Inherited Arrhythmias Associated with SCN5A mutations: A Translational Perspective

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COI Disclosure

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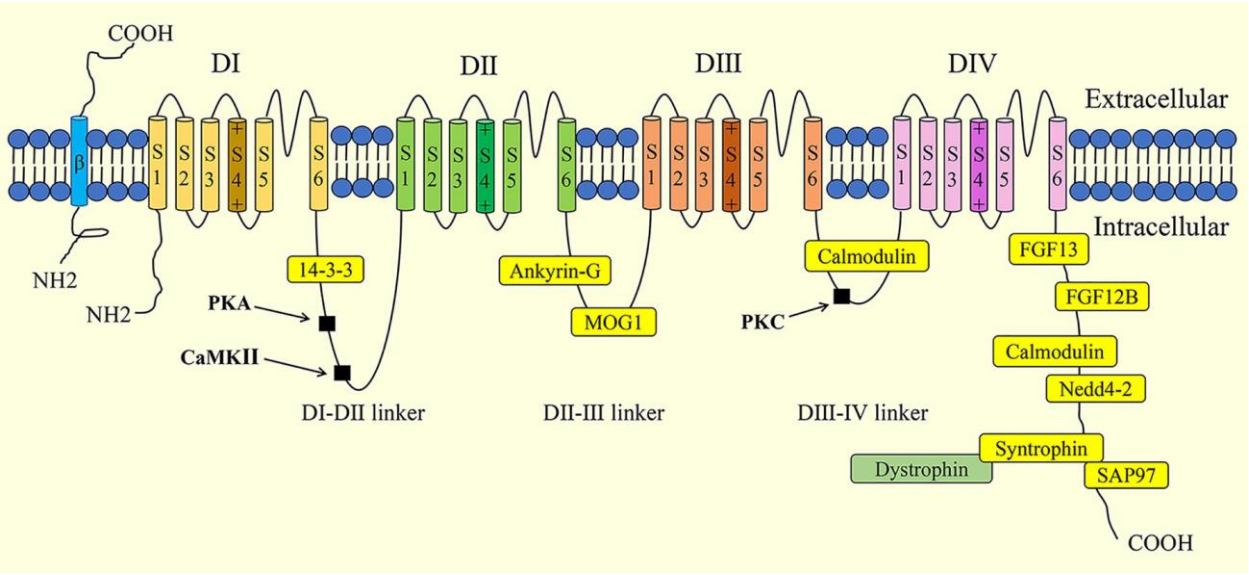
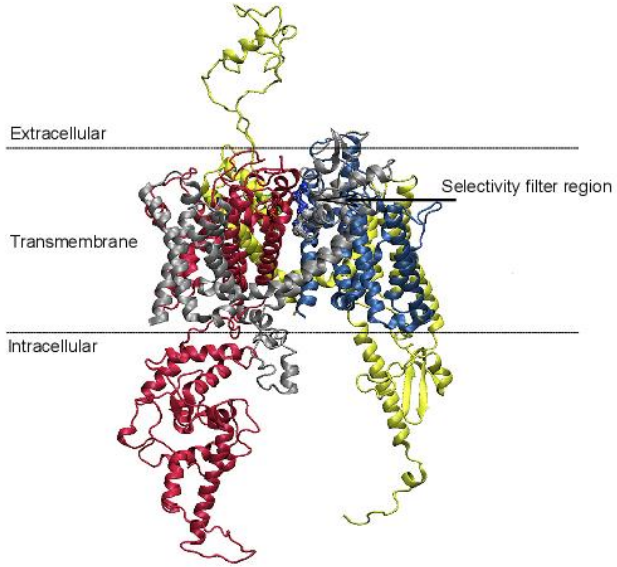
The authors have no financial conflicts of interest to disclose concerning the presentation

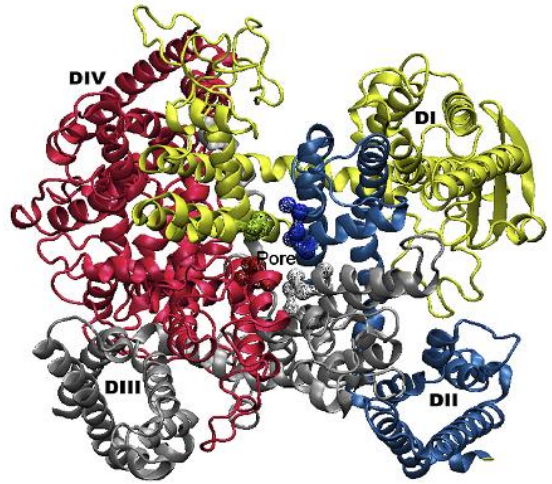
What is SCN5A

- SCN5A encodes an α subunit of cardiac sodium channel, Nav1.5.
- Nav1.5 consists of 4 domains with 6 transmembrane segments.
- Various proteins interact with Nav1.5
- Pathogenic variants in SCN5A cause various inherited cardiac diseases.





Side view



Top view

Dong C, et al.: Front Physiol, 11:609733,2020

Ahmed M, et al.: Drug Des Devel Ther, 11:2301-2324,2017

Disease caused by pathogenic SCN5A variants

Sodium Channelopathy

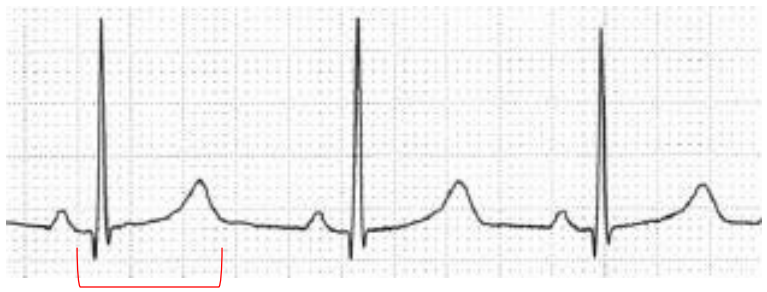
- Long QT syndrome type 3 (LQT3)
- Atrial fibrillation
- Brugada syndrome (BrS)
- Early repolarization syndrome (ERS)
- Idiopathic ventricular fibrillation
- Sick Sinus Syndrome (SSS)
- Progressive Cardiac Conduction Disease (PCCD)
- Dilated cardiomyopathy (DCM)

Gain of Function

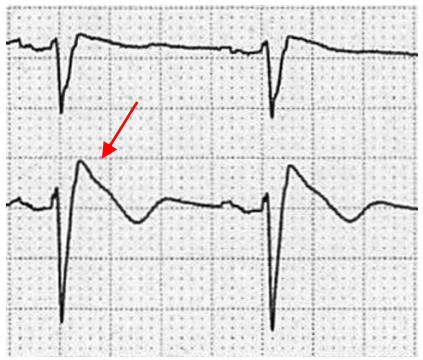
Loss or Gain of Function

Loss of Function

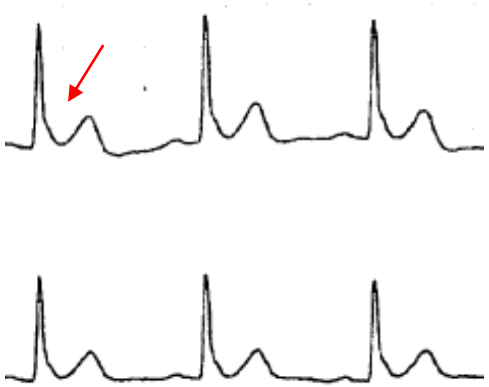
LQTS



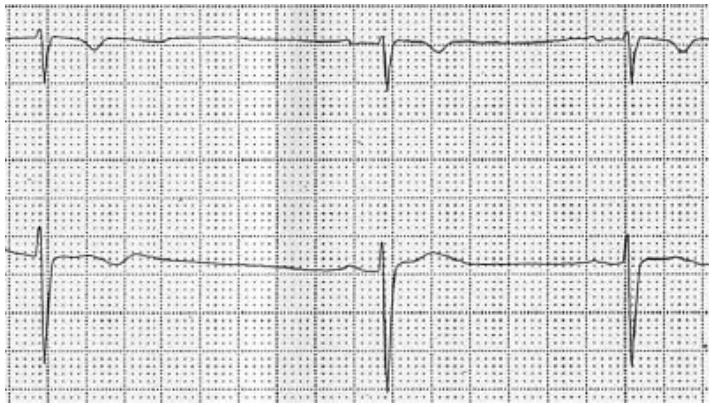
BrS



ERS



SSS

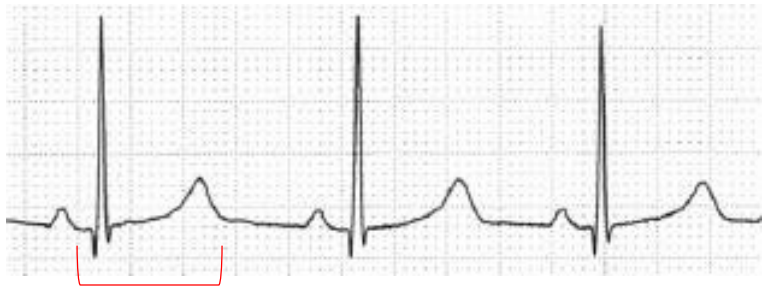


Disease caused by pathogenic SCN5A variants

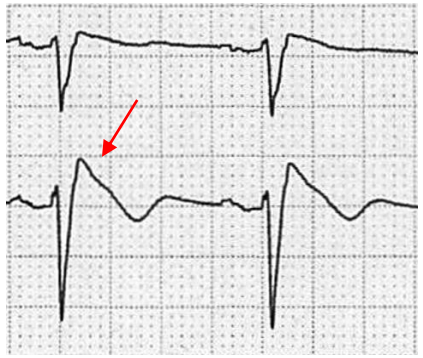
Sodium Channelopathy

- Long QT syndrome type 3 (LQT3) — Gain of Function
- Atrial fibrillation — Loss or Gain of Function
- Brugada syndrome (BrS) — Loss or Gain of Function
- Early repolarization syndrome (ERS) — Loss or Gain of Function
- Idiopathic ventricular fibrillation — Loss or Gain of Function
- Sick Sinus Syndrome (SSS) — Loss of Function
- Progressive Cardiac Conduction Disease (PCCD) — Loss of Function
- Dilated cardiomyopathy (DCM) — Loss or Gain of Function

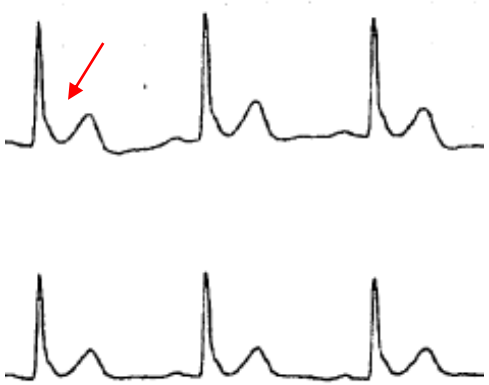
LQTS



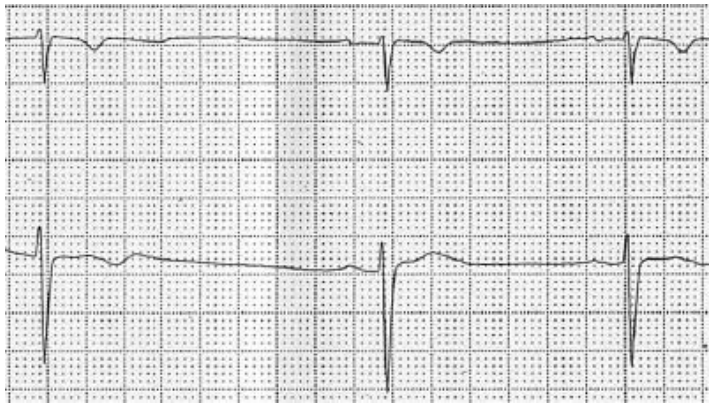
BrS



ERS

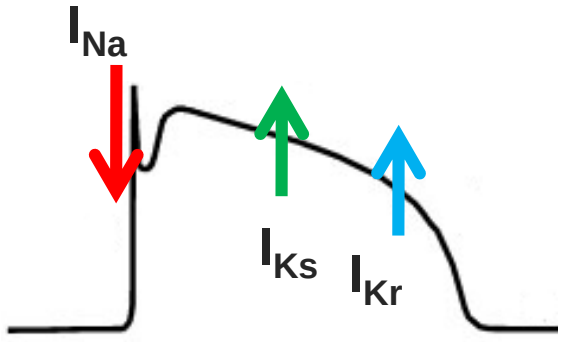


SSS

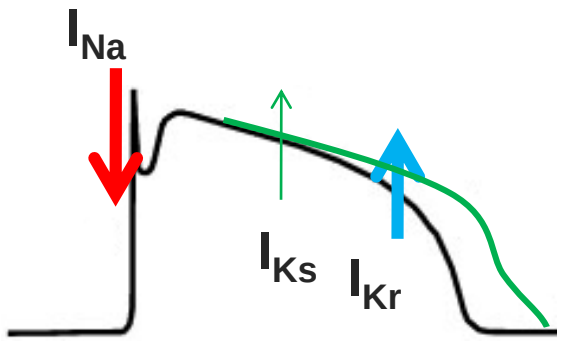


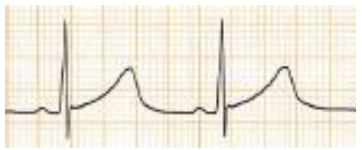
Mechanism of LQTS

Cardiac action potential



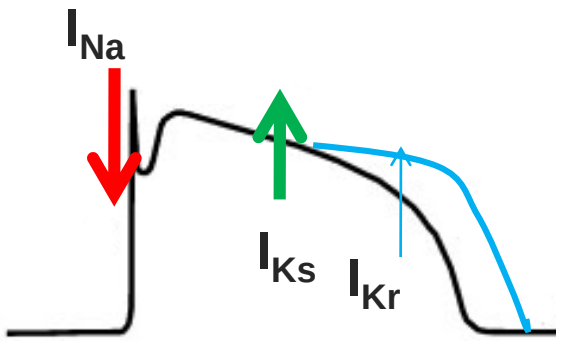
LQT1 (KCNQ1)
I_{ks} decrease

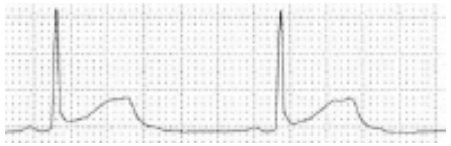




Wide based T

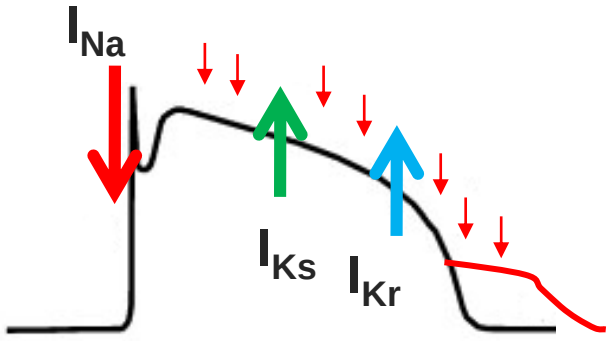
LQT2 (KCNH2)
I_{kr} decrease

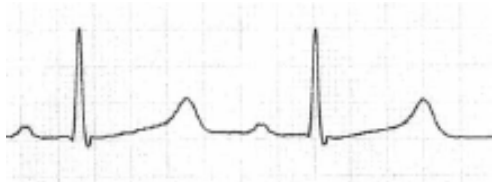




Notched T

LQT3 (SCN5A)
Late I_{Na} increase





Late onset T

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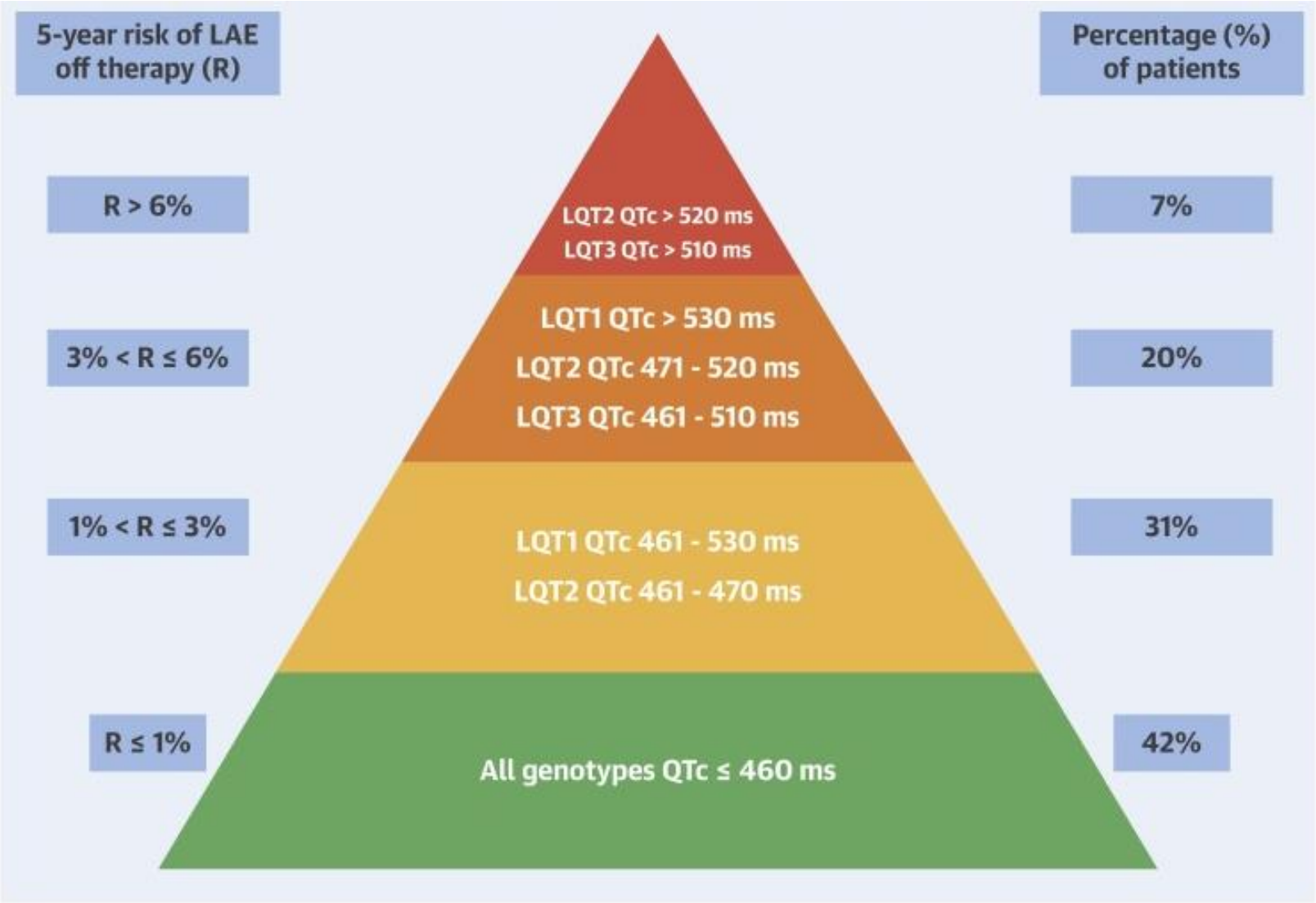
5-year risk of LARs by Genotype and QTc Interval

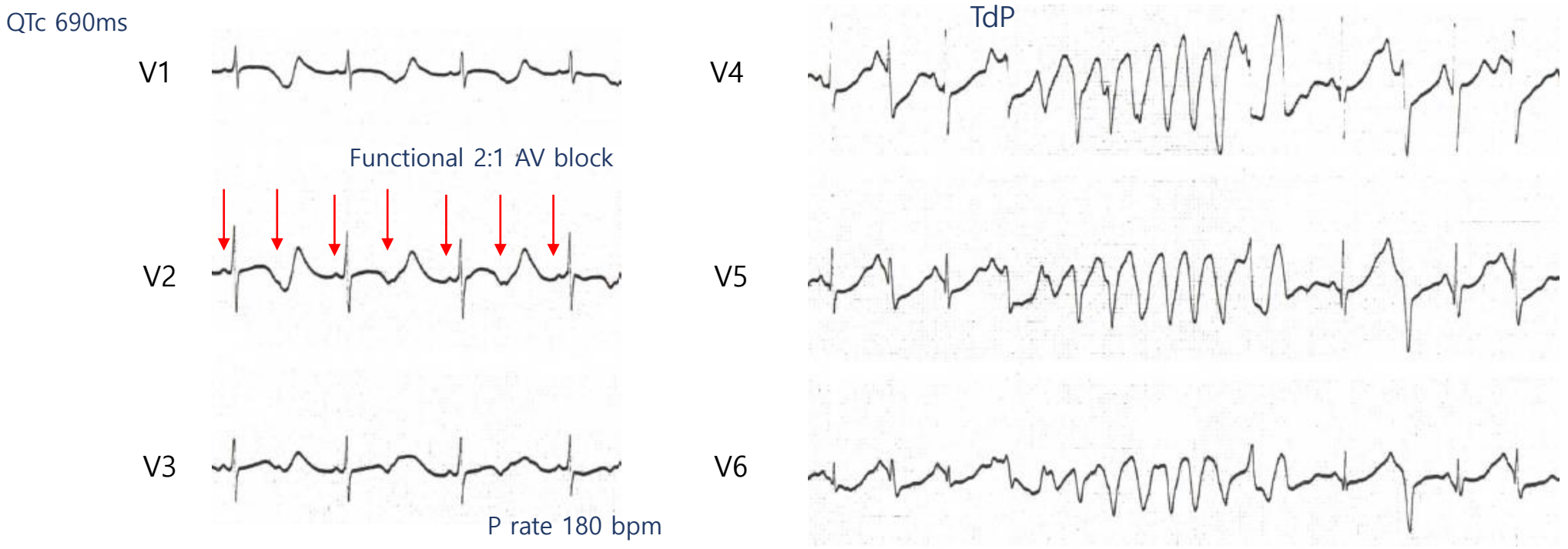


High risk in LQT3

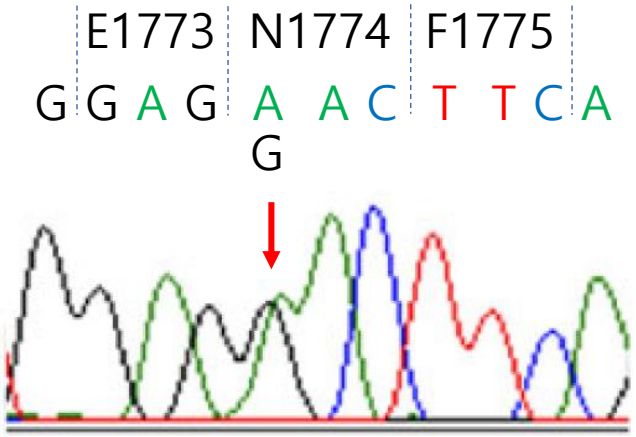
Mazzanti A, et al.: J Am Coll Cardiol, 71:1663-1671,2018

A LQT3 patient

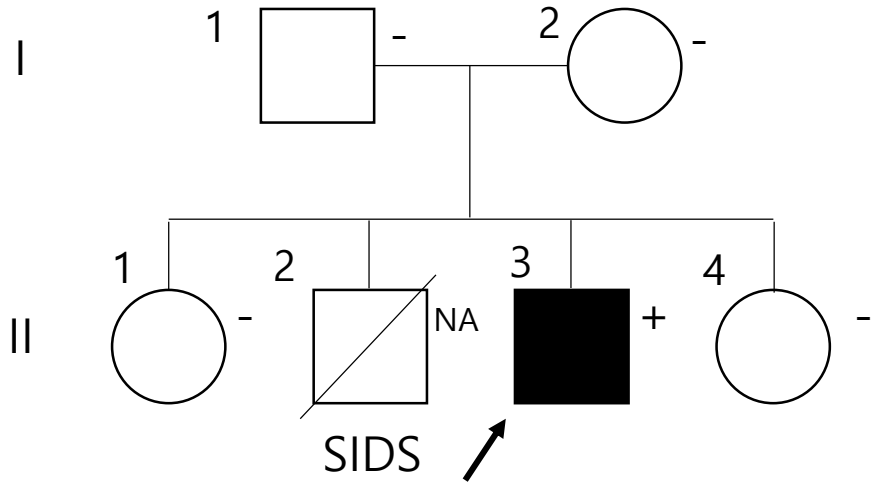
- ✓ A newborn boy who was pointed out bradycardia at the 27 weeks gestation age.
- ✓ He was delivered at 38 weeks by Caesarean section.
- ✓ Extremely prolonged QT intervals, 2:1 AV block and torsade des pointes (TdP) were observed in the ECG just after the birth.

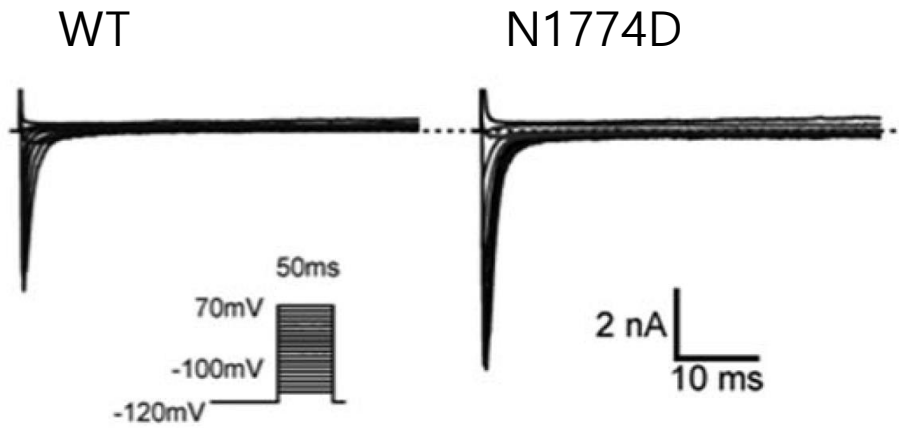


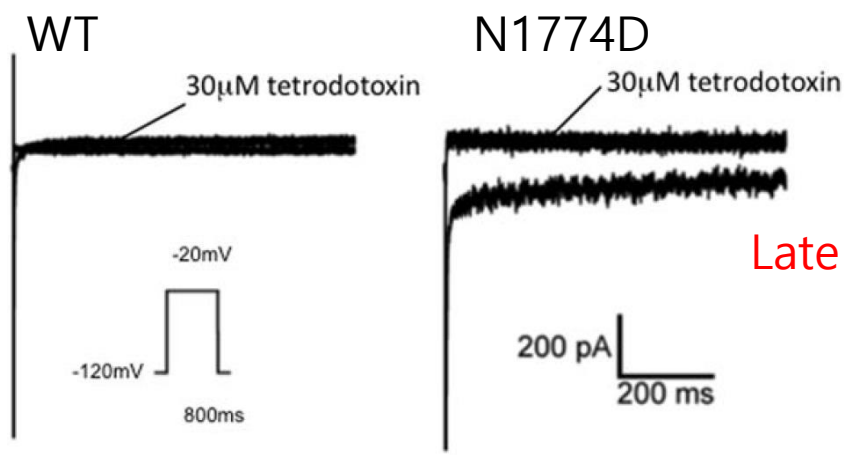
Genetic testing for the LQTS patient



c.5320A>G, p.N1774D







Late Na current

Kato K, Ohno S, et al.: J Cardiovasc Electrophysiol, 25:66-73,2014

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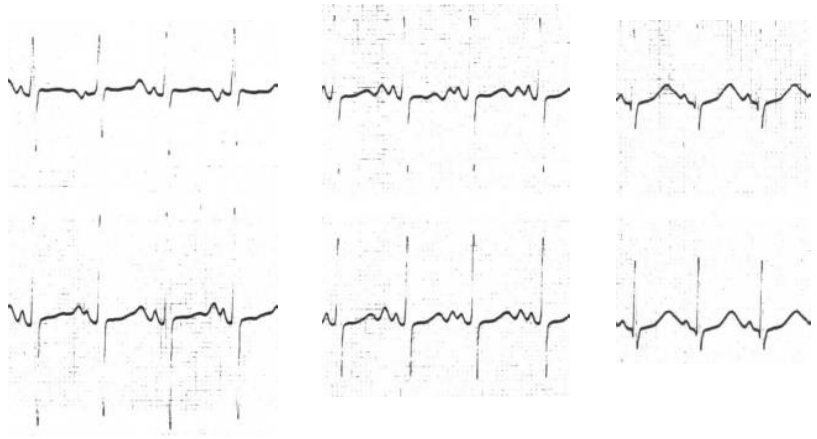
Therapy for LQTS

	LQT1	LQT2	LQT3
Gene	KCNQ1	KCNH2	SCN5A
Functional change	I_{Ks} ↓	I_{Kr} ↓	Late I_{Na} ↑
Trigger of QT prolongation	Tachycardia	Bradycardia	Bradycardia
Trigger of the symptom	Exercise Swimming	Sudden loud sound （Alarm, Telephone call at night） Pregnancy, Delivery	Rest
Time of occurrence	Daytime	Night, Early morning	Night
Age/Sex	Boy in teens	Women after puberty	
β blocker therapy	+++	++	+
Other therapy	Exercise Restriction	Pacemaker, ICD	ICD, Na channel blocker

A LQT3 patient: Clinical Course

- ✓ For the prevention of TdP, mexiletine, infusion of magnesium sulfate and Carteolol (non-selective β blocker) were effective.



2 days after birth

QTc 570ms

Are β blockers effective for LQT3?

- ✓ At 6-year-old, Carteolol was stopped.
- ✓ TdP was observed at 7-year-old.
- ✓ Carteolol was restarted and TdP was prevented.

β blocker therapy for LQT3 patients

406 LQT3 patients with 51 SCN5A variants

Cardiac event (Syncope, ACA, LQT3-related SCD)

Parameter	P Value	Hazard Ratio	95% Confidence Interval	
			LCL	UCL
β-Blockers among females*	0.014	0.17	0.04	0.7
β-Blockers among males*	0.895	0.94	0.4	2.21
E1784K mutation	< 0.001	0.35	0.19	0.62
D1790G mutation	0.007	0.32	0.14	0.73
QTc per 10 ms (up to 500 ms)	<0.0001	1.18	1.11	1.26
Year of birth (>1955)	<0.0001	1.05	1.04	1.07

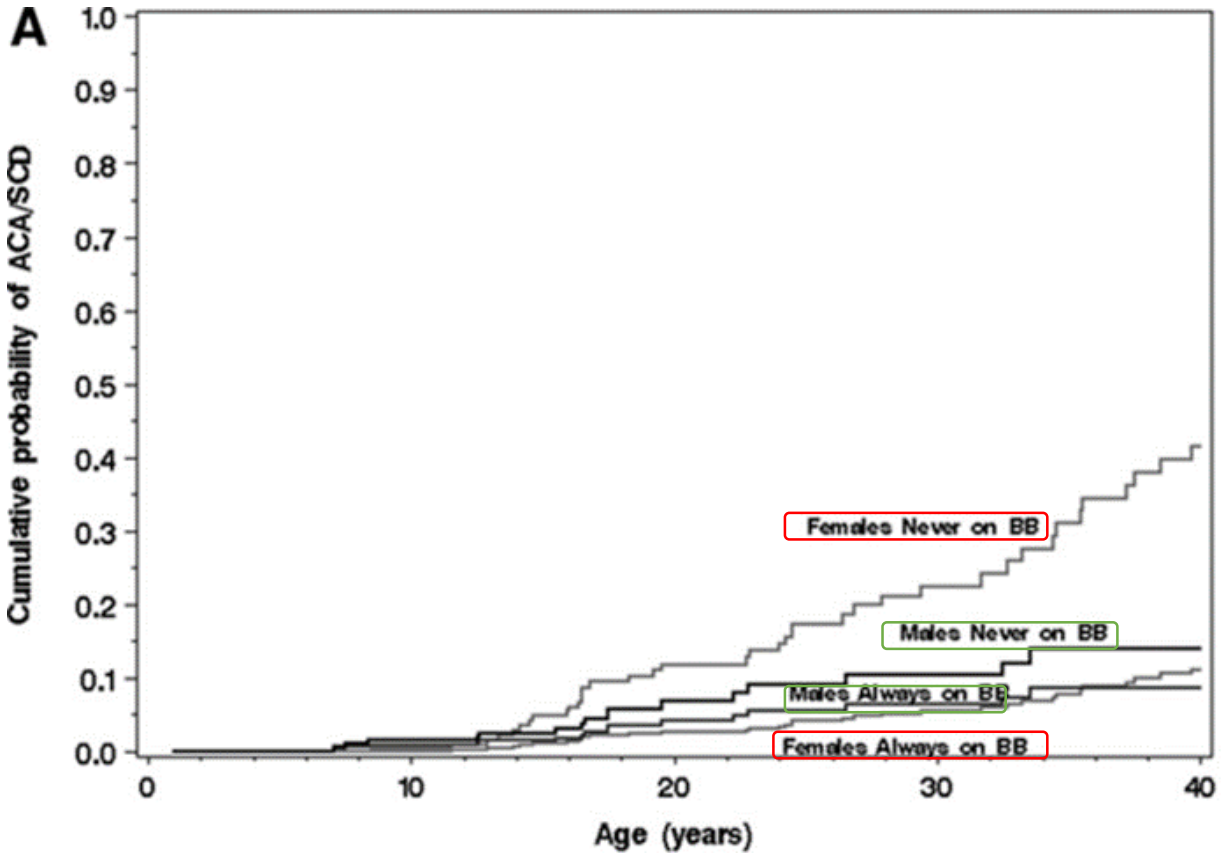
Cardiac event (ACA, LQT3-related SCD)

Parameter	PValue	Hazard Ratio	95% Confidence Interval	
			LCL	UCL
Syncope	0.023	2.03	1.1	3.72
β-Blockers among females*	0.032	0.2	0.05	0.87
β-Blockers among males*	0.308	0.51	0.14	1.88
E1784K mutation	0.001	0.09	0.02	0.37
D1790G mutation	0.049	0.3	0.09	0.99
QTc per 10 ms (up to 500 ms)	<0.001	1.33	1.19	1.48
Year of birth (>1955)	<0.001	1.06	1.03	1.09

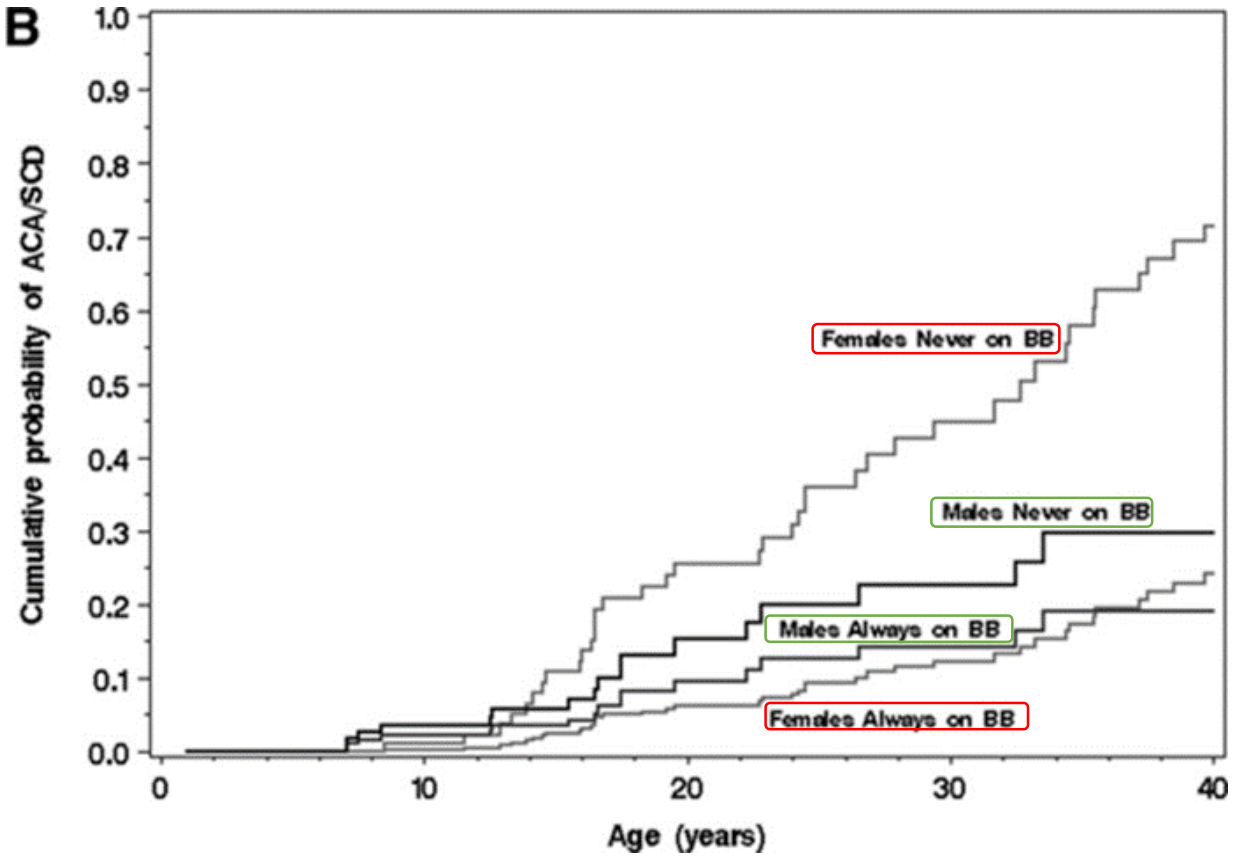
Wilde AA, et al. Circulation, 134:872-882,2016

β blocker therapy for LQT3 patients

Medium-risk patients
QTc: median 470 ms



High-risk patients
QTc: > 500 ms



Wilde AA, et al. Circulation, 134:872-882,2016

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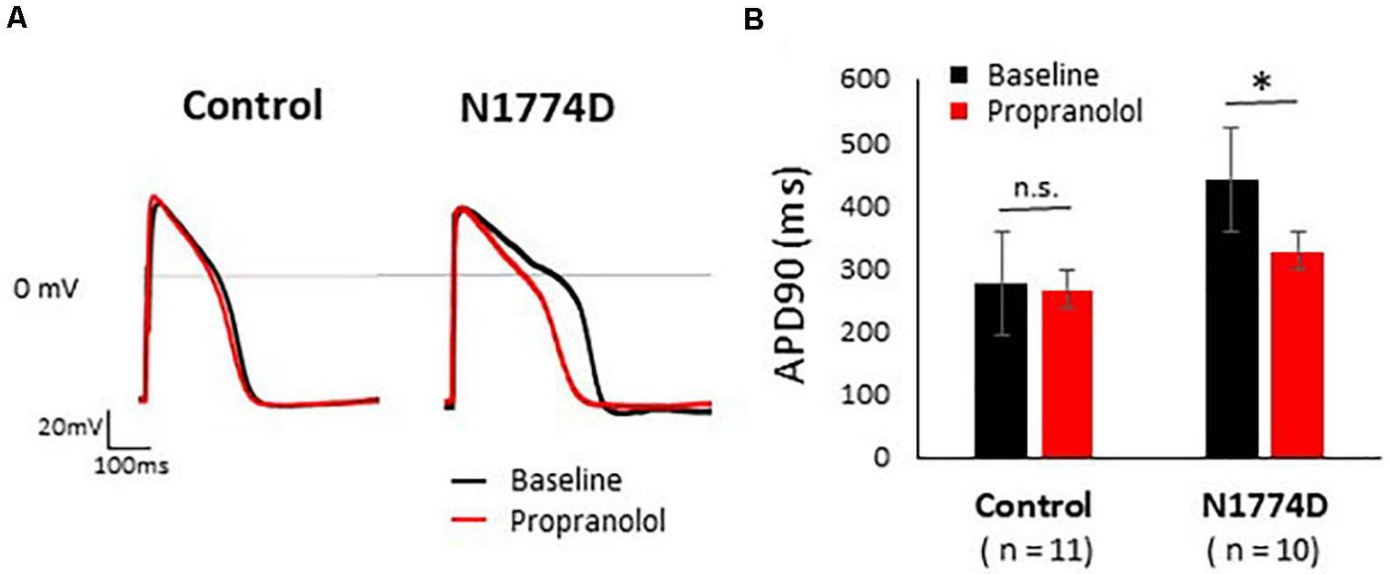
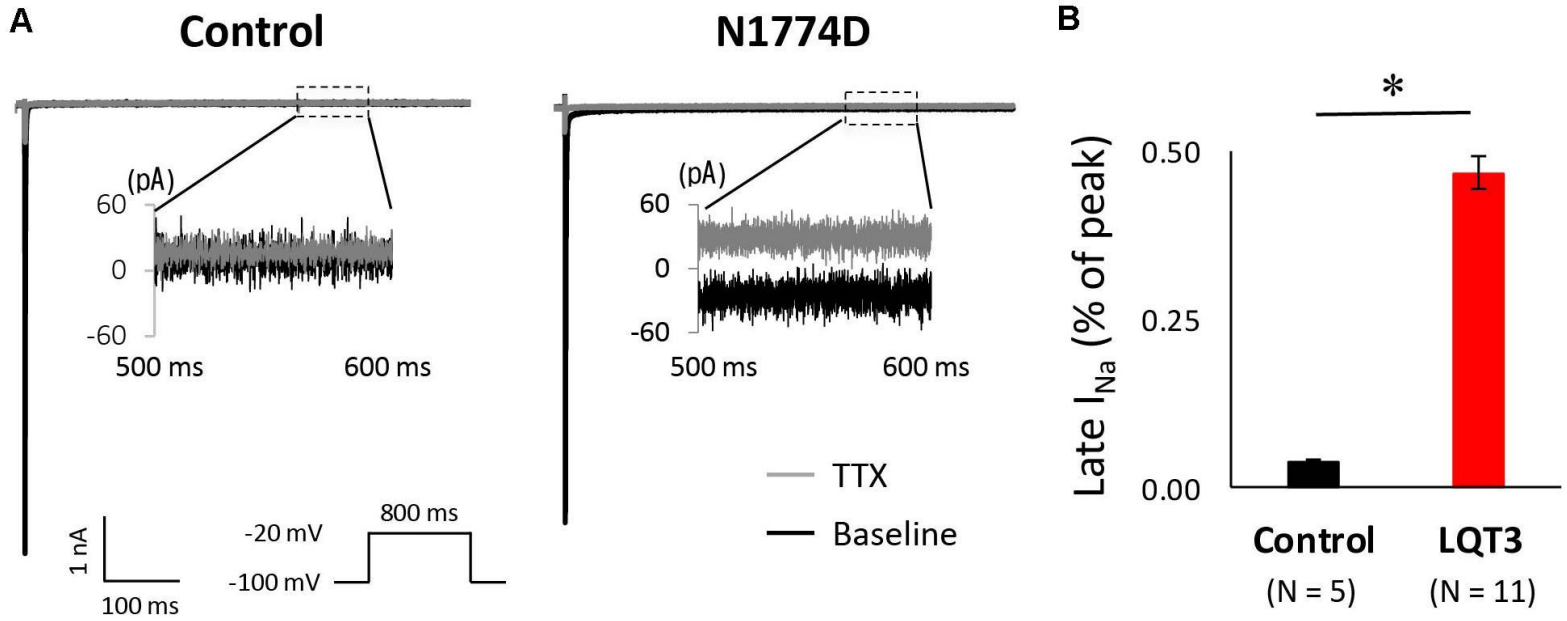
iPS derived cardiomyocytes from patients with N1774D



Propranolol is effective to shorten ac tion potentials only in iPS-CMs with N1774D



Late Na current is observed in iPS-CMs with N1774D

Hirose S, Ohno S, et al.: Frontiers in cell and developmental biology, 8:761,2020

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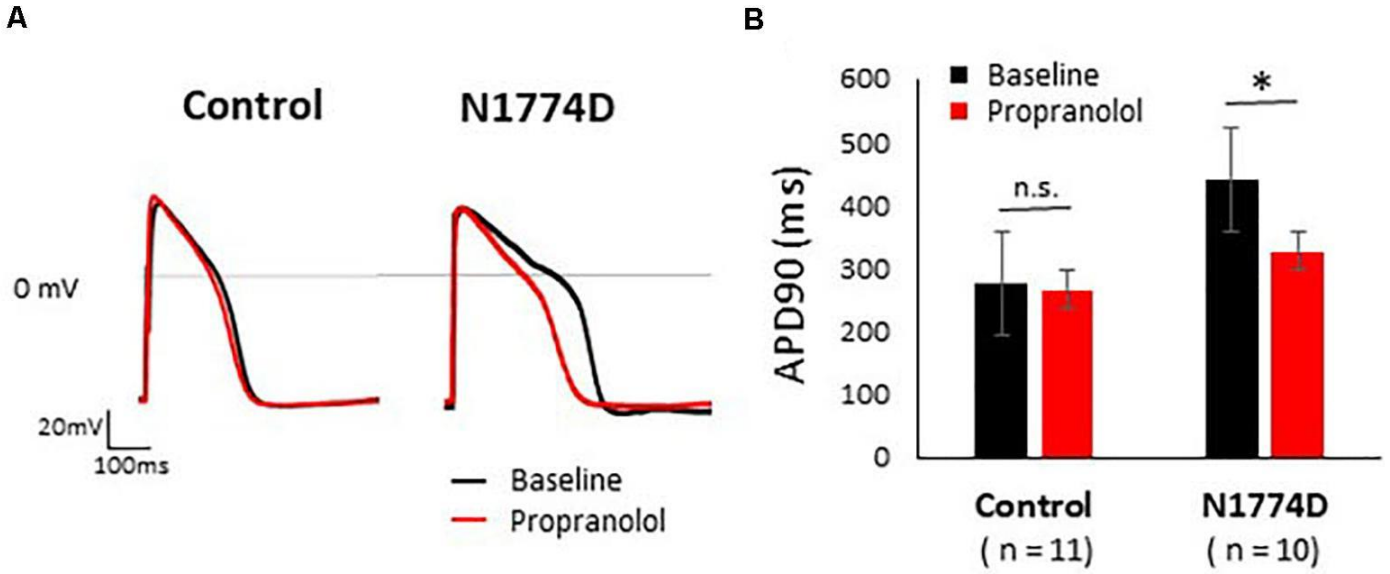

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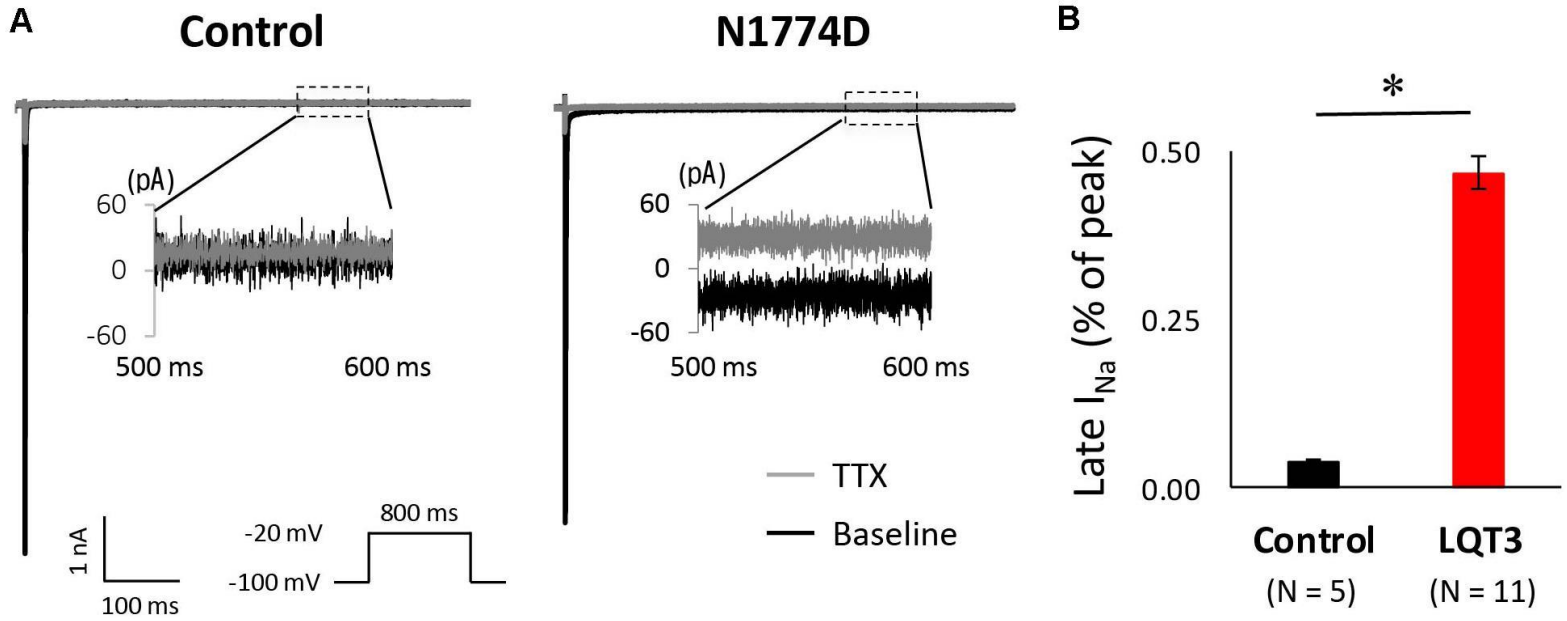

Late Na current is observed in iPS-CMs with N1774D

Hirose S, Ohno S, et al.: Frontiers in cell and developmental biology, 8:761,2020

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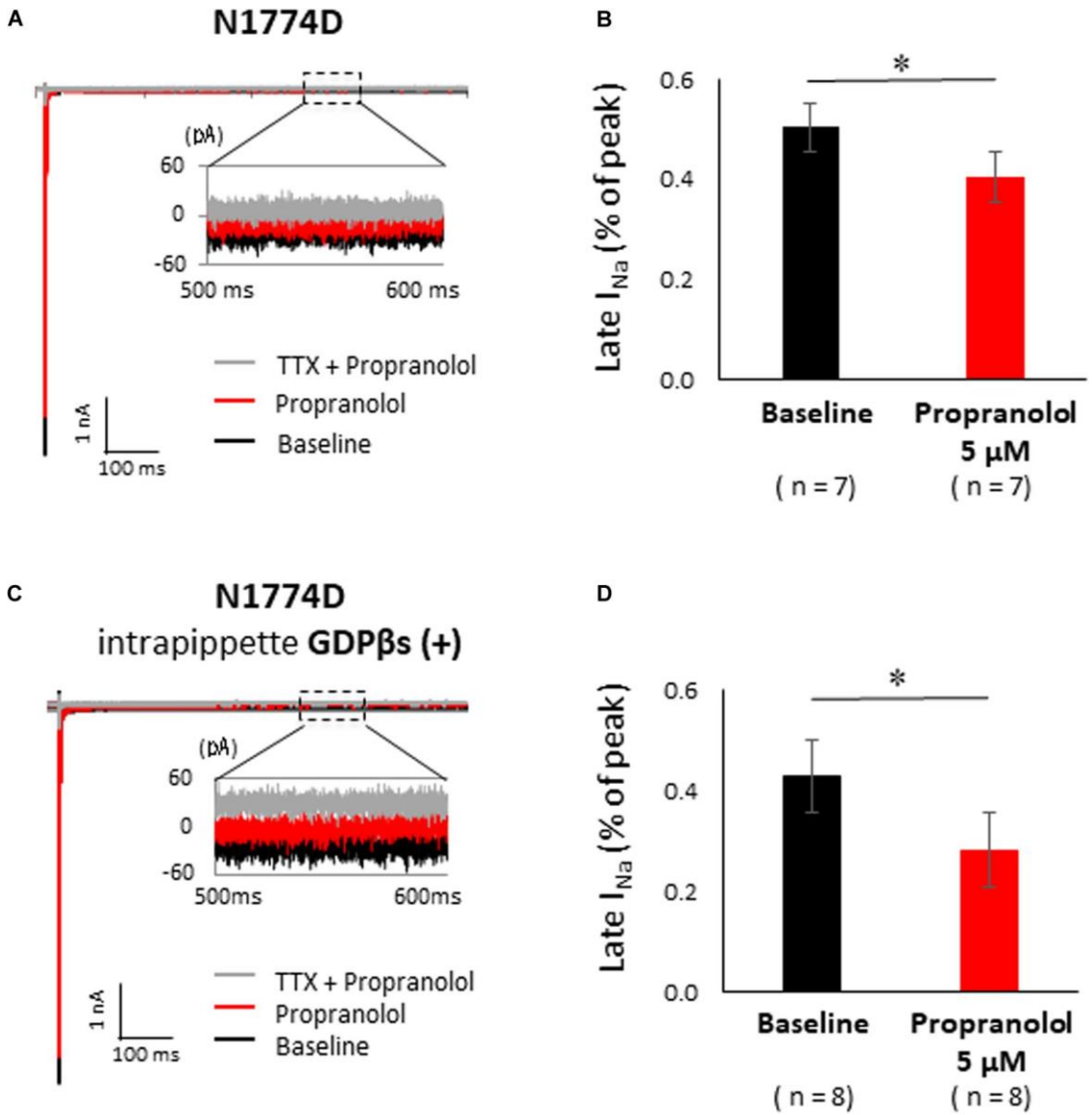
How does propranolol block late sodium current?



GDPβs: G protein inhibitor

Propranolol directly block late sodium current but not via G protein pathway.

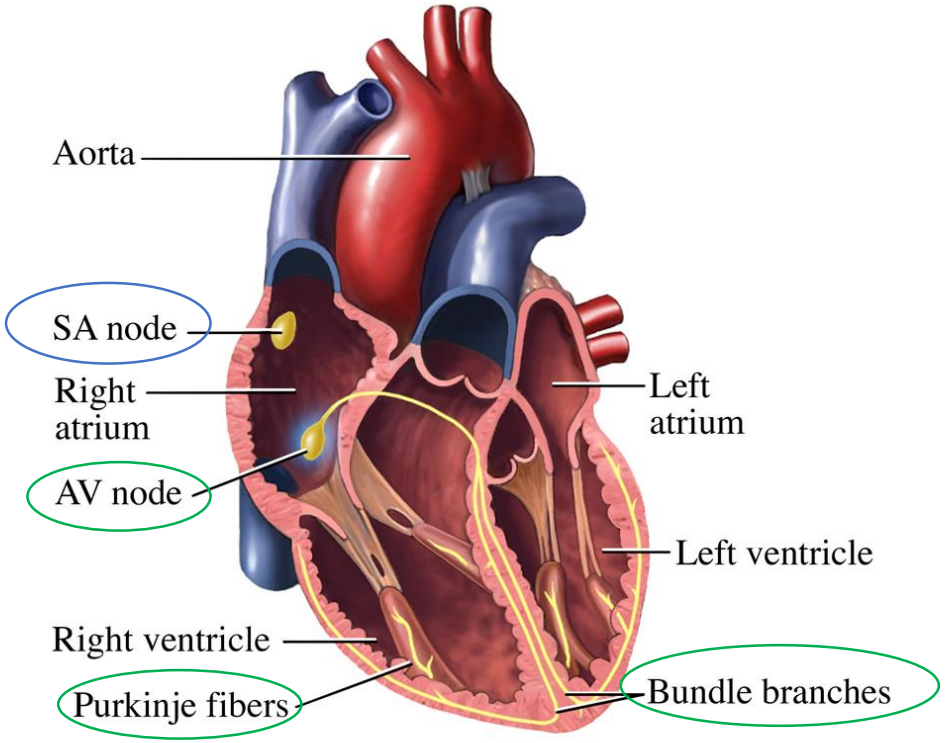
Hirose S, Ohno S, et al.: Frontiers in cell and developmental biology, 8:761,2020

SSS and PCCD

SSS Sinus bradycardia caused by dysfunction of sinus node

PCCD Progressive conduction block caused by fibrosis of conduction system

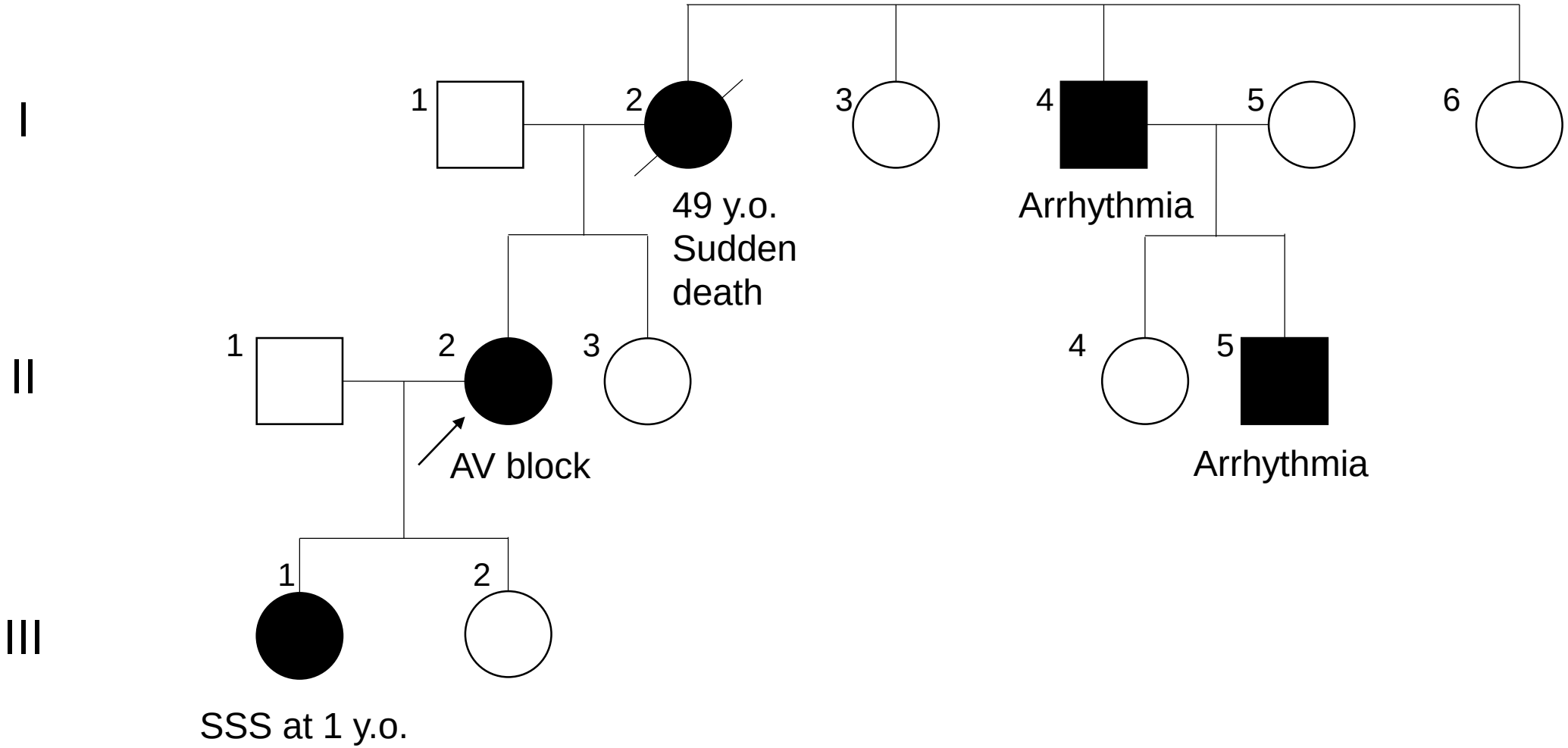
- ✓ Loss of function type of SCN5A variants are one of the causes of SSS and PCCD.
- ✓ One SCN5A variant sometimes cause both SSS and PCCD.
- ✓ Pacemaker implantation is required.
- ✓ In the family with Brugada syndrome, some members show only SSS or PCCD phenotype.



A family with SSS and PCCD

51-year-old female

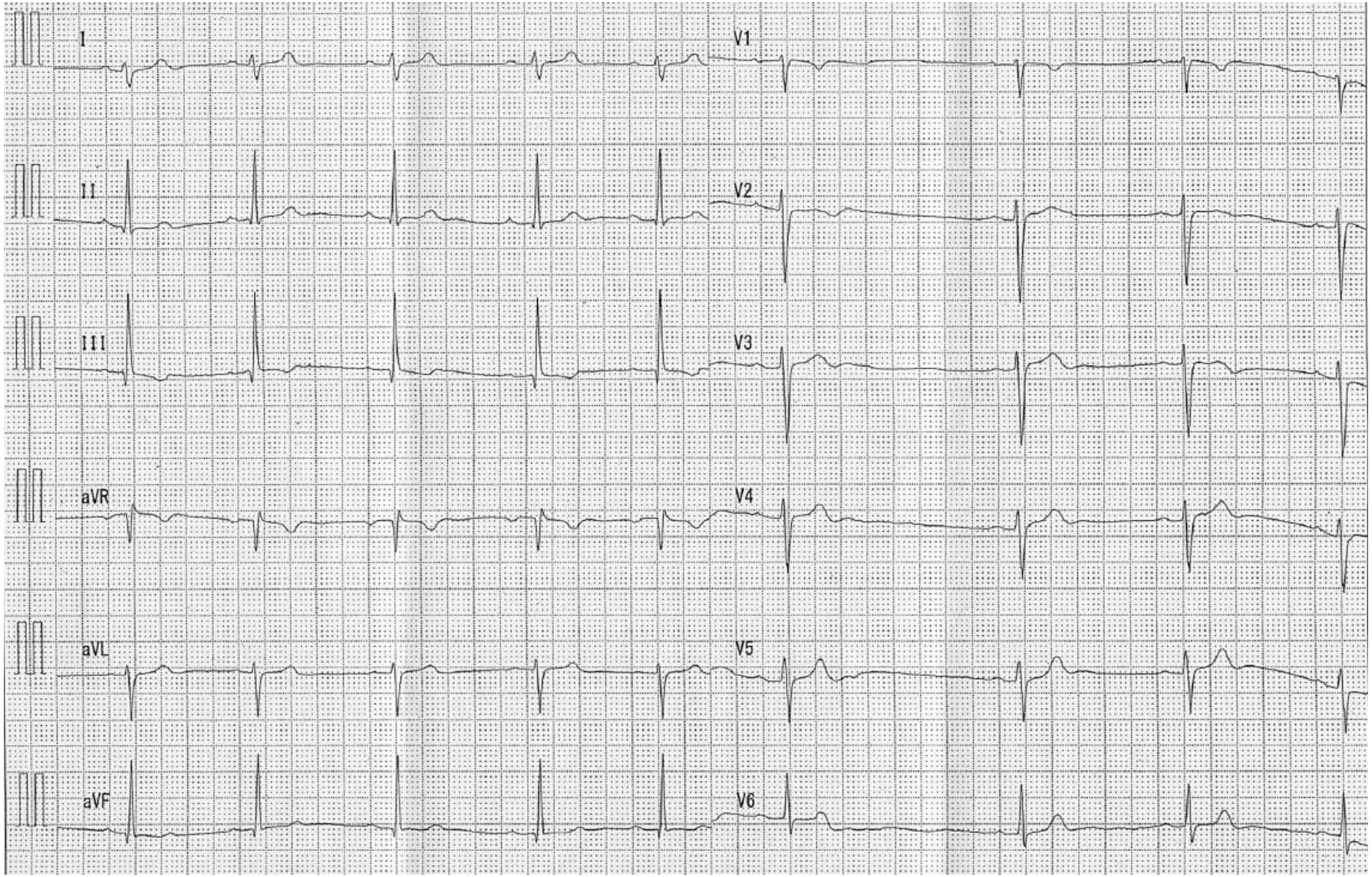
Pacemaker implantation for complete AV block at the age of 17.



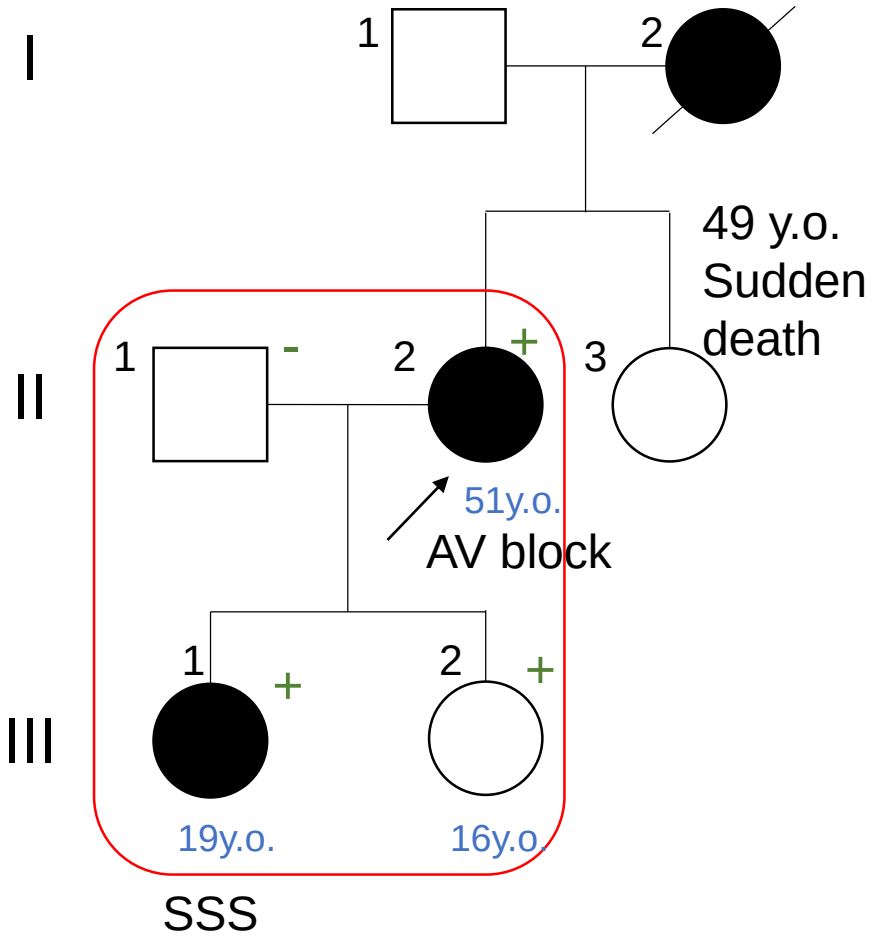
A family with PCCD

III-1 19 y.o.
Female

HR 51bpm
PR 220ms
QRS 110ms



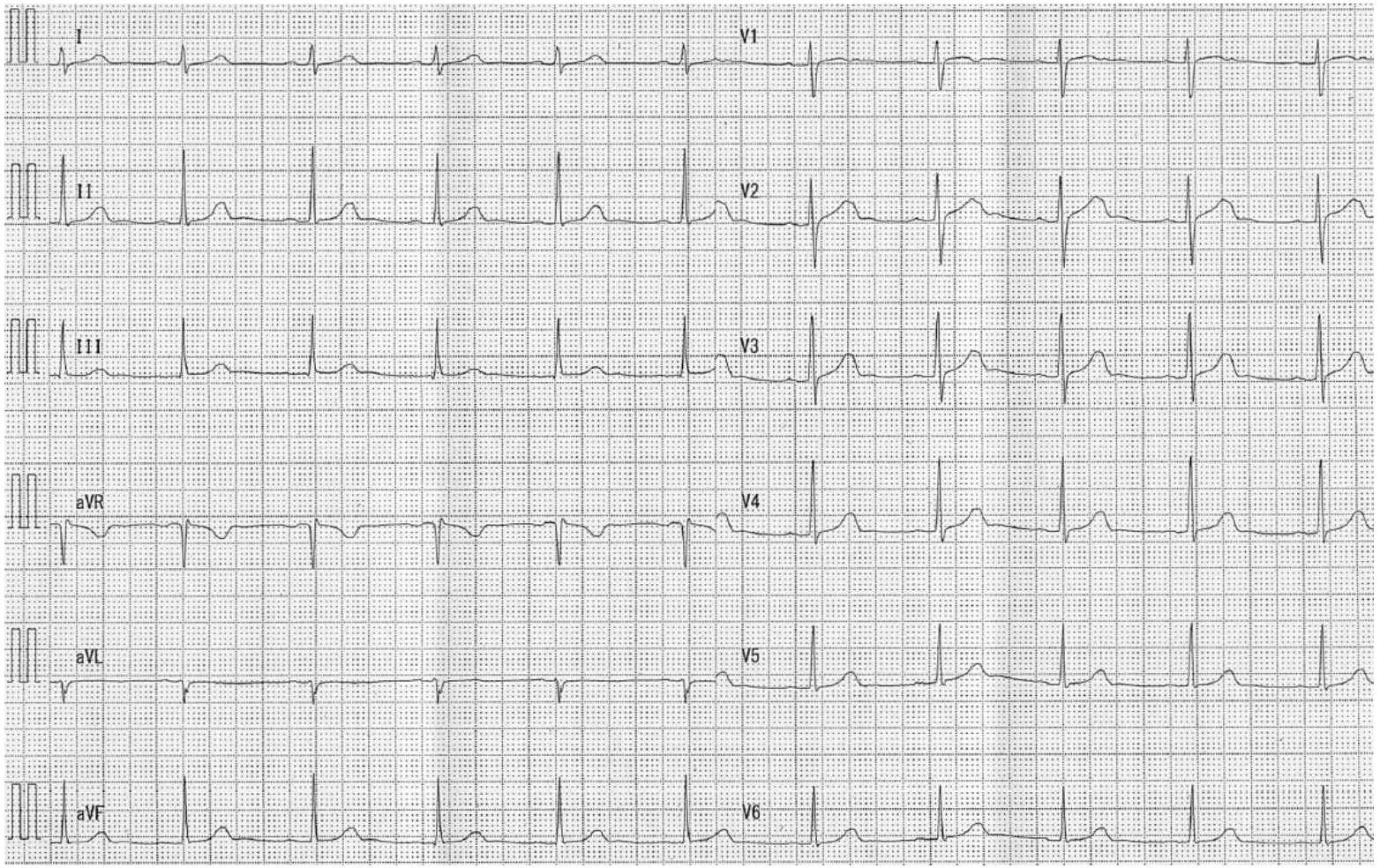
A family with PCCD



SCN5A c.5129 C>T, p.S1710L

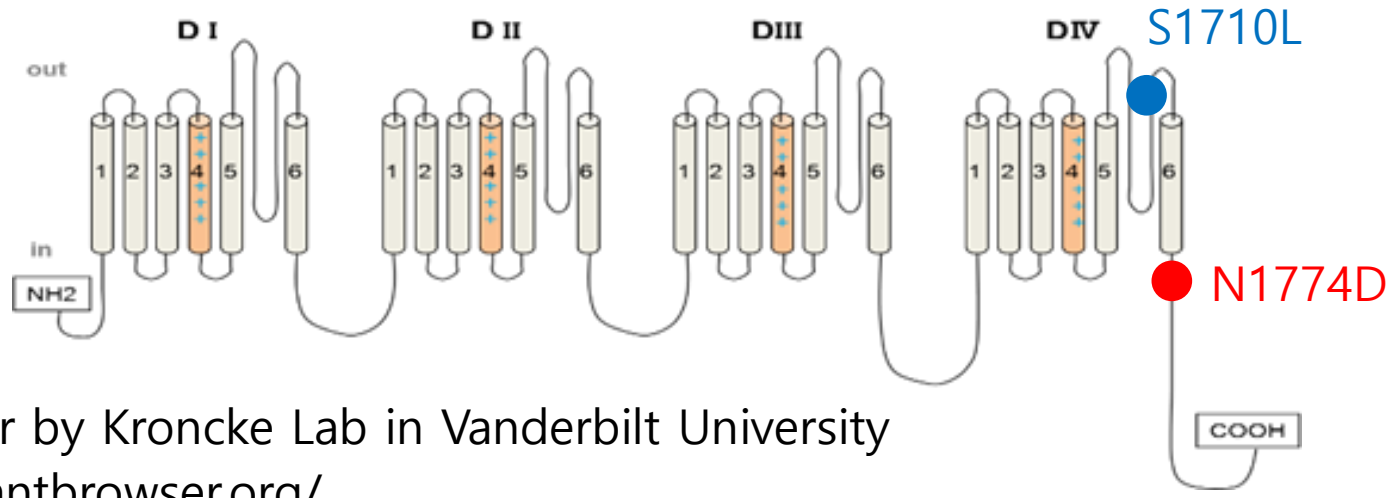
Loss of function type variant

III-2 HR 63bpm PR 180ms QRS 90ms



Sudden death of I-2 was suspected due to p.S1710L.

How to know the gain or loss of function in SCN5A variant?



Variant browser by Kroncke Lab in Vanderbilt University
https://variantbrowser.org/

A list of possible variants in KCNQ1, KCNH2 and SCN5A

N1774D

In Silico Data

PROVEAN	PolyPhen-2	BLAST-PSSM	REVEL	Penetrance Density BrS (%)	Penetrance Density LQT3 (%)
-4.62	0.998	-2.51	0.959	36	48

Functional Data

Peak and late/persistent current are relative to wildtype (100% being no different from wildtype). $V_{0.5}$ act/inact are the voltages at which half of the maximal current is reached during an activation and inactivation protocol, each is in units of mV and relative to wildtype.

PubMed ID	Year	Cell Type	Peak Current (%WT)	$V_{1/2}$ Act. (mV)	$V_{1/2}$ Inact. (mV)	Late/Persistent Current (%WT)
19996378	2010					
24112685	2014	CHO	216	-7.9	-0.9	170
30059973	2018					

S1710L

In Silico Data

PROVEAN	PolyPhen-2	BLAST-PSSM	REVEL	Penetrance Density BrS (%)	Penetrance Density LQT3 (%)
-5.55	1	-4.78	0.958	56	4

Functional Data

Peak and late/persistent current are relative to wildtype (100% being no different from wildtype). $V_{0.5}$ act/inact are the voltages at which half of the maximal current is reached during an activation and inactivation protocol, each is in units of mV and relative to wildtype.

PubMed ID	Year	Cell Type	Peak Current (%WT)	$V_{1/2}$ Act. (mV)	$V_{1/2}$ Inact. (mV)	Late/Persistent Current (%WT)
10940383	2000	HEK		17.7	-24.3	
19026623	2009					
26798387	2016					
30059973	2018					

Summary

- ✓ Various types of arrhythmias are caused by pathogenic variants in SCN5A.
- ✓ Gain of function type SCN5A variants cause LQT3.
- ✓ For the treatment of LQT3, β blockers are effective in addition to sodium channel blockers.
- ✓ Loss of function type SCN5A variants cause Brugada syndrome, SSS, PCCD and so on.
- ✓ In one family, phenotypes are sometimes different depending on the members.
- ✓ Functional changes of SCN5A variants can be searched in the database.

Brugada syndrome: A Translational Perspective

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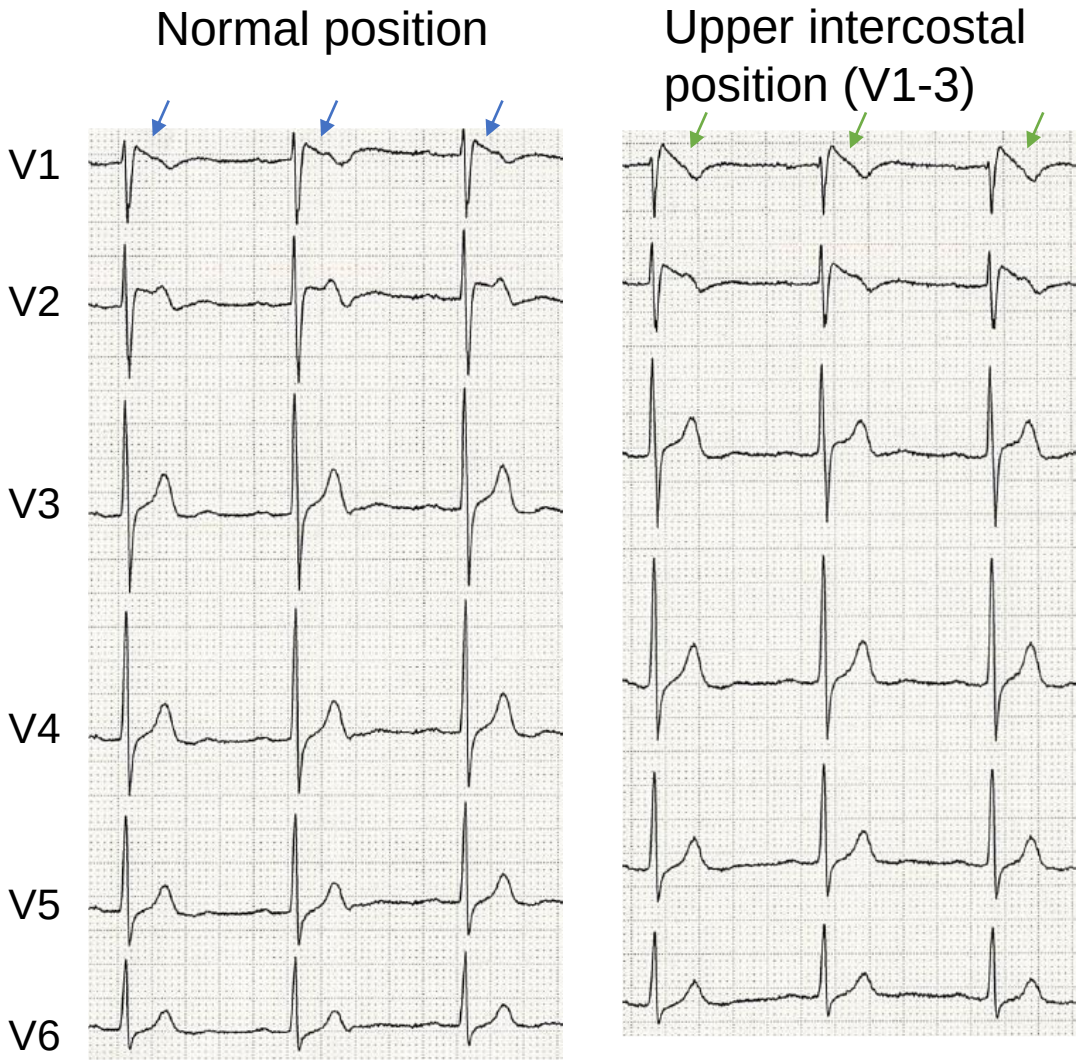
COI Disclosure

Seiko Ohno

The authors have no financial conflicts of interest to disclose concerning the presentation

What is Brugada syndrome?

- ✓ ST elevation in right precordial leads.
- ✓ One of the causes of sudden cardiac death due to ventricular fibrillation.
- ✓ Sudden cardiac death frequently occurred in adult male patients at night or early morning.
- ✓ Loss of function type SCN5A variants are identified in BrS patients.
- ✓ The variant detection rate is less than 20% in Asians
- ✓ The cardiac event rate in asymptomatic patients are around 0.5%/year.



Importance for Risk Stratification!

Brugada syndrome

Risk stratification

- ✓ SCN5A variants
- ✓ Brugada syndrome risk calculator

Pathogenesis of Brguada syndrome targeting for therapy

- ✓ Depolarization theory: conduction delay
- ✓ Repolarization theory: transmural dispersion

Diagnosis of Brugada syndrome

Shanghai Score

			Points
I.	ECG (12-Lead/Ambulatory)		
	A.	Spontaneous type 1 Brugada ECG pattern at	3.5
	B.	Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
	C.	Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
		*Only award points once for highest score within this category.	
		One item from this category must apply.	
II.	Clinical History*		
	A.	Unexplained cardiac arrest or documented VF/polymorphic VT	3
	B.	Nocturnal agonal respirations	2
	C.	Suspected arrhythmic syncope	2
	D.	Syncope of unclear mechanism/unclear etiology	1
	E.	Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
		*Only award points once for highest score within this category.	
III.	Family History		
	A.	First-or second-degree relative with definite BrS	2
	B.	Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second- degre e relative	1
	C.	Unexplained SCD <45 years in first- or second- degree relative with negative autopsy	0.5
		*Only award points once for highest score within this category.	
IV.	Genetic Test Result		
	A.	Probable pathogenic mutation in BrS susceptibility gene	0.5

Score
≥3.5 Probable/definite BrS
2~3 Possible BrS
<2 Non diagnostic

Antzelevitch C, et al.: Heart Rhythm, :e295-324,2016

Risk stratification of Brugada syndrome

415 (Male 403) Japanese Brugada syndrome

Univariate

	Hazard Ratio	95% CI	P value
History of ACA	6.6	3.9-11.0	<0.001
SCN5A mutation	2.1	1.1-3.8	0.020
History of Syncope (without ACA)	2.1	0.9-4.7	0.080
Male	1.4	0.2-10.3	0.722
ICD implantation	8.5	3.4-21.2	<0.001
Induced VF by EPS	1.7	1.0-3.0	0.058
Family history of SCD	1.1	0.6-2.2	0.769
Spontaneous type1 ECG	1.3	0.7-2.4	0.332
Documented AF	1.8	1.0-3.3	0.043
Late potential positive	1.5	0.8-3.0	0.249
P II ≥ 120ms	2.7	1.5-4.8	0.001
QRS V2 ≥ 120ms	2.4	1.3-4.3	0.005

Multivariate (without ICD)

	Hazard Ratio	95% CI	P value
History of ACA	6.5	3.8-11.0	<0.001
SCN5A mutation	2.0	1.0-3.8	0.045
QRS V2 ≥ 120ms	1.4	0.8-2.7	0.268
Documented AF	1.0	0.5-1.8	0.895

Detection of pathogenic SCN5A variants are useful for the risk stratification of Brugada syndrome

Yamagata K, Ohno S, et al.: Circulation, 135:2255-2270,2017

Variant of Unknown Significance: VUS

Classification of genetic variants

Pathogenic

Likely Pathogenic

VUS

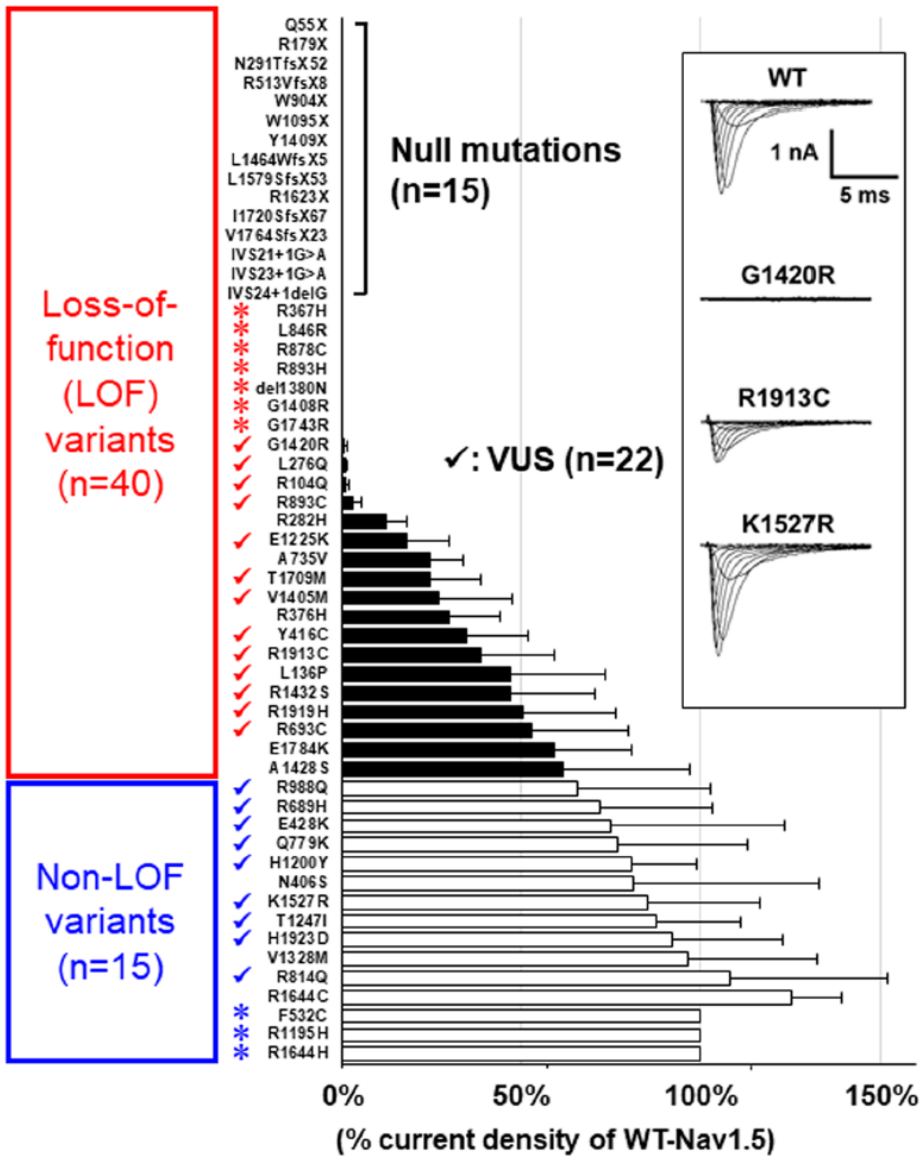
Likely Benign

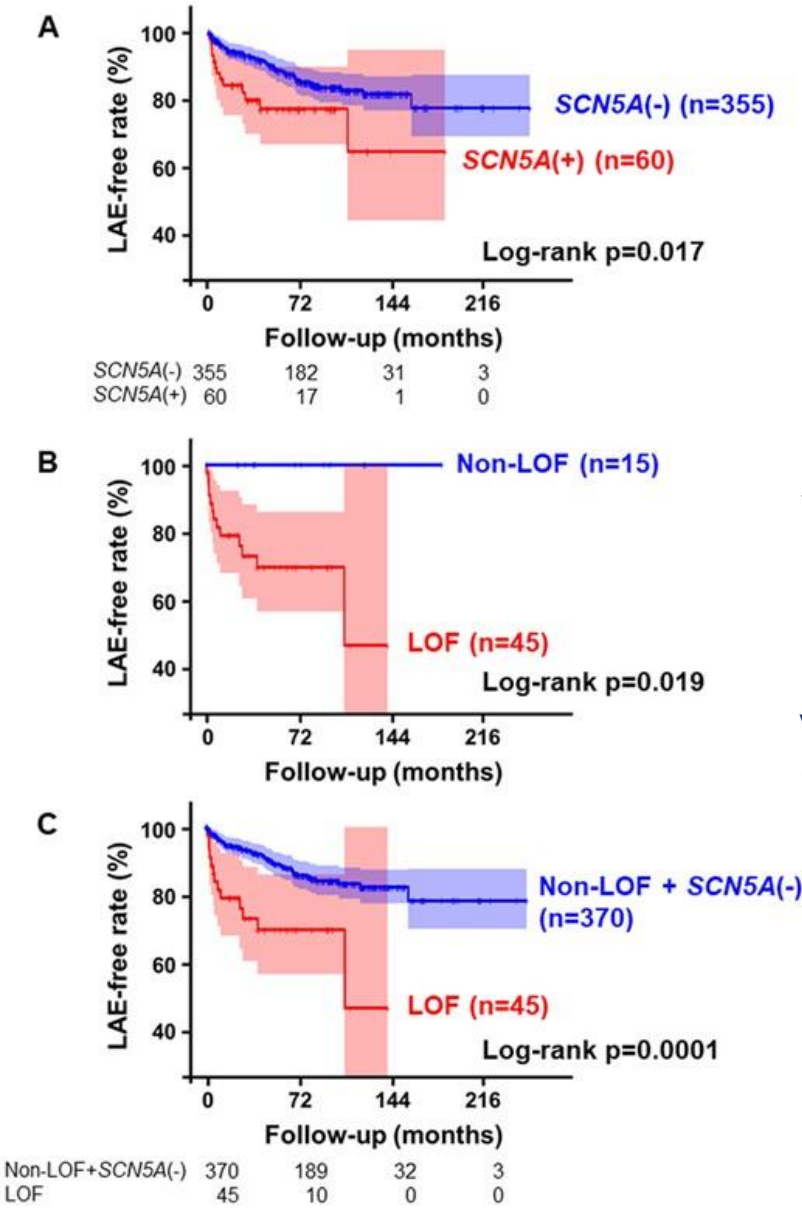
Benign

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Richards S, et al.: Genet Med, 17:405-424,2015

Risk stratification by SCN5A variants





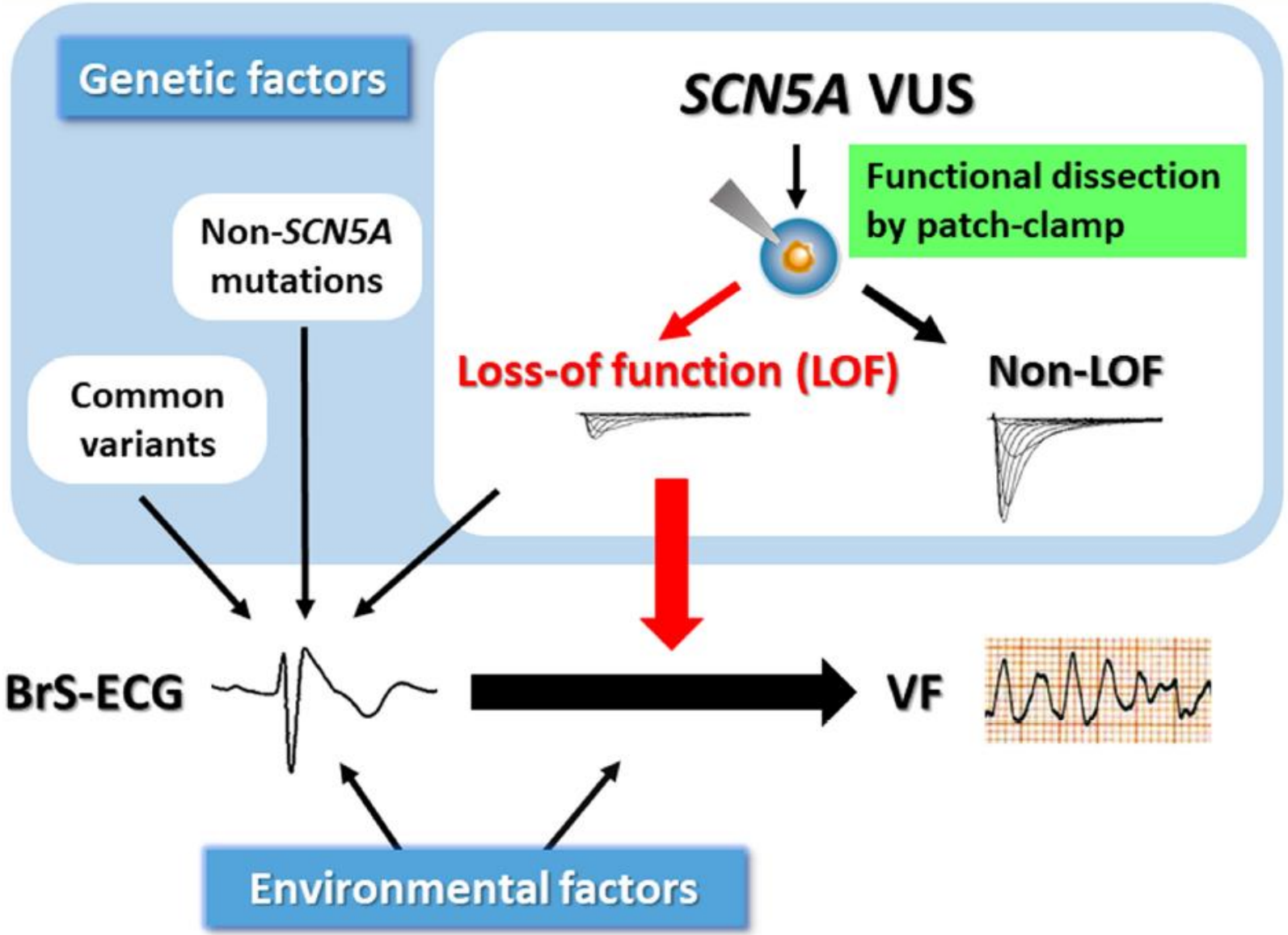
Higher risk of LAE in BrS patients with LOF SCN5A variants

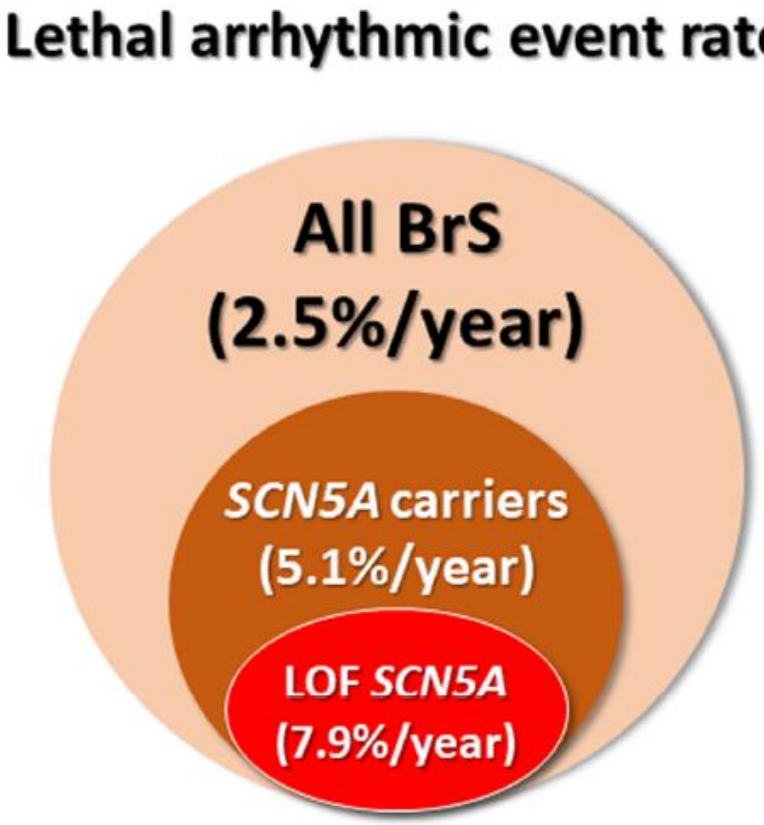
Importance of the variant evaluation for pathogenesis

Ishikawa T, Ohno S, Makita N, et al.: Eur Heart J, 42:2854-2863,2021

KHRS 2023

Risk stratification by SCN5A variants





Ishikawa T, Ohno S, Makita N, et al.: Eur Heart J, 42:2854-2863,2021

Brugada syndrome risk calculator

- ✓ 1100 (male 790) BrS patients without history of aborted cardiac arrest from 8 European countries.

(South 20 (1.8%) and East 16 (1.4%) Asians)

- ✓ Mean age at registration was 51.8 ± 13.6.
- ✓ Mean follow-up time was 5.33 ± 4.0 years.
- ✓ 103 (9.3%) patients had VA, and 11 (1%) suffered sudden cardiac death.

	VA/SCD (n = 114)	No VA/SCD (n = 996)	p Value
Age at diagnosis, yrs	43.2 ± 16.0	43.7 ± 13.4	0.85
Male	86 (75.4)	704 (70.7)	0.44
Probable arrhythmia–related syncope	67 (58.8)	137 (13.8)	<0.001
Diagnosis by family screening of SCD	13 (11.4)	40 (4.1)	0.002
Spontaneous type 1 Brugada ECG pattern	89 (78.1)	299 (30.0)	<0.001
Genetic testing	74 (64.9)	657 (66.0)	0.75
SCN5A mutation	21 (28.4)	154 (23.4)	0.39
Programmed ventricular stimulation	52 (45.6)	350 (35.1)	0.04
Inducible polymorphic VT or VF	23 (44.2)	105 (30.0)	0.06
VERP assessment	55 (48.2)	359 (36.0)	0.02
VERP <200 ms	11 (20.0)	77 (21.4)	1
SND	3 (2.6)	25 (2.5)	1
AF/atrial flutter	8 (7.0)	71 (7.1)	1
aVR sign	25 (21.9)	134 (13.5)	0.02
Significant S-wave in lead I	33 (28.9)	261 (26.2)	0.58
QRS duration >120 ms in V2	17 (14.9)	105 (10.5)	0.21
QRS fragmentation	12 (10.5)	88 (8.8)	0.6
Type 1 Brugada ECG pattern in peripheral leads	42 (36.8)	31 (3.1)	<0.001
ER	43 (37.7)	72 (7.2)	<0.001
Persistent ER	38 (88.4)	39 (54.2)	<0.001
Follow-up, yrs	6.7 ± 4.0	6.1 ± 4.0	0.11

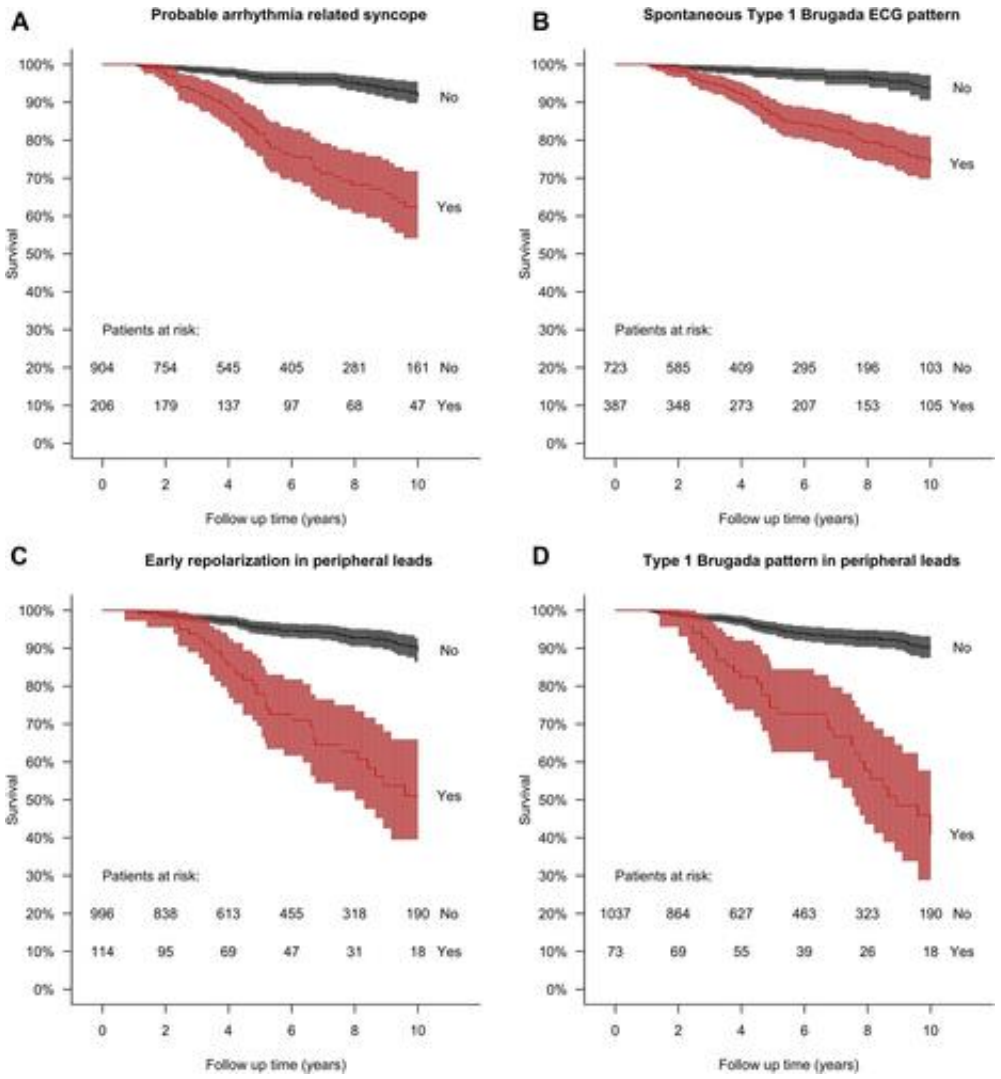
Honarbakhsh S, et al.: JACC. Clinical electrophysiology, 7:210-222,2021

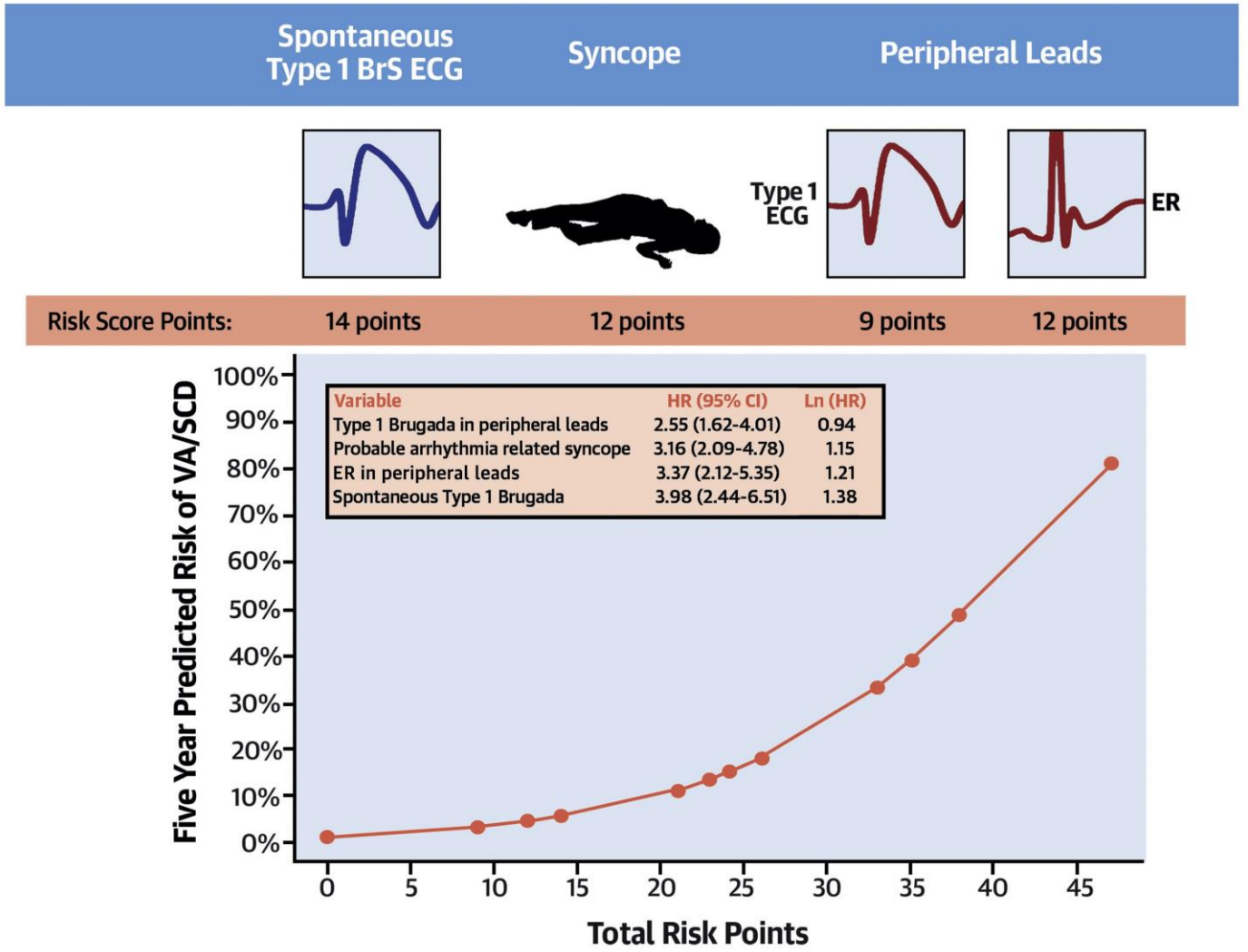
Brugada syndrome risk calculator

	Separate Univariate Models			Multivariate Model				
	HR	95% CI	p Value	HR	95% CI	p Value	Log(HR)	Score
Age at diagnosis	1	0.99–1.01	0.9					
Male	0.99	0.64–1.51	0.95					
Probable arrhythmia–related syncope	5.92	4.05–8.63	<0.001	3.71	2.41–5.70	<0.001	1.15	12
Diagnosis by family screening of SCD	3.31	1.85–5.91	<0.001	4.56	2.39–8.71	<0.001		
Spontaneous type 1 Brugada ECG pattern	5.93	3.71–9.48	<0.001	3.8	2.31–6.24	<0.001	1.38	14
SCN5A mutation	1.19	0.71–1.99	0.52					
Induced VT/VF by EPS	1.46	0.83–2.54	0.19					
VERp <200 ms	0.88	0.42–1.86	0.74					
SND	1.01	0.32–3.20	0.99					
AF/atrial flutter	0.91	0.44–1.86	0.79					
ER in peripheral leads	6.07	4.12–8.94	<0.001	3.42	2.17–5.41	<0.001	1.21	9
Type 1 Brugada ECG pattern in peripheral leads	6.86	4.69–10.04	<0.001	2.33	1.48–3.67	<0.001	0.94	12
aVR sign	1.62	1.04–2.52	0.03					
Significant S-wave in lead I	1.25	0.84–1.87	0.27					
QRS interval >120 ms in V2	1.26	0.75–2.11	0.39					
QRS fragmentation	1.09	0.61–1.95	0.77					

Honarbakhsh S, et al.: JACC. Clinical electrophysiology, 7:210-222,2021

Brugada syndrome risk calculator





Further study is needed for Asians.

Honarbakhsh S, et al.: JACC. Clinical electrophysiology, 7:210-222,2021

Pathogenesis of Brugada syndrome targeting for therapy

Brugada syndrome patients with ventricular septal defect

The Cohort in This Study

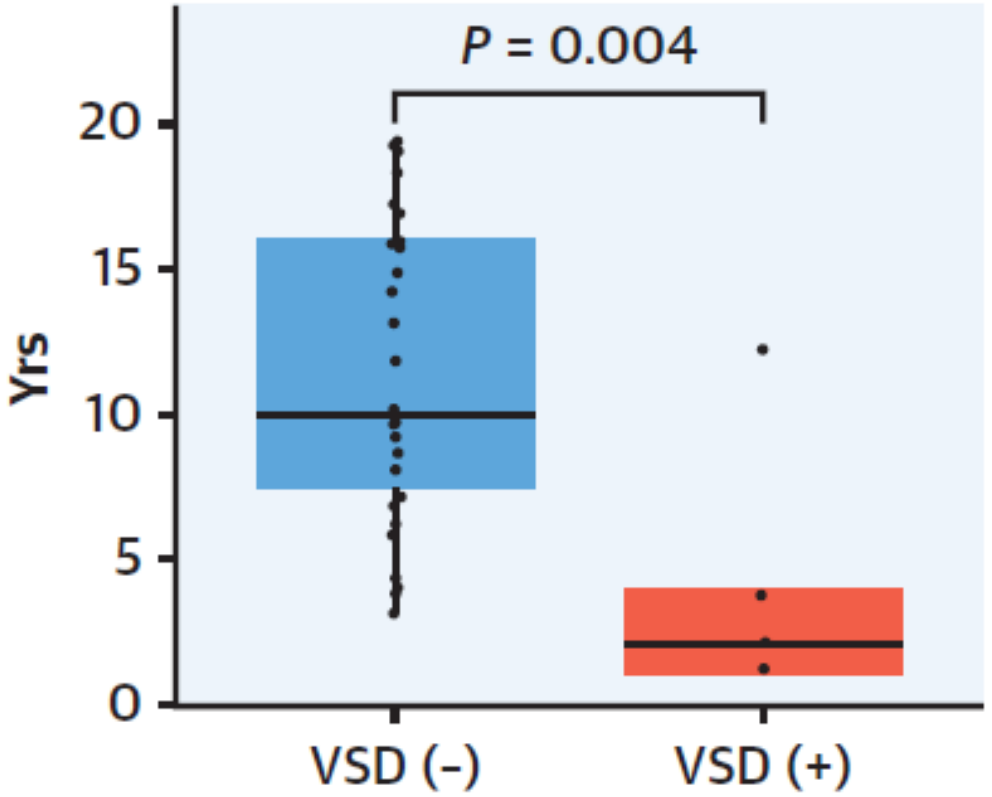
Young Brugada syndrome patients
N = 36

<20-year-old

SCN5A variant carriers
N = 15

Ventricular Septal Defect
N = 5

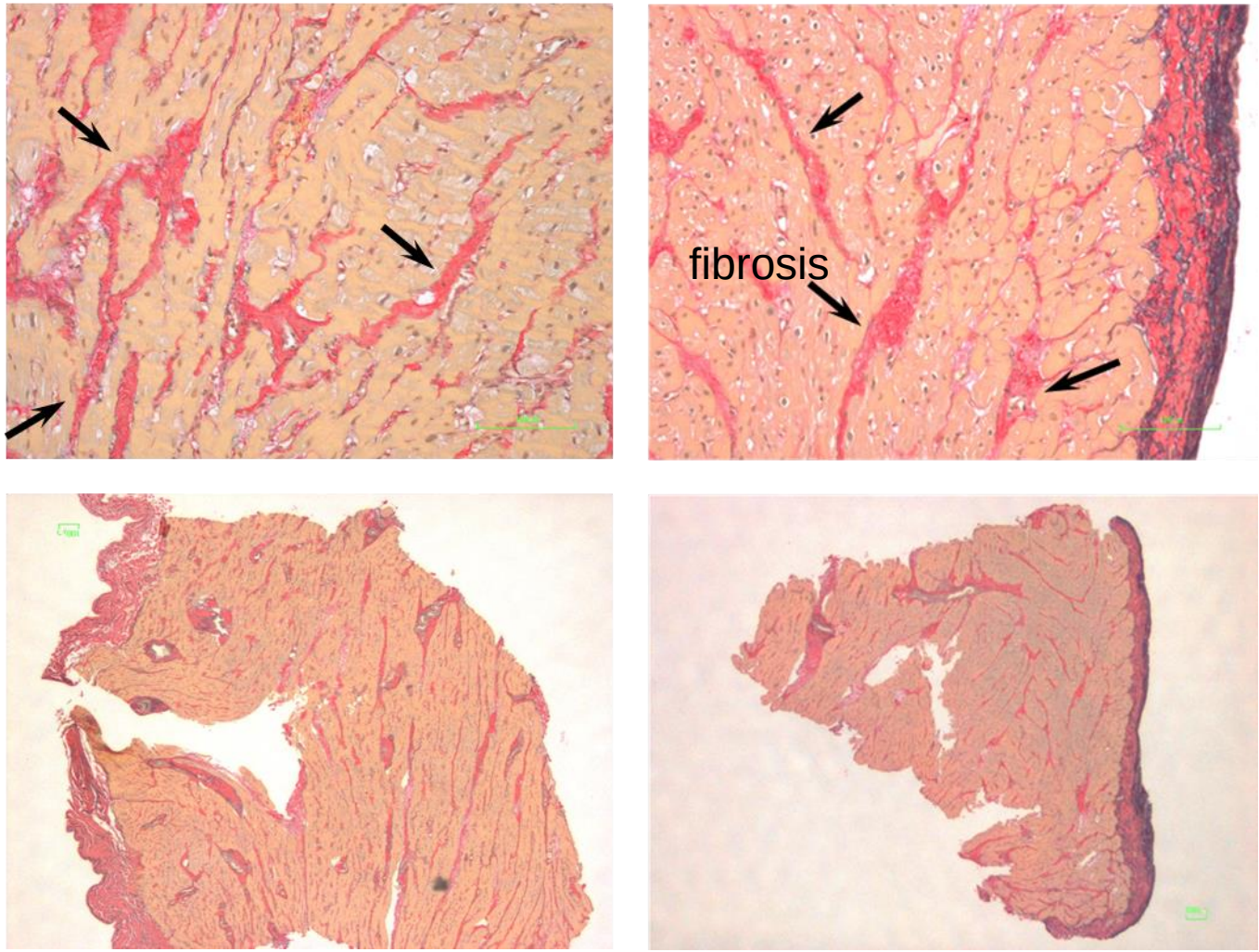
Age at Diagnosis of Brugada Syndrome



Suzuki K, Ohno S, et al.: JACC. Clinical electrophysiology, 8:297-305,2022

Pathogenesis of Brugada syndrome targeting for therapy

Fibrosis and conduction delay in Brugada syndrome patients

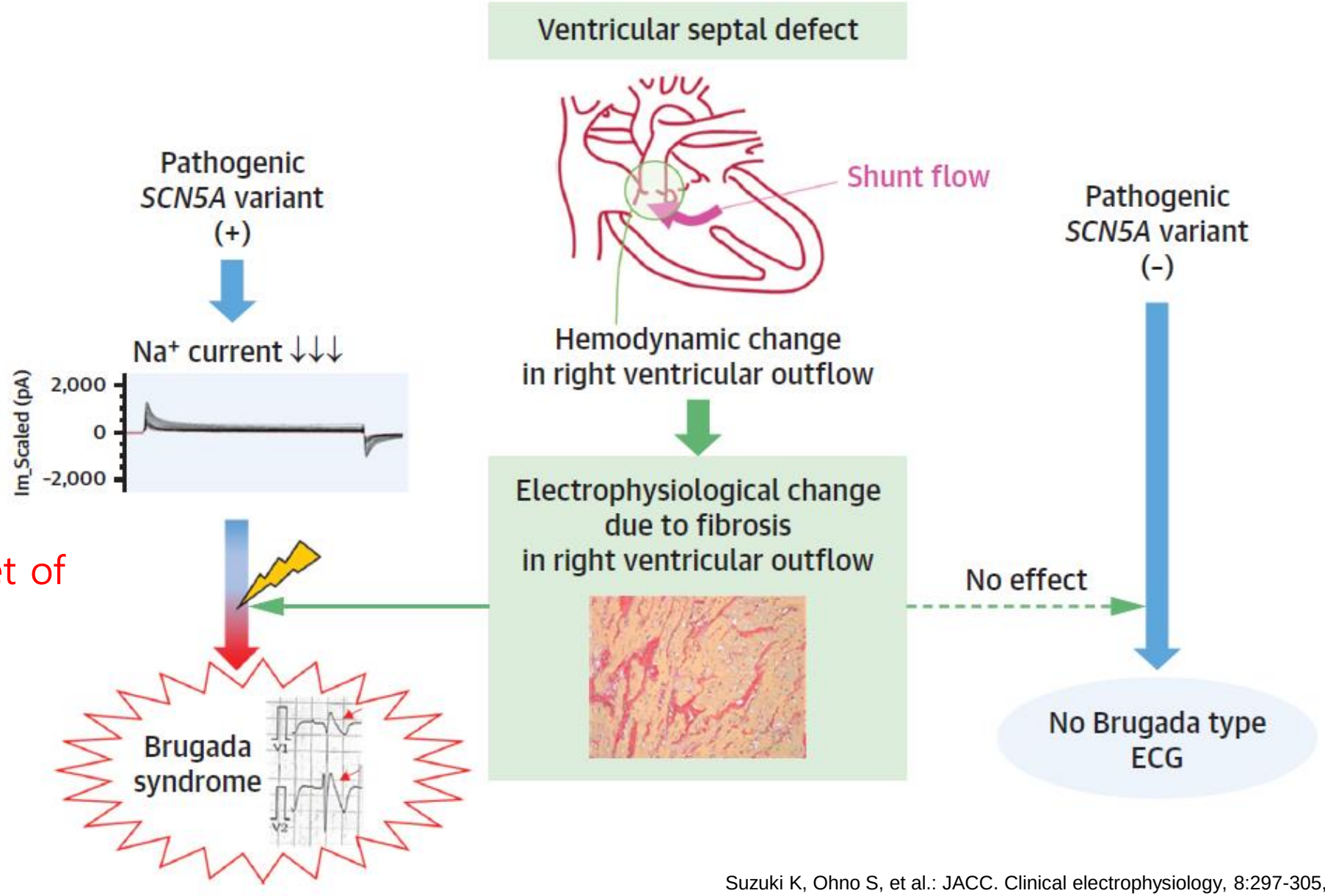


Cardiac fibrosis in the specimen obtained from 2-year-old Brugada syndrome patient with VSD

Elastica van Gieson staining.

Suzuki K, Ohno S, et al.: JACC. Clinical electrophysiology, 8:297-305,2022

Brugada syndrome patients with ventricular septal defect



Early onset of Brugada syndrome

Suzuki K, Ohno S, et al.: JACC. Clinical electrophysiology, 8:297-305,2022

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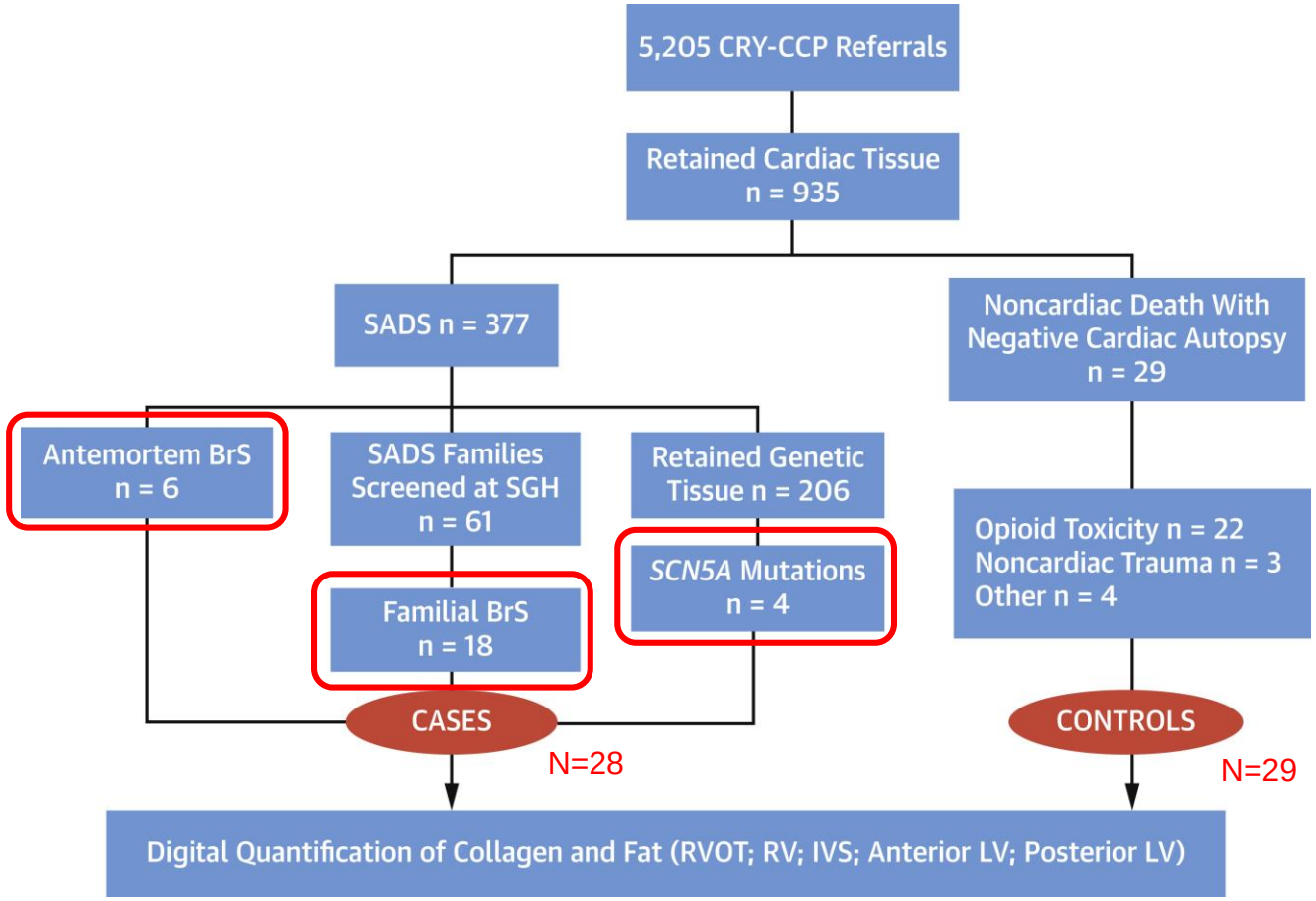
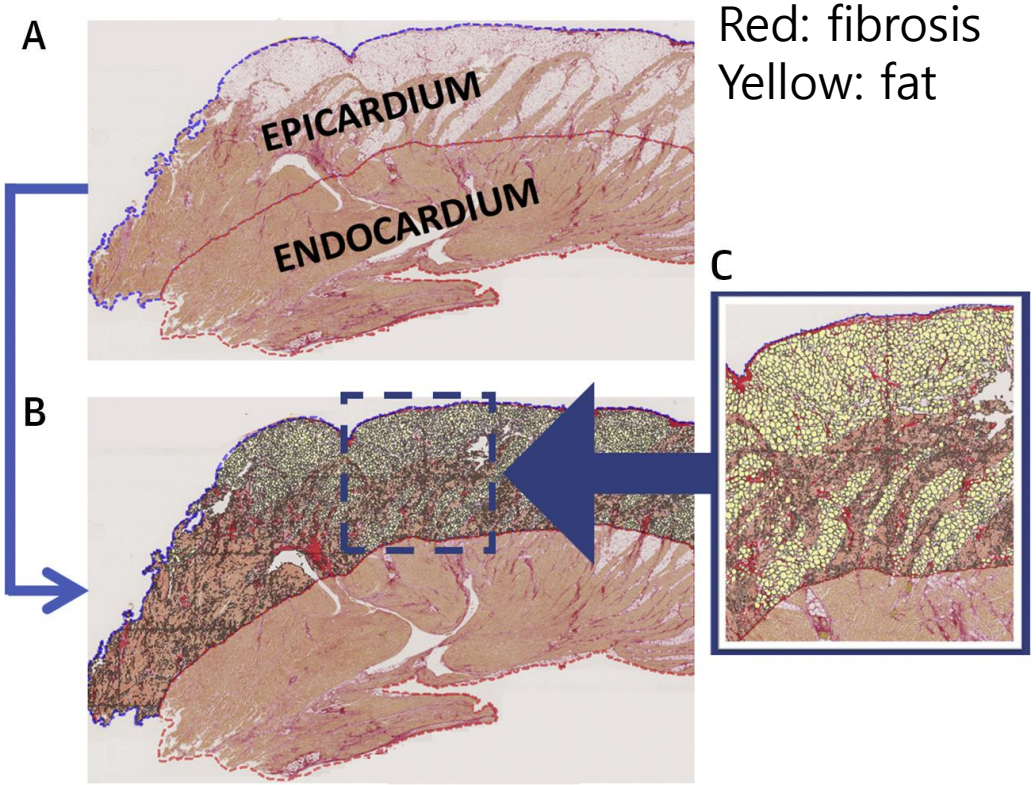
Cardiac fibrosis in Brugada syndrome patients



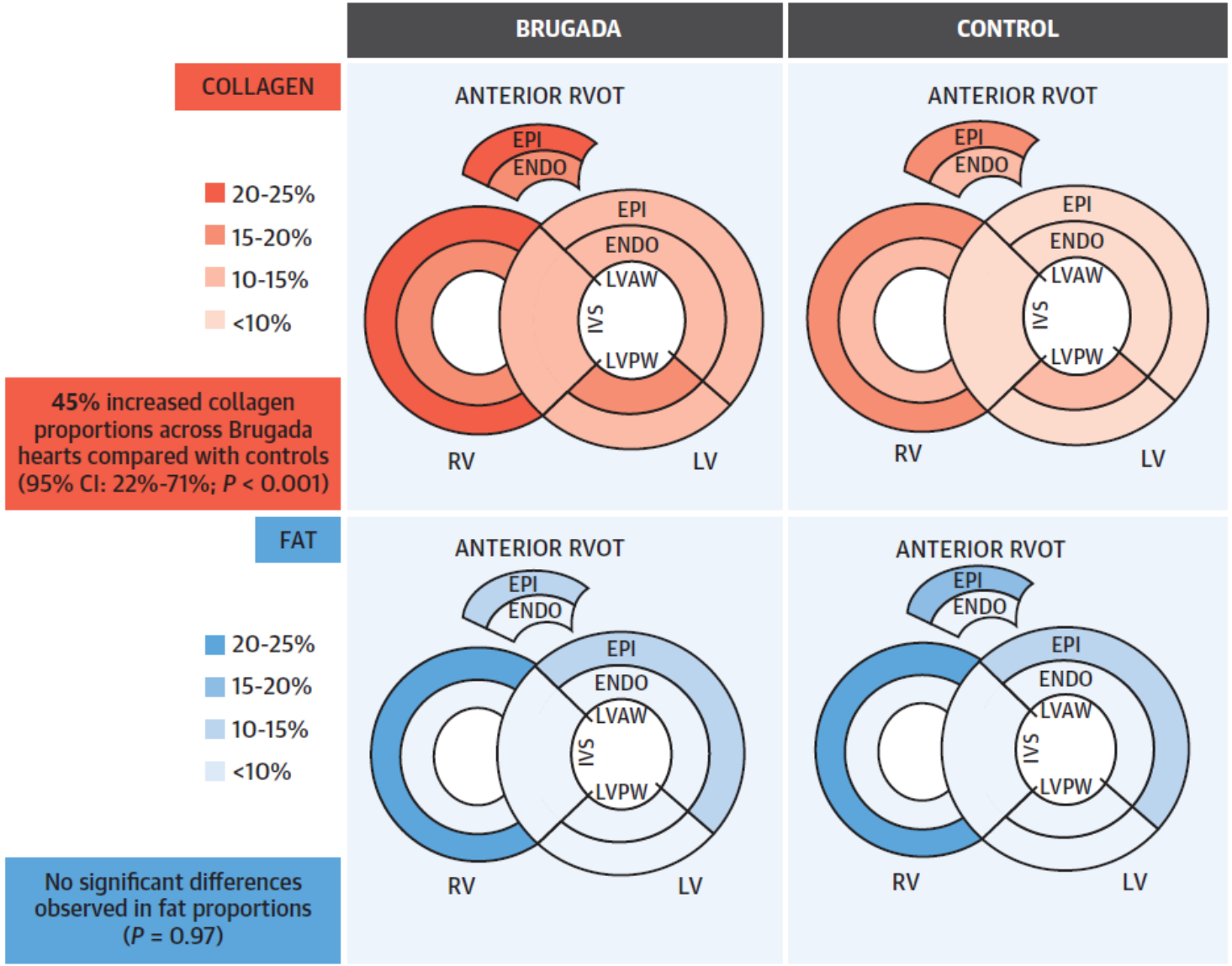


Cardiac Risk in the Young Centre for Cardiac Pathology (CRY-CCP)

Miles C, et al.: J Am Coll Cardiol, 78:1511-1521,2021

KHRS 2023

Cardiac fibrosis in Brugada syndrome patients

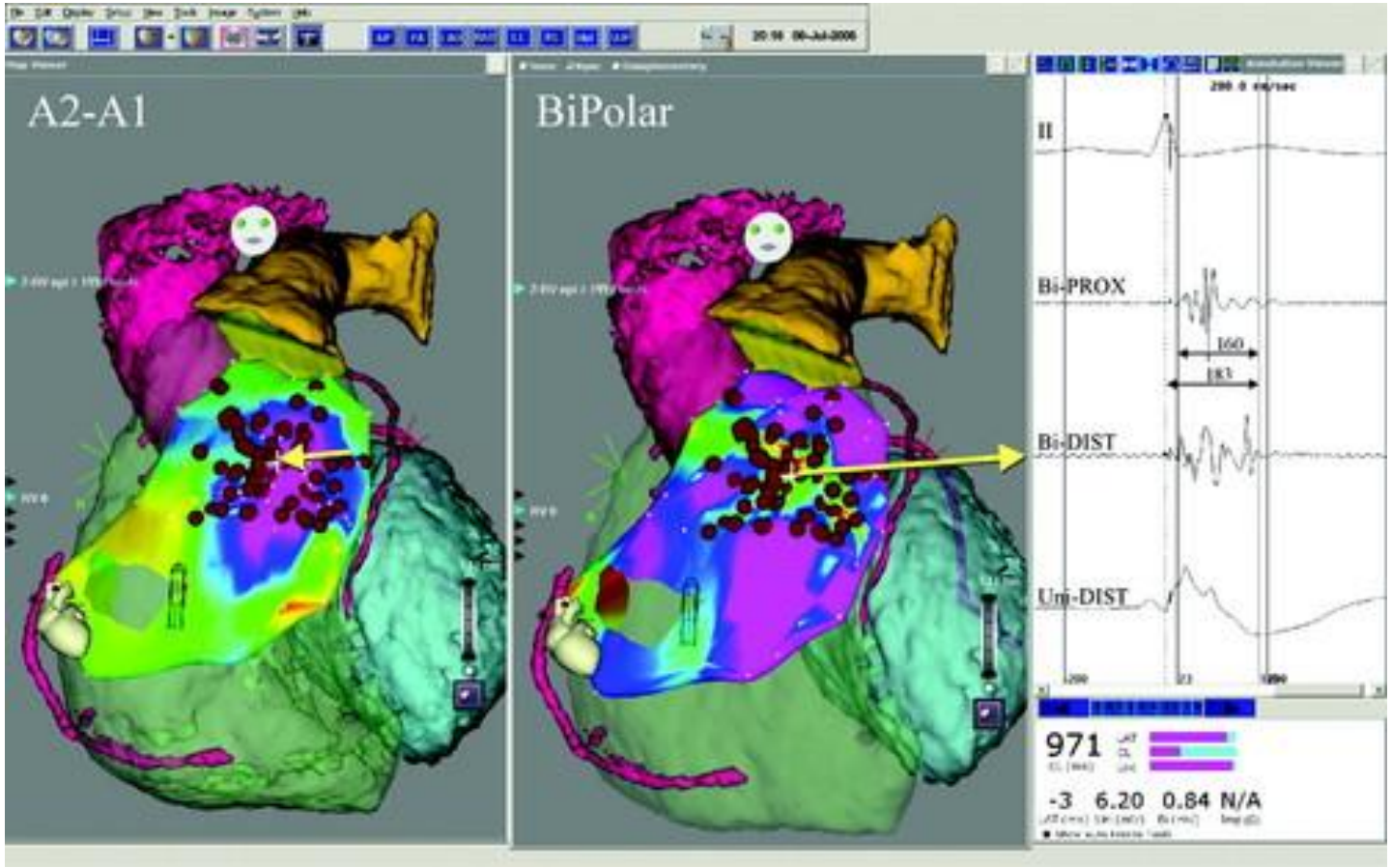


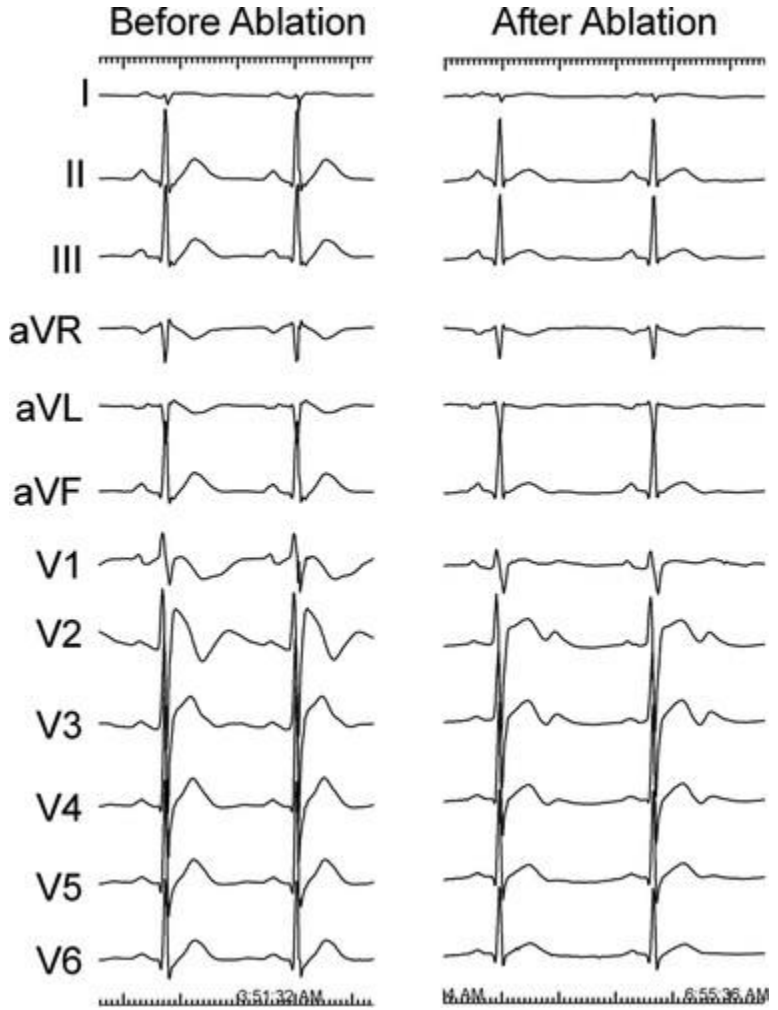
Brugada syndrome is associated with increased collagen content throughout right and left ventricular myocardium

Miles C, et al.: J Am Coll Cardiol, 78:1511-1521,2021

KHRS 2023

Ablation therapy for Brugada syndrome

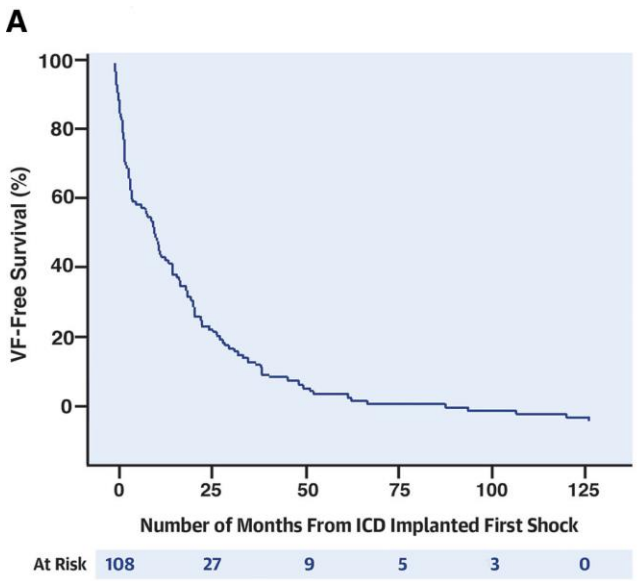


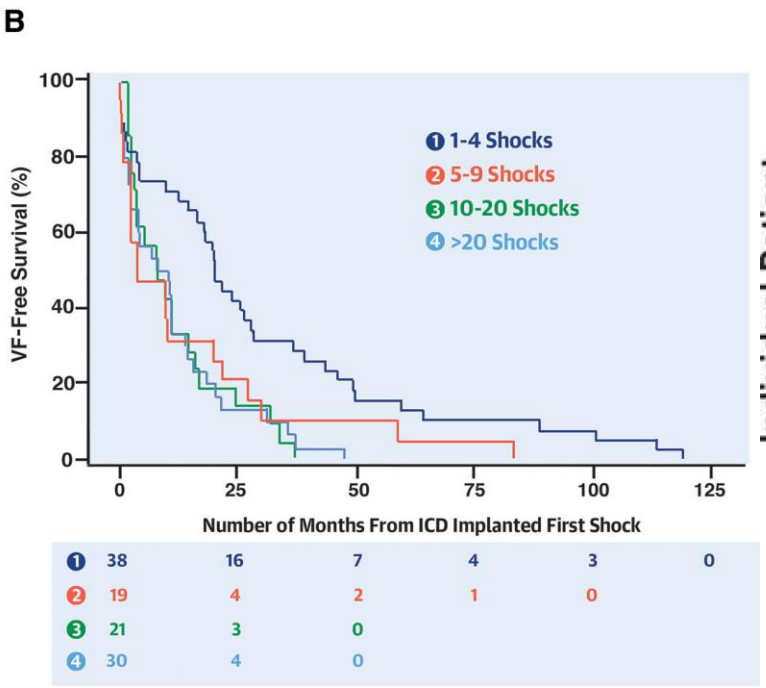


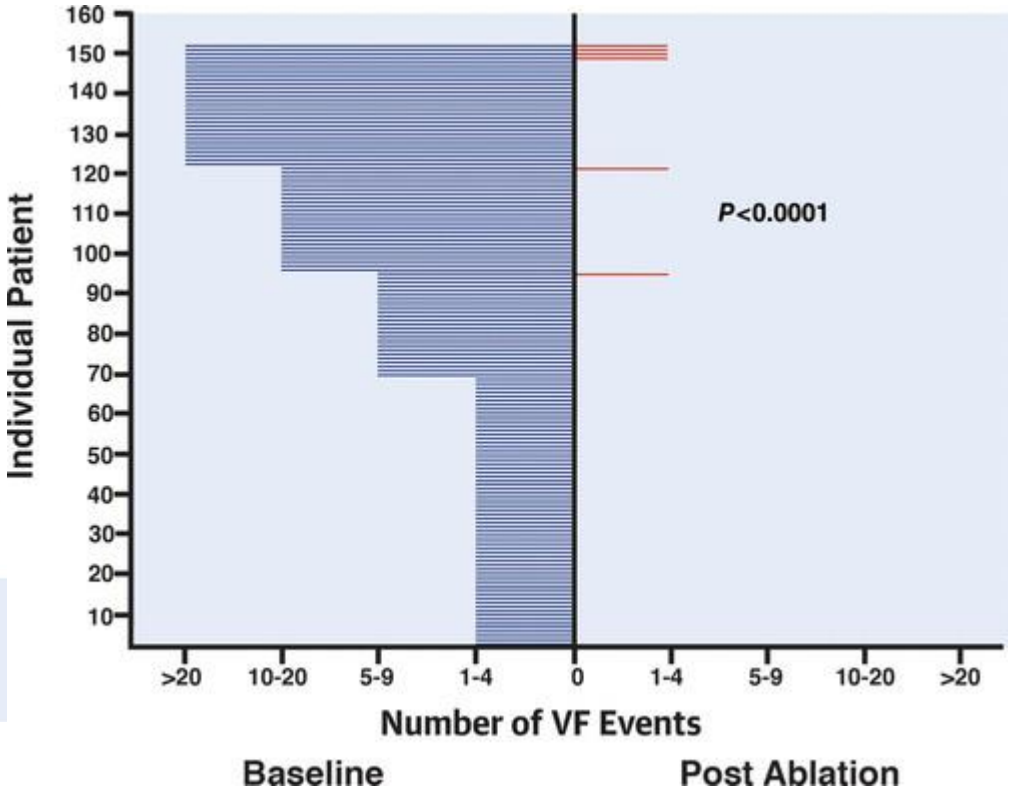
Nademanee K, et al.: Circulation, 123:1270-1279,2011

Epicardial ablation therapy for BrS: BRAVO

159 symptomatic Brugada paitents (156 male, median age 42) from Asia, Europe and North America.
125 aborted cardiac arrest,
34 arrhythmogenic syncope





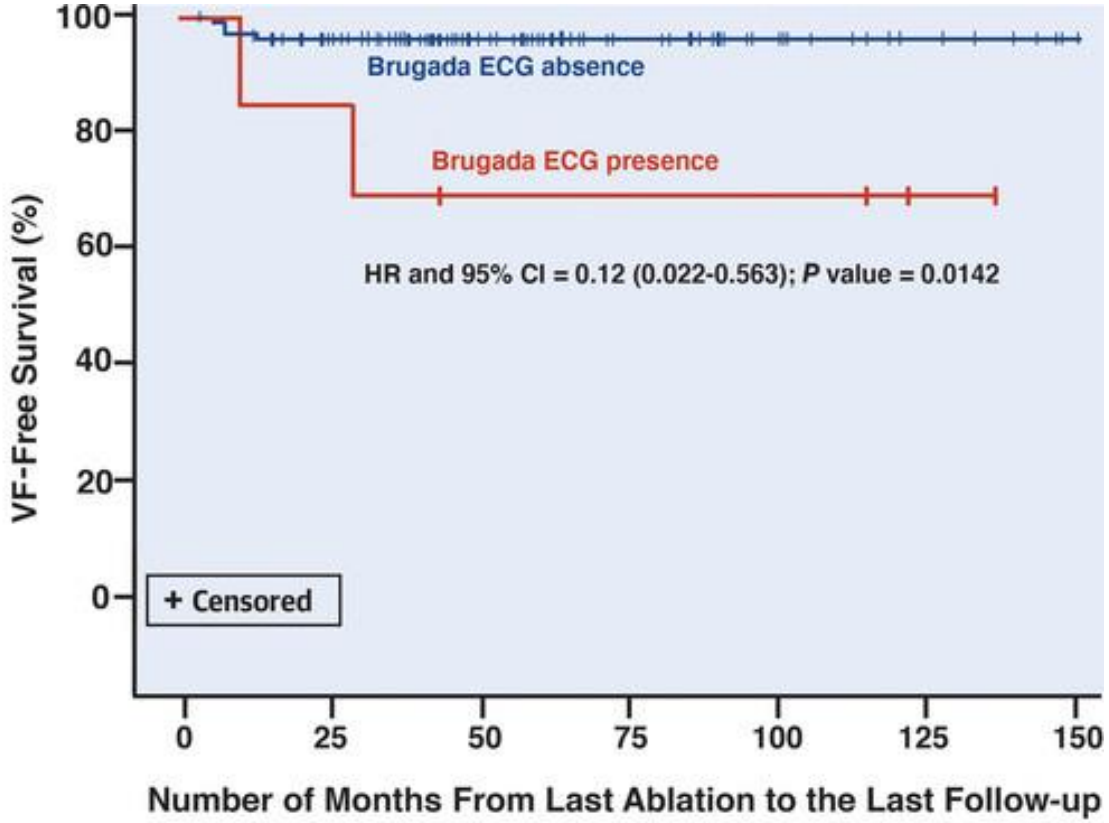


Nademanee K, et al.: Circulation, 147:1568-1578,2023

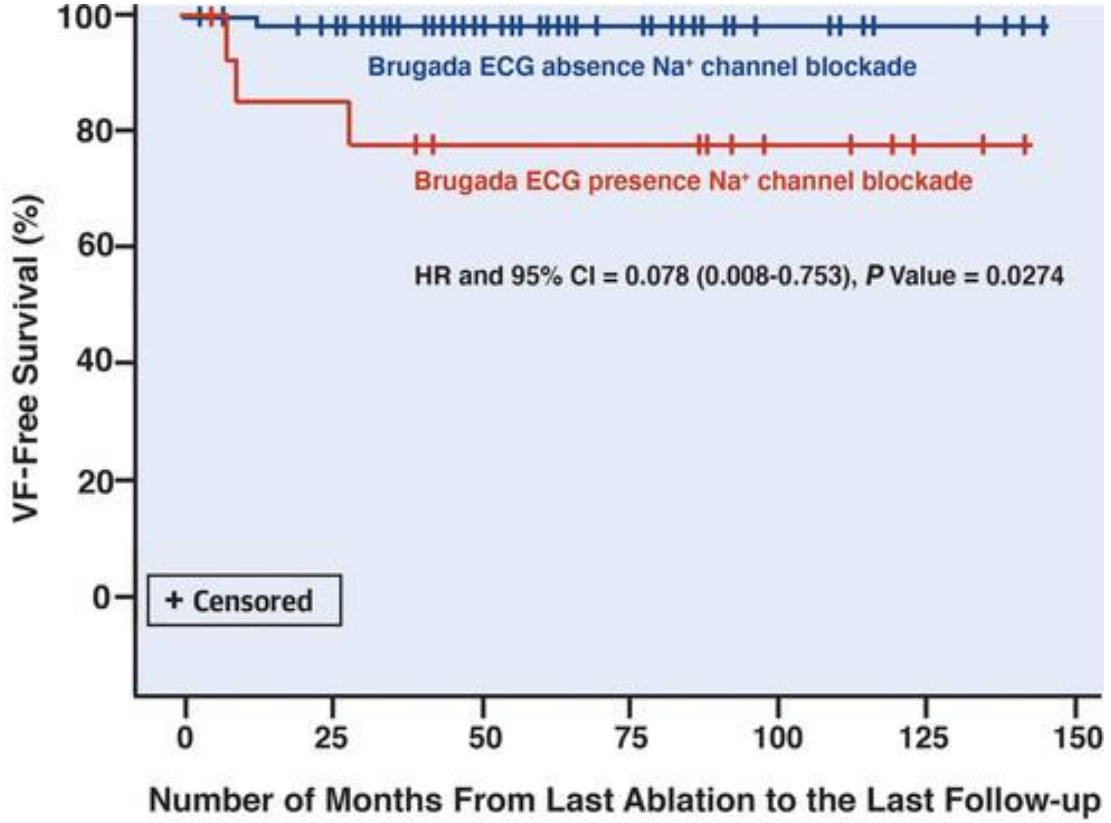
KHRS 2023

Epicardial ablation therapy for BrS: BRAVO

Normalization of type 1 Brugada ECG after ablation, both with and without sodium channel blockade, suggests elimination of ventricular fibrillation substrates and is associated with excellent outcomes.



Normal ECG	102	84	51	29	12	6	0
Brugada ECG	8	5	3	3	3	1	0



Normal ECG	58	51	32	20	8	4	0
Brugada ECG	16	12	9	9	5	2	0

Summary

- ✓ Pathogenic SCN5A variants can be used for the risk stratification in Japanese (Asian?) BrS patients.
- ✓ Fibrosis in cardiomyocytes may be related with Brugada syndrome.
- ✓ The ablation therapy for Brugada syndrome is effective for the prevention of ventricular fibrillation.

Thank you for your attention!