Genetic Basis of Early Repolarization Syndrome

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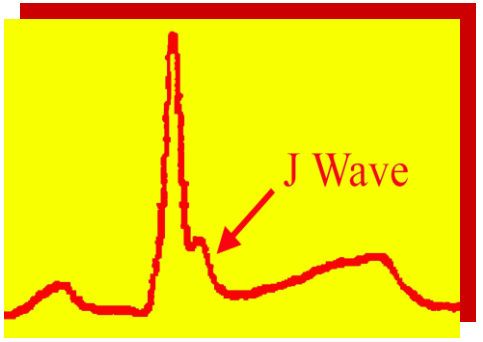
Invited Talk for KHRS2023

Characteristics of the J Wave

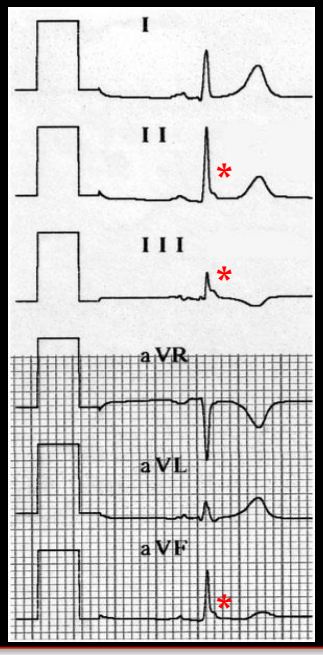


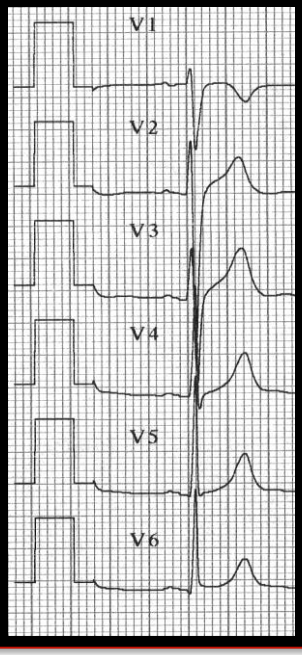
- Also referred to as an Osborn wave
- A distinct J wave is commonly observed in the baseline ECG of some animal species, including baboons and dogs.
- A distinct J wave is rarely observed in humans under normal conditions, although an elevated J point is commonly encountered
- In humans and animals, the appearance of a prominent J wave in the ECG is considered pathognomonic of hypothermia, hypercalcemia, the Brugada syndrome, early repolarization pattern or other arrhythmogenic syndromes

Definition and Epidemiology

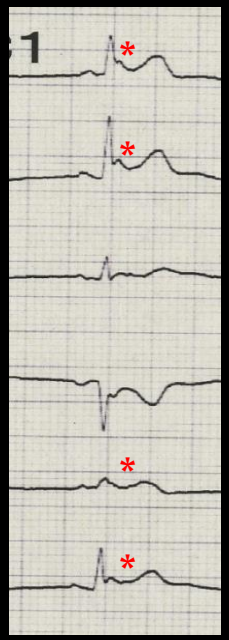
- The ER pattern on the ECG is characterized by ≥0.1mV J point elevation in two contiguous inferior and/or lateral ECG leads
- The prevalence estimates for the ER pattern in the general population are highly variable and range between 1~13%
- ER is significantly more common amongst males, young athletes and patients of African descent
- For decades, the ER pattern has been regarded as a benign ECG variant. However multiple contemporary studies have linked ER as a predictor of lethal arrhythmias that may lead to fatal heart conditions

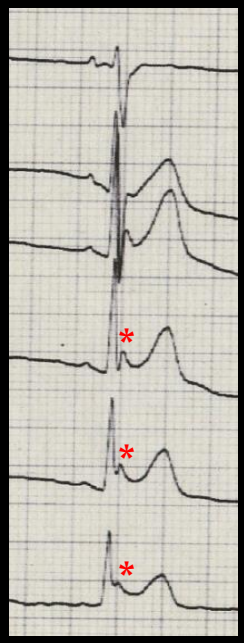
Inferior distribution



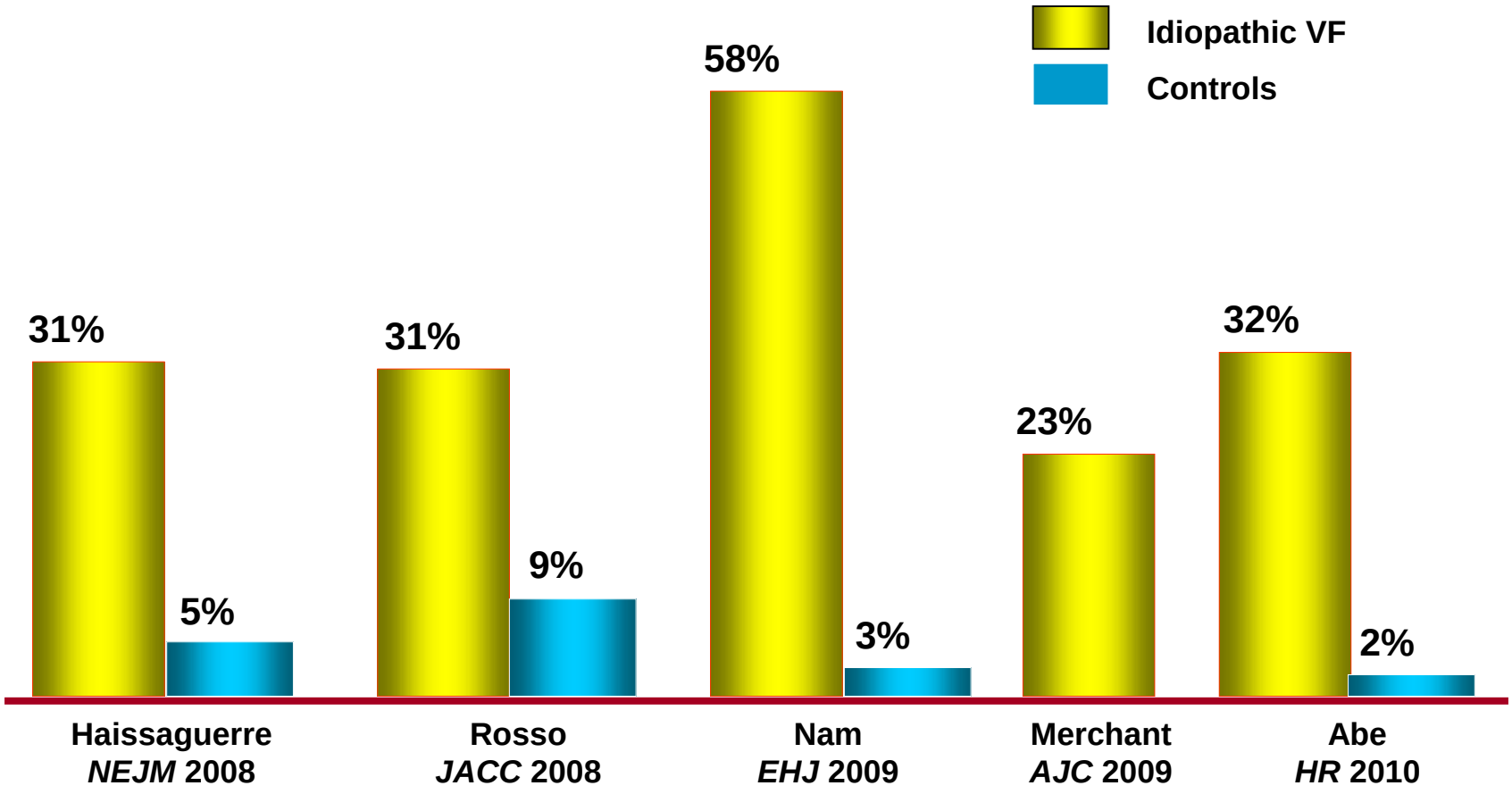


Infero-lateral distribution





Prevalence of ER in patients with IVF and controls



by courtesy of R. Rosso

J Wave Consensus Conference
Shanghai, China - April 2015

J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge

Heart Rhythm
EuroPace
临床心电学杂志
2016.9

Definition of ERS

- Early repolarization syndrome (ERS) is a new disease entity characterized by high probability of IVF, polymorphic VT, SCD/ASCD and ER pattern in the ECG

6. Early Repolarization (ER) *Expert Consensus Recommendations on* ***ER Diagnosis***

1. ER ***syndrome is diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT.
2. ER syndrome ***can be diagnosed*** in a SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.
3. ER pattern ***can be diagnosed*** in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.

Proposed Shanghai Score System for diagnosis of early repolarization syndrome

	Points
I. Clinical History	
A. Unexplained cardiac arrest, documented VF or polymorphic VT	3
B. Suspected arrhythmic syncope	2
C. Syncope of unclear mechanism/unclear etiology	1
**Only award points once for highest score within this category*	
II. Twelve-Lead ECG	
A. ER ≥0.2 mV in ≥2 inferior and/or lateral ECG leads with horizontal/descending ST segment	2
B. Dynamic changes in J-point elevation (≥0.1 mV) in ≥2 inferior and/or lateral ECG leads	1.5
C. ≥0.1 mV J-point elevation in at least 2 inferior and/or lateral ECG leads	1
**Only award points once for highest score within this category*	
III. Ambulatory ECG Monitoring	
A. Short-coupled PVCs with R on ascending limb or peak of T wave	2
IV. Family History	
A. Relative with definite ERS	2
B. ≥2 first-degree relatives with a II.A. ECG pattern	2
C. First-degree relative with a II.A. ECG pattern	1
D. Unexplained sudden cardiac death <45 years in a first- or second-degree relative	0.5
**Only award points once for highest score within this category*	
V. Genetic Test Result	
A. Probable pathogenic ERS susceptibility mutation	0.5
Score (requires at least 1 ECG finding)	
≥5 points: Probable/definite ERS	
3–4.5 points: Possible ERS	
<3 points: Nondiagnostic	

Genetics of ERS

Table 1 **Characteristics of the Population**

Variable	n (Available Data)	Mean ± SD or Percentage
Age (yrs)	122	36 ± 12.4
Sex		
Women	32	26%
Men	90	74%
Familial history of sudden death		
Yes	21	18%
No	98	82%
Syncope		
Yes	39	33%
No	78	67%
PR >200		
Yes	5	4%
No	110	96%
Amplitude of J-wave (mV)	112	0.21 ± 0.09
QRS duration (ms)	119	91.8 ± 10.4
QTc (ms)	117	394.7 ± 26.0
EP study: VF induced		
Yes	22	28%
No	57	72%

Haissaguerre M. *J Am Coll Cardiol*. 2009;53:612-619

Clinical characteristics of 53 patients in Japanese multicentric study

Male sex, N (%)	46 (87%)
Age, years	44±17
Family history of sudden death, N (%)	7 (13%)
Activity at initial cardiac arrest, N (%)	
Sleeping	14 (26%)
Rest	12 (23%)
Physical effort	10 (19%)
Other activities	17 (32%)
Atrial fibrillation, N (%)	12 (23%)
History of electrical storm, N (%)*	9 (17%)
Inducible ventricular fibrillation	15/31 (48%)
Mutation in *SCN5A* , N (%)	4/29 (14%)
Location of early repolarization, N (%)	
Inferior	37 (70%)
Lateral	37 (70%)
Right precordial	11 (21%)
Multiple locations of early repolarization	28 (53%)

* An electrical storm was defined as ≥3 episodes of VF within 24 hours.

Watanabe H, et al. *Int J Cardiol* 2012;159:238-240

Genetic defects associated with ERS and BrS

Genetic Defects Associated with ERS

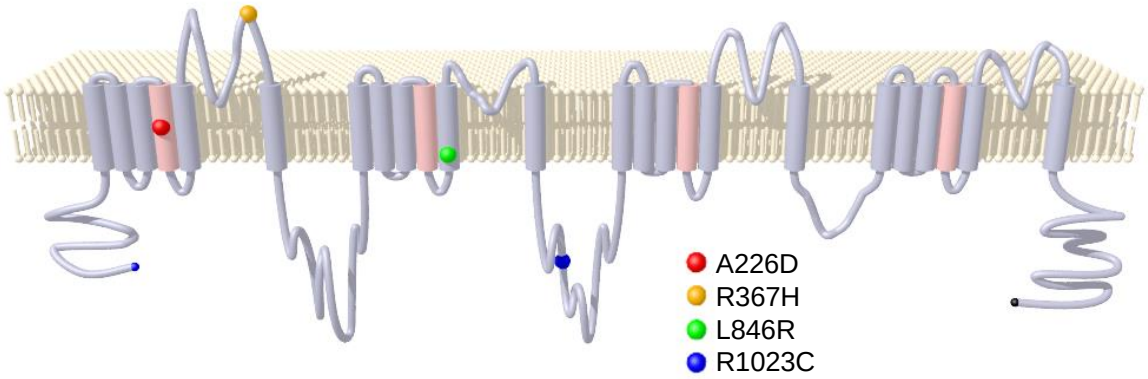
	Locus	Gene/protein	Ion channel	Percent of Probands
ERS1	12p11.23	*KCNJ8, Kir6.1*	$\uparrow I_{K\text{-}ATP}$	Rare
ERS2	12p13.3	*CACNA1C, $Ca_v1.2$*	$\downarrow I_{Ca}$	4.1%
ERS3	10p12.33	*CACNB2b, $Ca_v\beta 2b$*	$\downarrow I_{Ca}$	8.3%
ERS4	7q21.11	*CACNA2D1, $Ca_v\alpha 2\delta 1$*	$\downarrow I_{Ca}$	4.1%
ERS5	12p12.1	*ABCC9, SUR2A*	$\uparrow I_{K\text{-}ATP}$	Rare
ERS6	3p21	*SCN5A, $Na_v1.5$*	$\downarrow I_{Na}$	Rare
ERS7	3p22.2	*SCN10A, $Na_v1.8$*	$\downarrow I_{Na}$	Rare

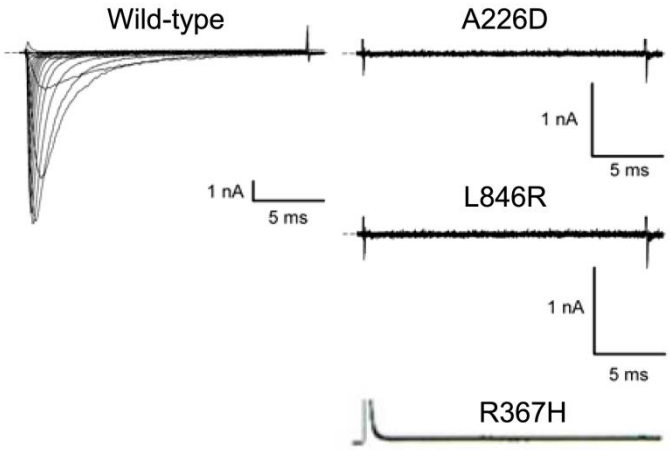
Genetic Defects Associated with BrS

	Locus	Gene/protein	Ion channel	Percent of probands
BrS1	3p21	*SCN5A, $Na_v1.5$*	$\downarrow I_{Na}$	11%–28%
BrS2	3p24	*GPD1L*	$\downarrow I_{Na}$	Rare
BrS3	12p13.3	*CACNA1C, $Ca_v1.2$*	$\downarrow I_{Ca}$	6.6%
BrS4	10p12.33	*CACNB2b, $Ca_v\beta 2b$*	$\downarrow I_{Ca}$	4.8%
BrS5	19q13.1	*SCN1B, $Na_v\beta 1$*	$\downarrow I_{Na}$	1.1%
BrS6	11q13-14	*KCNE3, MiRP2*	$\uparrow I_{to}$	Rare
BrS7	11q23.3	*SCN3B, $Na_v\beta 3$*	$\downarrow I_{Na}$	Rare
BrS8	12p11.23	*KCNJ8, Kir6.1*	$\uparrow I_{K\text{-}ATP}$	2%
BrS9	7q21.11	*CACNA2D1, $Ca_v\ \alpha 2\delta 1$*	$\downarrow I_{Ca}$	1.8%
BrS10	1p13.2	*KCND3, $K_v4.3$*	$\uparrow I_{to}$	Rare
BrS11	17p13.1	*RANGRF, MOG1*	$\downarrow I_{Na}$	Rare
BrS12	3p21.2-p14.3	*SLMAP*	$\downarrow I_{Na}$	Rare
BrS13	12p12.1	*ABCC9, SUR2A*	$\uparrow I_{K\text{-}ATP}$	Rare
BrS14	11q23	*SCN2B, $Na_v\beta 2$*	$\downarrow I_{Na}$	Rare
BrS15	12p11	*PKP2, Plakophillin-2*	$\downarrow I_{Na}$	Rare
BrS16	3q28	*FGF12, FHAF1*	$\downarrow I_{Na}$	Rare
BrS17	3p22.2	*SCN10A, $Na_v1.8$*	$\downarrow I_{Na}$	5%–16.7%
BrS18	6q	*HEY2 (transcriptional factor)*	$\uparrow I_{Na}$	Rare

Susceptibility genes of ERS - *SCN5A*

- SCN5A mutation positive, 4 of 29 (14%) patients with ERS
- Non-functional channel

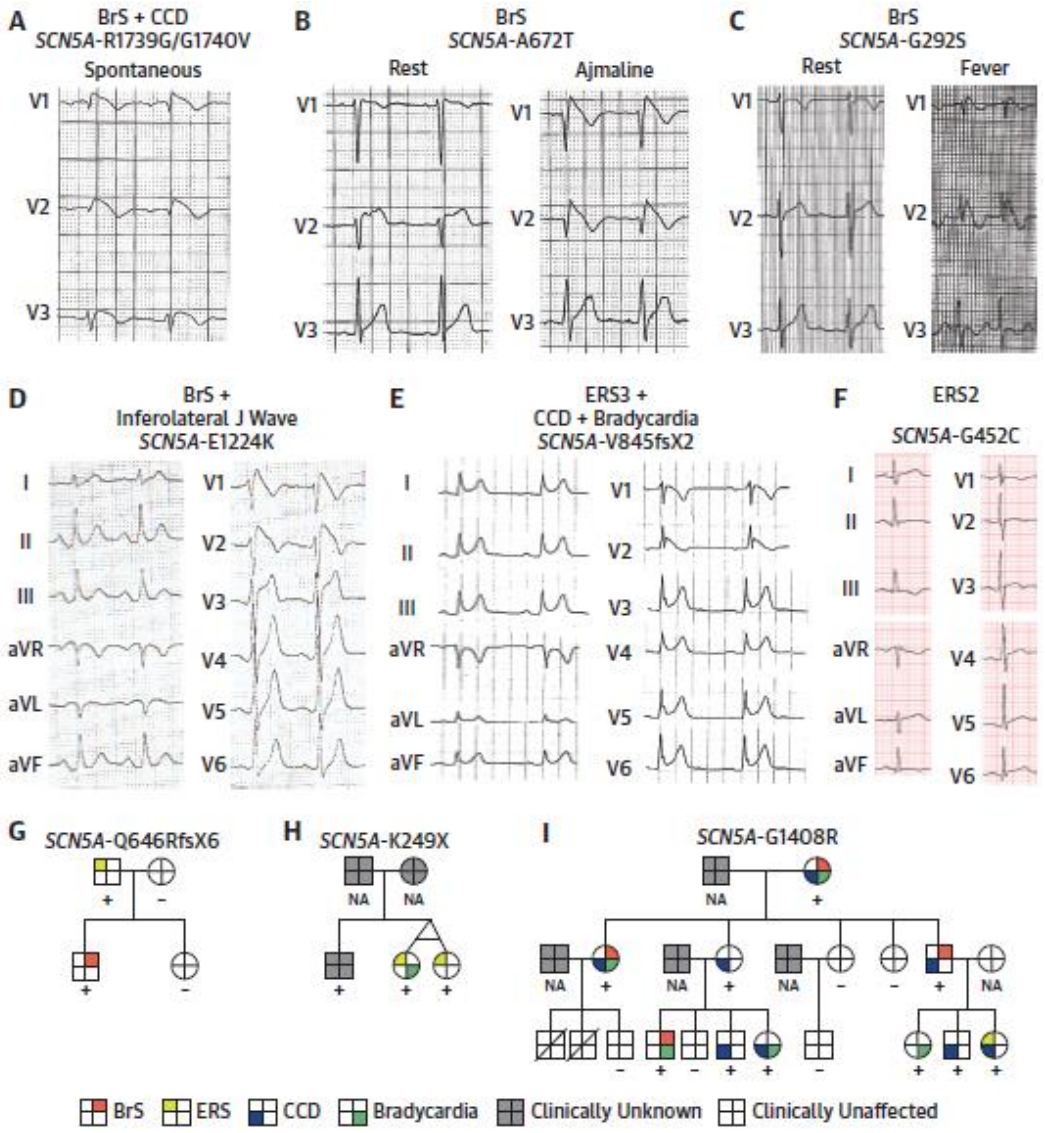




Watanabe H, et al. *Circ Arrhythm Electrophysiol*. 2011;4:874-881
Watanabe H, et al. *Int J Cardiol* 2012;159:238-240

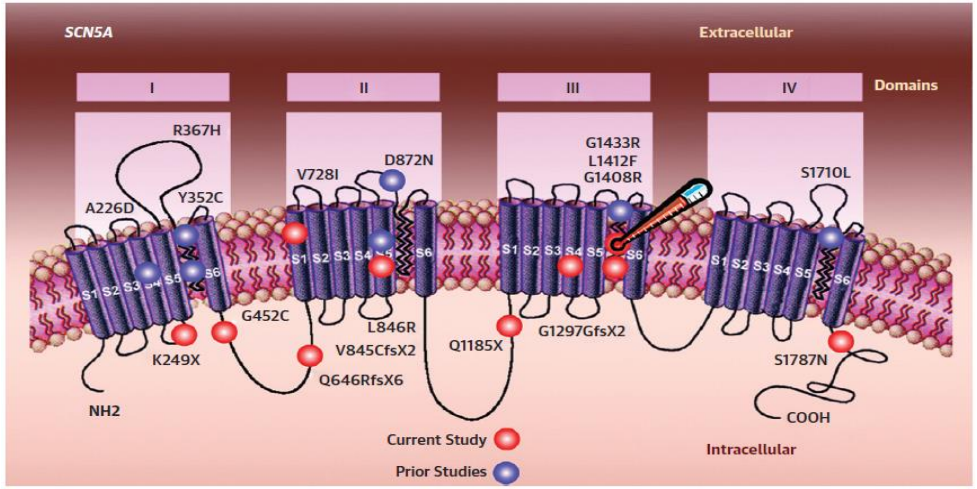
SCN5A gene defects associated with ERS

- Clinical assessment and gene sequencing were performed in 262 BrS and 104 ERS probands
- ERS patients had shorter QRS and QTc than BrS patients

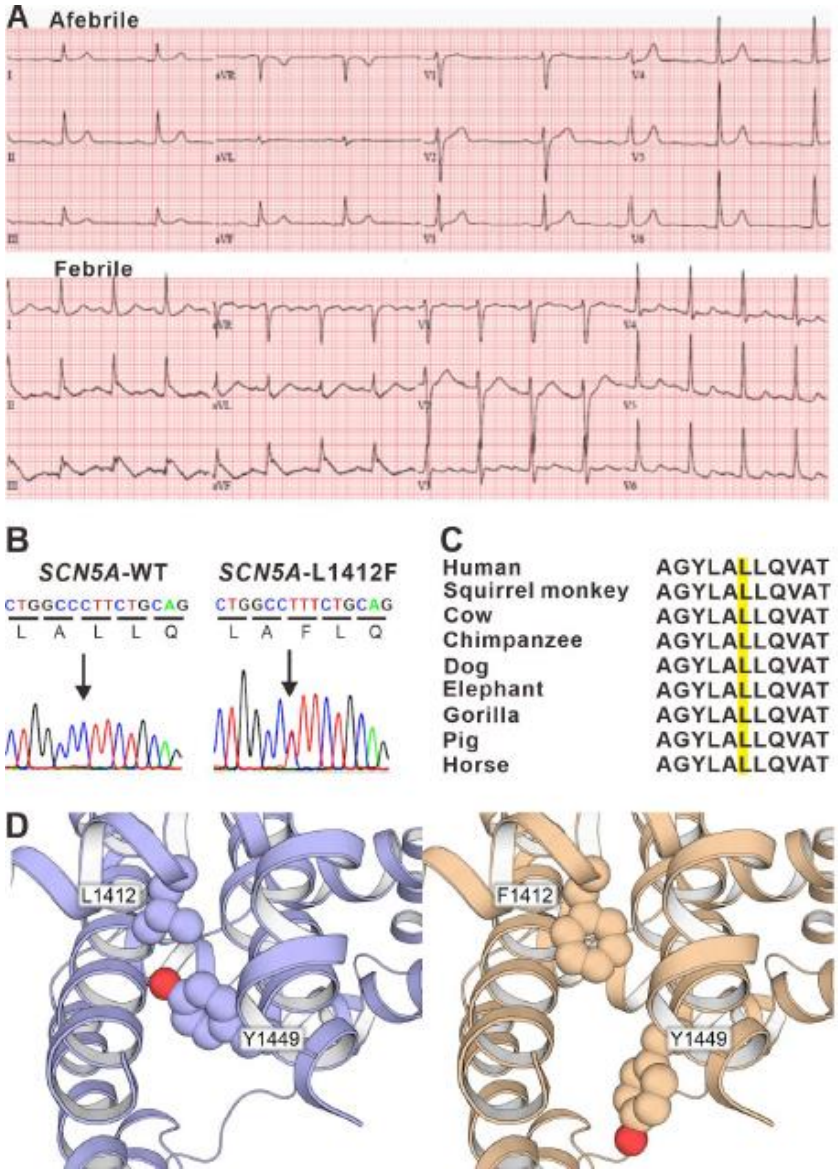


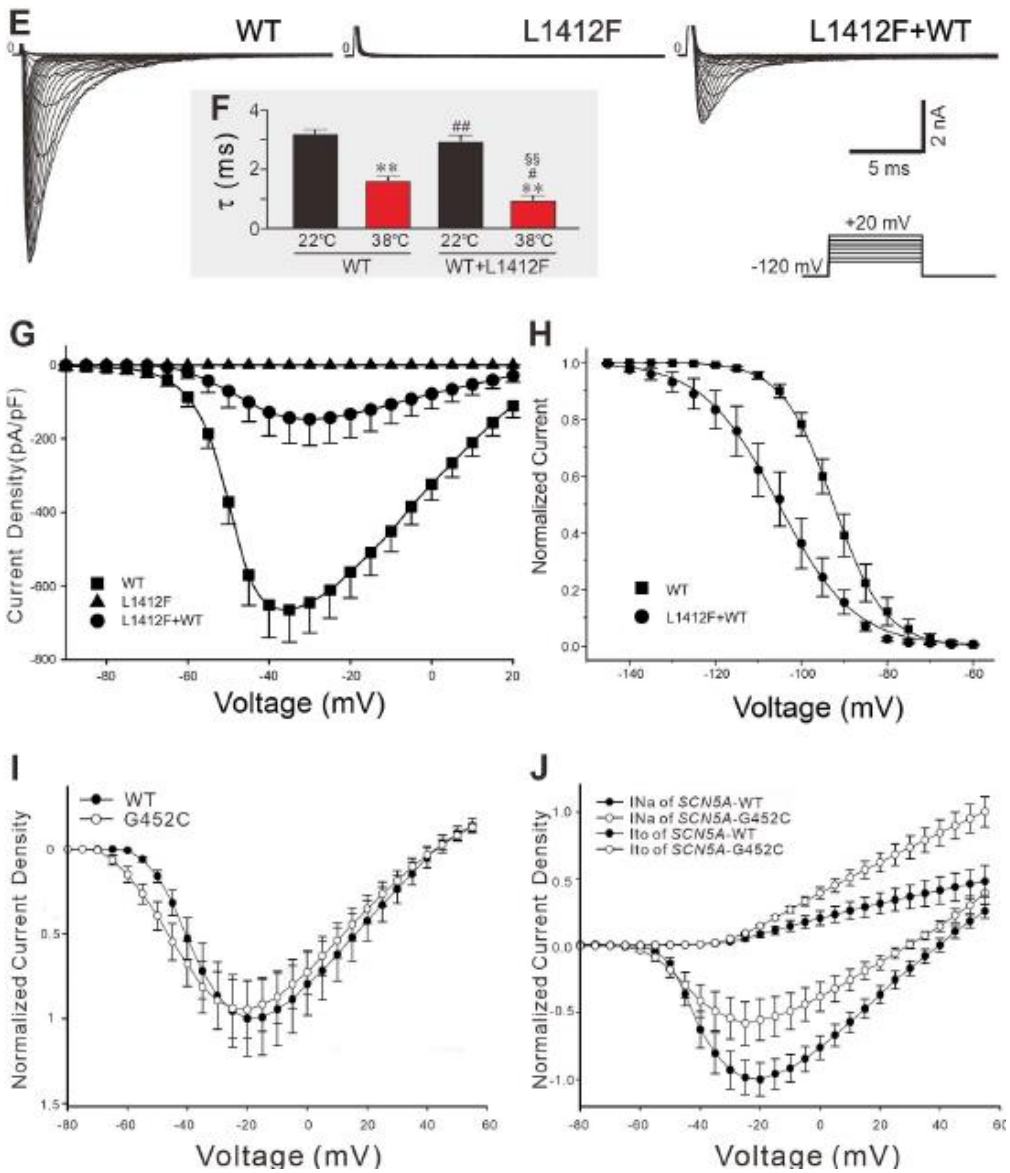
SCN5A gene defects associated with ERS

- Pathogenic SCN5A variants in 70 probands
  - 60 BrS and 10 ERS
  - 67 mutations, including 51 missense mutations
  - New mutations: 2 BrS (Q1695H and R1826P); ERS 10
- SCN5A+ ratio in ERS was lower than that in BrS
  - 9.62% vs. 22.90%
- More than two SCN5A mutations were found in five probands
  - PR↑、QRS↑、 MAE↑
- ERS type and SCN5A
  - ERS3 80%; ERS2 20%; ERS1 0%



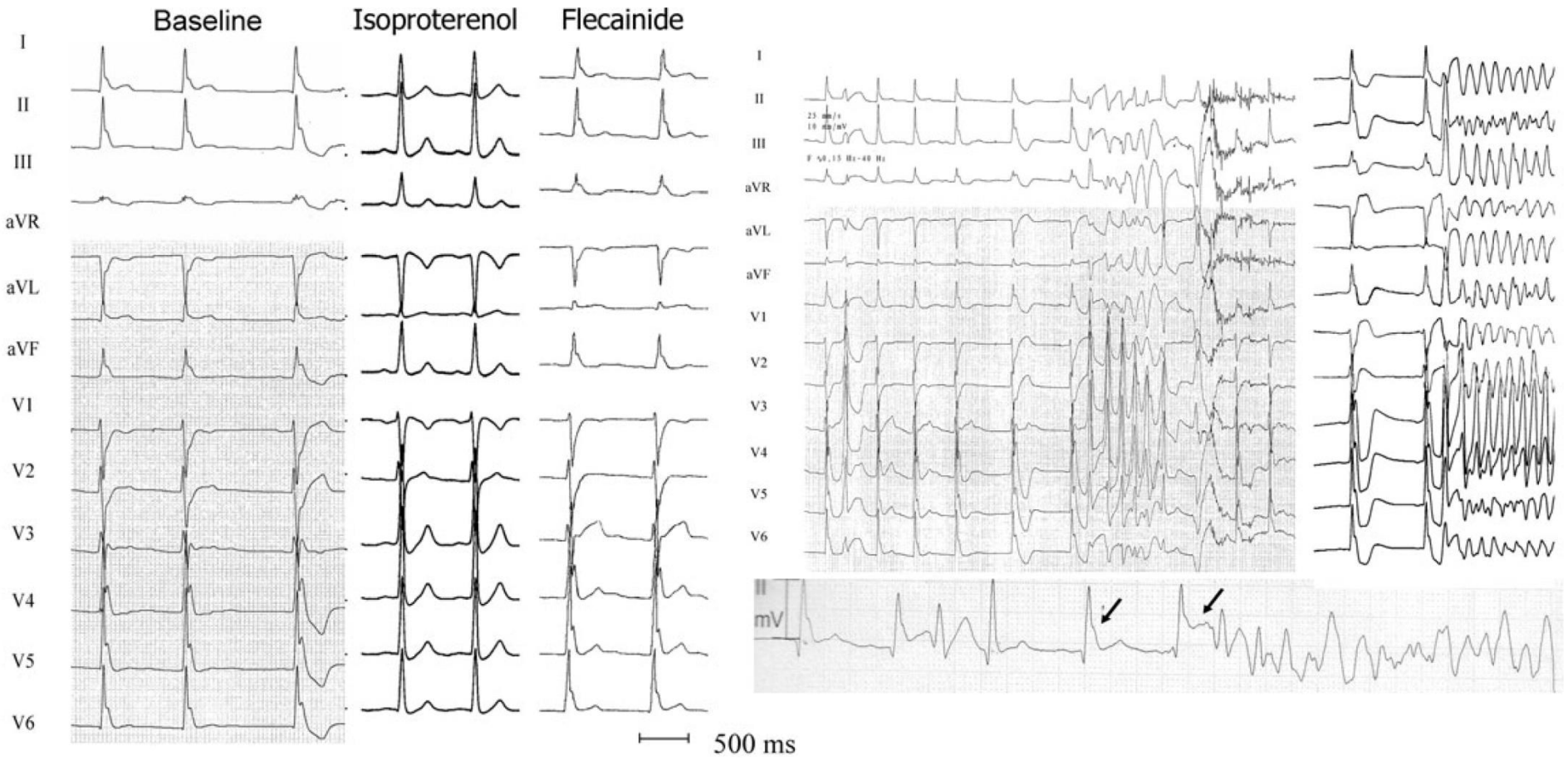
SCN5A gene defects associated with ERS





KCNJ8 mutation (S422L)

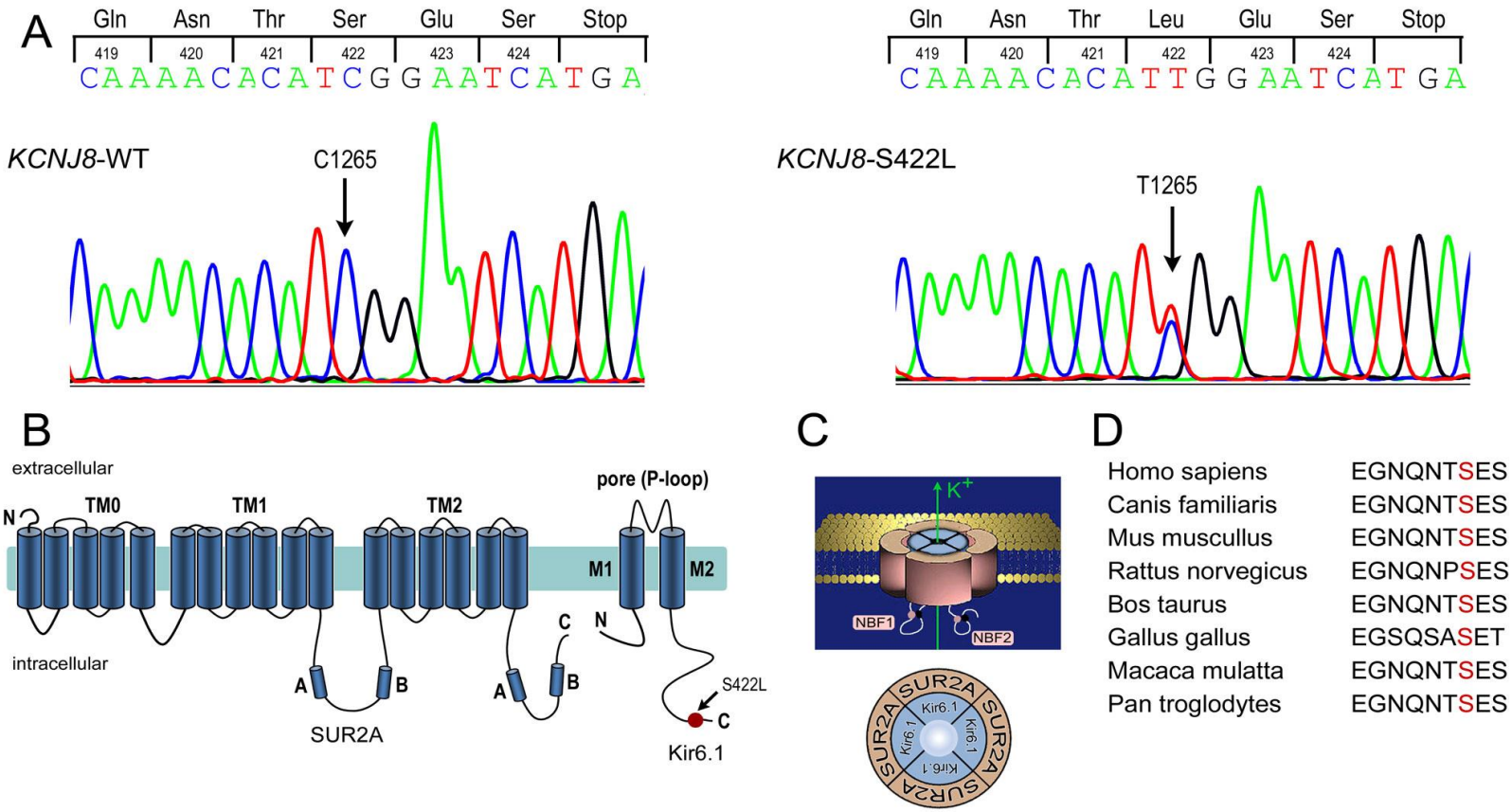
- An S422L mutation in *KCNJ8* was identified in a 14-years-old girl with no family history of sudden death



Haissaguerre M. ***J Cardiovasc Electrophysiol***. 2009;20:93-98

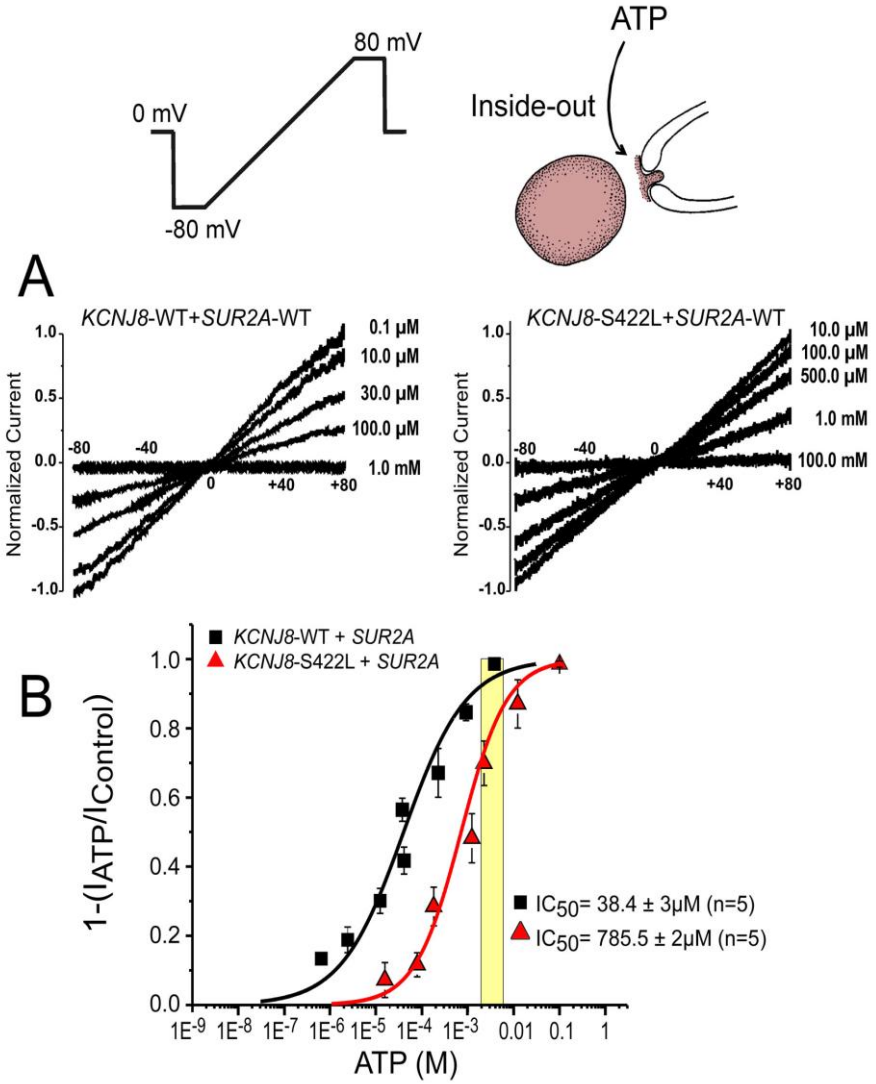
KCNJ8 mutation (S422L)

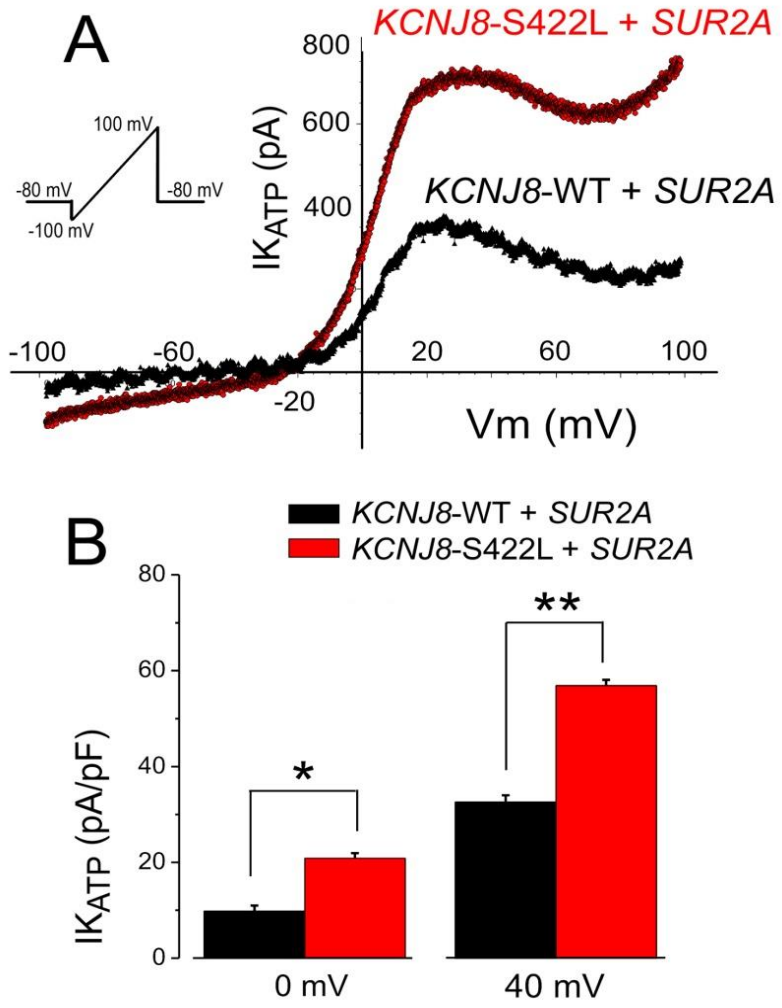
- *KCNJ8* encodes Kir6.1 subunit of ATP-sensitive K^+ channel
- Hotspot mutation S422L has been identified in 2 ERS patients and 4 Brugada patients



Barajas-Martinez Hector ,Dan Hu et al. Heart Rhythm, 2012

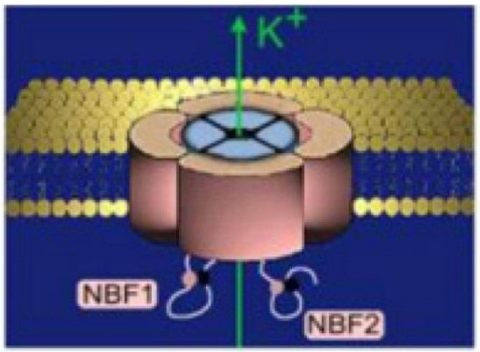
Biophysical studies of IKATP channels associated with KCNJ8-S422L





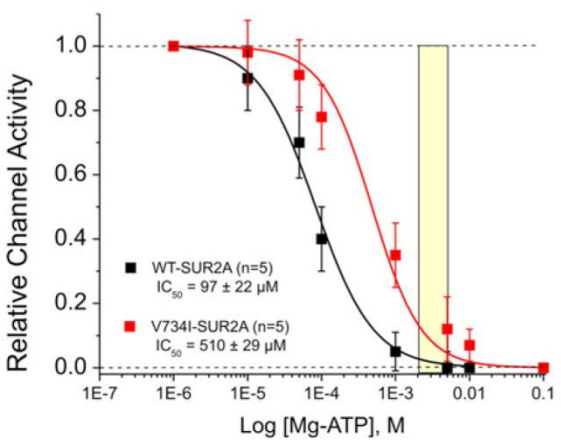
ABCC9 mutation (V734I)

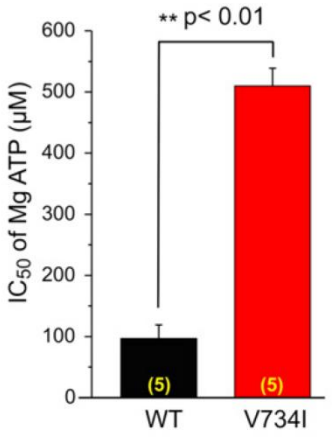
- ABCC9 encodes SUR2A subunit of ATP-sensitive K+ channel
- Hotspot mutation, V734I, causes a gain of function in KATP activity by reducing sensitivity of KATP channels to ATP



Genetic analysis in 150 patients with Brugada syndrome and/or ERS

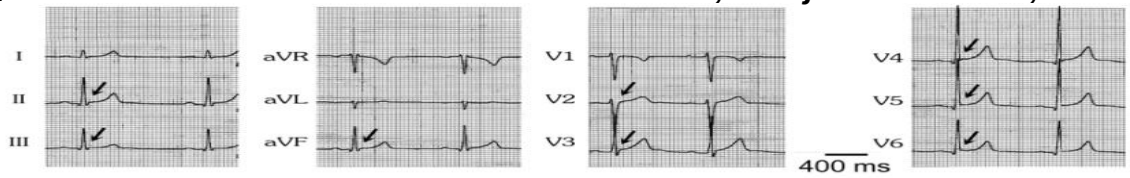
Proband no.	General information: Age for Dx (y/o)	Gender	Dx	VT/VF	FH[a]	Symptom: Syncope	SCD	Other[b]	Treatment	Other suspected genes	*ABCC9* Name
1	27	M	ERS3	Y	Y	Y	–	Y	–	–	R663C
2	38	M	ERS3	–	–	Y	Y	–	–	–	A665T
3	63	M	BrS + CAD	–	Y	–	Y	Y	ICD	–	N733D
4	20	M	ERS3 + bradycardia	–	Y	Y	–	Y	–	–	V734I
5	20	M	ERS3 + bradycardia	Y	Y	Y	Y	Y	ICD, quinidine	–	
6	40	M	ERS3 + AVB + bradycardia	Y	–	Y	Y	–	ICD	*SCN5A*	
7	20	M	ERS2 + bradycardia	–	–	Y	–	–	–	*CACNA1C*	
8	25	M	ERS2	–	–	–	Y	–	–	*SCN10A*	V1137I
9	65	M	BrS + SQTS	Y	–	Y	Y	–	ICD	*SCN10A, CACNA1C*	R1197C
10	18	M	BrS + SAB	–	Y	Y	–	Y	–	*SCN5A*	S1402C
11	39	M	BrS	Y	–	Y	Y	Y	ICD	–	L1524K fs*5



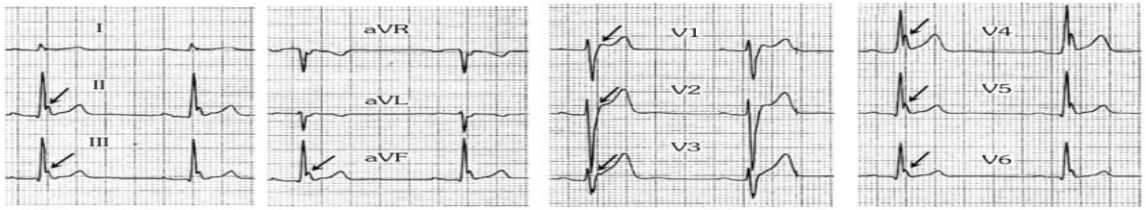


Hu D, Barajas-Martinez H, et al. Int J Card: 2014,171:431-42

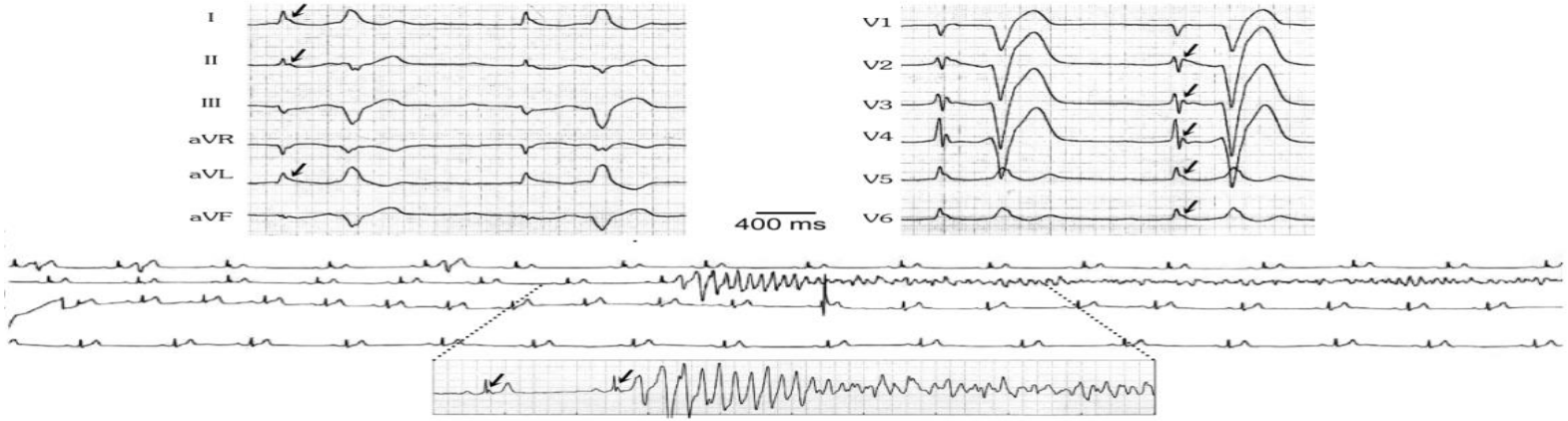
A: *ABCC9*-V734I



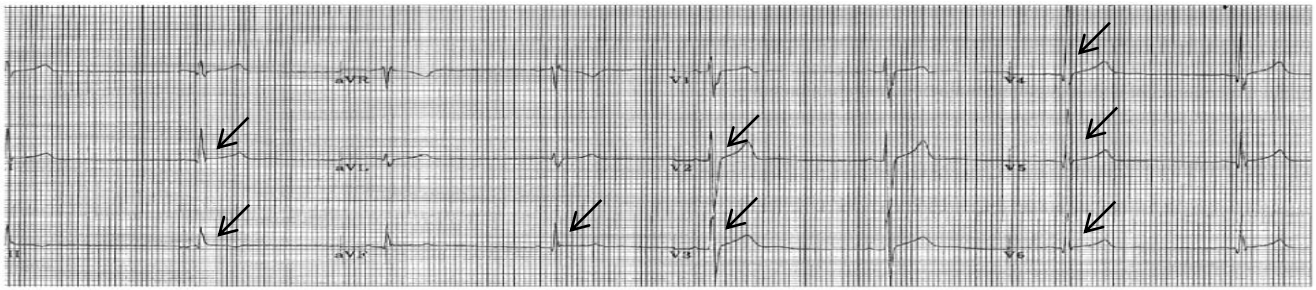
B: *ABCC9*-V734I



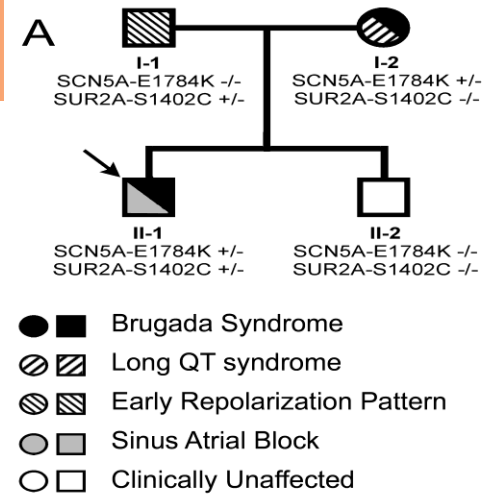
C: *ABCC9*-V734I + *SCN5A*-G1297Gfsx22

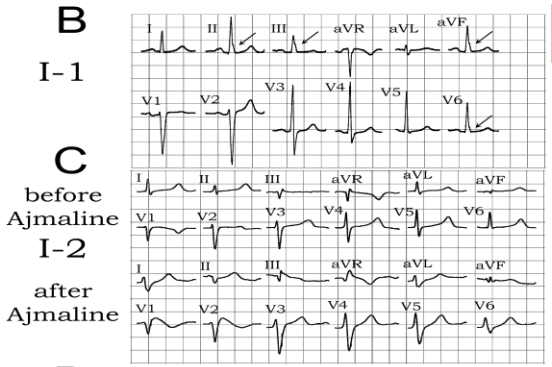


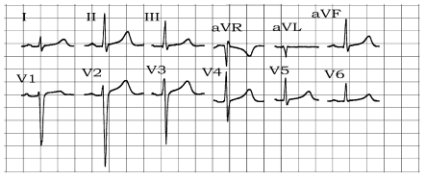
D: *ABCC9*-V734I + *CACNA1C*-P817S

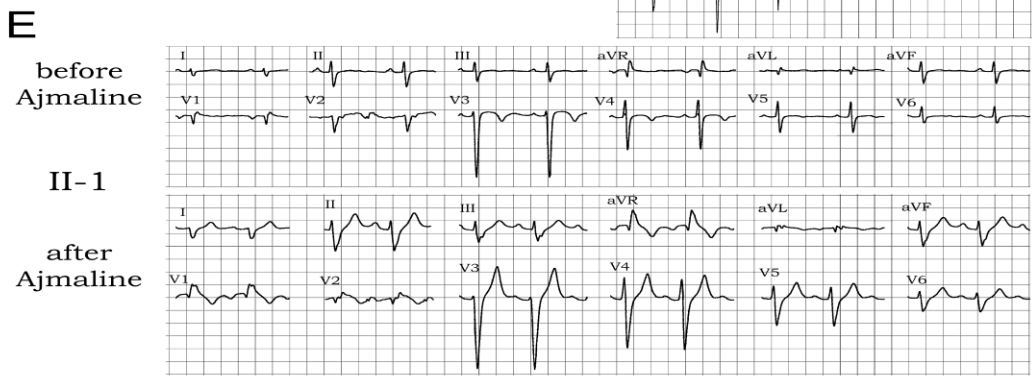


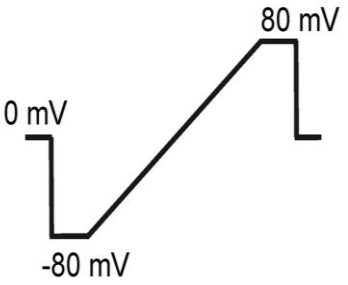
- ECGs of 4 *ABCC9*-V734I variant carriers with ERS

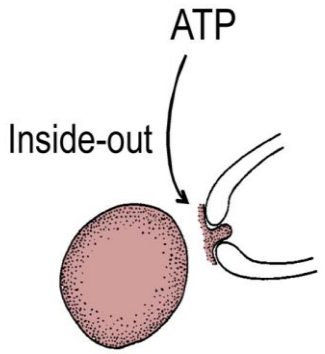


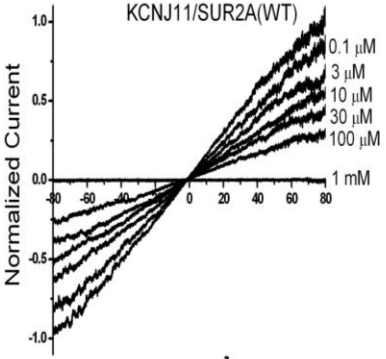


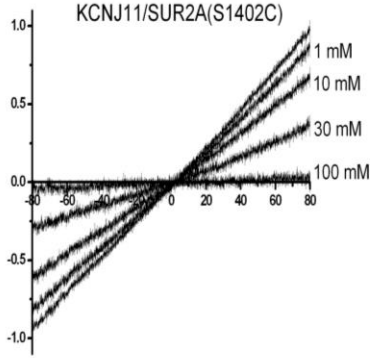


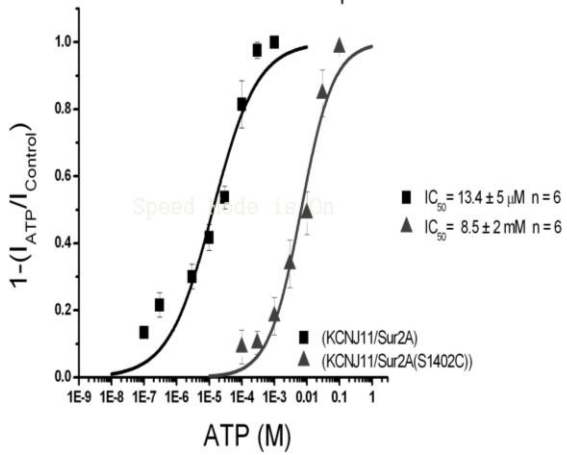












Overlap Syndrome

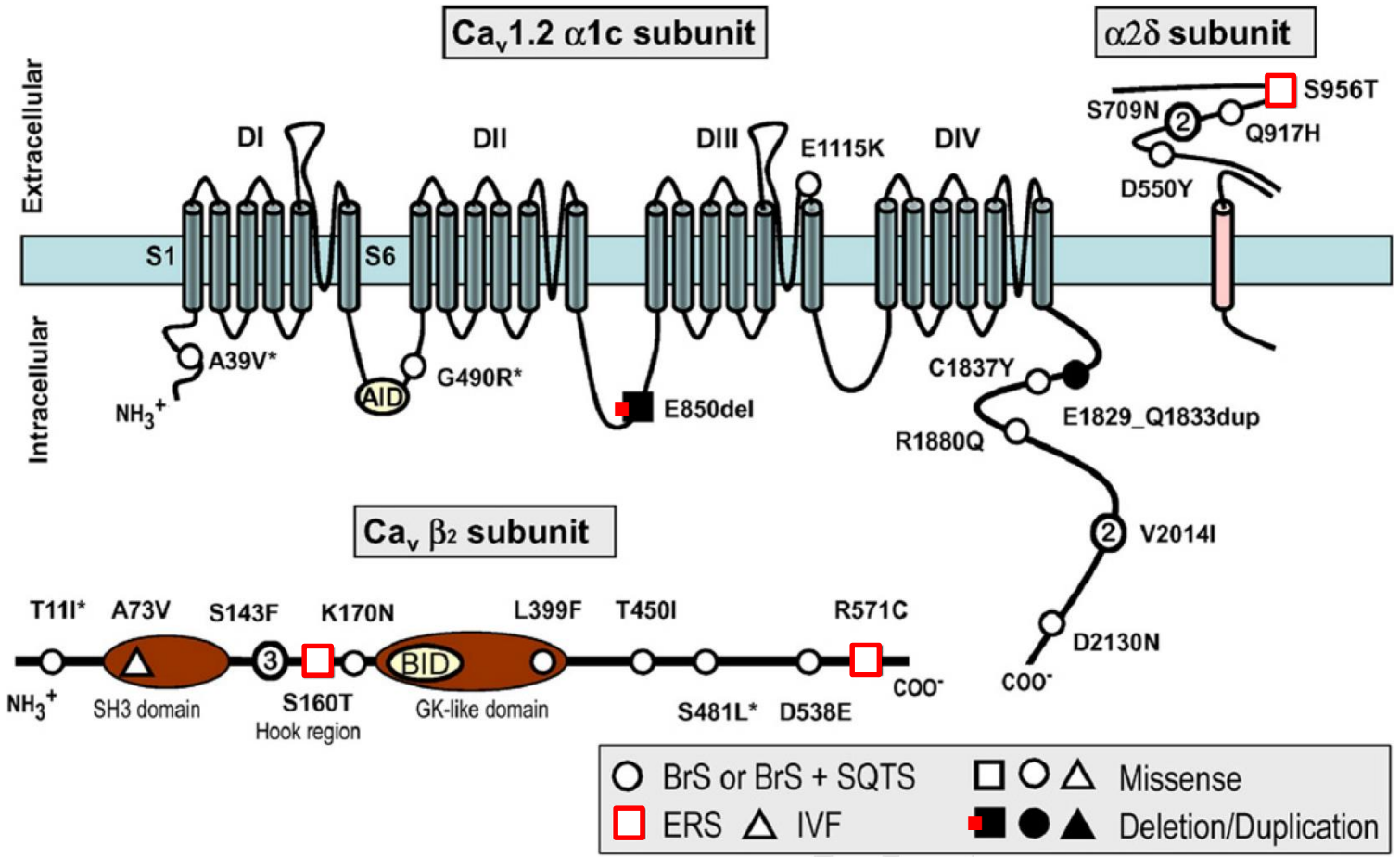
ERS, BrS, LQTS, SAB

Gain of Function in IK-ATP due to reduced sensitivity of the *ABCC9 (SUR2A)-S1402C* mutant KATP channels to ATP

Hu Dan et al., Int J Card, 2014

Susceptibility genes of ERS, Ca^{2+} channel genes

- 4 mutations in 3 Ca^{2+} channel genes (*CACNA1C, CACNA2D1, CACNB2*)
- Loss-of-function



Burashnikov E , Hu D, Heart Rhythm. 2010;7:1872-1882

Calcium-related gene defects are associated with ERS

- ECG features
  - HR slowed down
  - QTc shortened
  - TP-E /QT ratio increased

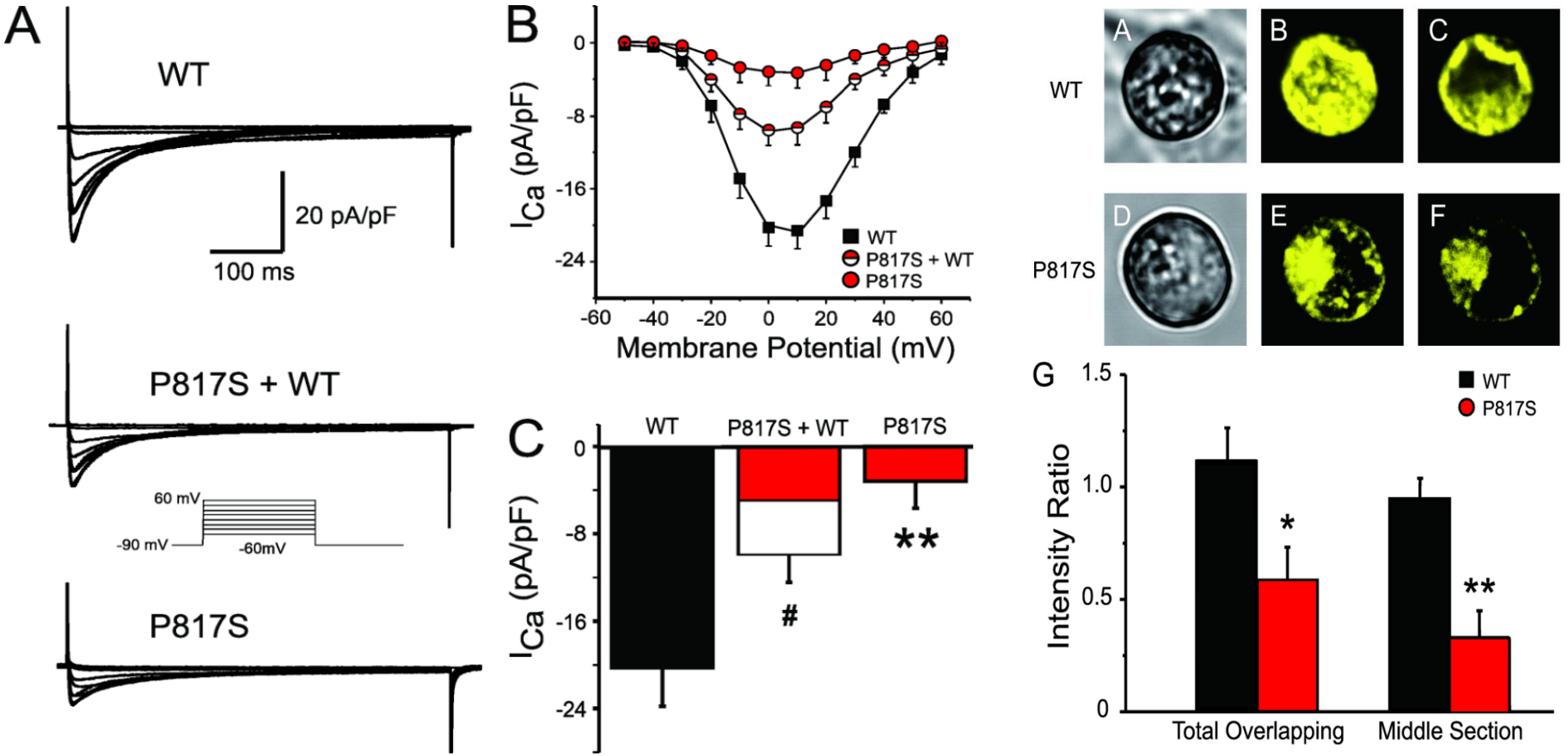
Index	Healthy control (*n* = 150)	ERS probands with calcium mutation (*n* = 16)			
		Single calcium mutation (*n* = 8)	*P*-value	With additional mutation(s) (*n* = 8)	*P*-value
HR (bpm)	72.7 ± 8.9	65.6 ± 16.1	**0.0378**	60.9 ± 9.6	**<0.001**
P wave (ms)	87.6 ± 9.1	90.9 ± 13.5	0.3318	89.4 ± 19.4	0.6133
PR interval (ms)	170.7 ± 18.7	178.0 ± 51.0	0.3448	184.3 ± 32.5	0.0567
QRS duration (ms)	89.4 ± 14.6	94.6 ± 16.1	0.3302	96.3 ± 25.9	0.2154
QTc interval (ms)	408.2 ± 21.4	386.8 ± 16.9	**0.0061**	389.5 ± 23.6	**0.0177**
Tp-e	82.3 ± 9.9	104.7 ± 18.5	**<0.001**	102.0 ± 27.6	**<0.001**
Tp-e/QT	0.22 ± 0.05	0.28 ± 0.04	**0.0011**	0.26 ± 0.07	**0.0324**

Calcium-related gene defects are associated with ERS

- Information of single calcium channel mutation was obtained in 8 cases, and the incidence of calcium channel mutation was 16.5% in ERS

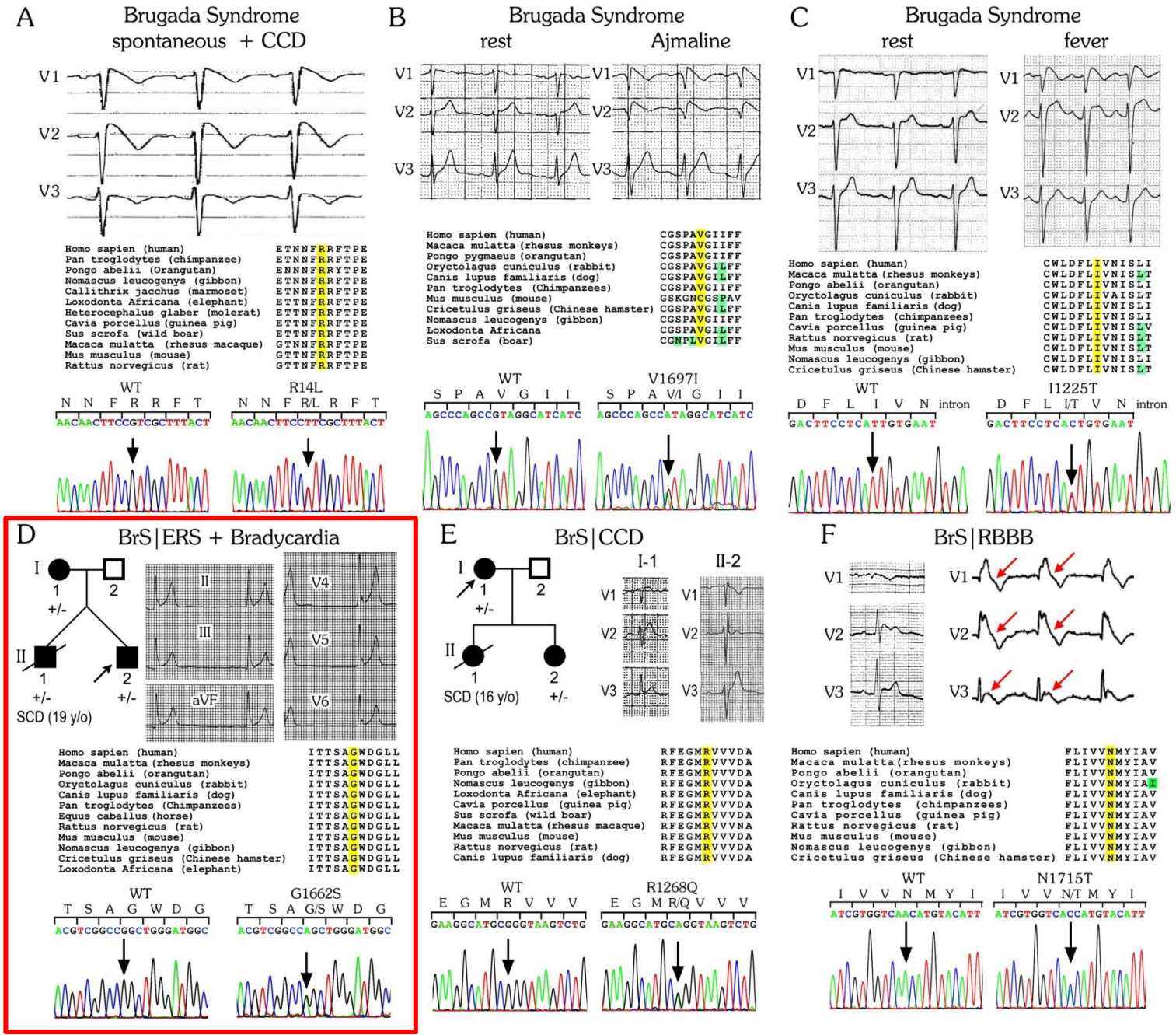
	CACNA1C				*CACNB2b*			
Variant	P817S	G37R	G490R	E850del	S160T	A170V	S503L	R571C
Reported ID	rs112532048	rs34534613	rs121912775	rs575583988	rs149253719	NA	rs137886839	rs1060499847
Type	Missense	Missense	Missense	Frameshift	Missense	Missense	Missense	Missense
Change in Nucleotide	2449C>T	109G>A	1468G>A	2548-2550del	479G>C	509C>T	1508C>T	1711C>T
Exon Location	17	2	10	19	5	6	13	13
MAF								
GnomAD	0.003488	0.004555	0.000162	0.00042	0.000581	NA	0.001099	NA
ExAC	0.003534	0.007385	0.000809	0.000526	0.001007	NA	0.001162	NA
1000 gnome	0.001597	0.000399	0.000399	NA	0.001797	NA	0.001398	1.62686e-05
SIFT								
Score	0.212	0	0.133	NA	0.01	0.062	0.001	0
Prediction	Tolerated	Damaging	Tolerated	NA	Damaging	Tolerated	Damaging	Damaging
MetaLR								
Score	0.839	0.9028	0.83	NA	0.3893	0.5276	0.5305	0.6806
Prediction	Damaging	Damaging	Damaging	NA	Tolerated	Damaging	Damaging	Damaging
Muation Taster								
Score	0.99975	1	0.999727	NA	1	1	0.999999	1
Prediction	Disease causing	Disease causing	Disease causing	NA	Disease causing	Disease causing	Disease causing	Disease causing
PolyPhen2								
Score	0.999	1	1	NA	0.787	0.007	0.996	1
Prediction	Probably damaging	Probably damaging	Probably damaging	NA	Probably damaging	Benign	Probably damaging	Probably damaging
FATHMMM								
Score	-3.83	-3.88	-3.33	NA	-1.67	-1.81	-1.85	-2.17
Prediction	Damaging	Damaging	Damaging	NA	Damaging	Damaging	Damaging	Damaging

Calcium-related gene defects are associated with ERS

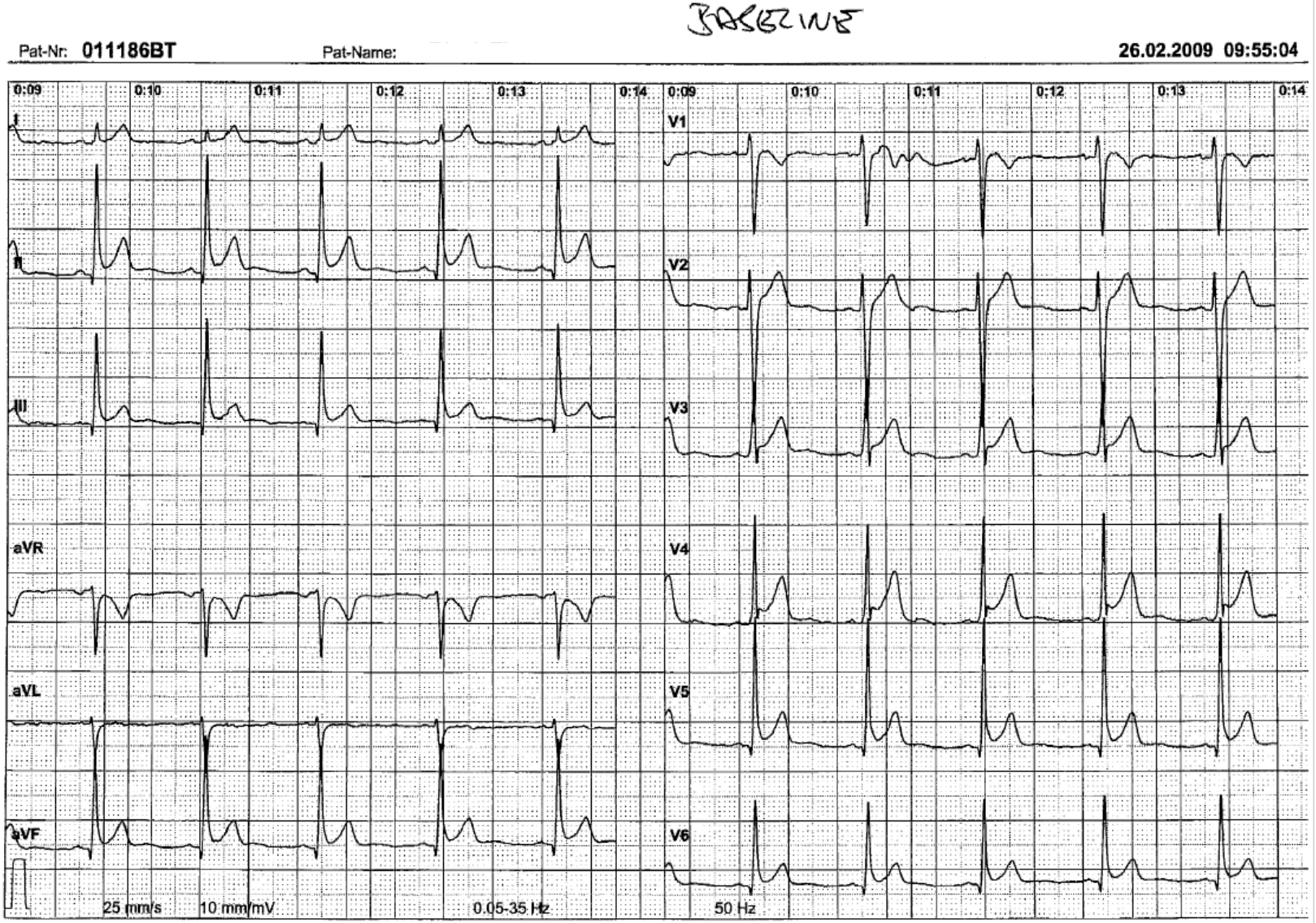


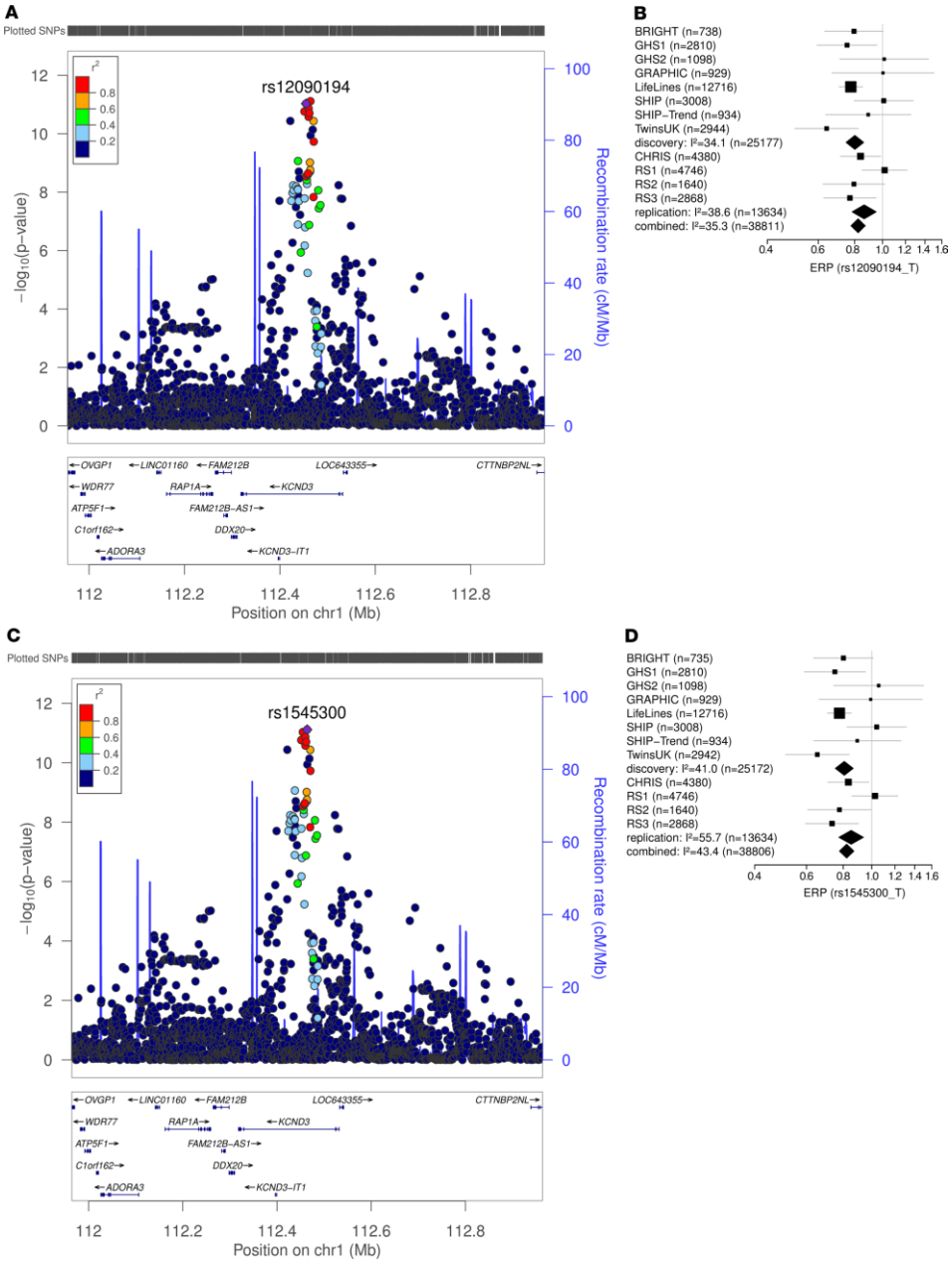
SCN10A Mutations and BrS

Dan Hu, et al. JACC, 2014



ERS3 case – 27 y/o Male, with syncope and aborted SCD, carried *SCN10A* Mutation





- For the first time in GWAS, a significant association between a gene variant and ERP was identified
- Not only discover a KCND3 locus as a possible ERP gene determinant, but also provide a promising candidate for functional studies to understand the pathophysiological mechanism

A *de novo* gain-of-function *KCND3* mutation in early repolarization syndrome

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BACKGROUND Early repolarization syndrome (ERS) is characterized by J-point elevation on electrocardiograms and ventricular fibrillation (VF). Early repolarization arises from augmentation of the transmural electrical gradient in the cardiac action potential; therefore, the transient outward potassium current (I_{to}) has been regarded as a key candidate current for elucidating the mechanism of ERS. *KCND3* encoding Kv4.3, an α-subunit of the I_{to} channel, is considered as one of target genes.

OBJECTIVE The purpose of this study was to search for novel *KCND3* mutations associated with ERS and to clarify the pathogenesis.

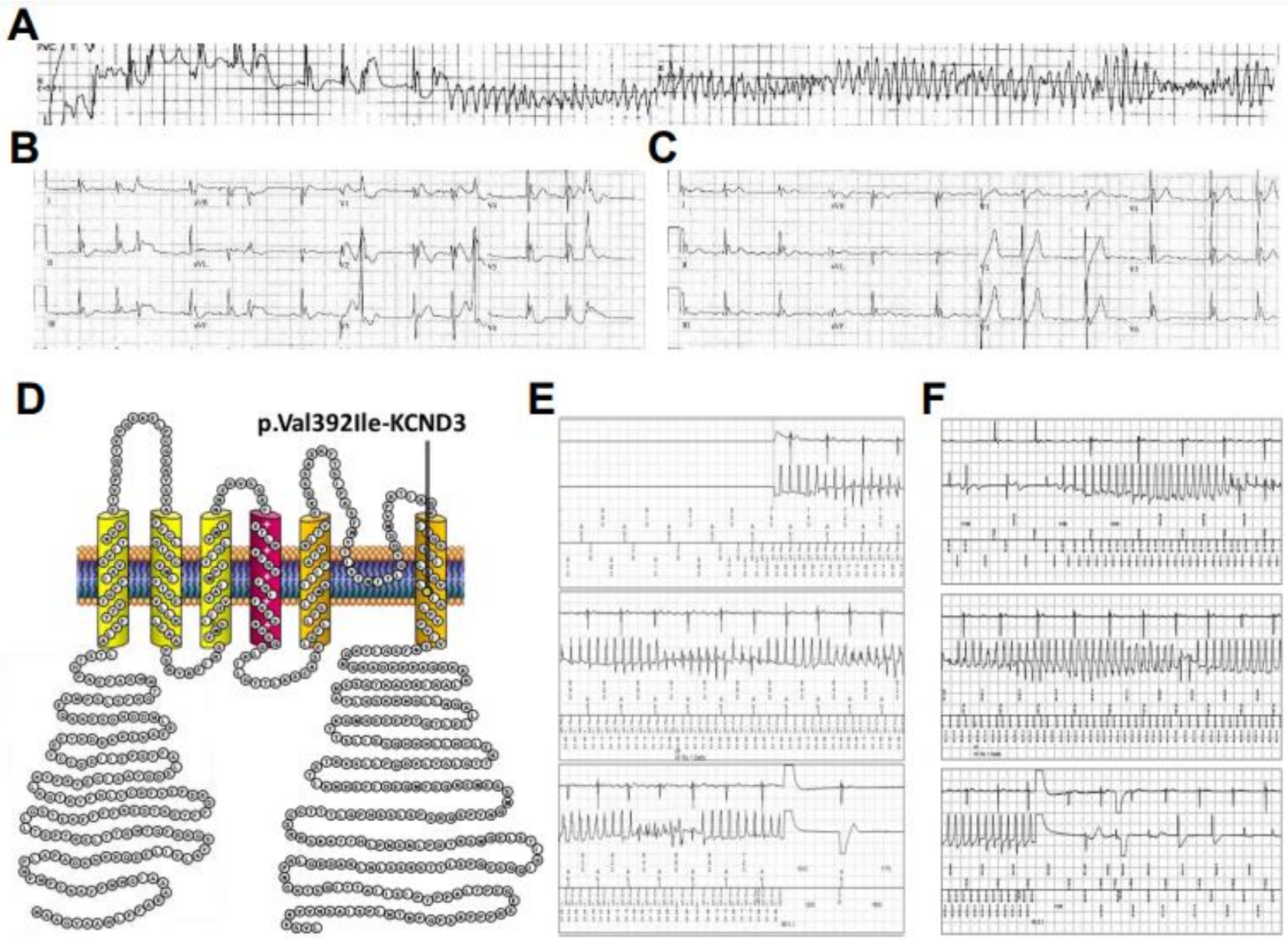
METHODS We performed genetic screening for 11 unrelated probands with ERS and analyzed the electrophysiological properties of detected mutations by patch-clamp methods.

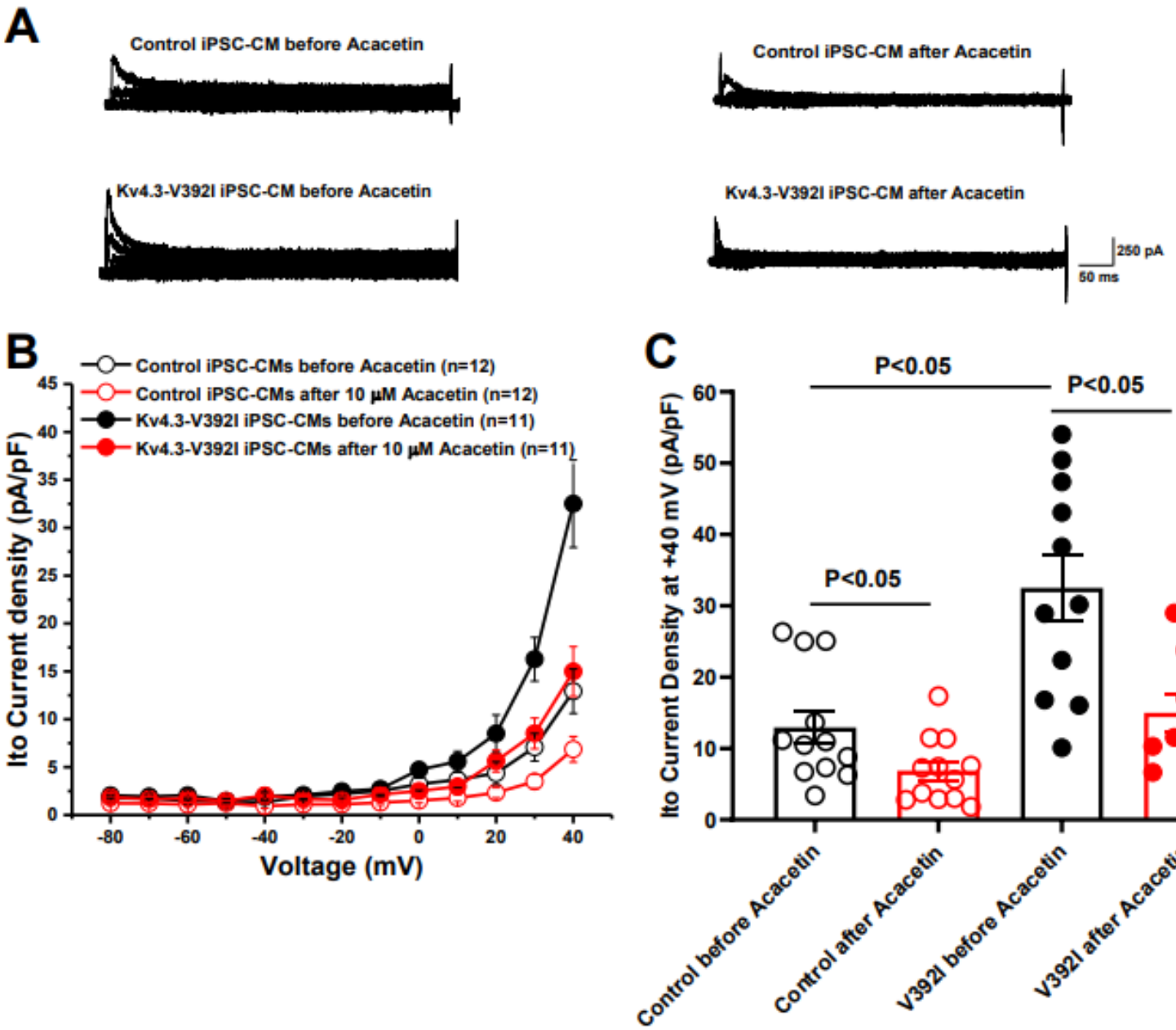
RESULTS A novel *de novo* *KCND3* heterozygous mutation, Gly306Ala (c.917g>c), was found in 1 proband. The proband was a 12-year-old boy, who suffered VF storm and showed significant J-point elevation in multiple leads. Intravenous isoproterenol and subsequent administration of quinidine were effective in preventing VF recurrence and restored the J-point elevation. In electrophysiological analysis, cultured cells expressing mutant Kv4.3 showed significantly increased current densities, slow inactivation, and slow recovery from inactivation compared to wild type. Extracellular application of quinidine significantly restored the inactivation time course in mutant Kv4.3. A simulation study confirmed the relationship between the novel *KCND3* mutation and early repolarization on electrocardiograms.

CONCLUSION A novel *KCND3* heterozygous mutation was found to be associated with ERS. The pathogenesis can be explained by the increased I_{to}. Genetic screening for *KCND3* could be useful for understanding the pathogenesis and selecting effective treatment.

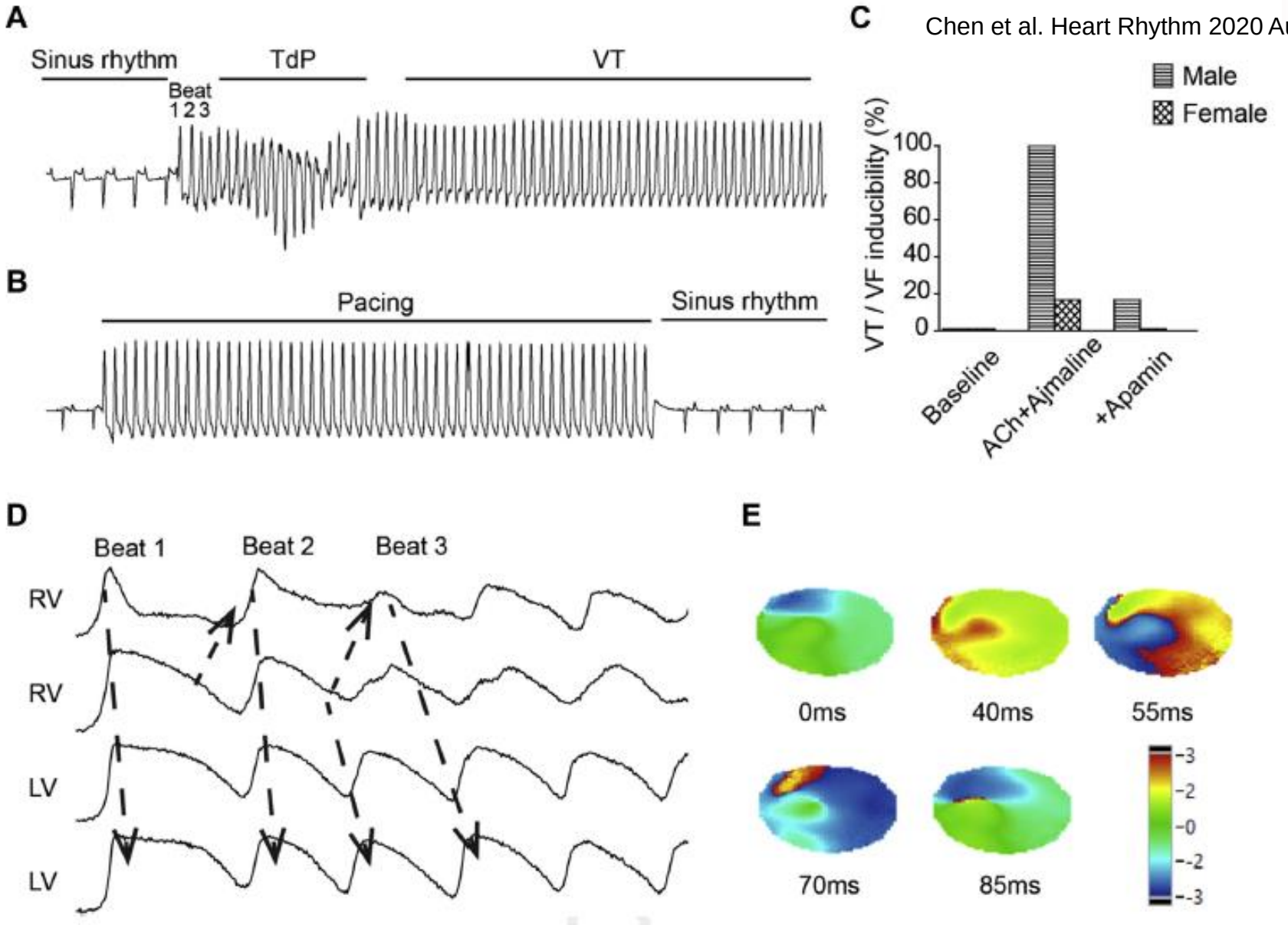
KEYWORDS Early repolarization syndrome; *KCND3*; Kv4.3; Transient outward potassium current; Quinidine

(Heart Rhythm 2019;16:1698–1706)


A
B
C
D
p.Val392Ile-KCND3
E
F


A
Control iPSC-CM before Acacetin
Control iPSC-CM after Acacetin
Kv4.3-V392I iPSC-CM before Acacetin
Kv4.3-V392I iPSC-CM after Acacetin
250 pA
50 ms
B
Control iPSC-CMs before Acacetin (n=12)
Control iPSC-CMs after 10 μM Acacetin (n=12)
Kv4.3-V392I iPSC-CMs before Acacetin (n=11)
Kv4.3-V392I iPSC-CMs after 10 μM Acacetin (n=11)
Ito Current density (pA/pF)
Voltage (mV)
C
P<0.05
P<0.05
P<0.05
Ito Current Density at +40 mV (pA/pF)
Control before Acacetin
Control after Acacetin
V392I before Acacetin
V392I after Acacetin

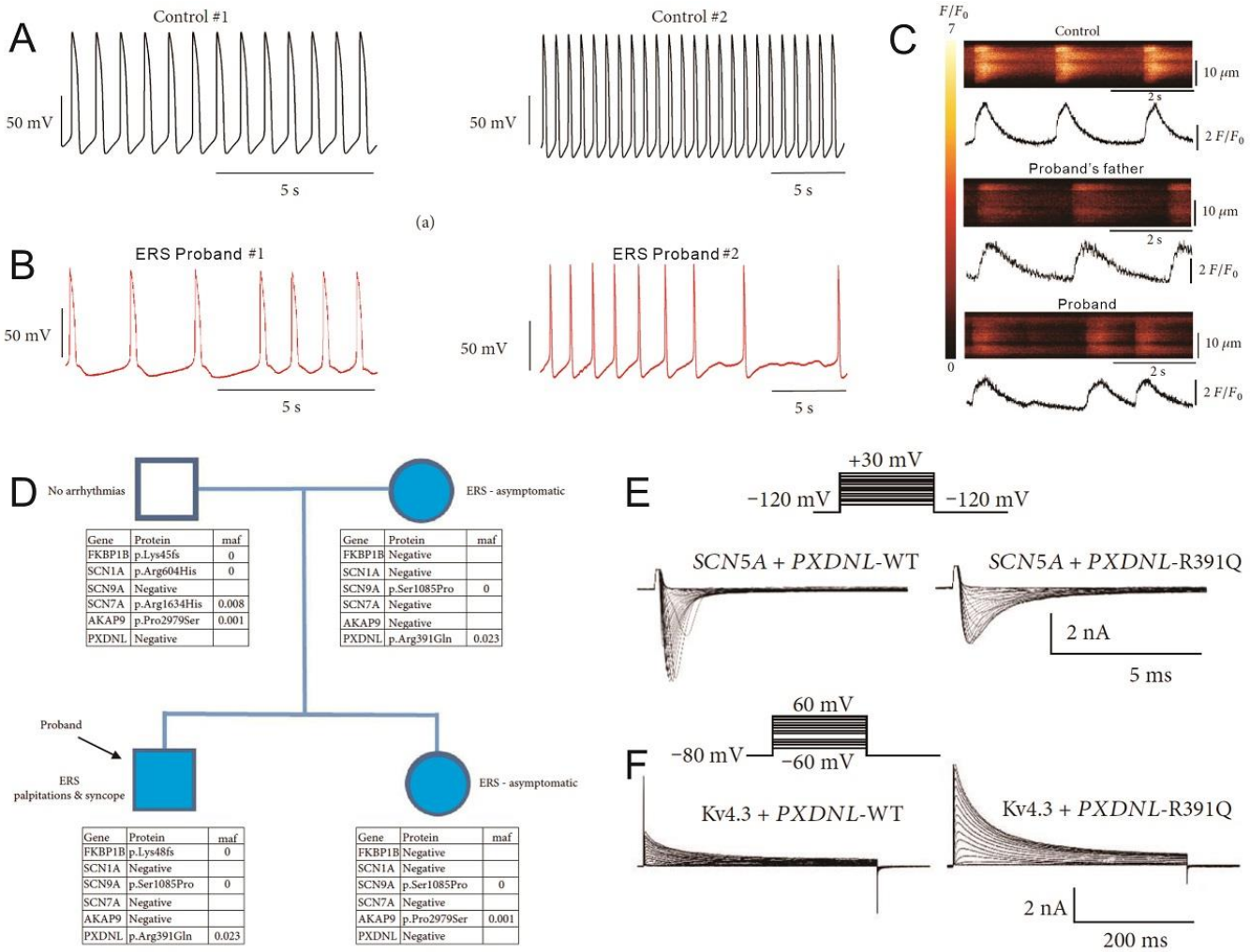
Chen et al. Heart Rhythm 2020 Aug 04



Ach activates ventricular IKAS

ACh and Ajmaline can induce JWS, and male are more likely to induce ventricular arrhythmias than female

Establishment and identification of the first hiPSC-CM system in ERS patients



Stem cell international, 2021;16:781–790

Conclusion

- Clinical characteristics of ERS are heterogeneous and there have been multiple causative genes
- ERS is genetically complicated, but Ito-INa complex is still the key to pathogenicity


Thank You