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Early Repolarization Pattern Inheritance in the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER)

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ABSTRACT

OBJECTIVES This study explored early repolarization (ER) pattern inheritance between survivors of unexplained cardiac arrest (UCA) and their first-degree relatives.

BACKGROUND ER is considered a factor that confers an increased risk of sudden death. A monogenic explanation for ER is seldom evident after cascade screening.

METHODS UCA survivors and their first-degree relatives enrolled in the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry were included in the study. ER was defined and characterized according to accepted criteria. Logistic regression was performed to explore the association between ER status in the UCA survivor and first-degree relative groups based on the presence of an ER pattern in their related family members after adjusting for age, sex, and ethnicity.

RESULTS A total of 289 patients from 14 Canadian sites were studied (age: 43.0 ± 15.9 years; 148 women), and 945 electrocardiograms were analyzed. Seventy-five patients had the ER pattern. There was a significantly higher prevalence of the ER pattern in UCA survivors who had first-degree relatives with the ER pattern (adjusted odds ratio: 5.79; 95% confidence intervals [CI]: 1.79 to 18.7). There was also a nonsignificant higher prevalence of the ER pattern in first-degree relatives of UCA survivors with the ER pattern (OR: 2.43; 95% CI: 0.70 to 8.43). The highest prevalence of the ER pattern was seen in first-degree relatives of UCA survivors with ER syndrome (29%).

CONCLUSIONS The ER pattern appeared to be more common among UCA survivors and first-degree relatives whose related family members had similar changes on electrocardiography, which suggested that genetically complex factors contribute to electrocardiographic patterns that predispose to cardiac arrest. (J Am Coll Cardiol EP 2018;■:■–■) Crown Copyright © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

ER = early repolarization

ERS = early repolarization syndrome

UCA = unexplained cardiac arrest

The early repolarization (ER) pattern is a common electrocardiographic finding that has been historically considered benign. However, there is a growing body of evidence to suggest that ER carries an increased risk of sudden death, especially if localized in the inferior leads with a horizontal and/or descending ST segment (1–11). The pathophysiology underlying ER and J-wave development remains uncertain; however, it has been suggested to be secondary to transmural dispersion of repolarization that involves the transient outward current (I_{to}) (12).

Recent studies have suggested that the ER pattern may be a heritable phenotype, although clear evidence of a Mendelian monogenic inheritance is seldom evident after cascade screening, making rare variant association with the ER syndrome (ERS) at best tenuous (13–17). To date, a series of genes that encode voltage-gated sodium, potassium, and calcium channels have been implicated in ER, although all have been identified using a candidate gene approach. A robust genotype–phenotype segregation that supports genetic causality has yet to be provided (18).

We sought to explore inheritance of the ER pattern by examining the prevalence of the ER pattern in survivors of unexplained cardiac arrest (UCA) and their first-degree relatives.

METHODS

Details of the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry) study have previously been reported (19). Briefly, CASPER is a national registry involving 14 Canadian sites that enrolled UCA survivors and their first-degree relatives. In the present study, patients with a digitized electrocardiogram (ECG) were enrolled in the CASPER registry between January 2004 and May 2017. Patients were eligible if they had experienced an UCA with ventricular tachycardia or fibrillation that required direct-current cardioversion or defibrillation. Follow-up testing demonstrated normal left ventricular function (left ventricular ejection fraction ≥50%), normal coronary arteries (no stenosis >50% or anomalous coronary arteries), and a resting QTc of ≤460 ms in men and of ≤480 ms in women. Patients could be included in the study if they had transient left ventricular dysfunction or QT prolongation immediately after the cardiac arrest that resolved promptly. The comparison group consisted of first-degree relatives of UCA survivors.

Patients were excluded if they were younger than 12 years of age or if a reversible cause of ER (e.g., marked hypokalemia or drug overdose) was present. Patients were also excluded if they had persistent ST-segment elevation with ≥2 mm ST elevation in leads V_1 and/or V_2 (type 1 Brugada pattern).

CASPER investigators were asked to review the entire patient record, including the nature and context of symptoms, family history, and the results of clinical and genetic testing. They were asked to render a working diagnosis and a qualitative descriptor of the strength of the diagnosis as definite, probable, and possible, based on the weight of the evidence (19,20). The working diagnosis could be revised over time based on events during follow-up, repeat clinical or genetic testing, or determination of previously unrecognized diagnoses, such as early repolarization or short QT syndrome. A diagnosis strength of definite required that both clinical and genetic testing be positive and/or disease-causing, or the clinical testing was clearly positive. A diagnosis strength of probable was applied when either clinical or genetic testing suggested diagnosis, but the other did not. A diagnosis strength of possible was applied when ≥1 tests were borderline but not conclusive.

Cardiac arrest survivors from the CASPER registry were labeled as UCA survivors because they did not have an explanation for their cardiac arrest at the time of enrollment in the registry. A portion of these patients did eventually receive primary diagnoses after workup with the CASPER protocol. These diagnoses included long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, dilated cardiomyopathy, myocarditis, short QT syndrome, and coronary spasm. The ER pattern could be present on ECG in a patient with 1 of the preceding diagnoses; these patients were not considered not to have ERS. In keeping with the 2015 J-wave syndrome consensus report, UCA survivors were diagnosed with ERS if they demonstrated the ER pattern in the absence of another cause of cardiac arrest (no other cause of cardiac arrest identified after diagnostic workup with the CASPER protocol) (21).

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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For UCA survivors, 12-lead ECGs were recorded on hospital presentation, on days 4 to 5 during hospitalization, and at pre-discharge; up to 5 follow-up ECGs were analyzed. ECGs on days 2 to 3 were excluded because J-point elevation is often observed during therapeutic hypothermia. For first-degree relatives, the enrollment ECG and up to 5 follow-up ECGs were used. The ER pattern was defined as J-point elevation ≥1 mm above the isoelectric line in ≥2 contiguous inferior (leads II, III, avF) or lateral leads (leads I, avL, V_4 to V_6), excluding leads V_1 to V_3 on any of the available ECGs (21).

The ER pattern was further characterized according to accepted criteria by its morphology (notched vs. slurring) and the pattern of the associated ST segment: horizontal and/or descending, defined as ≤0.1 mV elevation within 100 ms after the J point; rapidly ascending and/or upsloping, defined as >0.1 mV within 100 ms after the J point; or persistently elevated >0.1 mV throughout the ST segment (21). Because of the known intermittent nature of the ER pattern, patients were coded as having ER if any of the sampled ECGs met criteria for the ER pattern (21). If a subject had an ER pattern demonstrated in 1 ECG, but not all ECGs, this was coded as intermittent ER. The ECG lead with the most prominent ER pattern was used for analysis.

The population was divided into 2 groups: cardiac arrest survivors and first-degree relatives. The groups were further stratified by the diagnoses of the UCA survivors (ERS vs. UCA with ER but another primary diagnoses vs. UCA without ER). Baseline demographic characteristics were compared between the groups, as well as ER characteristics that included prevalence and pattern (notch vs. slurred, location, slope [upsloping vs. horizontal and/or downsloping], and J-point amplitude). All 12-lead ECGs were independently reviewed by 2 physicians experienced in ECG interpretation who were blinded to patient status.

Data were reported as mean ± SD or median and interquartile range. In both UCA survivors and first-degree relatives, logistic regression was performed to evaluate for association between ER status and for the presence of the ER pattern in a related family member, adjusting for known predictors of the ER pattern, including age, sex, and ethnicity. p Values for single variables between comparator groups were calculated using a chi-square or Fisher's exact test depending on cell size for comparison. A p value <0.05 was considered statistically significant.

All patients provided written informed consent. This project was conducted in compliance with the protocol and principles in the Declaration of Helsinki and Good Clinical Practice, as defined by the International Conference on Harmonization, where applicable, along with all other local regulatory requirements. Written approval from the institutional review boards and/or independent ethics committees of the 14 sites was obtained before study initiation.

TABLE 1 Study Population Characteristics

	All	UCA Survivors	UCA Survivors With ER Syndrome	UCA Survivors With ER With Other Diagnoses	First-Degree Relatives
N	289	159	38	19	132*
Age, yrs	43 ± 16	47 ± 15	42 ± 13	40 ± 15	40 ± 16
Female	148 (51)	74 (47)	14 (37)	9 (47)	74 (56)
Ethnicity†					
White/Caucasian,	210 (84)	119 (86)	28 (76)	50 (86)	91 (82)
Other	40 (16)	20 (14)	9 (24)	8 (14)	20 (18)
Median ECGs	2 (4)	4 (3)	5 (4)	5 (3)	1 (1)

Values are n (%), mean ± SD, and median (interquartile range 1-5). *Thirty-six parents, 59 siblings, and 37 children; 2 unexplained cardiac arrest (UCA) survivors are siblings. The total number of subjects was 289, but first-degree relatives + UCA survivors equalled 291. †Ethnicity information was available for 139 UCA survivors and 111 first-degree relatives.

ECG = electrocardiogram; ER = early repolarization.

RESULTS

A total of 945 ECGs from 289 subjects were analyzed (median 2 per subject; IQR 1 to 5). Approximately one-half of all patients were women, and the mean age was 43 ± 16 years (Table 1). Of the 159 UCA survivors, 80 had at least 1 first-degree relative enrolled. Parents, siblings, and children accounted for 27%, 45%, and 28% of first-degree relatives, respectively.

UCA survivors were further divided by ERS versus other diagnoses. Of the 57 UCA survivors with the ER pattern, 38 UCA survivors had a primary diagnosis of ERS, whereas ER was a cofactor in 19 additional UCA survivors with other diagnoses (those who had a primary diagnosis after following the CASPER protocol; the other diagnoses included primarily long QT syndrome, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy) (Table 2).

Overall, the ER pattern was observed in 26% of the patient population. A higher proportion of the ER pattern was seen in UCA survivors compared with the first-degree relative cohort (36% vs. 14%; p = 0.0001). The ER pattern was seen in 25% of UCA survivors on the first ECG from the time of event (Online Table 1). The ECG prevalence at last and median ECG was similar (21% and 23%) (Online Table 1). Of the 56 UCA survivors and 4 first-degree relatives with an ER pattern who had >1 ECG available for interpretation, 41 (73%) and 3 (75%), respectively, had evidence of intermittent ER (at least 1 ECG that did not demonstrate ER). The ER pattern most frequently

TABLE 2 Breakdown of the ER Pattern Prevalence and Characteristics

	Total	UCA Survivors	UCA Survivors With ER Syndrome	UCA Survivors With ER With other Diagnoses*	First-Degree Relatives	UCA Survivors With IVF†	First-Degree Relatives of UCA Survivors With IVF‡
N	289	159	38	19	132	46	21
ER positive	75 (26)	57§ (36)	38 (100)	19 (100)	18 (14)	0 (–)	1 (4.8)
ER location							
Inferior	35 (47)	23 (40)	19 (50)	4 (21)	12 (67)	0 (–)	1 (100)
Lateral	18 (24)	15 (26)	8 (22)	7 (37)	3 (17)	0 (–)	0 (0)
Inferolateral	22 (29)	19 (34)	11 (28)	8 (42)	3 (17)	0 (–)	0 (0)
ER pattern							
Notched	32 (43)	20 (35)	14 (37)	6 (32)	12 (67)	0 (–)	0 (0)
Slurring	36 (48)	30 (53)	19 (50)	11 (58)	6 (33)	0 (–)	1 (100)
Notched and slurring	7 (9.3)	7 (12)	5 (13)	2 (10)	0	0 (–)	0 (0)
Slope							
Horizontal/descending	47 (63)	37 (64)	25 (66)	12 (63)	10 (56)	0 (–)	0 (0)
Ascending	28 (37)	20 (36)	13 (34)	7 (37)	8 (44)	0 (–)	1 (100)
Intermittent ER‖	44 (73)	41 (73)	28 (76)	13 (68)	3 (75)	0 (–)	NA
J-point amplitude (mm)	1.5 ± 0.6	1.6 ± 0.6	1.5 ± 0.7	1.6 ± 0.6	1.5 ± 0.4	0 (–)	1.5
Heart rate (beats/min)	71 ± 15	73 ± 16	73 ± 13	69 ± 16	68 ± 14	73 ± 13	70 ± 13
QT (ms)	399 ± 35	401 ± 37	395 ± 30	414 ± 39	397 ± 32	396 ± 27	397 ± 26
QTc (ms)	429 ± 33	436 ± 34	431 ± 28	437 ± 39	418.2 ± 30	432 ± 33	423 ± 27

Values are n (%) and mean ± SD. Breakdown was between UCA survivors with ER syndrome, UCA survivors with ER pattern but another primary diagnosis, UCA survivors with IVF, and first-degree relatives. *Other diagnoses include: arrhythmogenic right ventricular cardiomyopathy (n = 8), Brugada syndrome (n = 5), coronary spasm (n = 1), catecholaminergic polymorphic ventricular tachycardia (n = 6), dilated cardiomyopathy (n = 3), hypertrophic cardiomyopathy (n = 1), long QT syndrome (n = 34), and short QT syndrome (n = 2). †There were 46 total patients with idiopathic ventricular fibrillation (IVF), and by definition, none exhibited ER. ‡There were 21 total first-degree relatives of UCA survivors with IVF. One of these subjects demonstrated ER. §Thirty of 80 (37.5%) UCA survivors with enrolled first-degree relatives demonstrated the ER pattern. ‖Fifty-six ER-positive UCA survivors (37 with ER syndrome, and 19 with other diagnoses) and 4 first-degree relatives had >1 ECG available. No first-degree relatives of UCA survivors with IVF had >1 ECG available.

Abbreviations as in Figure 1.

manifested in a slurred pattern and was located in the inferior leads, with a horizontal and/or descending ST segment. The mean magnitude of the J-point elevation was 1.5 ± 0.6 mm (Table 2).

After adjusting for age, sex, and ethnicity, the ER pattern in first-degree relatives was independently associated with ER in UCA survivors (adjusted odds ratio: 5.79; 95% confidence interval: 1.79 to 18.7; p = 0.003). Similarly, the ER pattern in the UCA survivors was associated with ER in first-degree relatives (adjusted odds ratio: 2.43; 95% confidence interval 0.70 to 8.43; p = 0.16), although this was nonsignificant (Table 3).

The prevalence of the ER pattern in first-degree relatives was influenced by the apparent role of ER in the UCA survivor to whom they were related. The relationships of first-degree relatives to UCA survivors stratified by ER characteristics are outlined in Online Table 2. The highest proportion of first-degree relatives with the ER pattern were those whose family members had experienced arrest attributed to ERS (29%), followed by those whose family members had the ER pattern but who had a primary diagnosis for arrest other than ERS (17%), and finally, followed by those whose family members had no evidence of ER (8.4%) (Figure 1). Sample tracings from a UCA survivor and 2 first-degree relatives are presented in Figure 2.

Eighty-seven first-degree relatives had follow-up data available. Overall, events in the first-degree relative cohort were low, and all events occurred in subjects without the ER pattern. There was only 1 cardiac arrest in the first-degree relative cohort, over the 178 person-years followed (2.00 ± 2.87 years per patient). One first-degree relative with sarcoidosis experienced sustained ventricular tachycardia, and another experienced asymptomatic nonsustained ventricular tachycardia. There were 17 episodes of syncope experienced by 5 first-degree relatives; all were considered nonarrhythmic in etiology. Outcomes in UCA survivors, measured by recurrent implantable cardioverter-defibrillator shocks, were similar in between groups, regardless of ER status and diagnosis characteristics (Online Table 3). There was no statistical difference in implantable cardioverter-defibrillator shock recurrence in UCA survivors with ER versus those without ER (22% vs. 18%; p = 0.49).

DISCUSSION

This prospective multicenter registry demonstrated a higher proportion of the ER pattern in UCA survivors

compared with the first-degree relative cohort. There was a significantly higher proportion of the ER pattern in UCA survivors whose first-degree relatives had ER, compared with those whose first-degree relatives did not. Similarly, there was an association between an increased ER pattern in first-degree relatives of UCA survivors with ER, compared with those without ER, particularly in those related to UCA survivors with ERS versus those whose survivors had other diagnoses. These findings support the notion that the ER pattern is at least partially an inherited trait in this unique population of latent causes of cardiac arrest. The strength of association outlined in Figure 1 suggests a gradient of risk that could represent a genetic dose–response curve of sorts, with the greatest evidence of ER heritability found in relatives of ERS patients.

Several studies explored the heritability of the ER pattern. A study of 4 large French families with familial sudden death attributed to ERS reported a higher ER rate of 36% in multigenerational family members, and the ER pattern appeared to be transmitted in an autosomal dominant fashion with incomplete penetrance (33% to 90%) (15). In the present study, the ER pattern was also seen in the first-degree relatives whose UCA survivors did not have ER. Although a monogenic explanation of the ER pattern might be evident in some families, this observation, in conjunction with infrequent evidence of a candidate monogenic explanation for ERS, supports a multiple hit hypothesis that included oligo- or polygenic factors that interacted with environmental factors such as exercise and/or hypertrophy, ischemia, race, and sex. This is supported by the sporadic nature of ER, and its "ambient" prevalence in the general population (2,7,10,18,22).

In the present study, the ER pattern was found in 36% of UCA survivors. This was similar to previous studies in patients with idiopathic ventricular fibrillation (1-4,13-16). The ER pattern was seen in 8.4% of the first-degree relatives whose UCA survivors did not have ER. This was comparable to the ER pattern prevalence of 5.8% to 13% reported in population-based studies (2,3). We observed a 2.5-fold increase in ER pattern prevalence in first-degree relatives whose related survivors had ER, which is consistent with previous reports that demonstrated a 1.9- to 2.5-fold higher likelihood in an unselected population (13,14).

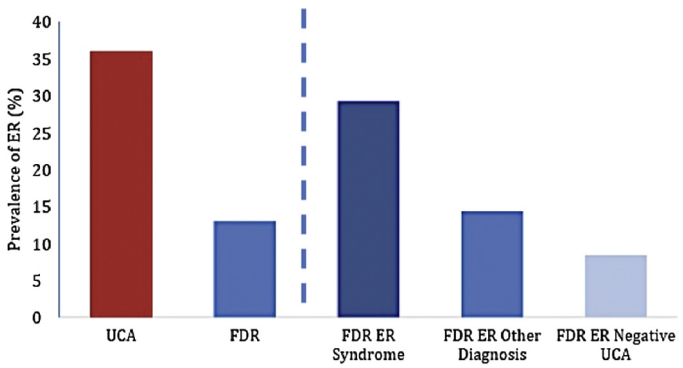
Reinhard et al. (14) also investigated ER pattern heritability and reported that subjects with a parent with the ER pattern had a 2.5-fold risk of ER. Noseworthy et al. (13) found that the ER pattern was present in 243 of 3,955 (6.1%) patients from the Framingham Heart Study. Siblings of subjects with the ER pattern had a significantly higher probability of having the ER pattern (12%), which correlated to a sibling risk ratio of 1.89. Although the study by Noseworthy et al. demonstrated a similar relative risk of the ER pattern in first-degree relatives of subjects with ER, we found a higher prevalence of the ER pattern in this cohort. This might be because their study enrolled first-degree relatives of patients in the Framingham Heart Study and not UCA survivors in whom ER might play a larger role in the propensity for arrhythmias, as well as what was more readily observed surrounding the time of arrhythmic events (13).

TABLE 3 Logistic Regression Analysis of Predictors of Positive ER Stratified by Patient Type

	Univariate		Multivariate	
Covariate	OR (95% CI)	p Value	OR (95% CI)	p Value
Logistic regression analysis of predictors of positive ER in FDRs				
Male sex	5.78 (1.79-18.69)	0.003	4.84 (1.19-19.6)	0.03
Age at enrollment*	1.00 (0.97-1.03)	0.94	1.00 (0.96-1.04)	0.90
Ethnicity†	0.46 (0.13-1.67)	0.24	0.61 (0.15-2.46)	0.49
UCA survivor with ER	3.14 (1.13-8.76)	0.03	2.43 (0.70-8.43)	0.16
Logistic regression analysis of predictors of positive ER in UCA survivors				
Male sex	1.48 (0.77-2.85)	0.24	1.85 (0.64-5.30)	0.25
Age at enrollment*	0.99 (0.97-1.02)	0.53	1.01 (0.98-1.05)	0.54
Ethnicity†	0.35 (0.12-0.98)	0.05	0.64 (0.16-2.65)	0.64
FDR with ER	4.37 (1.48-12.9)	0.007	5.79 (1.79-18.7)	0.003

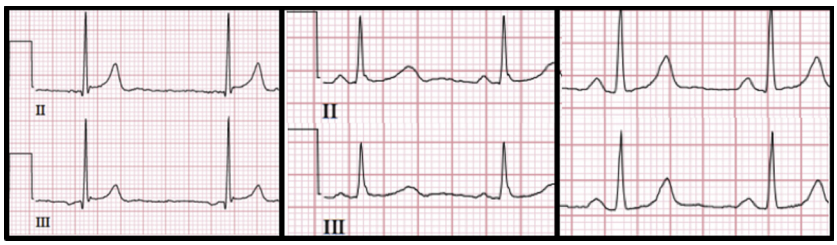
*Odds ratio (OR) reflects risk per year with increasing age †OR for White/Caucasian ethnicity versus other.
CI = confidence interval; FDR = first-degree relatives; other abbreviations as in Table 1.

FIGURE 1 ER Prevalence by Patient Type



The early repolarization (ER) pattern was much more common in unexplained cardiac arrest (UCA) survivors than in first-degree relatives (FDRs) (36% vs. 14%; $p < 0.001$). FDRs with the highest proportion of the ER pattern were those related to a UCA survivor who was diagnosed with the ER syndrome (cardiac arrest attributed to ER), followed by those related to a UCA survivor with the ER pattern on electrocardiography but who had another primary diagnosis (FDR ER Other Diagnosis). The lowest prevalence of ER was seen in FDRs related to a UCA survivor with no evidence of the ER pattern.

FIGURE 2 ER Examples



Example of horizontal notched ER pattern in a UCA survivor **(left panel)**; slurred, horizontal sloping ER pattern in a FDR **(middle panel)**, and no ER pattern in a FDR **(right panel)**. Abbreviation as in Figure 1.

First-degree relatives of UCA survivors might have a higher probability of having the ER pattern. A recent study by Mellor et al. (16) investigated the proportion of the ER pattern in 401 first-degree relatives of individuals who died from sudden arrhythmic death syndrome (16). This study found that 21% of first-degree relatives of sudden arrhythmic death syndrome patients had ER versus 8% of first-degree relatives in the control group. This contributes to the growing body of literature supporting that the ER pattern is a heritable trait associated with an increased risk of sudden death.

Ultimately, these observations provide mechanistic insights, but do not provide actionable risk markers that drive clinical decisions regarding the ER pattern. A reliable provocation test for ERS has been elusive, and the only reliable measure of risk is a combination of ECG markers of amplitude and ST-segment pattern, along with symptomatic history. These simple measures make family screening and management empiric at best, supported by guideline recommendations to withhold interventions unless arrhythmic symptoms are present, which are variably informed by family history (22).

STUDY LIMITATIONS. The ER pattern for the cardiac arrest survivors was identified after their primary arrhythmic event, and thus, we could not establish a causal relationship between the ER pattern and the cardiac arrest. The present study compared the cardiac arrest survivors and their family members, and the latter was not an a priori a control group. Moreover, the ER pattern could occur intermittently (13), and its prevalence could be underestimated in subjects with only a single resting ECG. This was the case for 100 study subjects, who were predominantly first-degree relatives. Future larger scale familial studies that assess serial ECGs with genetic testing and with extended follow-up on clinical outcomes are necessary to determine the implication of the present findings.

CONCLUSIONS

The ER pattern is more common among individuals whose family members also have ER in the CASPER registry. Furthermore, there appears to be a gradient of risk among first-degree relatives of UCA survivors, with first-degree relatives of UCA survivors with ERS having the highest prevalence of the ER pattern among first-degree relatives. This suggests that genetically complex factors contribute to ECG patterns that predispose to cardiac arrest.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The ER pattern is more prevalent in UCA survivors than that in unaffected individuals, and is demonstrated to likely be at least partly inheritable.

TRANSLATIONAL OUTLOOK: Inheritance patterns of the ER pattern and subsequent risk of sudden death for first-degree relatives of UCA survivors needs to be explored in large-scale studies.

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APPENDIX For supplemental tables, please see the online version of this paper.