56</td>
</tr>
<tr>
<td>ER by territory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>0.30 (-0.35 to 0.94)</td>
<td>0.38</td>
</tr>
<tr>
<td>Lateral</td>
<td>0.36 (-0.40 to 1.12)</td>
<td>0.36</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>0.00 (-1.18 to 1.18)</td>
<td>1.00</td>
</tr>
<tr>
<td>ER by ST-segment morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapidly ascending</td>
<td>0.31 (-0.46 to 1.08)</td>
<td>0.42</td>
</tr>
<tr>
<td>Horizontal/descending</td>
<td>0.00 (-0.51 to 0.51)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

h²SNP: GREML estimate of the common SNP heritability; CI, confidence interval.
[30]. J-point elevation ≥0.1 mV is required as part of the definition of ER and the J-point was not included in the analysis. Heritability estimates of the inferior ST-segment voltage were however on the low side, in part supporting our data.

4.3. Definitions

Our definition of ER stayed as true as possible to those used in studies that have associated ER with SCD events in the general population and in survivors of IVF [1–4]. Although accurate measurement of the notched ER pattern is usually straightforward, when transition from the terminal QRS into the ST-segment is unclear J-point elevation may be more subjective and this poses a problem for identifying slurred ER [29]. Despite this the interobserver reliability in the TwinsUK cohort was high with 98% concordance as well as 96% concordance between GRAPHIC and BRIGHT, indicating that our measurements are reliable.

4.4. Limitations

GREML can be used to analyse quantitative traits in family members, as it enables estimation of the narrow-sense heritability using identity-by-descent sharing rather than identity-by-state information, that is more accurate than the heritability estimates from structural equation modeling in Mx [22,23,31]. Unfortunately, current versions of GREML cannot be used for narrow-sense heritability estimation using relatives for binary traits such as ER, because the liability correction that is applied requires unrelated individuals. Mx heritability estimates which were derived from female twins only, were not statistically significant due to the low disease prevalence resulting in low power to differentiate between additive genetic factors and common environment in classical twin estimates. We attempted to estimate the percentage of phenotypic variance explained by common SNPs using GREML. However, all common SNP heritability estimates were non-significant, implying that analysis of a binary trait with a low prevalence with GREML has insufficient power resulting in unreliable estimates of the common SNP heritability. In addition $h_{SNP}^2$ does not capture the contribution of rare variants.

5. Conclusion

ER and ER subtypes are traits with a modest to high familial component, but our analyses could not determine whether these are genetic or shared environmental factors. It therefore appears that although ER may show some genetic predisposition, there is significant environmental influence. These modest heritability estimates may explain why GWAS have been unable to find significant genetic signals for ER. Furthermore, we observed no significant differences between heritability of the ST-segment morphology subtypes.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.119.

References


