Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 2, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.09.040

Identification of Large Families in Early Repolarization Syndrome

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Objectives The aim of this study was to identify families affected by early repolarization syndrome (ERS) and to determine the mode of transmission of the disease.

Background Early repolarization (ER) has recently been linked to idiopathic ventricular fibrillation. Familial inheritance of the disease has been suggested but not demonstrated.

Methods We screened relatives of 4 families affected by ERS. ER was defined as a distinct J-wave in at least 2 consecutive leads and a 1-mm amplitude above baseline. The Valsalva maneuver was performed in affected and unaffected family members to decrease heart rate and thus increase or reveal an ER pattern.

Results Twenty-two sudden cardiac deaths occurred in the 4 families including 10 before 35 years of age. In the 4 families, the prevalence of ER was 56%, 34%, 61%, and 33% of, respectively, 30, 82, 29, and 30 screened relatives. In these families, transmission of an ER pattern is compatible with an autosomal dominant mode of inheritance. All probands were screened for genes identified in ERS, and no mutation was found. The Valsalva maneuver was performed in 80 relatives, resulting in increased J-wave amplitude for 17 of 20 affected patients and revealing an ER pattern in 17 relatives in whom 5 are obligate transmitters of an ER pattern.

Conclusions ERS can be inherited through autosomal dominant transmission and should be considered a real inherited arrhythmia syndrome. Familial investigation can be facilitated by using the Valsalva maneuver to reveal the electrocardiographic pattern in family members. The prognosis value of this test remains to be assessed. (J Am Coll Cardiol 2013;61:164–72) © 2013 by the American College of Cardiology Foundation

Over the past 70 years, early repolarization (ER) has been considered a benign electrocardiographic finding affecting more predominantly asymptomatic young and healthy men (1–3). The high prevalence of this pattern in the general population (1% to 5.8%) was considered the best argument to reinforce the benign nature of this electrocardiographic pattern (1,3–6). However, new evidence has recently highlighted the importance of this abnormality, defined as a positive deflection on the S-wave in at least 2 consecutive inferior or lateral leads and at least 1-mm amplitude above baseline, with identification of this electrocardiographic pattern in 31% of patients presenting with idiopathic ventricular fibrillation (7). Recent studies also found a higher risk of sudden cardiac death (SCD) in the general population in ER pattern carriers (8,9). The high prevalence of ER in the general population contrasts with a relatively low risk of SCD, requiring further investigation to understand the pathogenic consequences of ER and risk stratification for various types of the malignant forms (10).

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In 2008, our group identified the first mutation associated with ER syndrome (ERS) in a sporadic case, located on the *KCNJ8* gene (11), suggesting genetic factors in ERS occurrence. The same mutation was found in another patient by

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Manuscript received March 29, 2012; revised manuscript received August 6, 2012, accepted September 22, 2012.

Medeiros-Domingo et al. (12), who showed that this amino acid change could lead to a gain of function of K_{ATP} channel. Genes encoding calcium channels also appear to be involved in a few unrelated ERS cases (13). However, to our knowledge, no familial cases have been previously described. The mode of transmission and genetic basis of this syndrome remain essentially unknown.

A major limitation in diagnosis is the high variability of the ER pattern over time, partly due to variation in autonomic tone and heart rate (14–17). For other arrhythmias such as Brugada syndrome and long QT syndrome, pharmacological challenges have proved their efficiency in unmasking the pattern. Because ER is modulated by vagal tone, we tested the ability of the Valsalva maneuver (VM) to reveal an ER pattern.

The aim of the study was to recruit large families affected by a malignant form of ERS and to evaluate the efficiency of the VM to unmask ER.

Abbreviations and Acronyms

ECG = electrocardiogram
ER = early repolarization
ERS = early repolarization syndrome
SCD = sudden cardiac death
VM = Valsalva maneuver

Methods

Probands were included in the study after experiencing SCD associated with an ER pattern in French university hospitals (Bordeaux, Nantes, and Rennes), from a database of 148 symptomatic cases. This study was conducted according to French guidelines for clinical and genetic research. Informed written consent was obtained from each family member who agreed to participate in the clinical and genetic study.

Clinical investigation. The ER pattern was the only cardiac abnormality in at least 1 case of SCD in each family. Coronary artery disease, nonischemic cardiomyopathy, and other known inherited cardiac arrhythmias were excluded (echocardiography, exercise test, coronary angiography, Na blocker test) in family A, B, and C probands according to the guidelines for management of ventricular arrhythmia (18).

Familial investigation included a review of medical history and a complete physical examination. A 12-lead electrocardiogram (ECG) was obtained for family member at rest and, when possible, during a VM. The VM was performed by closing one's mouth and pinching one's nose shut to obtain forceful attempted expiration against a closed airway. We performed continuous 12-lead rhythm strips during the VM and measured the J-wave amplitude when heart rate was the lowest.

Blinded interpretation of electrocardiographic data was done by 2 physicians for each patient. Heart rate, PR interval, QRS axis, J-point amplitude, QT interval, and QT interval corrected for heart rate (Bazett's formula) were measured at rest and during the VM.

Patients were considered to be affected by ER in the presence of a distinct J-wave defined as a positive deflection on the S-wave in at least 2 consecutive inferior or lateral leads and with at least 1-mm amplitude above baseline (7). ST-segments after ER were classified as horizontal/descending or rapidly ascending/upsloping (19).

The phenotype was classified as major (J-wave amplitude >2 mm), minor (J-wave amplitude between 1 and 2 mm), probably unaffected (J-wave amplitude <1 mm, or J-wave observed in only 1 lead), and unaffected (normal ECG). The VM was considered positive for affected patients when J-wave increased by >0.5 mm in 2 consecutive leads or when a significant J-wave as previously described appeared in a new territory. Appearance of a significant J-wave as previously described (>1 mm) defined a positive test for unaffected patients.

Cases of unexplained SCD without any available ECG were included in the estimation of ER prevalence if an ER pattern was found in first-degree relatives.

Penetrance of ER within the families was evaluated by the frequency of an ER pattern in obligate transmitters defined as family members with descendants affected by ER or SCD.

Genetic investigation. Genomic DNA was isolated from peripheral blood lymphocytes using a Macherey-Nagel kit according to manufacturer recommendations. Genes implicated in ERS were excluded for each proband by DNA sequencing.

Statistical analysis. Continuous variables were reported as mean ± SD or median (lower quartile, upper quartile), as appropriate. A comparison between families and patients was performed with 1-way analysis of variance, the Kruskal-Wallis test, Student *t* test, or chi-square test, as appropriate. A comparison between heart rate before and after a VM was performed with a paired Student *t* test as appropriate. All tests were 2 tailed, and a p value <0.05 was considered as statistically significant.

Results

We identified 4 large French families in which SCD occurred in, respectively, 11, 4, 4, and 3 young adults.

Identification and description of the families. Family A (Fig. 1A) was recruited after examination of the ECG of a 45-year-old woman (V:15) who died during an electrical storm due to ERS even though she had an implantable cardioverter-defibrillator (Figs. 2A, 3A, and 4A).

Familial screening identified a large family of 72 members. Eleven SCDs occurred (5 during the day, 4 at night, and 2 undetermined) including 7 before 35 years of age. The mean age at SCD was 41 years (range, 20 to 72 years), occurring more frequently in males (sex ratio = 1.7) (Table 1). Four individuals had normal cardiac investigation findings and negative toxicological test results. The autopsy was negative for 3 individuals (V:3, V:9, V:22). No cardiac information or ECG was available for the 3 others.

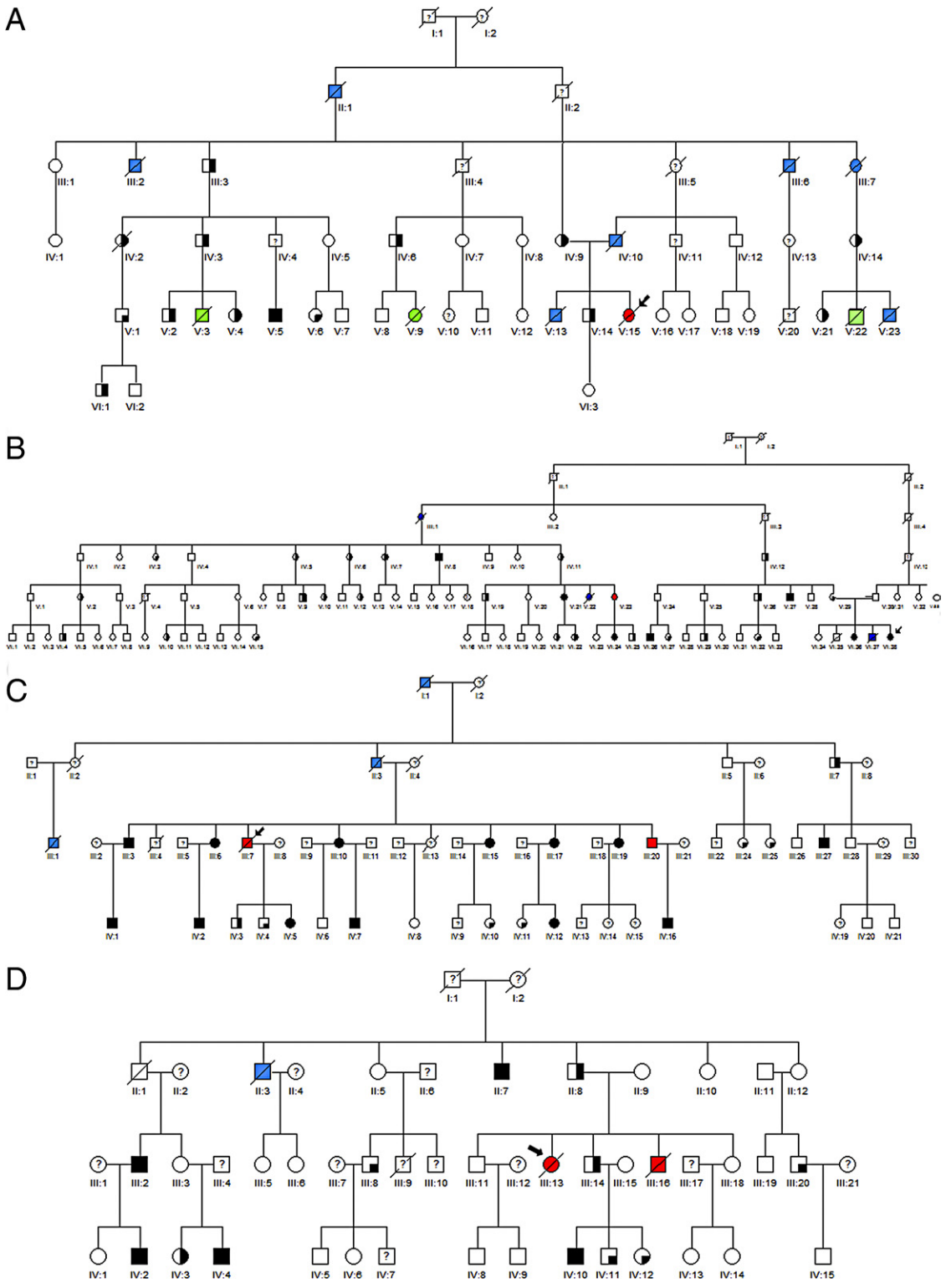

Figure 1 **Familial Segregation of ER in 4 Families**

(A) Pedigree of family A (1 early repolarization syndrome [ERS], 3 negative autopsies, 7 unexplained sudden deaths, 12 other early repolarization [ER] patterns). **(B)** Pedigree of family B (1 ERS, 3 unexplained sudden deaths, 25 other ER patterns). **(C)** Pedigree of family C (2 ERS, 3 unexplained sudden deaths, 15 other ER patterns). **(D)** Pedigree of family D (2 ERS, 1 unexplained sudden death, 8 other ER patterns). ERS: ER pattern + arrhythmia; unexplained sudden death: no available autopsy or antemortem clinical examination; probably a normal electrocardiogram: ER in only 1 lead or with amplitude <1 mm above baseline.

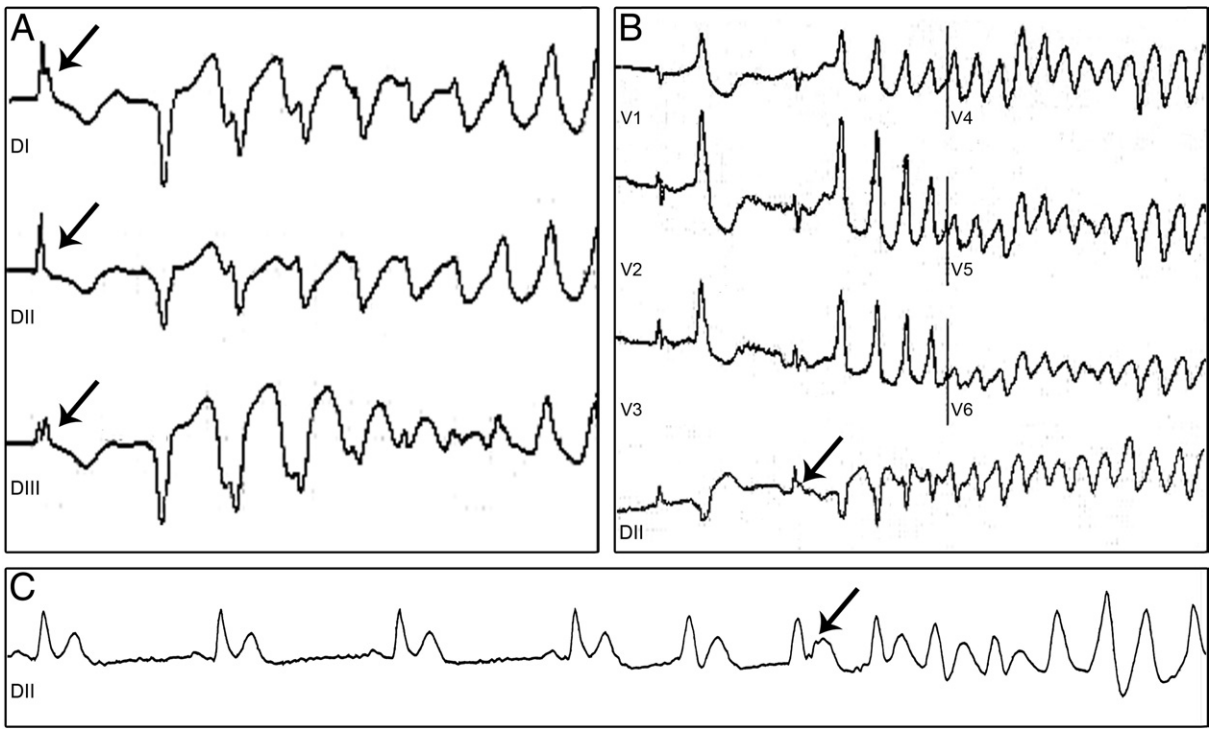

Figure 2 **Mode of Onset of Ventricular Fibrillation in the Probands**

The first **(A)**, second **(B)**, and fourth **(C)** families. Note that the J-wave increases before ventricular fibrillation in **B** and **C** (**arrows**).

ECGs were available for 30 members and revealed a major ER pattern in 2 patients and a minor form of ER in 11 (Figs. 1A, 3A, and 3B, Table 1).

Family B was identified after the individual VI:37 died without previous symptoms at 17 years of age (Fig. 1B). No ECGs were available, but 2 asymptomatic sisters presented a major ER pattern with no other cardiac abnormalities (Figs. 3C and 4B).

In this family, 4 SCDs occurred. The mean age at SCD was 39 years (range, 17 to 56 years), with a predominance of SCD in females (sex ratio = 0.3) (Table 1). No cardiac information or ECG was available for 3 of these individuals. Individual V:23 experienced an electrical storm aborted by isoprenaline. The ECG showed a typical ER pattern (Figs. 2B and 3D).

Familial screening identified a large family with 119 members including 82 with an available ECG. Eight individuals presented a major ER pattern and 17 a minor one (Figs. 1B, 3C, and 3D).

Family C was identified when individual III:7 experienced an aborted SCD associated with a major ER pattern on the ECG (Figs. 1C and 3E). Findings on cardiac testing were normal, and toxicological test results were negative. He finally died during an electrical storm 2 years after he received an implantable cardioverter-defibrillator.

Familial screening identified 61 patients spanning 4 generations. In this family, 3 SCDs occurred at a mean age of 49 years (range, 45 to 52 years), but no ECGs were available. The SCDs occurred exclusively in males (Table 1).

Individual III-20 experienced 2 unexplained syncope episodes with no other cardiac abnormality than an ER pattern. He finally received an implantable cardioverter-defibrillator after asymptomatic monomorphic ventricular tachycardia was identified by an implantable loop recorder.

ECGs were available for 29 individuals and revealed a major ER pattern in 14 and a minor pattern in 3 (Figs. 1C, 3E, 3F, and 4C).

Family D was identified after individual III:13 died during an electrical storm with no cardiac abnormality except a major ER pattern (Figs. 1D and 2C). Her brother died 2 years earlier during ventricular fibrillation. He presented a major ER pattern in inferolateral leads (Figs. 3G and 4D).

Familial screening identified a large family of 50 members. In this family, 3 SCDs occurred (2 related to ERS). The mean age at SCD was 40 years (range, 26 to 55 years) with a predominance of SCDs in males (sex ratio = 2) (Table 1).

ECGs were available in 30 relatives and revealed a major ER pattern in 5 other patients and a minor pattern in 3 (Figs. 1D, 3G, and 3H).

Global analysis of families. No statistical differences were found between heart rate, PR interval, QRS duration, and QT interval in the different families. We found a statistical

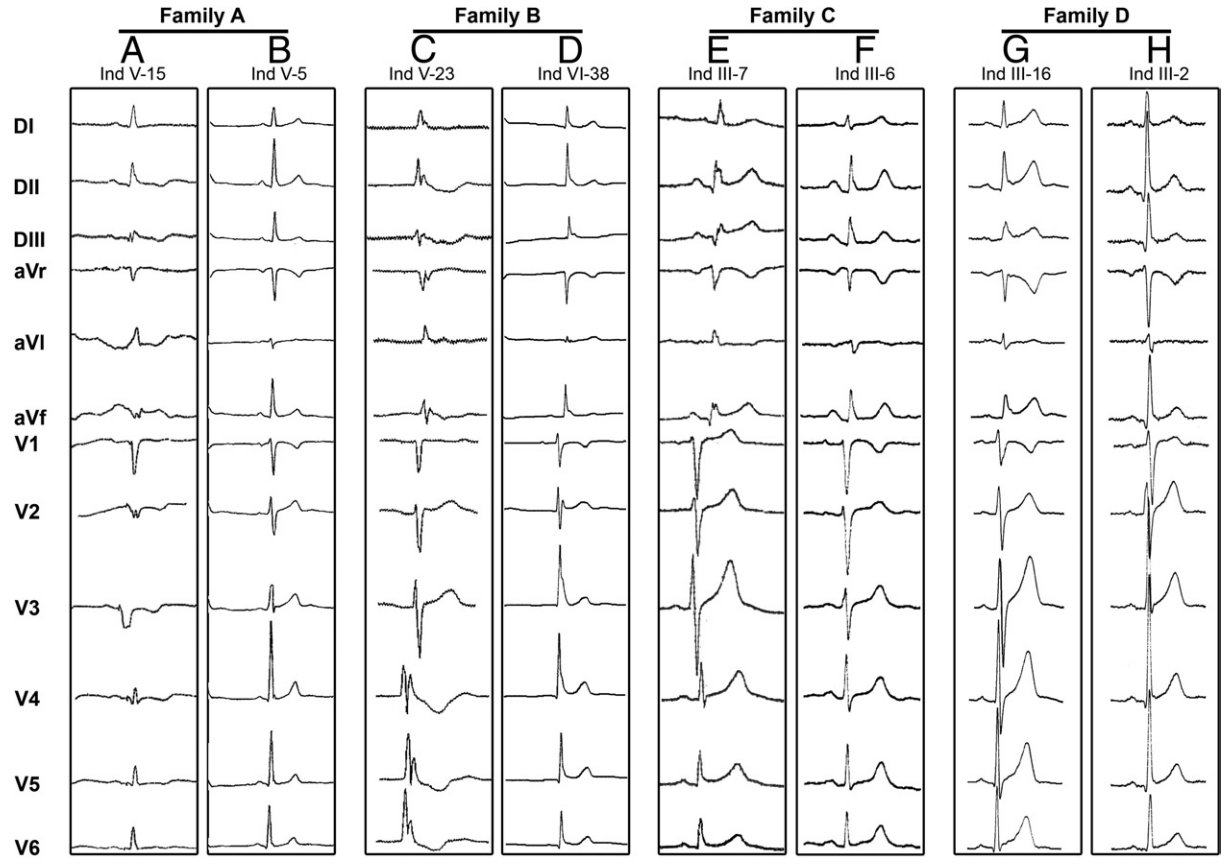

Figure 3 **Typical Aspect of Early Repolarization Patterns in Symptomatic (Left) and Asymptomatic (Right) Patients**

Electrocardiography was performed at 10 mm/mV and 25 mm/s.

difference between affected and unaffected patients in age, heart rate, and QRS duration (Table 2).

Localization of ER was mostly inferior, with a predominance of notching and a horizontal/descending ST-segment in the families (Table 1). All patients with ERS, except for individual III-16 in the family D, presented a notched ER with a horizontal/descending ST- segment.

In these 4 families, the ER pattern is probably transmitted by an autosomal dominant mode of inheritance because we found ER in males and females and a father-to-son transmission of ER pattern in each family. Penetrance of the ER pattern was, respectively, 90%, 33%, 90%, and 60% in families.

Within the family, most of the unexplained SCDs occurred in the presence of ERS or an ER pattern in first-degree relatives (Table 1).

Analysis of a VM. We performed a VM in 80 members of families B and C. This maneuver increased ER amplitude in 17 of 20 baseline affected patients tested. It revealed an ER pattern in 17 of 60 individuals previously considered unaffected. The VM succeeded in unmasking the pattern for 5 of 11 obligate transmitters previously considered unaffected. Using this test, penetrance of the ER pattern increases from 33% to 60% in family B and from 90% to 100% in family C. Finally, the VM made it possible to reclassify 45% (5/11) of obligate transmitters first considered with a baseline ECG as unaffected as ER cases (Table 3, Fig. 5).

The mean heart rate was 75 ± 13 beats/min (median, 75 beats/min [range, 65 to 80 beats/min]) at rest and was not different between patients with a positive (VM+) or negative (VM−) outcome ($p = 0.141$). Heart rate decreased by 3.87 ± 7.93 beats/min during the test ($p < 0.001$), but no difference was observed between the VM+ and VM− groups ($p = 0.304$).

After performing the VM in families B and C, an ER pattern was found in, respectively, 56%, 34%, 58%, and 33% of relatives in each family (Table 1).

Genetic analysis. Mutations in *KCNJ8*, *SCN5A*, *CACNA1C*, *CACNB2*, and *CACNA2D1*, were excluded by DNA sequencing in the probands of each family.

Discussion

Starting with a database of 148 ER cases, this study allowed the identification of 4 large families affected by a malignant form of ERS. Our familial studies demonstrated for the first

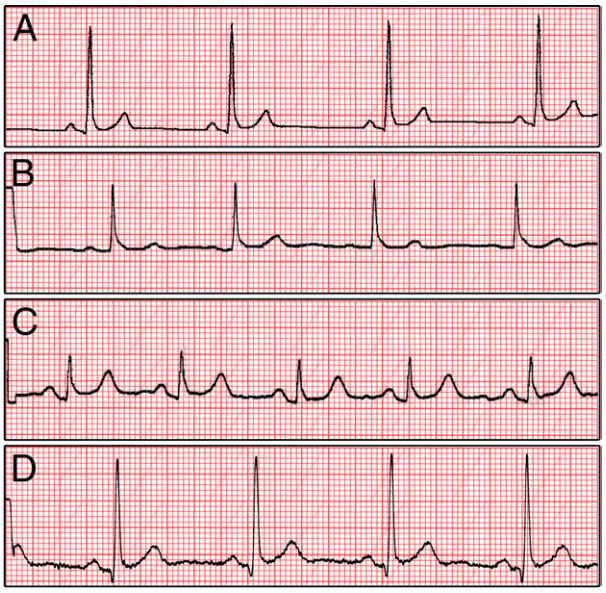

Figure 4 Aspect of Early Repolarization Pattern in the DII Lead Rhythm Strips in the 4 Families

(A) Individual V:5, family A. **(B)** Individual VI:38, family B. **(C)** Individual III:6, family C. **(D)** Individual III:16, family D. Electrocardiography was performed at 25 mm/s and 10 mm/mV for each proband.

time that an ER pattern can be inherited with an autosomal dominant mode of transmission. Since the description of ER as a potential factor for the occurrence of SCD by our group in 2008, the involvement of this electrocardiographic pattern in the occurrence of SCD remains a matter of debate owing to the frequency of this pattern in the general population (20,21). Tikkanen et al. (8) and Sinner et al. (9) demonstrated in 2 distinct populations that an ER pattern is associated with an increased risk of SCD (respective relative risks: 1.28 and 1.96; 95% confidence interval: 0.04 to 1.59 and 1.05 to 3.68; $p < 0.05$). The present demonstration of a high occurrence of SCD in multigenerational families presenting a far higher prevalence of ER pattern than in the general population adds strong evidence that these patients may face an increased risk of SCD due to ER, emphasizing that ERS should be considered a potentially inherited arrhythmia syndrome along with Brugada or long QT syndrome. Similar results on J-point elevation prevalence were recently reported by published by Nunn et al. (22) and Noseworthy et al. (23) among relatives of sudden arrhythmic death syndrome probands and among relatives of ER pattern probands. Even if we have no definitive proof that an ER pattern is responsible for SCD occurring in these

Table 2 Clinical and Electrocardiographic Data of Affected (ER+) and Unaffected (ER−) Patients in 4 Families

	ER+ (n = 64)	ER− (n = 112)	p Value
Age, yrs	44 (25–63)	33 (16–48)	0.002
Sex ratio	1.18	0.85	0.307
Heart rate, beats/min	70 (60–80)	77 (68–86)	0.001
PR, ms	165 (40–180)	155 (140–170)	0.202
QRS interval, ms	88 (80–97)	80 (78–90)	0.001
QT interval corrected for heart rate, ms	407 ± 19	410 ± 24	0.314

Values are median (lower quartile–upper quartile) or mean ± SD.
ER = early repolarization.

Table 1 Clinical Characteristics of Families: History of SCD, Clinical Data, and Characteristics of ER

	Family				
	A	B	C	D	p Value
Sudden death	11	4	4	3	—
ERS	1	1	1	2	—
SCD with negative autopsy	3	0	0	0	—
Unexplained sudden death	7	3	3	1	—
With ER pattern in relatives	3	3	3	1	—
Mean age, yrs (range)	41 (20–72)	39 (17–56)	49 (45–52)	40 (26–55)	—
Sex ratio	1.7	0.3	∞ (100% male)	2	—
No. of screened relatives	30	82	29	30	—
No. of relatives with an ER pattern	12	25	16	8	—
Early repolarization pattern					
Prevalence of ER pattern (in probands and relatives), %	56	34	58	33	—
Mean amplitude, mm	1.61 ± 0.654	1.50 ± 0.452	1.93 ± 0.805	2.0 ± 0.79	0.385
Localization, %					
Inferior	61	61	76	92	0.146
Lateral	22	32	33	25	0.773
Inferolateral	33	37	44	58	0.300
Notching repolarization, %	78	88	92	89	0.668
Horizontal/descending ST segment, %	78	68	67	72	0.888

Values are n, median (lower quartile–upper quartile), or mean ± SD. Distinction has been established in unexplained SCD, which was considered related with ER when ERS occurred in descendant or an ER pattern was found in first-degree relatives.
ER = early repolarization; ERS = early repolarization syndrome; SCD = sudden cardiac death.

Table 3 VM in Affected and Unaffected Patients at Rest

	No. of Screened Relatives	No. of VM+	No. of VM−	Positive VM, %
Affected	20	17	3	85
Unaffected	60	17	43	28
Nonobligate transmitter	49	12	37	24
Obligate transmitter	11	5	6	45
Total	80	34	46	42

The VM was considered positive (VM+) through an increasing J-wave (affected patients) or when the J-wave was unmasking during the test (unaffected patients). Obligate transmitters were defined as family members with descendents affected by early repolarization or sudden cardiac death.

VM = Valsalva maneuver.

families, we have several lines of evidence to consider that the ER pattern is the cause of SCD. In 3 families (families A, B, and D), 1 patient with recorded ventricular fibrillation also displays a major ER pattern increasing before arrhythmia. In all patients who experienced SCD, at least 1 first-degree relative is clearly a carrier of a major ER pattern, and all parents (except 1) of symptomatic individuals present an ER pattern on an ECG. Patient V:29 (family B) is probably unaffected with an ER pattern, but she is the mother of VI:37 who died suddenly at 17 years of age. We have a major argument to consider that SCD is related to ER because the 2 young sisters of the patient showed canonical ER aspect. Moreover, no other cardiac abnormalities have been found in affected family members, although a complete cardiac examination was performed, and autopsies were negative for 3 patients who experienced SCD.

The identification of large families also provides a unique opportunity to allow insight into the genetic basis of the disease and probably, in a second step, to better characterize this particular electrocardiographic pattern, which would make it possible to identify the truly malignant form of ER in the general population.

The ER pattern is transmitted by an autosomal dominant trait in the 4 families. Genetic studies have already demonstrated a strong genetic component for other inherited cardiac arrhythmias such as congenital long QT syndrome, short QT syndrome, and or Brugada syndrome. Most of the mutations described affect genes encoding ion channels, with an autosomal dominant trait that results in a 50% risk of transmission through Mendelian inheritance. In the 4 families described here for the first time, penetrance seems to be incomplete with an autosomal dominant model, particularly in the second family, despite the use of the VM to unmask the pattern.

The second important finding of this study is the identification of the VM as an interesting tool to unmask an ER pattern on an ECG. In this study, the VM unmasked an ER pattern in 17 patients, including 5 obligate transmitters of ER. Similar to other genetic arrhythmias, the ER pattern is highly variable over time, partly because of the variation of autonomic tone and heart rate (14–17). Indeed, ER has been shown to increase at a lower rate and during a higher vagal tone (10,24,25). This variability of the electrocardiographic pattern over time has led to widespread use of unmasking tests such as an ajmaline or flecainide challenge for Brugada syndrome or adrenaline challenge or stress test for long QT syndrome. These tests have proved their efficacy in unmasking abnormal electrocardiographic patterns in the context of familial screening or in the case of a borderline ECG. Until now, no reliable test could reveal the ER pattern. In the present study, we demonstrated that the

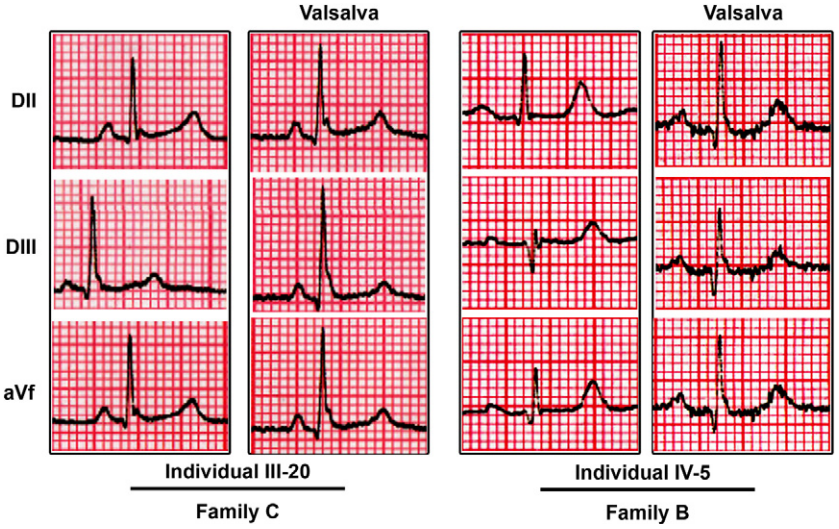

Figure 5 Effect of the Valsalva Maneuver in the ER Patterns of 2 Obligate Transmitters of Families B and C (Electrocardiography Performed at 25 mm/s and 10 mm/mV)

(A) Electrogram (ECG) of individual III:20 (family C) first performed at rest with an inferior early repolarization (ER) increased during the Valsalva maneuver. **(B)** ECG of individual IV:5 (family B) without ER at rest. The Valsalva maneuver unmasks an inferior pattern.

VM is helpful in unmasking the syndrome in the context of familial screening. However, it should be noted that a negative VM result is not enough to rule out the diagnosis because the sensitivity of the test is only 45% in our study. Further investigations are required to estimate the ability of this test to differentiate the malignant and benign forms of the ER pattern in the general population and to estimate the prognostic value of this test in arrhythmic status of relatives.

In the 4 families, the affected patients appeared to present a significantly longer PR and QRS duration. This observation does not underlie conduction disease in the ER pattern because in the families, the affected patients are older and because ER can lead to an overestimation of QRS duration through the J-wave length. Heart rates tend to be lower in affected patients, but, as previously shown, autonomic tone decreases heart rate, increasing the chances of observing an ER pattern (14–16). The proportion of ER pattern fluctuating between 34% and 61% among families is a far higher prevalence than in the general population in which previous studies have reported 1% to 5.8% of ER (1,3–9,26–28). This higher prevalence confirms the genetic foundations of ERS suggested by previous identification of a heterozygous mutation in unrelated cases reported and by population-based studies (11–13,29). Identification of the familial forms of malignant ER moves us to recommend systematic familial screening of first-degree relatives in ERS.

The ER pattern is sometimes found in association with other pathologies such as Wolff-Parkinson-White, short QT syndrome, and Brugada syndrome (30–32). Some similarities were observed between ERS and Brugada syndrome, including sex and arrhythmia triggers. However, no other pathologies and, more specifically, no Brugada syndrome were found during the familial screening, suggesting a differential mechanism between ER in the inferolateral leads and ST-segment elevation in the right precordial leads (33).

Study limitations. The main limitation of the study is the limited capacity to detect the ER, which can lead to underestimation of the prevalence of ER in families, although the VM can be used to unmask the ER pattern in asymptomatic individuals. The prognostic value of this test remains to be assessed using a control population, but we can already suppose that with the use of the VM, some familial segregation of ERS could be revealed and some idiopathic ventricular fibrillation cases could be reclassified as ERS cases. Another issue is the difficulty in applying measurement and characterization of J-wave amplitude to clinical practice, especially because differences of <1 mm have been shown to modify the risk of SCD (14–16).

Conclusions

ERS is an inherited arrhythmia that is, at least in some families, compatible with an autosomal dominant trait. Familial screening should be performed, at least in first-degree relatives, for each proband. Because the VM can unmask the ER pattern, it should be used to reveal inherited malignant forms. The prognostic value of this test remains to be assessed in relatives and the general population. Identification of these first large families is the first step toward understanding the genetic basis of the malignant familial forms of ER.

Acknowledgments

The authors thank Christine Fruchet, Annabelle Rajalu, and Patricia Bouillet for their assistance in familial screening. They also thank these families for participation.

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Key Words: early repolarization syndrome ■ familial inheritance ■ ventricular fibrillation.