VENICE 2015 ARRHYTHMIAS

Brugada syndrome

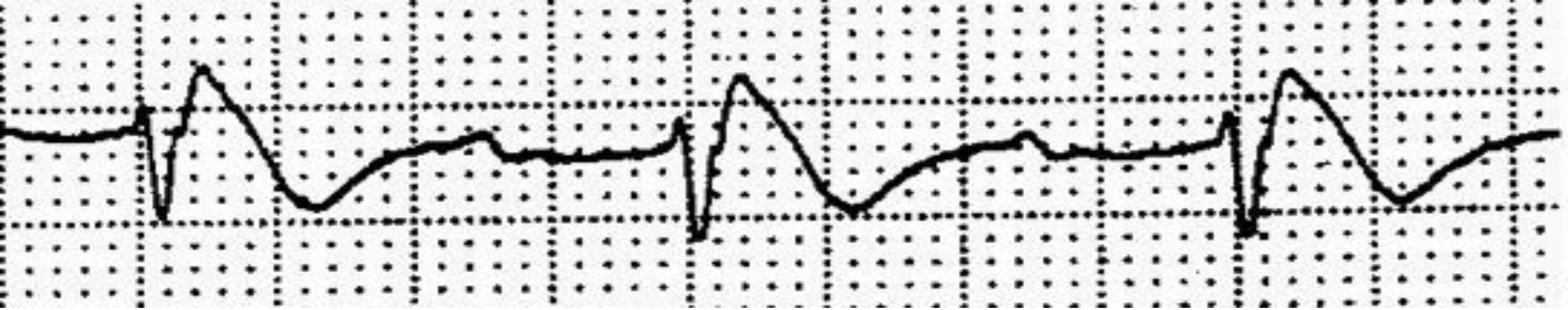
The role of genetic mutations

Venice Arrhythmia 2015

Arthur A.M. Wilde

October 16 - 18
14th EDITION 2015

NO CONFLICT OF INTEREST TO DECLARE



Brugada syndrome

The diagnosis

Special Report

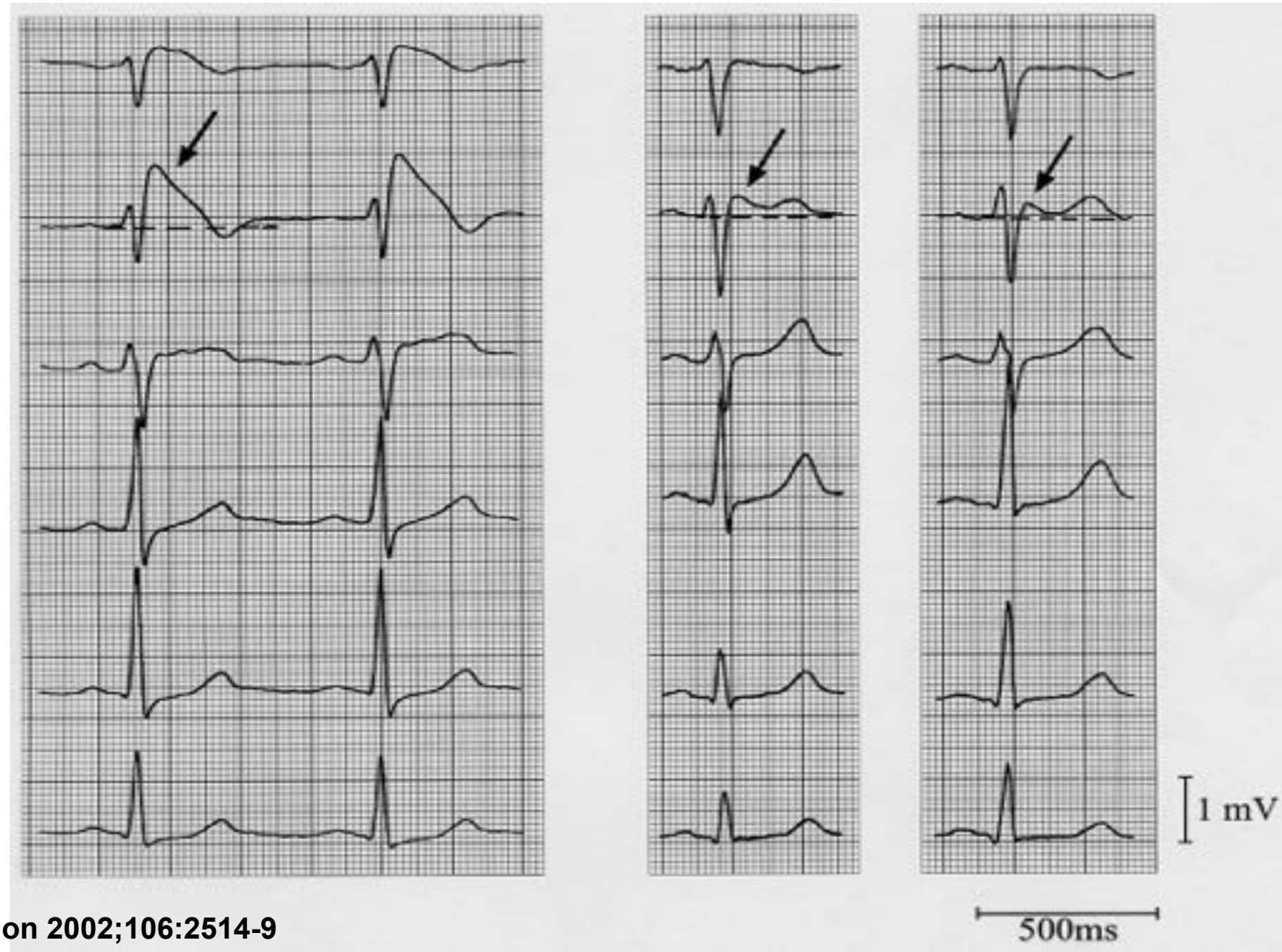
Brugada Syndrome

Report of the Second Consensus Conference

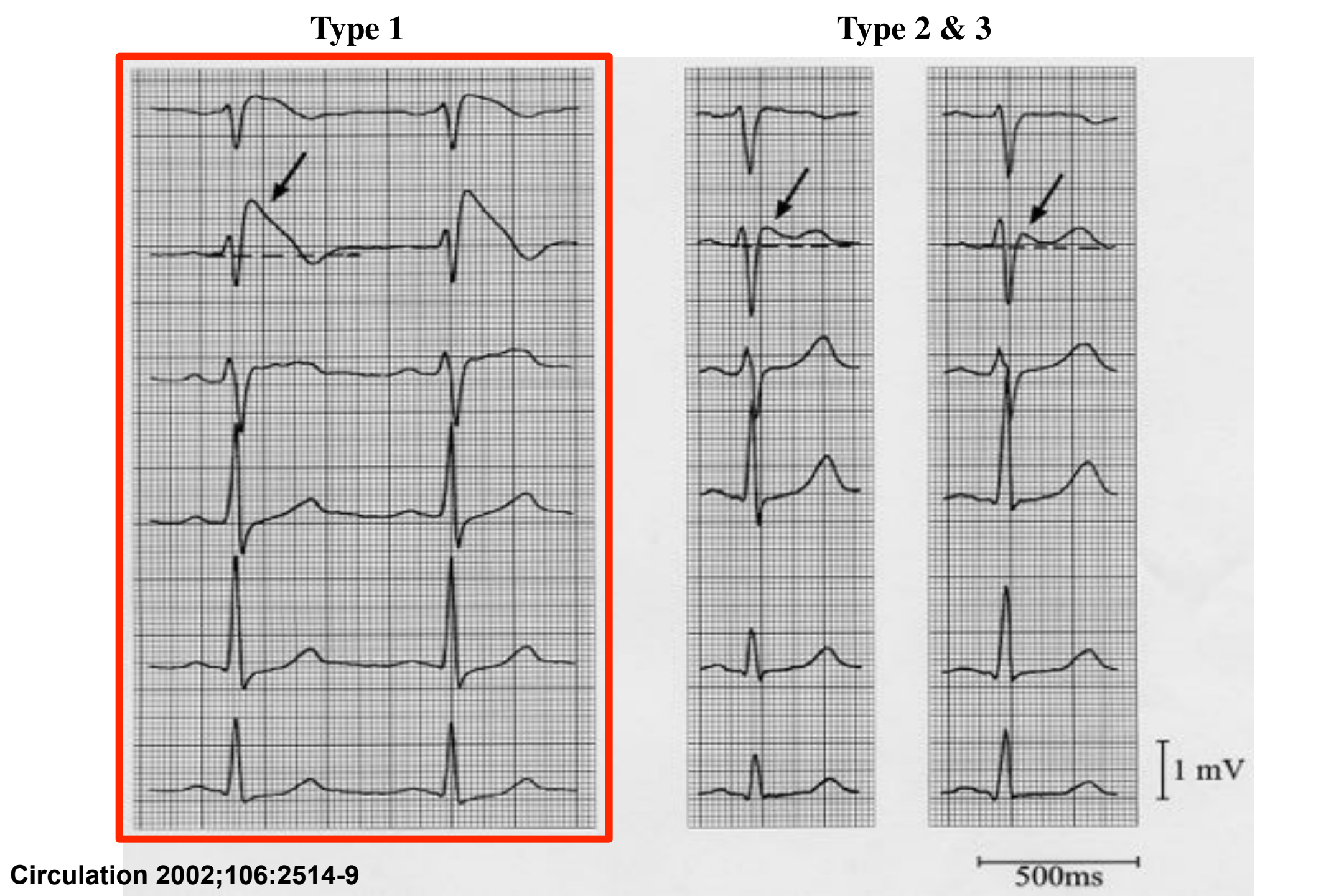
Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association

Charles Antzelevitch, PhD; Pedro Brugada, MD, PhD; Martin Borggrefe, MD, PhD; Josep Brugada, MD; Ramon Brugada, MD; Domenico Corrado, MD, PhD; Ihor Gussak, MD, PhD; Herve LeMarec, MD; Koonlawee Nademanee, MD; Andres Ricardo Perez Riera, MD; Wataru Shimizu, MD, PhD; Eric Schulze-Bahr, MD; Hanno Tan, MD, PhD; Arthur Wilde, MD, PhD

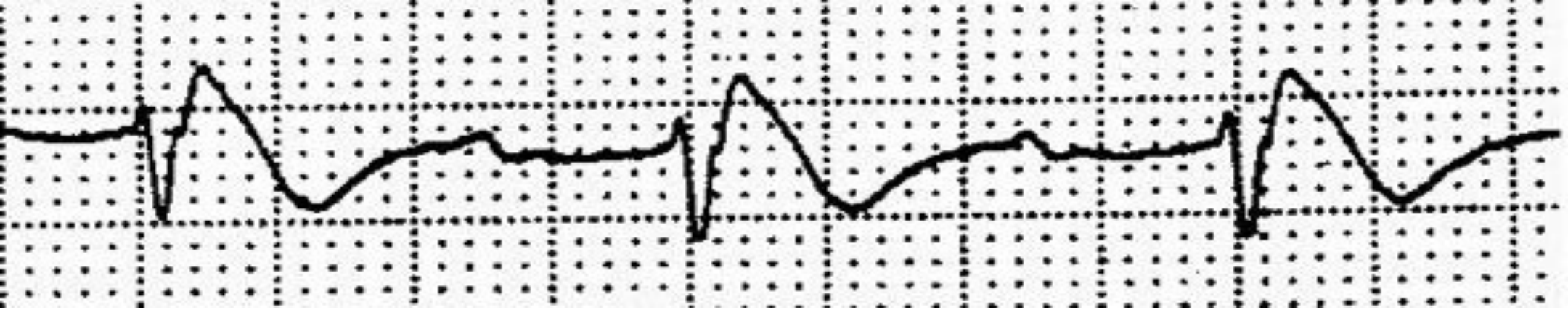
Heart Rhythm 2005;2:429-440



Circulation 2002;106:2514-9



Circulation 2002;106:2514-9



Brugada syndrome should be considered:

- Type 1 ECG (± drugs) and
- documented VF or self terminating PMVT
- Family history of SCD < 45 y.
- Type 1 ECG in family members
- EPS inducibility, syncope
- Nocturnal agonal respiration

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)[1], Arthur A. Wilde, (EHRA Chairperson)[2], Minoru Horie, (APHRS Chairperson)[3], Yongkeun Cho, (APHRS Chairperson)[4], Elijah R. Behr[5], Charles Berul[6], Nico Blom[7*], Josep Brugada[8], Chern-En Chiang[9], Heikki Huikuri[10], Prince Kannankeril[11‡], Andrew Krahn[12], Antoine Leenhardt[13], Arthur Moss[14], Peter J. Schwartz[15], Wataru Shimizu[16], Gordon Tomaselli[17†], Cynthia Tracy[%18]

Document Reviewers: Michael Ackerman (USA), Bernard Belhassen (Israel), N. A. Mark Estes III (USA), Diane Fatkin (Australia), Jonathan Kalman (Australia), Elizabeth Kaufman (USA), Paulus Kirchhof (UK and Germany), Eric Schulze-Bahr (Germany), Christian Wolpert (Germany), Jitendra Vohra (Australia), Marwan Refaat (USA), Susan P. Etheridge (USA), Robert M. Campbell (USA), Edward T. Martin (USA), Swee Chye Quek (Singapore)

Brugada Syndrome

Bottom line: one right precordial lead at any position

1. BrS ***is diagnosed*** in patients with ST segment elevation with type 1 morphology ≥ 2 mm in ≥ 1 lead among the right precordial leads V1,V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously *or* after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

2. BrS ***is diagnosed*** in patients with type 2 or type 3 ST segment elevation in ≥ 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type 1 ECG morphology

Heart Rhythm 2013, Europace 2013

Insights into the location of type I ECG in patients with Brugada syndrome: Correlation of ECG and cardiovascular magnetic resonance imaging

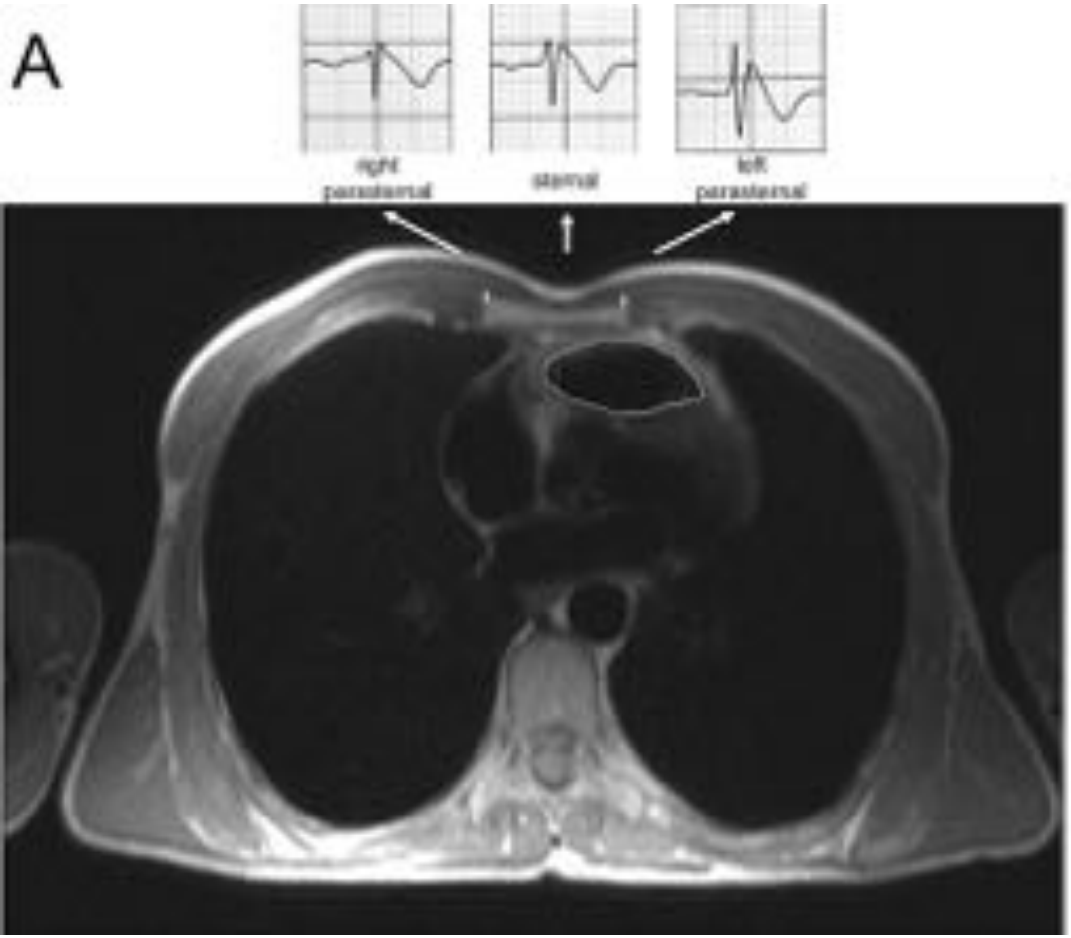
C. Veltmann, MD,* T. Papavassiliu, MD,* T. Konrad, MD,* C. Doesch, MD,* J. Kuschyk, MD,* F. Streitner, MD,* D. Haghi, MD,* H.J. Michaely, MD,† S.O. Schoenberg, MD,† M. Borggrefe, MD,* C. Wolpert, MD,‡ R. Schimpf, MD*

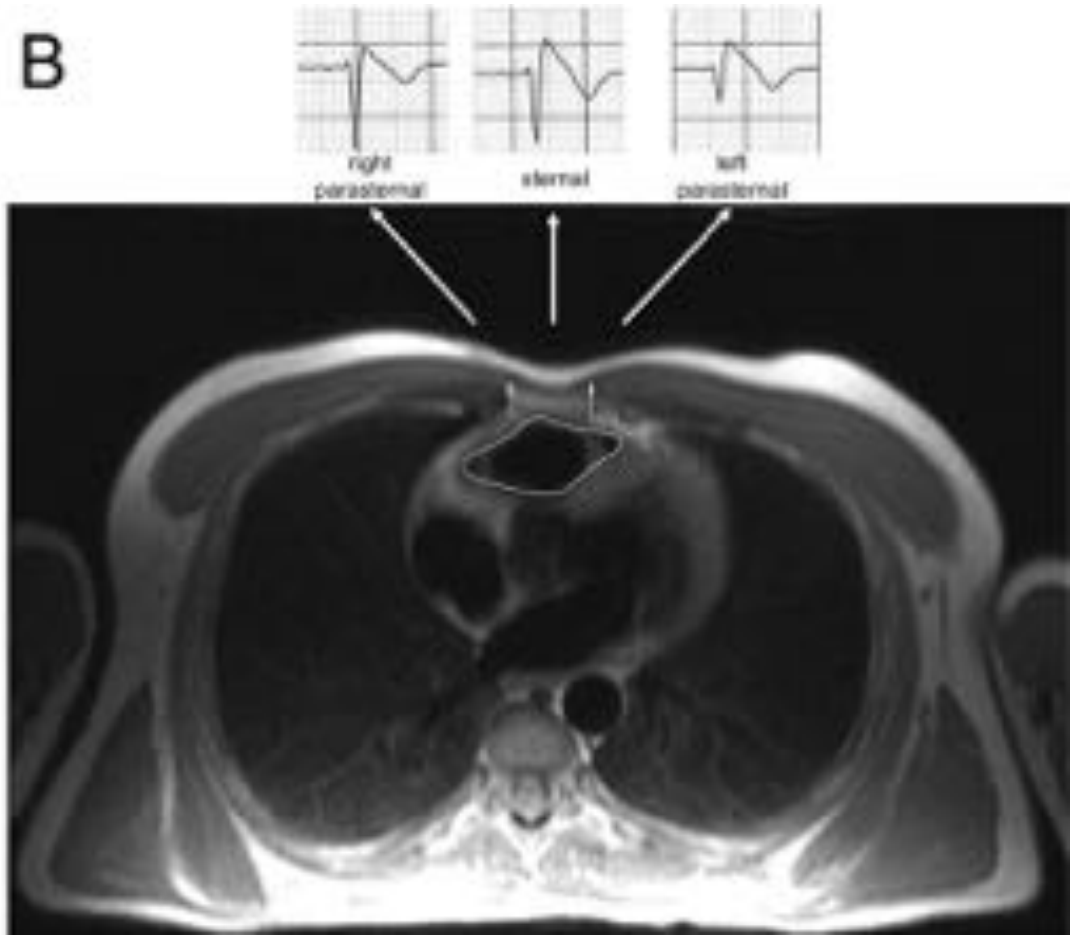
*From the *1st Department of Medicine-Cardiology, University Medical Centre Mannheim, Mannheim, Germany; †Department of Radiology, University Medical Centre Mannheim, Mannheim, Germany; ‡Department of Medicine-Cardiology, Klinikum Ludwigsburg, Ludwigsburg, Germany.*

Table 3 Diagnostic yield of single right-precordial leads for the detection of a Brugada type I ECG pattern

	Ajmaline-induced type I ECG			Spontaneous type I ECG		
	Right parasternal	Sternal	Left parasternal	Right parasternal	Sternal	Left parasternal
2nd ICS	20%	50%	55%	0%	40%	50%
3rd ICS	30%	100%	100%	0%	100%	100%
4th ICS	15%	100%	85%	20%	70%	70%
5th ICS	0%	5%	5%	0%	0%	0%

ICS = intercostal space.

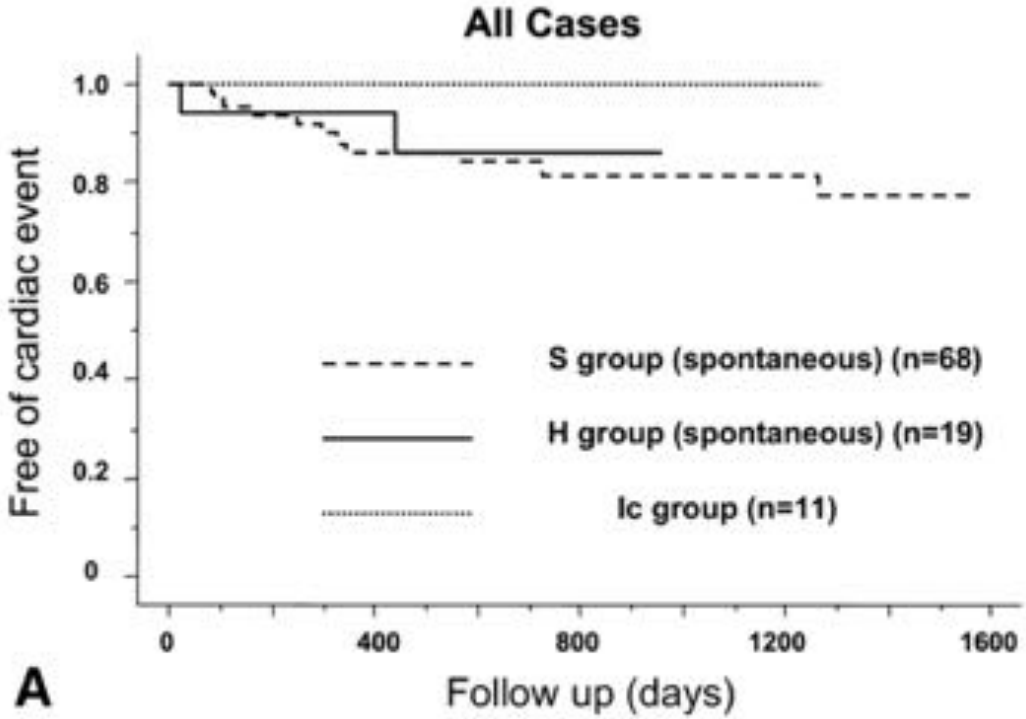


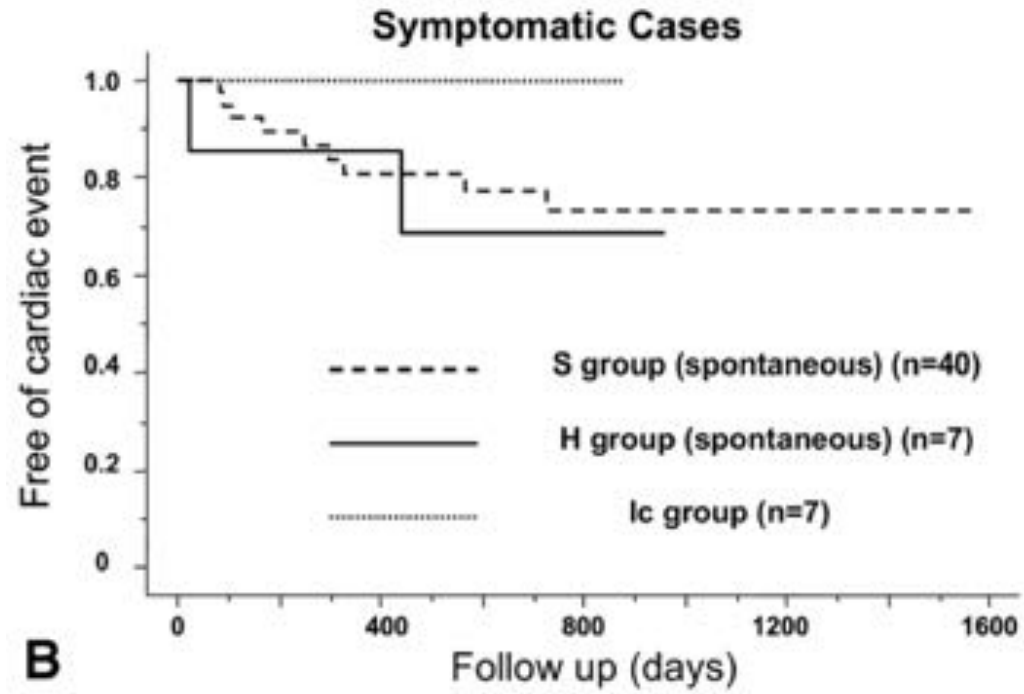


Veltmann et al, HR 2012;9:414-421

Diagnostic and Prognostic Value of a Type 1 Brugada Electrocardiogram at Higher (Third or Second) V_1 to V_2 Recording in Men With Brugada Syndrome

Koji Miyamoto, MD, Miki Yokokawa, MD, Koji Tanaka, MD, Takayuki Nagai, MD, Hideo Okamura, MD, Takashi Noda, MD, PhD, Kazuhiro Satomi, MD, PhD, Kazuhiro Suyama, MD, PhD, Takashi Kurita, MD, PhD, Naohiko Aihara, MD, Shiro Kamakura, MD, PhD, and Wataru Shimizu, MD, PhD*

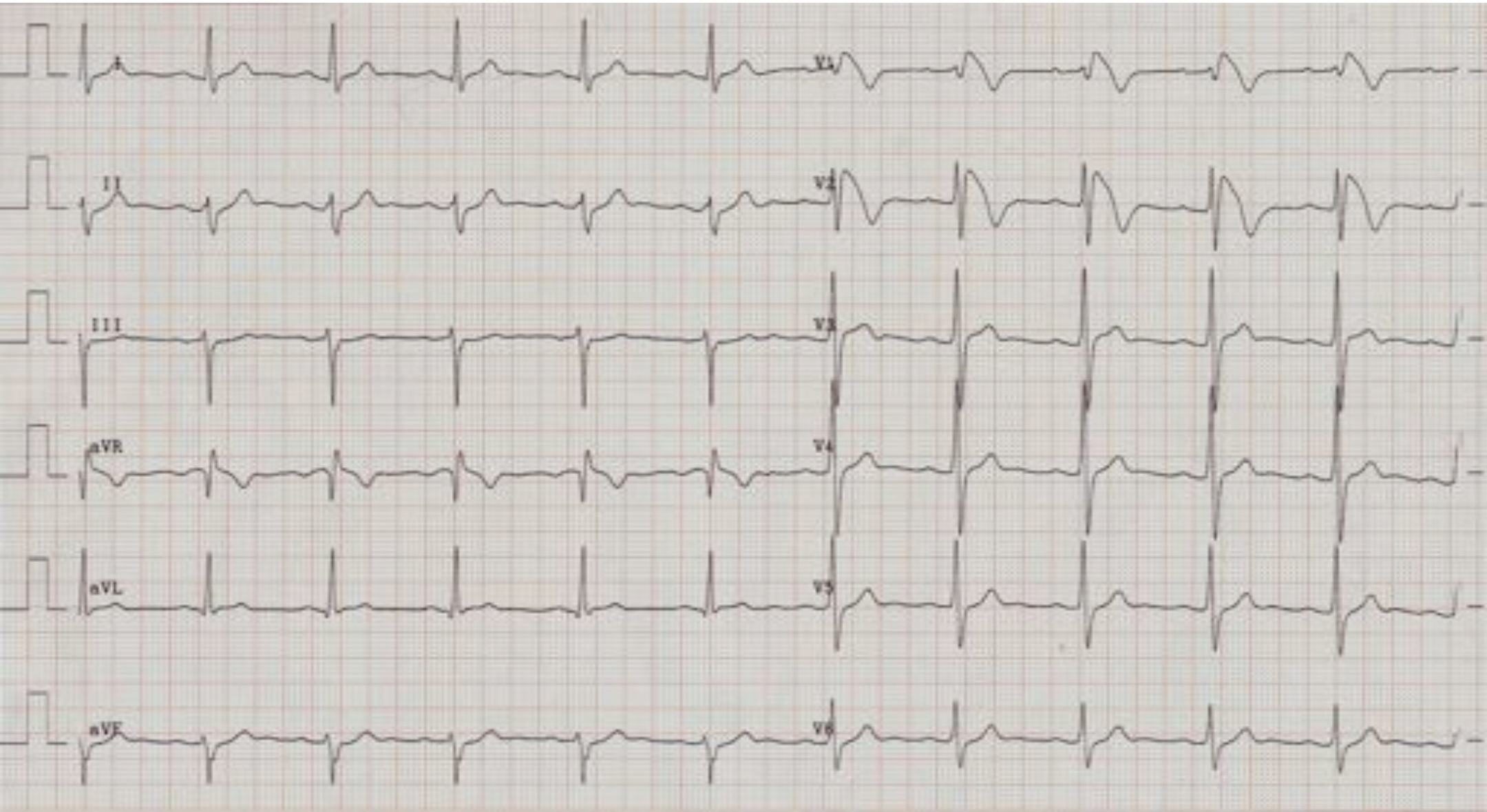


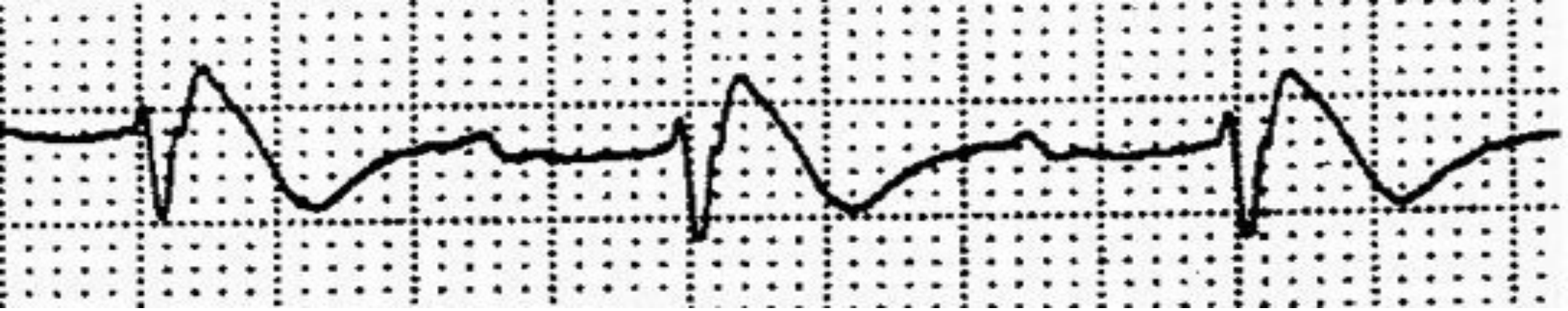


Miyamoto et al, AJC 2007;99:53-57

S = 4th ICS, H = higher (2nd and 3rd), Ic = drug induced

Male 39 years (resuscitated)





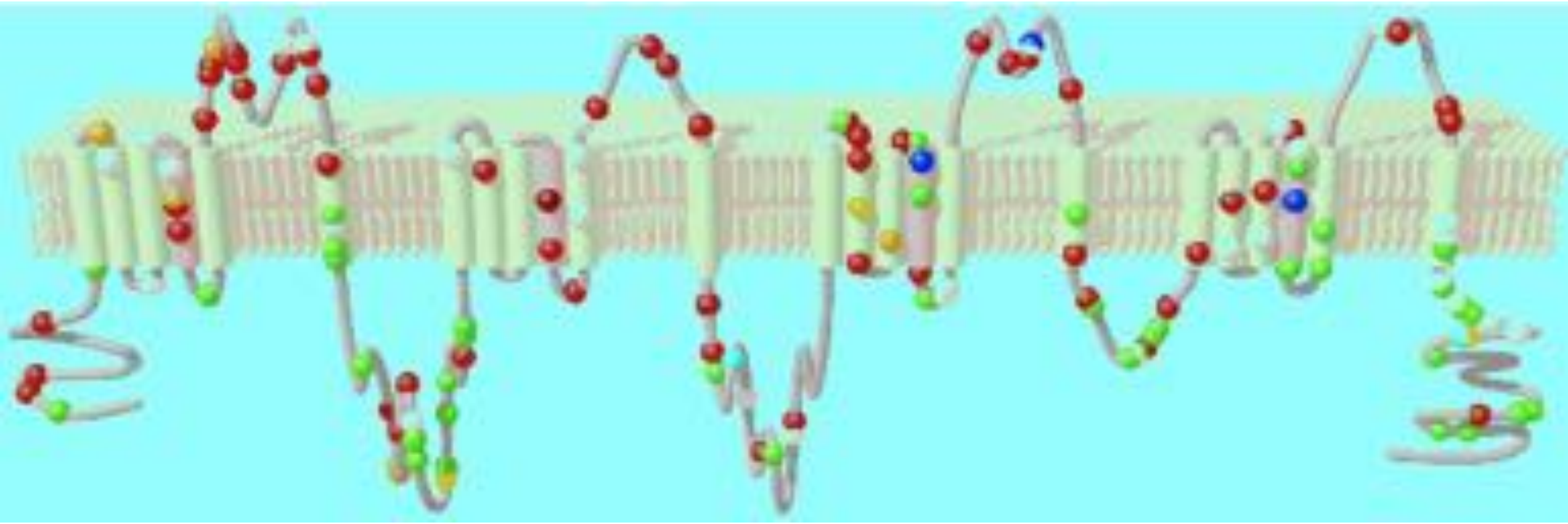
Brugada syndrome

Genetics

Brugada syndrome, genetics

- Genetically heterogeneous

SCN5A (3p21) mutations



● : Brugada syndrome

● : (P)CCD

● : LQTS

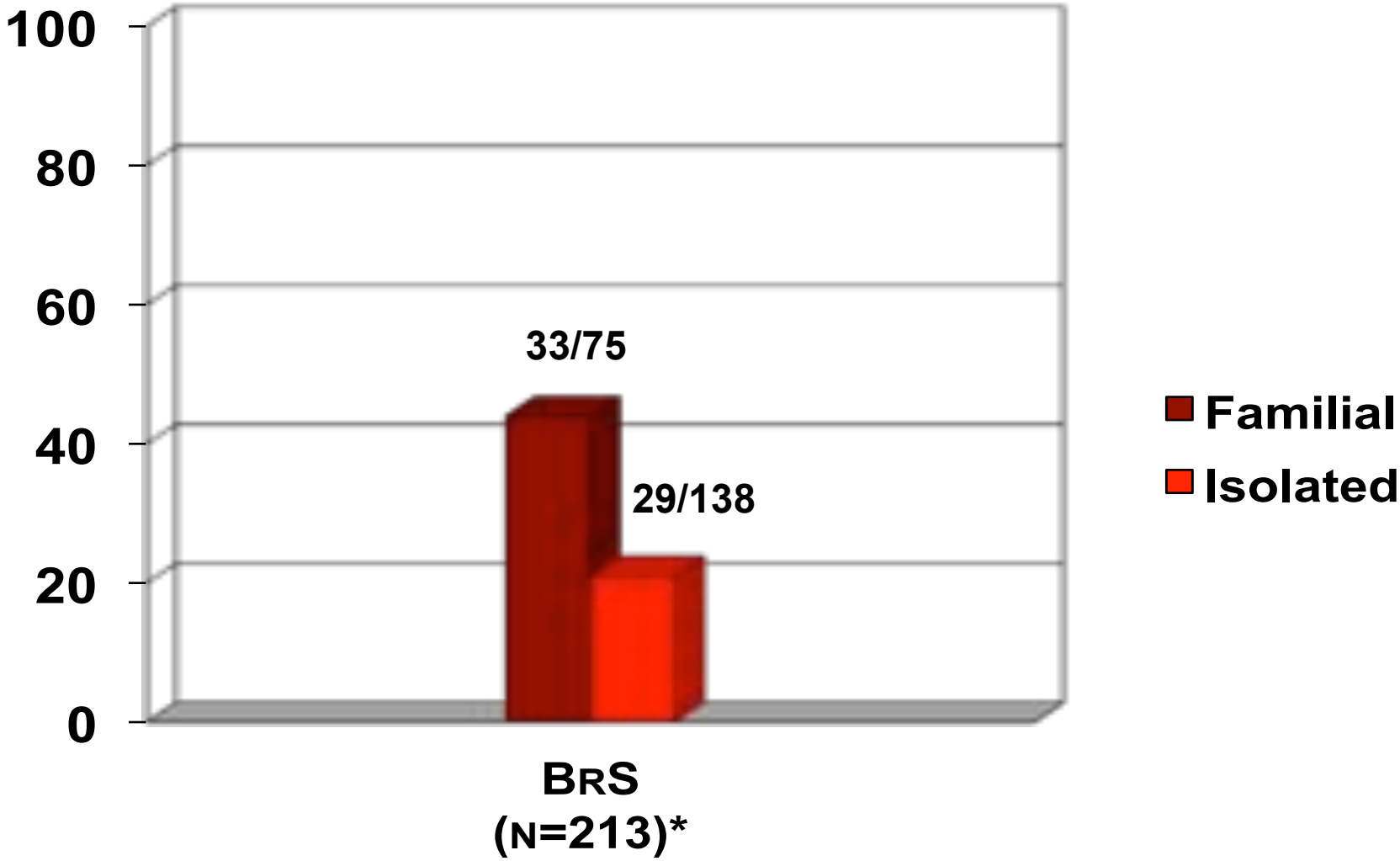
Brugada syndrome, genetics

28/130 (22%) : Priori et al., 2002 (mostly Italian)

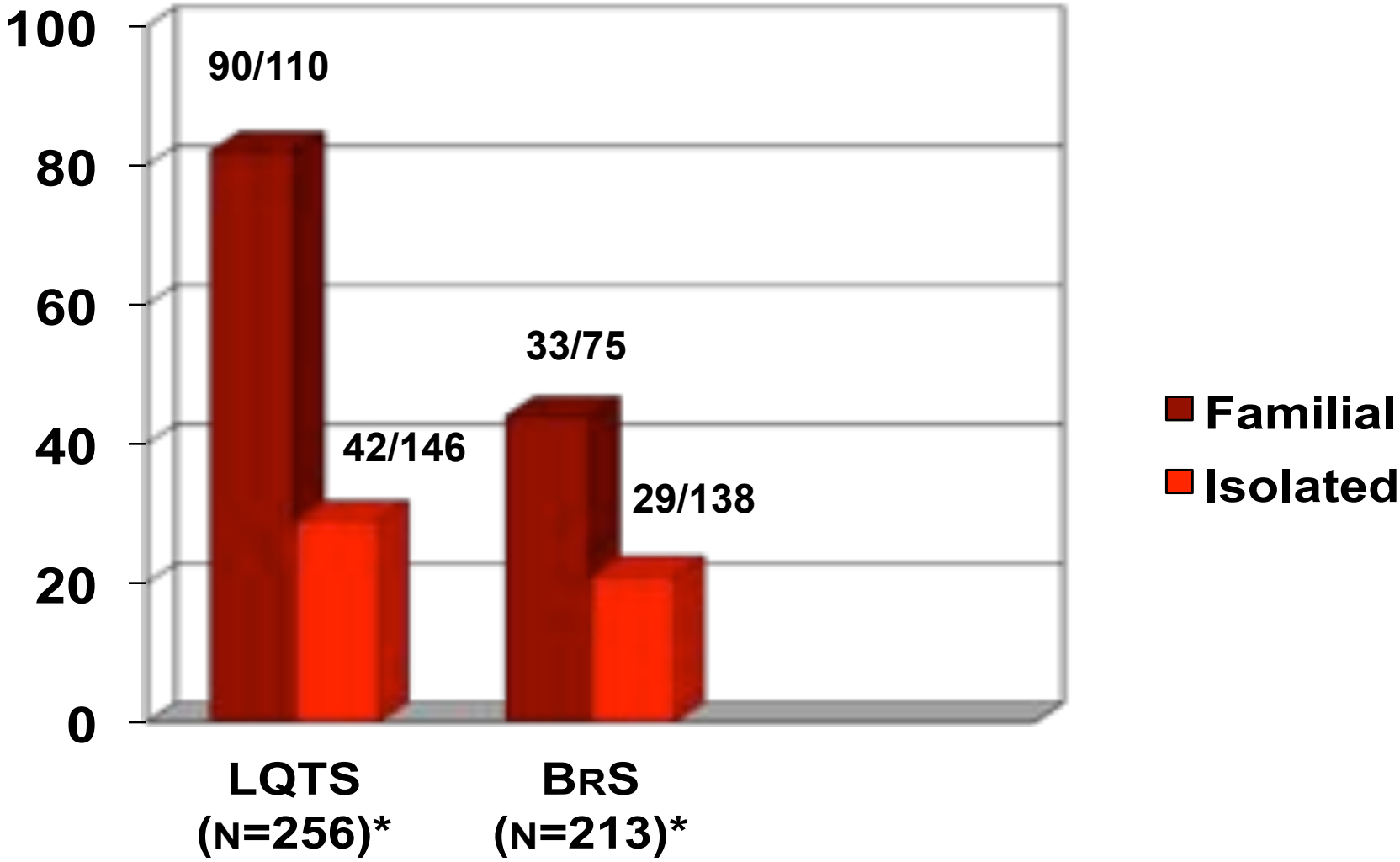
23/77 (30%) : Smits et al., 2002 (NL, Fr, GER)

3/10 (30%) : Vatta et al., 2002 (Japan, Thailand)

4/39 (10%) : Makiyama ea., 2005 (Japan)



Hofman et al., Circulation 2013



Hofman et al., Circulation 2013

Brugada syndrome, genetics

	Locus	Ion channel	Gene/Protein
BrS 1	**3p21**	**I_{Na}** ↓	**SCN5A, $Na_v1.5$**

Brugada syndrome, genetics

	Locus	Ion channel	Gene/Protein
BrS 1	**3p21**	**I_{Na}** ↓	**SCN5A, $Na_v1.5$**

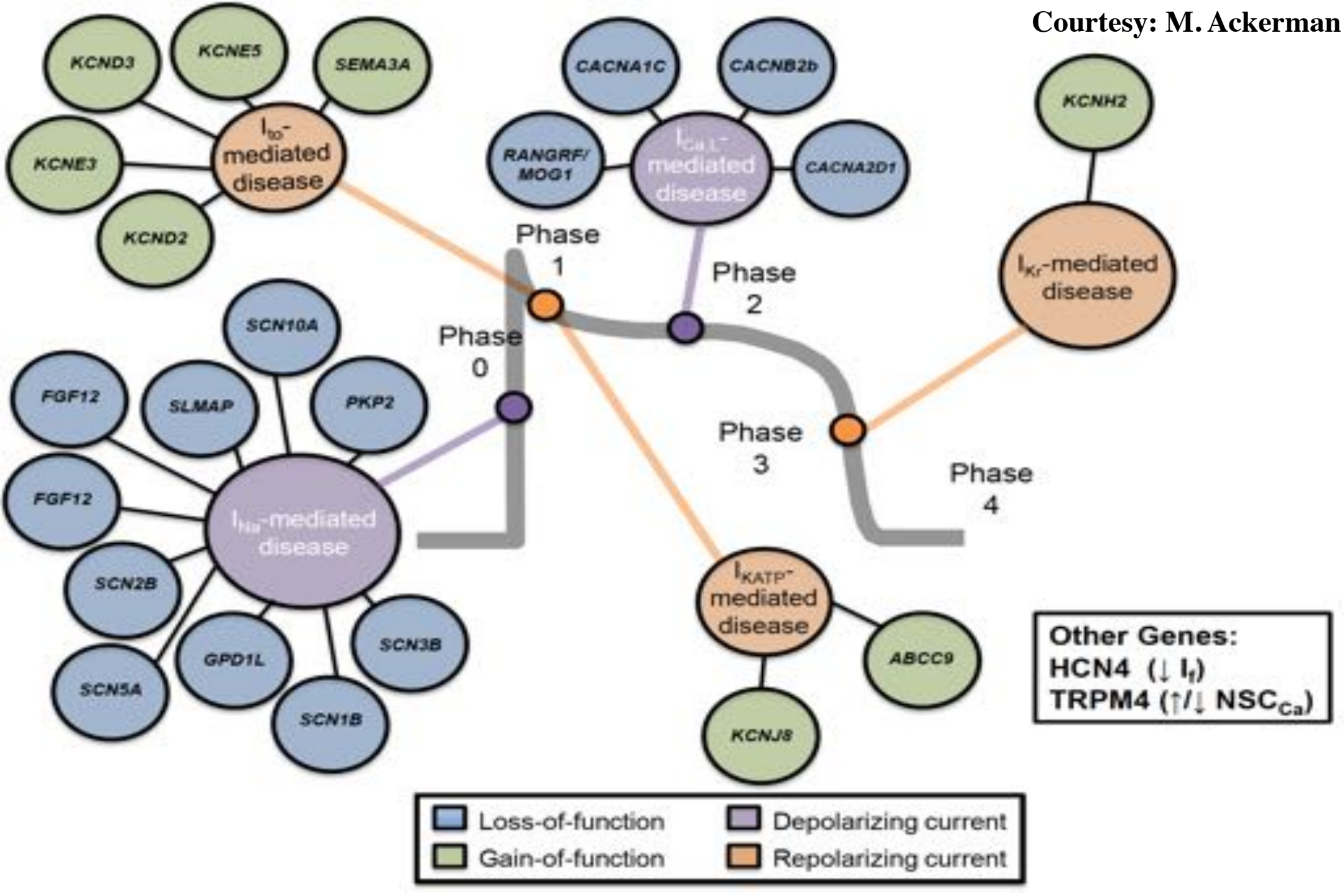
Brugada syndrome, genetics

	Locus	Ion channel	Gene/Protein
BrS 15	**12p11**	I_{Na} ↓	**PKP2**
BrS 16	**3q28**	I_{Na} ↓	**FGF12**
BrS 17	**3q22.2**	I_{Na} ↓	**SCN10A**
BrS 18	**7p12.1**	I_{TO} ↑	**SEMA3A**

Brugada syndrome, genetics

	Locus	Ion channel	Gene/Protein
BrS modifying	**15q24-25**	I_F ↓	**HCN4**
BrS modifying	**7q35**	I_{Kr} ↑	**KCNH2**
BrS modifying	**Xq22.3**	I_{to} ↑	**KCNE5**
BrS modifying	**6q22**	I_{Na} ↓	**HEY2**

Courtesy: M. Ackerman

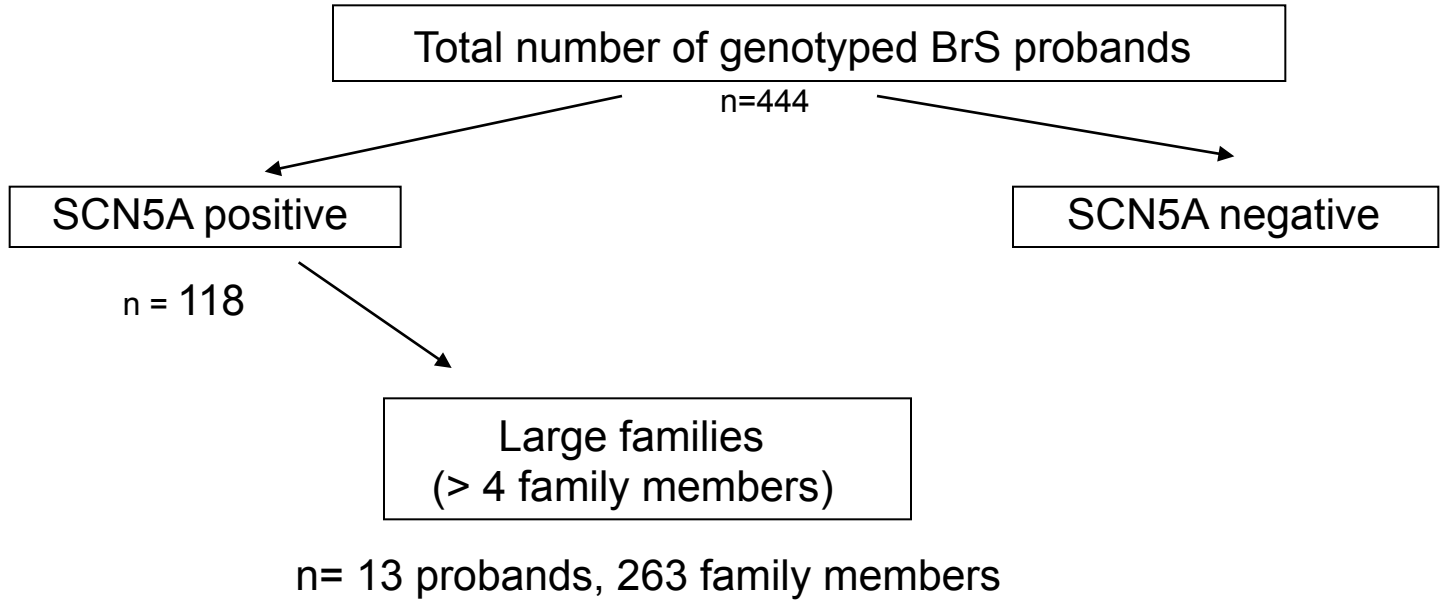


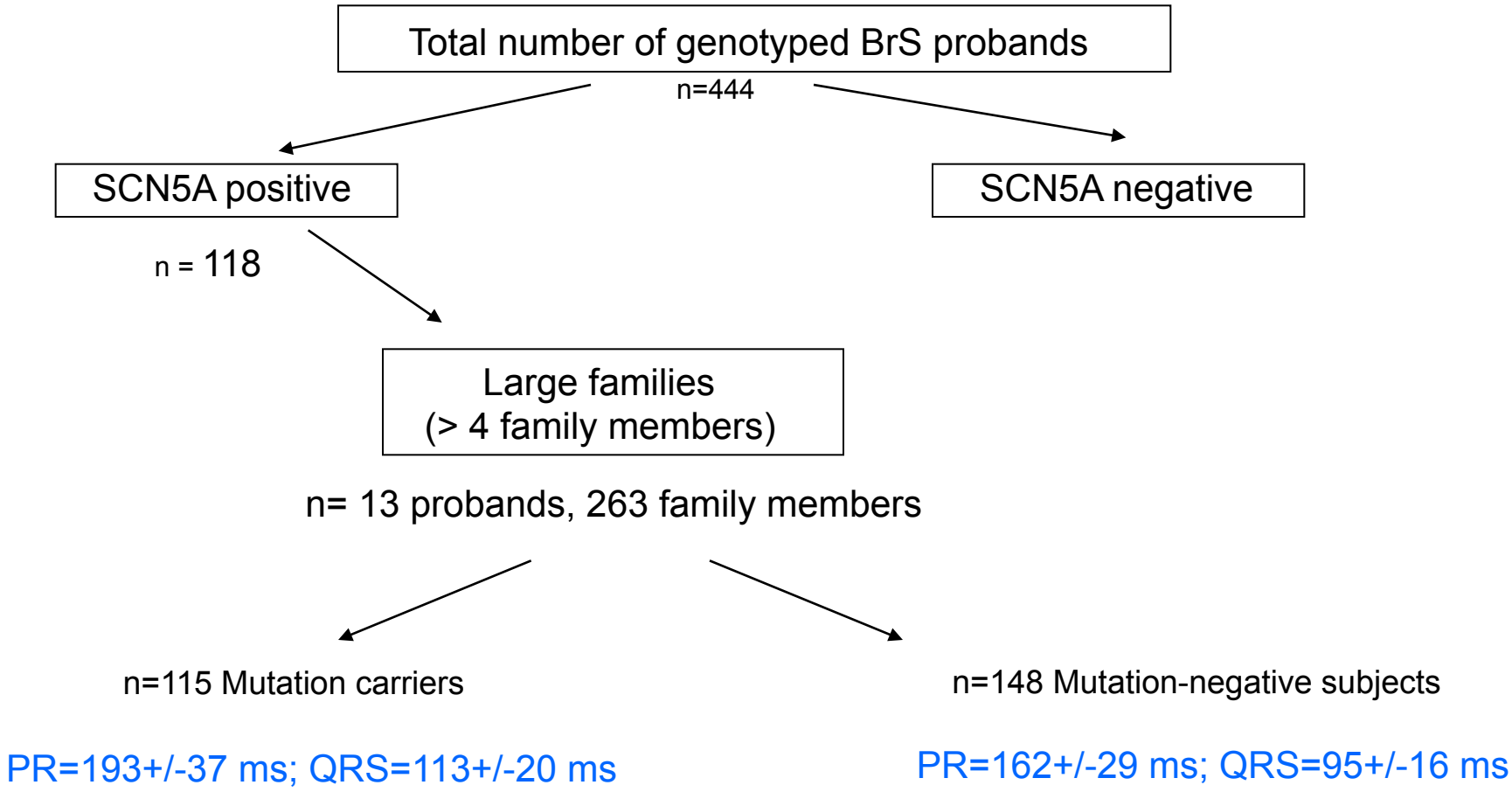
Circulation
Cardiovascular Genetics
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

SCN5A Mutations and the Role of Genetic Background in the Pathophysiology of Brugada Syndrome

Vincent Probst, Arthur A.M. Wilde, Julien Barc, Frederic Sacher, Dominique Babuty, Philippe Mabo, Jacques Mansourati, Solena Le Scouarnec, Florence Kyndt, Cedric Le Caignec, Pascale Guicheney, Laetitia Gouas, Juliette Albuisson, Paola G. Meregalli, Hervé Le Marec, Hanno L. Tan and Jean-Jacques Schott

Circ Cardiovasc Genet 2009;2;552-557; originally published online Sep 29, 2009;
DOI: 10.1161/CIRCGENETICS.109.853374


Total number of genotyped BrS probands
n=444
SCN5A positive
SCN5A negative
n = 118
Large families
(> 4 family members)
n= 13 probands, 263 family members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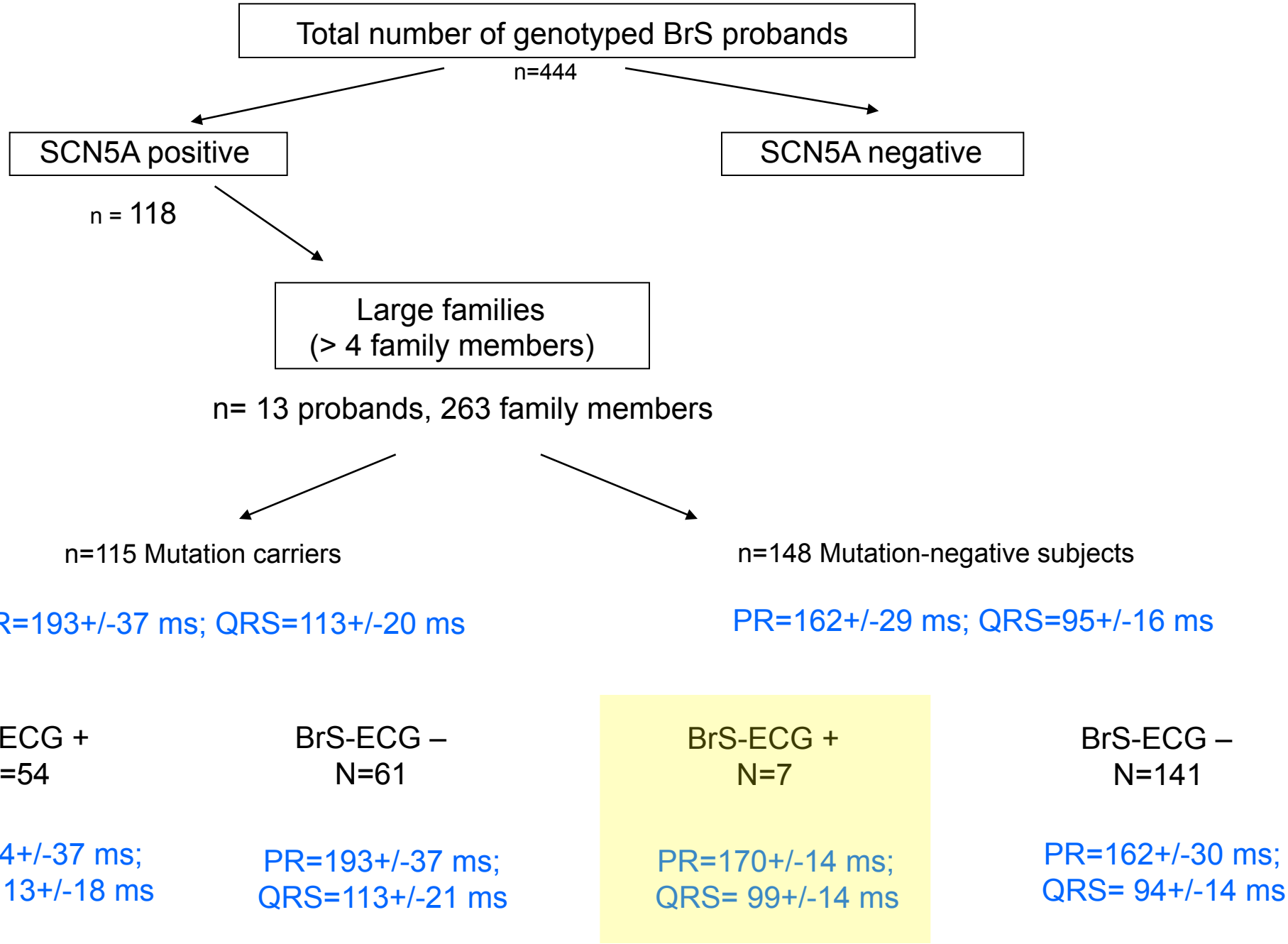
n= 13 probands, 263 family members
n=115 Mutation carriers
n=148 Mutation-negative subjects
PR=193+/-37 ms; QRS=113+/-20 ms
PR=162+/-29 ms; QRS=95+/-16 ms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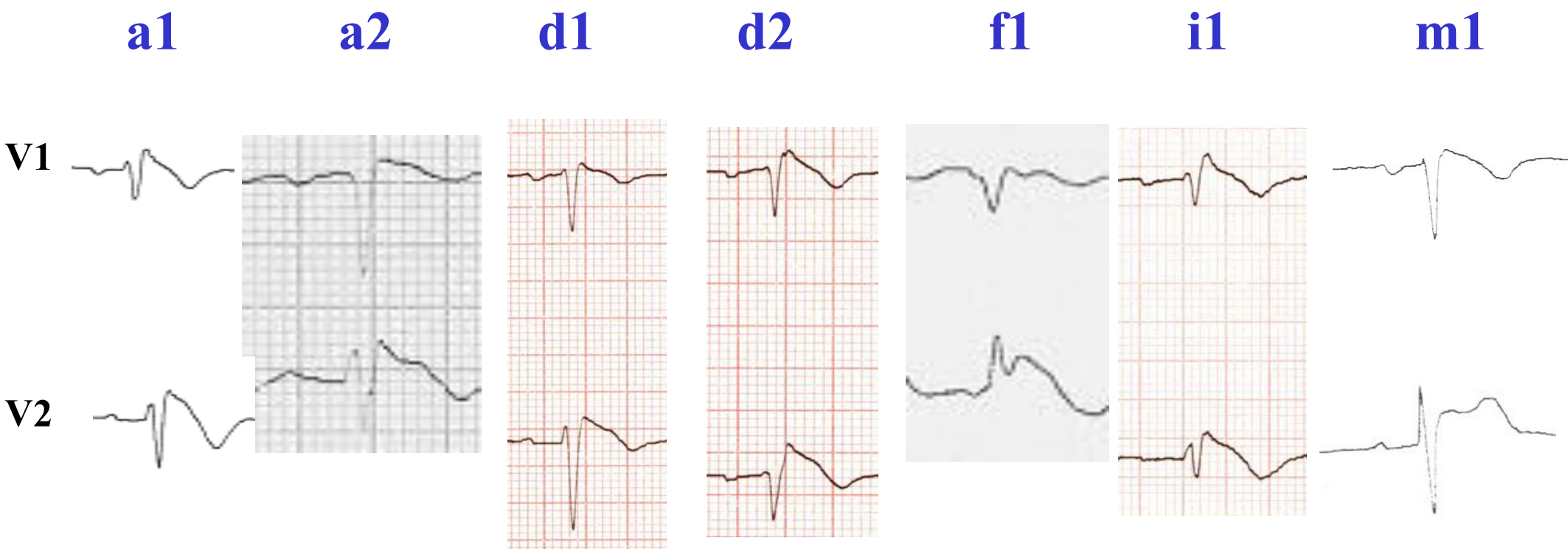
PR=193+/-37 ms; QRS=113+/-20 ms
PR=162+/-29 ms; QRS=95+/-16 ms
BrS-ECG +
N=54
PR=194+/-37 ms;
QRS= 113+/-18 ms
BrS-ECG –
N=61
PR=193+/-37 ms;
QRS=113+/-21 ms
BrS-ECG +
N=7
PR=170+/-14 ms;
QRS= 99+/-14 ms
BrS-ECG –
N=141
PR=162+/-30 ms;
QRS= 94+/-14 ms


a1
a2
d1
d2
f1
i1
m1
V1
V2

BrS, genetics

Does SCN5a play a role?:

- there are no linkage data for SCN5a!
- loss-of-function mutation not mandatory!
- could it be an important modifier?

- if this would have been the first family then…

OXFORD

Human Molecular Genetics, 2015, Vol. 24, No. 10 2757–2763

doi: 10.1093/hmg/ddv036
Advance Access Publication Date: 3 February 2015
Original Article

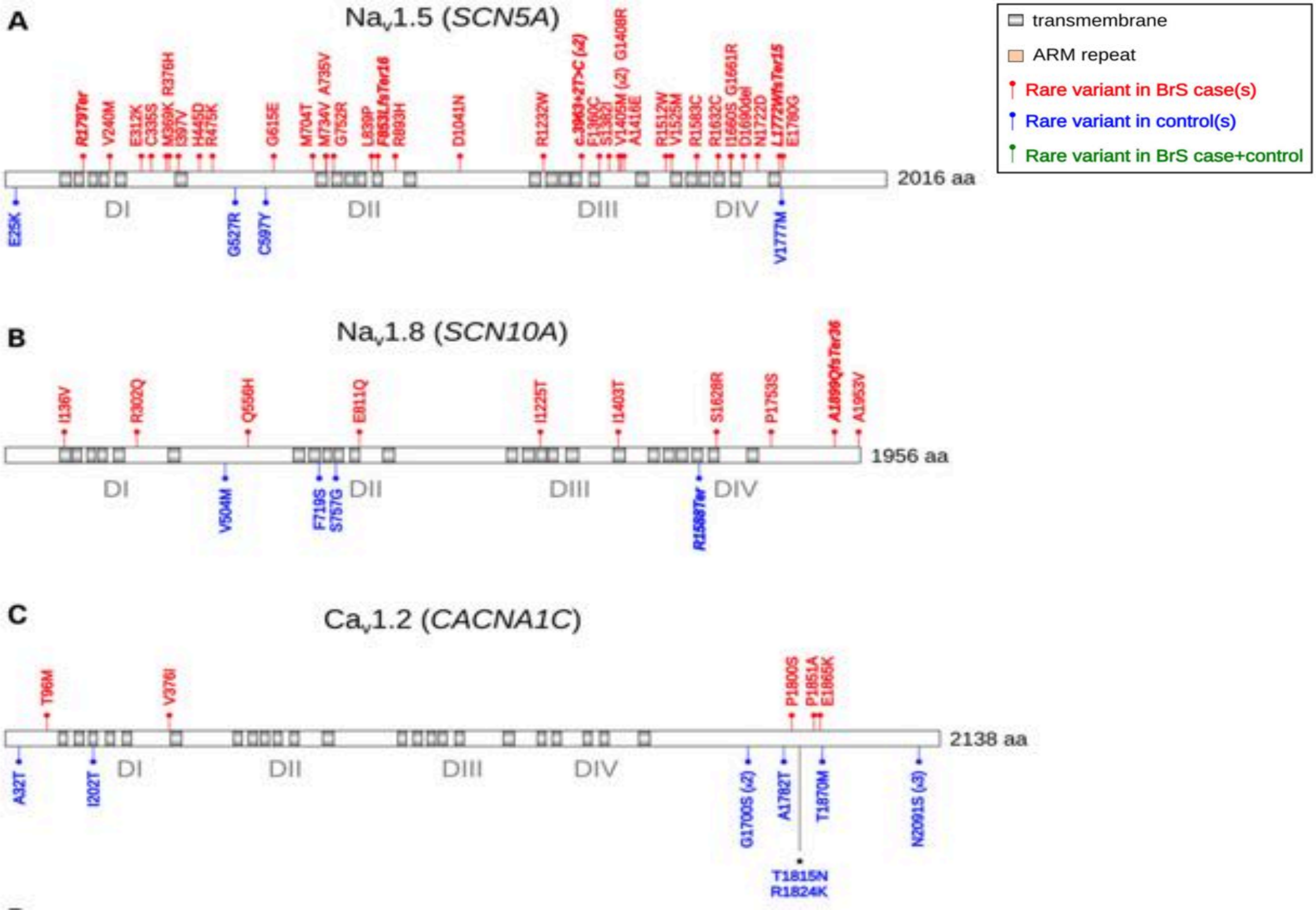
ORIGINAL ARTICLE

Testing the burden of rare variation in arrhythmia-susceptibility genes provides new insights into molecular diagnosis for Brugada syndrome

Solena Le Scouarnec[1,2,3,†], Matilde Karakachoff[1,2,3,4,†], Jean-Baptiste Gourraud[1,2,3,5,†], Pierre Lindenbaum[1,2,3,5], Stéphanie Bonnaud[1,2,3,5], Vincent Portero[1,2,3], Laëtitia Duboscq-Bidot[1,2,3], Xavier Daumy[1,2,3], Floriane Simonet[1,2,3], Raluca Teusan[1,2,3], Estelle Baron[1,2,3], Jade Violleau[1,2,3,5], Elodie Persyn[1,2,3], Lise Bellanger[3,6], Julien Barc[7,8], Stéphanie Chatel[1,2,3,5], Raphaël Martins[9], Philippe Mabo[9], Frédéric Sacher[10], Michel Haïssaguerre[10], Florence Kyndt[1,2,3,5], Sébastien Schmitt[3,11], Stéphane Bézieau[3,11], Hervé Le Marec[1,2,3,5], Christian Dina[1,2,3,5], Jean-Jacques Schott[1,2,3,5], Vincent Probst[1,2,3,5] and Richard Redon[1,2,3,5,*]

Table 1 Burden tests results for 45 genes linked to cardiac arrhythmias

Gene	BrS cases ($n = 167$)	Internal controls ($n = 167$)	P-value 1	UK10K controls ($n = 881$)	P-value 2
BrS-susceptibility genes					
SCN5A	20.4% (34)	2.4% (4)	1.4×10^{-7a}	2.4% (21)	1.7×10^{-15a}
SCN10A	6% (10)	2.4% (4)	0.170	3.5% (31)	0.131
CACNA1C	3% (5)	6.6% (11)	0.199	2% (18)	0.395
PKP2	3% (5)	2.4% (4)	1	1.7% (15)	0.348
CACNB2	1.8% (3)	1.2% (2)	1	0.9% (8)	0.396
KCNH2	1.2% (2)	3.6% (6)	0.283	1.6% (14)	1
TRPM4	1.2% (2)	3% (5)	0.448	1.9% (17)	0.754
KCND3	0.6% (1)	1.2% (2)	1	1.6% (14)	0.488
CACNA2D1	0.6% (1)	0.6% (1)	1	3.3% (29)	0.072
HEY2	0.6% (1)	0.6% (1)	1	0.1% (1)	0.293
SCN2B	0.6% (1)	0.6% (1)	1	0.5% (4)	0.581
SCN3B	0.6% (1)	0.6% (1)	1	0.5% (4)	0.581
ABCC9	—	3% (5)	0.061	1.1% (10)	0.379
SCN1B	—	1.8% (3)	0.248	0.3% (3)	1
RANGRF	—	0.6% (1)	1	0.2% (2)	1
FGF12	—	—	—	0.7% (6)	0.597
GPD1L	—	—	—	0.1% (1)	1
HCN4	—	—	—	1.6% (14)	0.144
KCNE1L	—	—	—	1% (9)	0.369
KCNE3	—	—	—	0.1% (1)	1
KCNJ8	—	—	—	0.5% (4)	1


A
Na$_v$1.5 (*SCN5A*)
transmembrane
ARM repeat
Rare variant in BrS case(s)
Rare variant in control(s)
Rare variant in BrS case+control
R179Ter
V240M
E312K
C335S
R376H
M399K
E397V
H445D
R475K
G615E
M704T
M734V
A735V
G752R
L839P
F853LfsTer16
R893H
D1041N
R1232W
c.3963+2T>C (x2)
F1360C
S1382I
V1405M (x2)
G1408R
A1416E
R1512W
V1525M
R1583C
R1632C
I1660S
G1661R
D1690del
N1722D
L1772WfsTer15
E1780G
2016 aa
DI
DII
DIII
DIV
E25K
G527R
C597Y
V1777M
B
Na$_v$1.8 (*SCN10A*)
I136V
R302Q
Q556H
E811Q
I1225T
I1403T
S1628R
P1753S
A1899QfsTer36
A1953V
1956 aa
DI
DII
DIII
DIV
V504M
F719S
S757G
R1568Ter
C
Ca$_v$1.2 (*CACNA1C*)
T96M
V376I
P1800S
P1851A
E1865K
2138 aa
DI
DII
DIII
DIV
A32T
I202T
G1700S (x2)
A1782T
T1870M
N2091S (x3)
T1815N
R1824K

Gene	Signal-to-Noise	Case	ExAC All	ExAC Euro.	ExAC African	ExAC Asian	ExAC Latino	ExAC Other
SCN5A	5 - 7.5 : 1	20-30%	3.95%	1.21%	4.00%	3.29%	2.13%	2.09%
CACNA1C	1.5 - 3.8 : 1	3-7%	1.85%	0.76%	1.14%	1.32%	0.95%	0.99%
SCN10A	1.2 : 1	6%	4.95%	1.89%	2.82%	3.66%	3.30%	2.31%
CACNB2	1.5 - 3.7 : 1	2-5%	1.36%	0.49%	1.38%	0.79%	1.01%	0.66%
PKP2	1.4 : 1	3%	2.18%	0.70%	2.55%	1.62%	1.14%	1.21%
KCNJ8	2.2 - 8.7 : 1	<0.5-2%	0.23%	0.10%	0.22%	0.13%	0.09%	0.00%
CACNA2D1	<1 - 1.8 : 1	0.6-1.8%	1.02%	0.40%	0.33%	0.80%	0.76%	0.33%
SCN1B	1.9 - 3.8 : 1	<0.5-1%	0.26%	0.10%	0.13%	0.21%	0.09%	0.33%
KCNH2	1 : 1.2	1.2%	1.41%	0.49%	1.02%	1.06%	1.02%	1.21%
TRPM4	1 : 2.5	1.2%	3.03%	1.10%	2.52%	2.38%	1.38%	1.76%
KCND3	1.2 : 1	0.6%	0.50%	0.26%	0.40%	0.15%	0.24%	0.33%
SCN2B	1.2 : 1	0.6%	0.52%	0.25%	0.12%	0.39%	0.18%	0.44%
SCN3B	1.5 : 1	0.6%	0.40%	0.20%	0.16%	0.24%	0.17%	0.11%
ABCC9	<1 : 2.2	<0.5%	1.12%	0.44%	0.86%	0.78%	0.54%	1.21%
FGF12	<6.2 : 1	<0.5%	0.08%	0.03%	0.04%	0.08%	0.03%	0.00%
GPD1L	<1 : 1	<0.5%	0.58%	0.21%	0.49%	0.47%	0.27%	0.22%
HCN4	<1 : 2.6	<0.5%	1.32%	0.55%	1.01%	0.90%	0.57%	0.66%
KCND2	<1.1 : 1	<0.5%	0.47%	0.18%	0.81%	0.18%	0.15%	0.11%
KCNE3	<1.9 : 1	<0.5%	0.26%	0.10%	0.20%	0.17%	0.16%	0.22%
KCNE1L	<4.5 : 1	<0.5%	0.11%	0.05%	0.06%	0.08%	0.02%	0.11%
RANGRF	<1.2 : 1	<0.5%	0.43%	0.13%	0.40%	0.33%	0.31%	0.11%
SEMA3A	<1 : 2.9	<0.5%	1.47%	0.38%	2.13%	1.03%	1.08%	0.66%
SLMAP	<1 : 1.8	<0.5%	0.88%	0.43%	0.39%	0.50%	0.47%	0.22%
Total			28.30%	10.40%	23.10%	20.50%	16.00%	15.20%

Background Rate of Rare Variants in ExAC Exomes

Kapplinger … Ackerman. *Circ Cardiovasc Genet*. 2015 (In-Press)

BrS, genetics

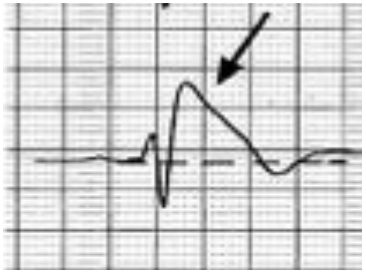
Which genes do play a role?:

- SCN5a probably yes, but……
- All the other genes doubtful

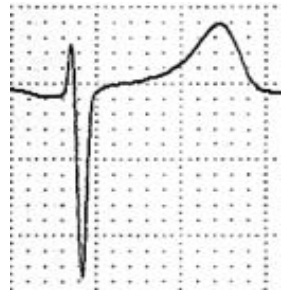
- Modifying role for all?
- some stronger than others?

Genetics of Brugada Syndrome: new strategy

Genome Wide Association Study



N=312
Type-I BrS index cases



N=1115
General population

Bezzina et al., Nature Genetics 2013

Brugada Syndrome patients ascertained at 13 clinical centers in Europe, U.S., Japan

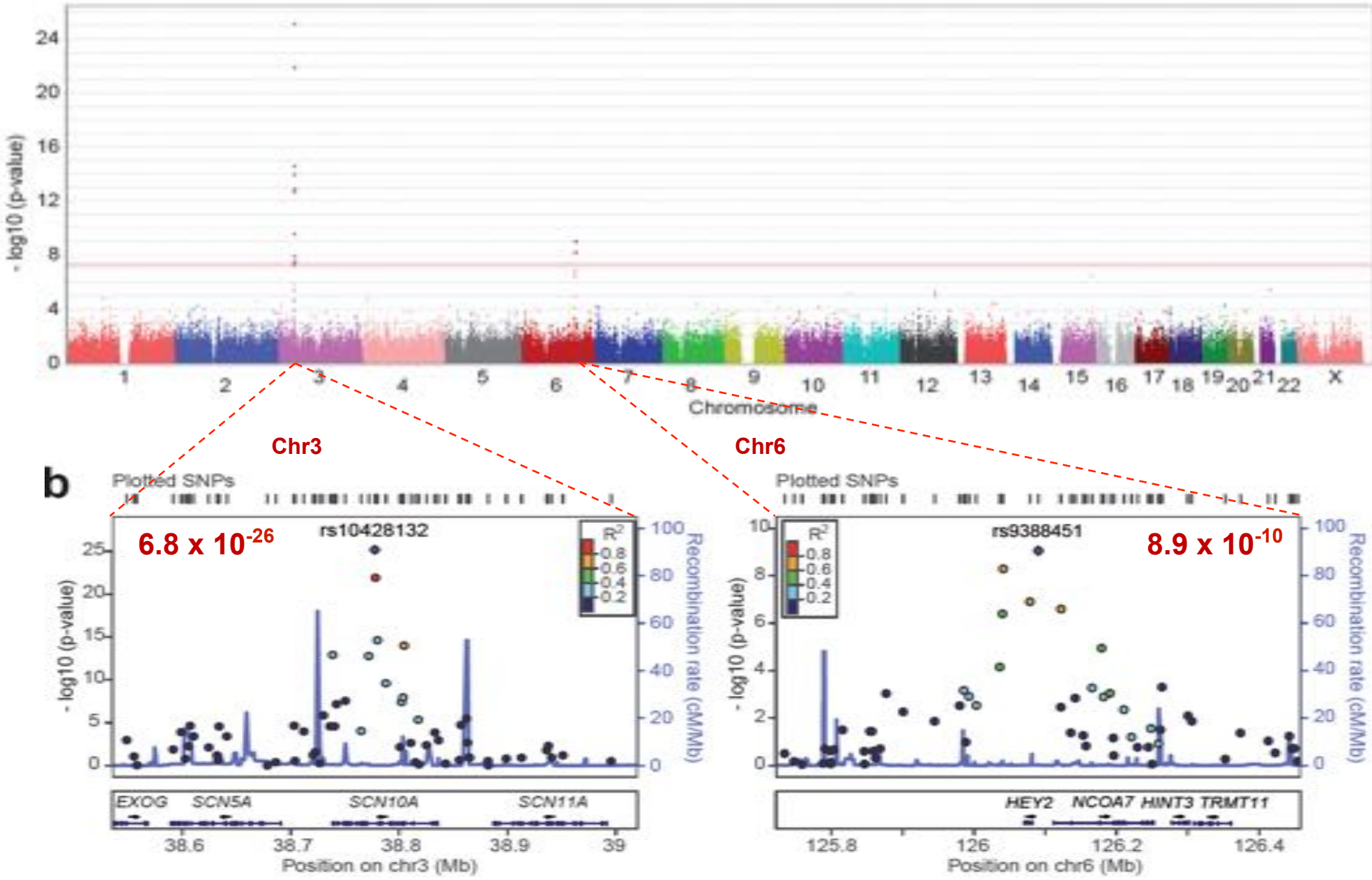
Clinical Centre	*n*	*Males*	*Age at diagnosis*	*Baseline BrS ECG*	*Symptoms* [1]	*SCN5A carriers*
Nantes (FR)	422	323 (77%)	48 (+/-13)	295 (46%)	153 (36%)	71 (17%)
Pavia (IT)	126	105 (83%)	42 (+/-14)	46 (37%)	16 (13%)	20 (16%)
Amsterdam (NL)	101	84 (83%)	48 (+/-13)	46 (46%)	52 (51%)	23 (23%)
Paris (FR)	93	84 (90%)	44 (+/-13)	56 (60%)	28 (30%)	15 (16%)
Utica (US)	74	49 (66%)	42 (+/-17)	24 (32%)	41 (55%)	10 (14%)
Other Centers [2]	90	71 (79%)	44 (+/-14)	47 (52%)	42 (47%)	21 (23%)
Japan [3]	208	190 (91%)	46 (+/-15)	95 (46%)	84 (40%)	29 (14%)

[1] Ventricular tachycardia, ventricular fibrillation, syncope and near syncope

[2] Munster (DE), London (UK), Copenhagen (DK), Munich (DE), Nashville (US)

[3] Osaka, Nagasaki, Shiga

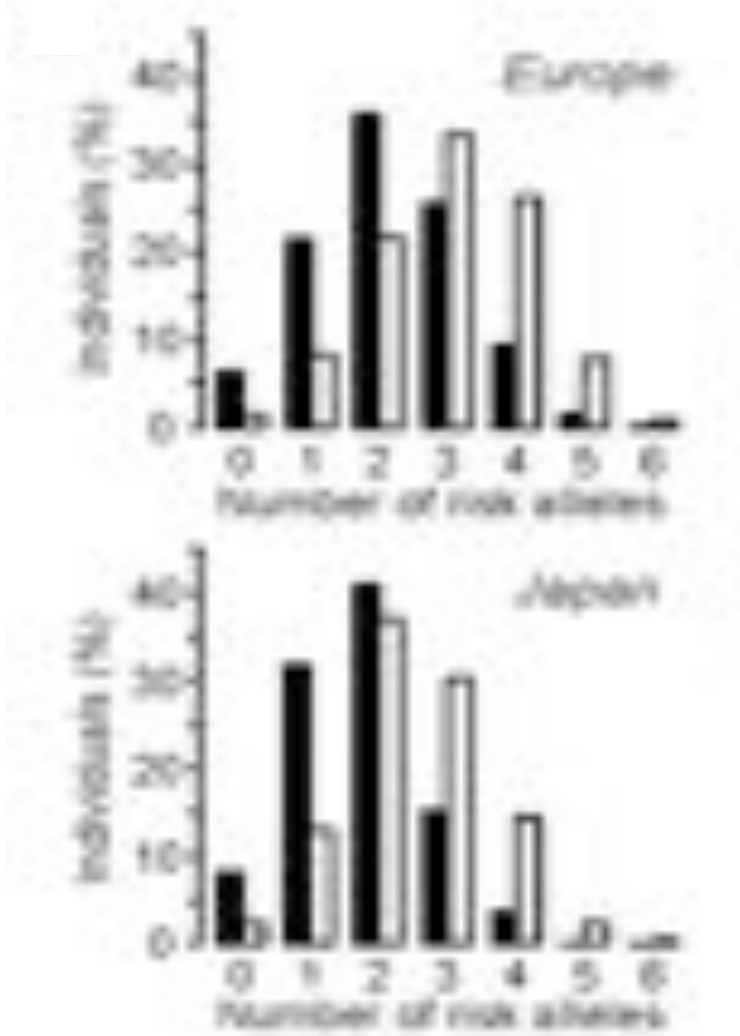
Identification of 2 loci associated with BrS



Cumulative effect of alleles at the three loci on susceptibility to BrS

Controls

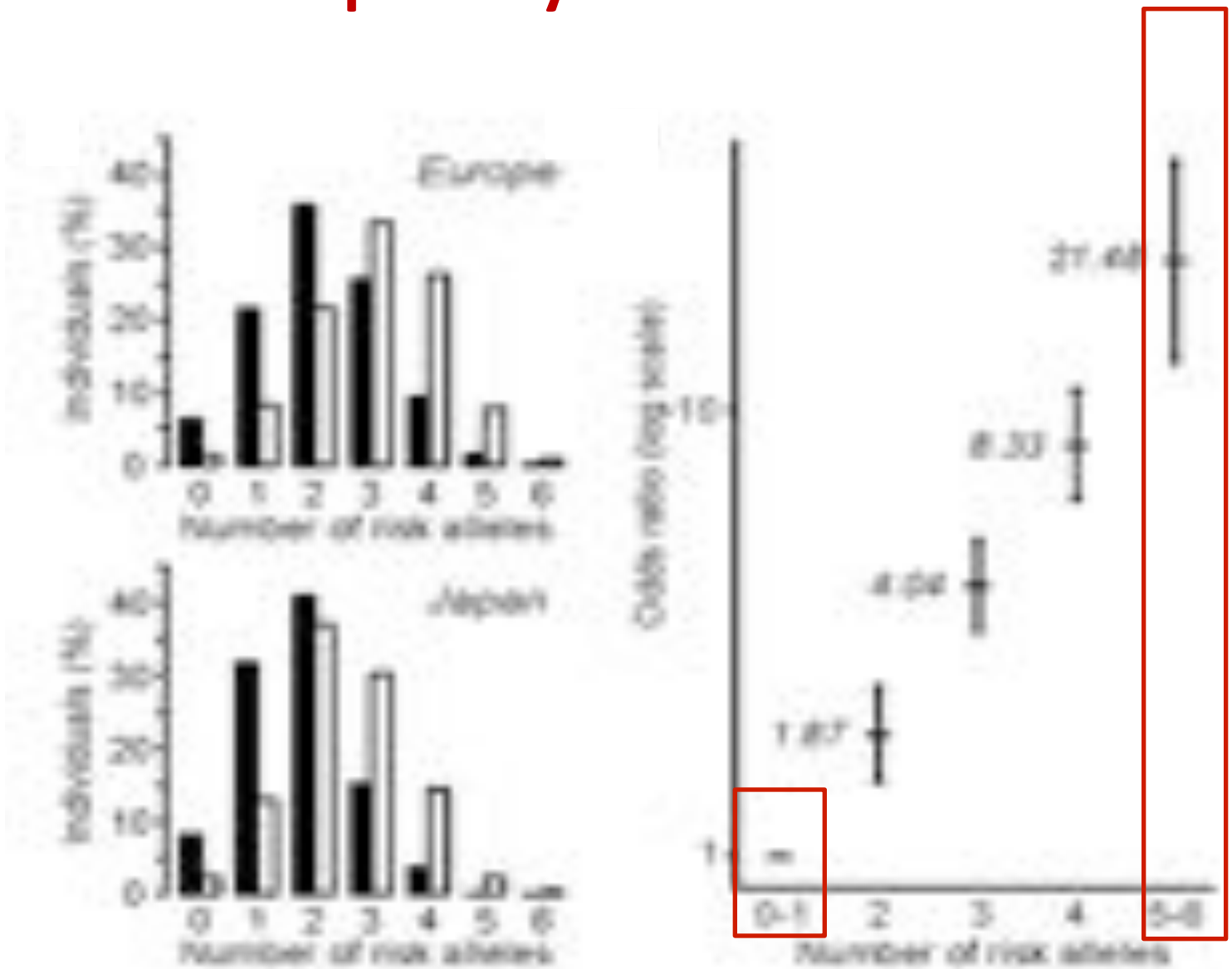
BrS cases



Cumulative effect of alleles at the three loci on susceptibility to BrS

Controls

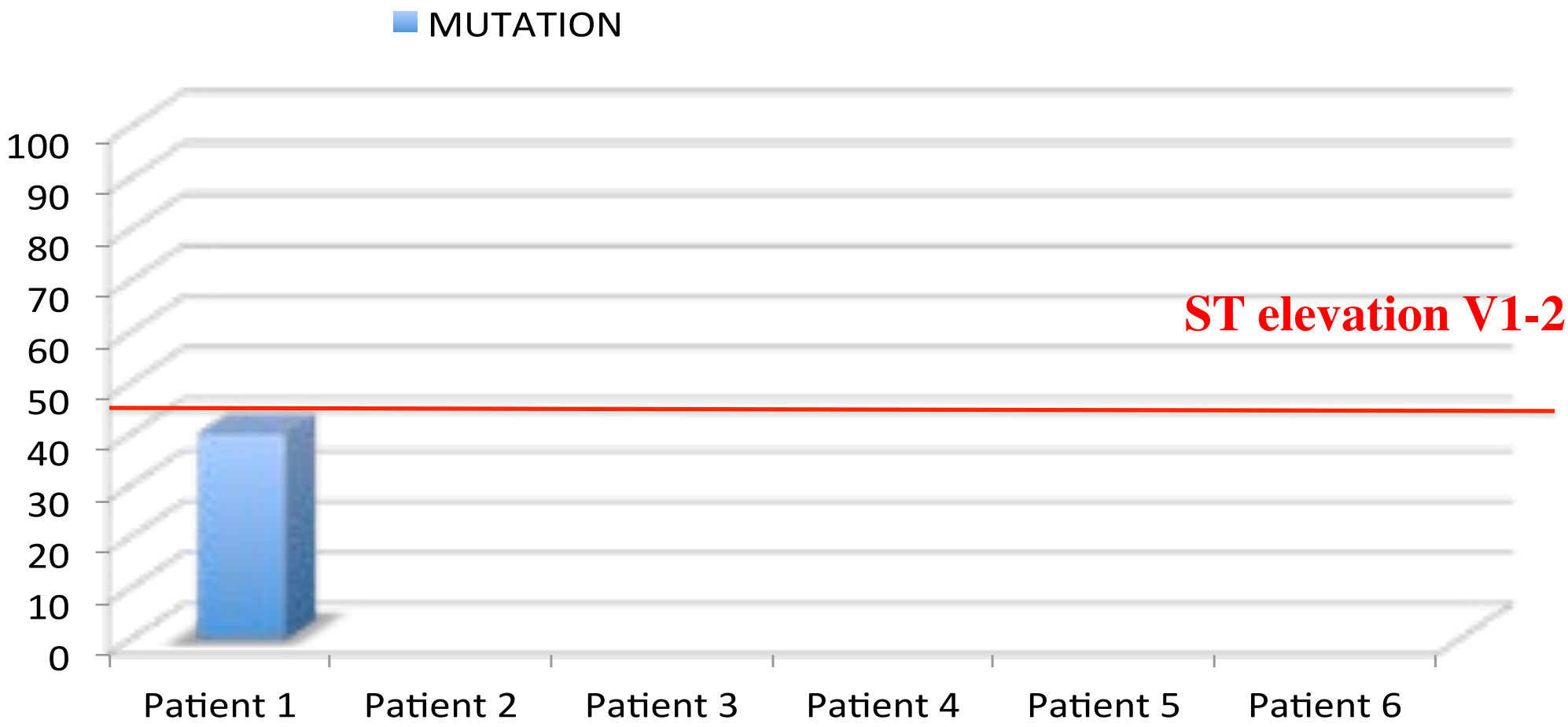
BrS cases



Brugada syndrome, genetics

Conclusions:

- Genetically heterogeneous
- SCN5a 15-30% of patients
- likely oligogenetic


MUTATION
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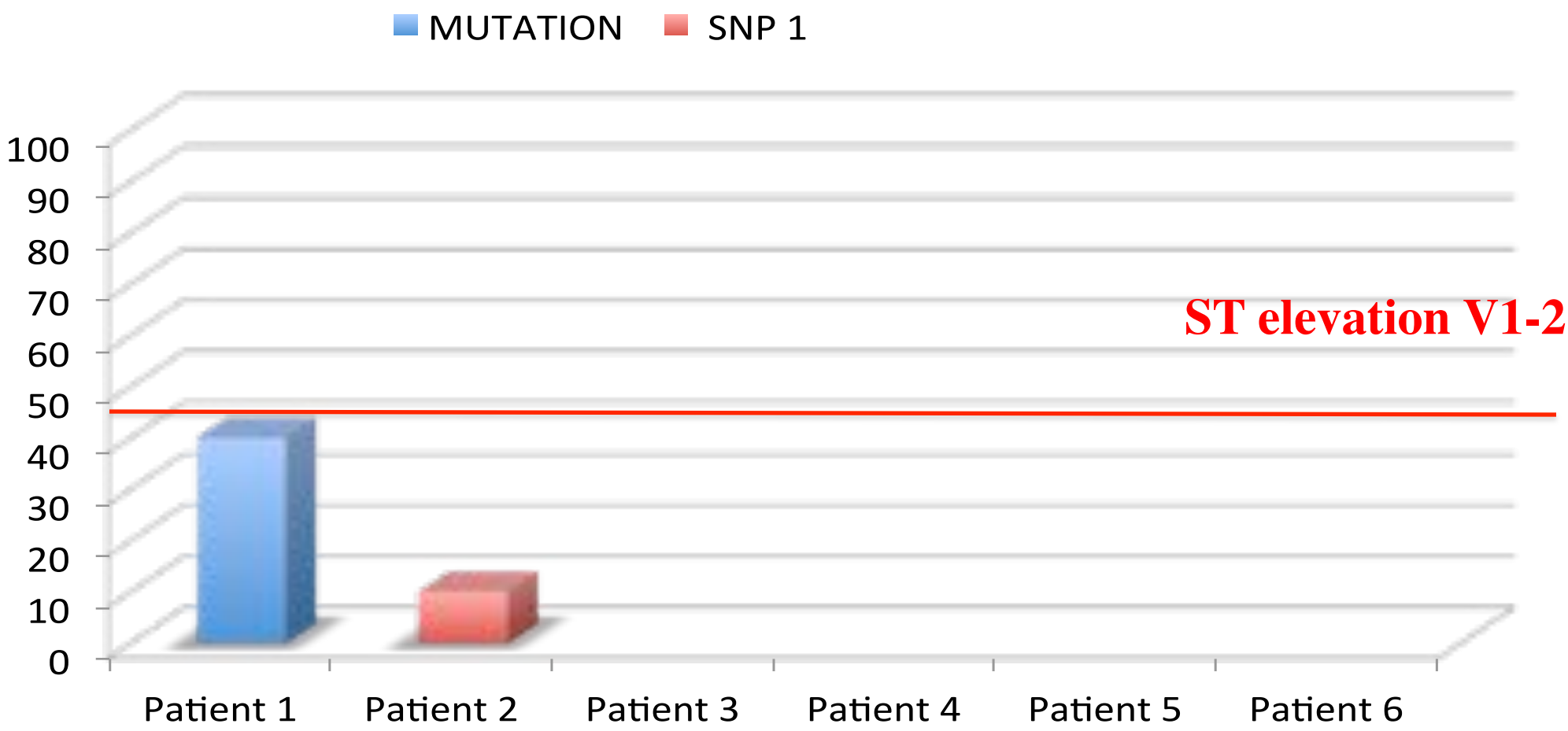
ST elevation V1-2
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6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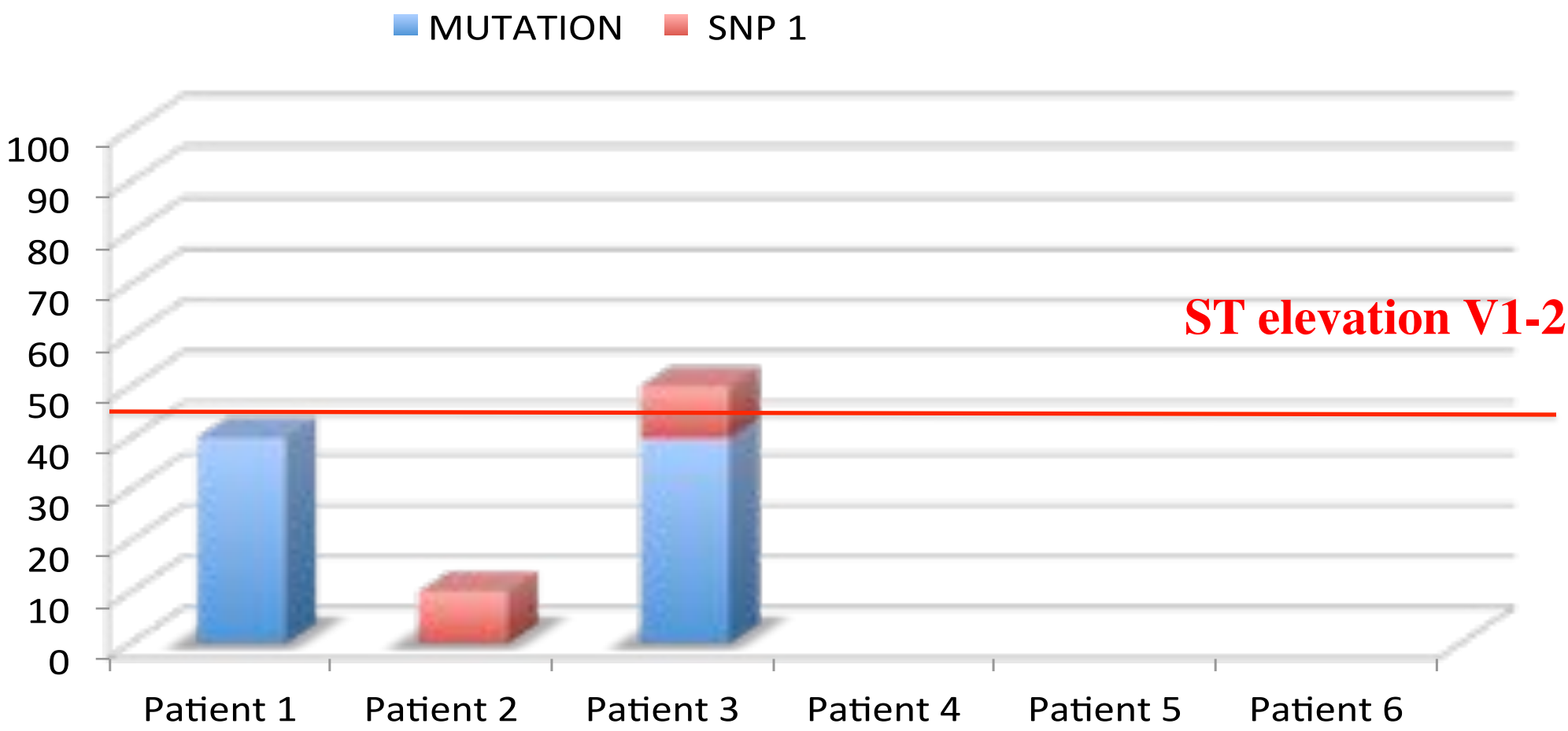
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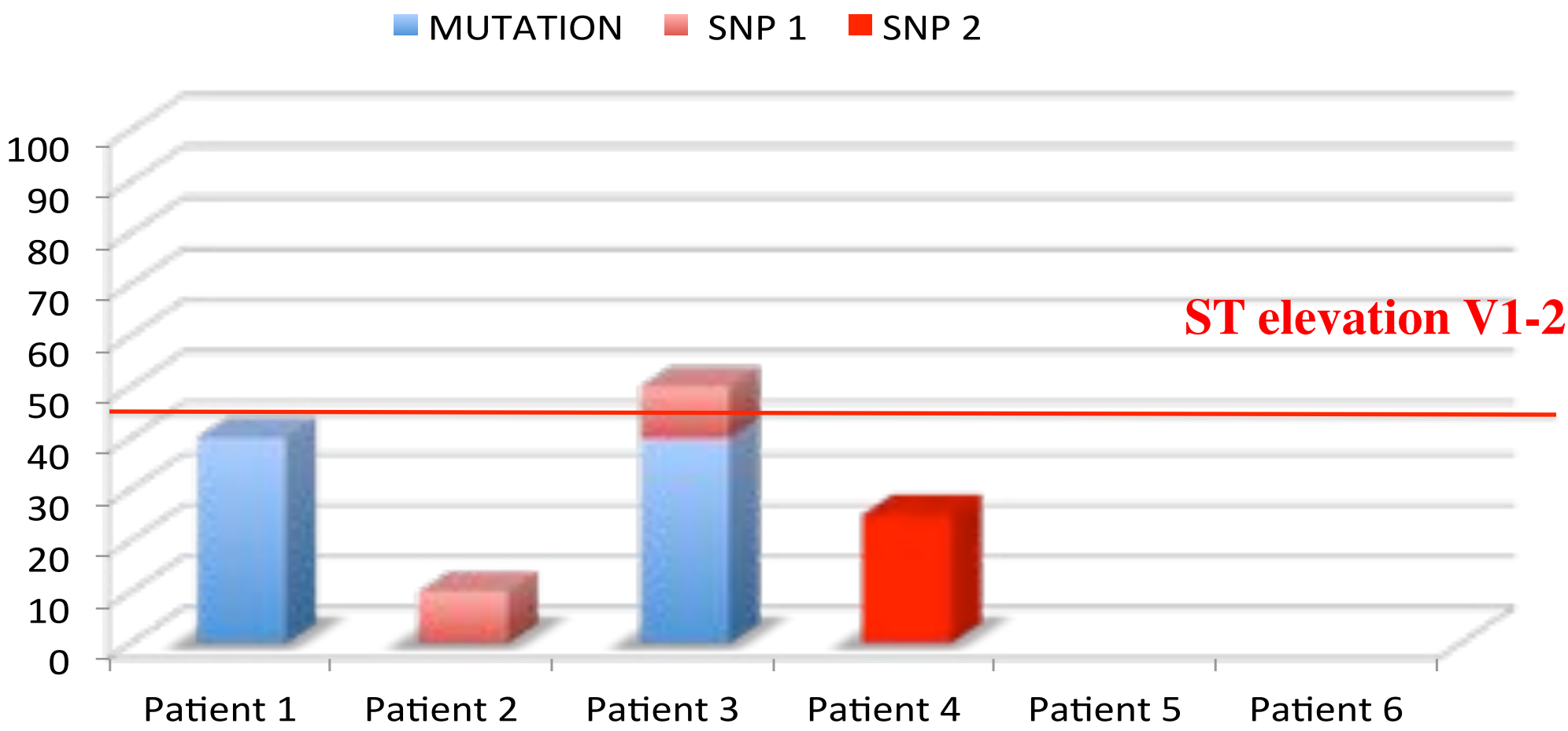
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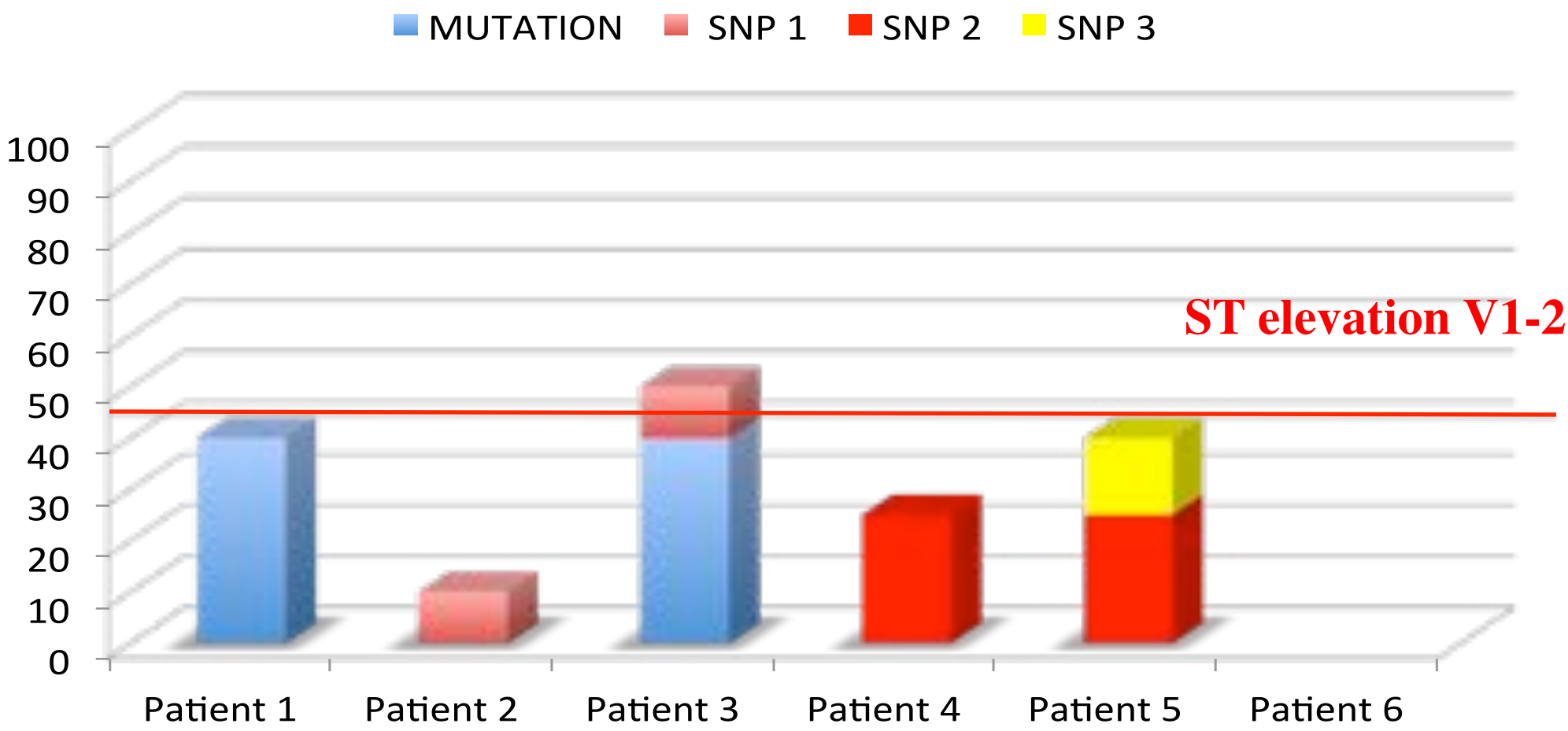
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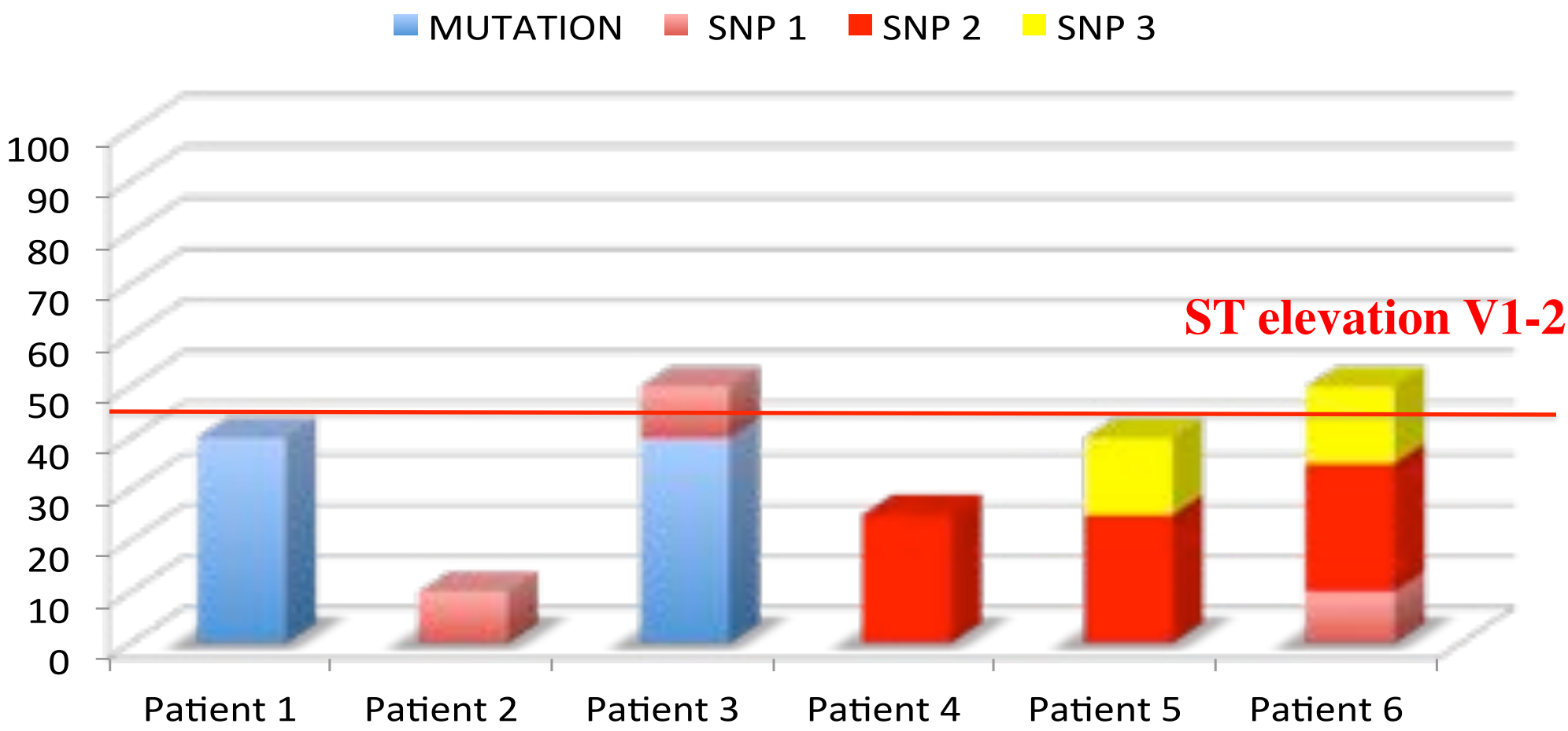
MUTATION
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ST elevation V1-2
Patient 1
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Patient 4
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Patient 6

Brugada syndrome, genetics

whether this impacts on prognosis remains to be proven

Brugada syndrome
Genotype-phenotype relation

Type of *SCN5A* mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies

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Tamara T. Koopmann, PhD,† Michael W. Tanck, PhD,# Zahurul A. Bhuiyan, MD, PhD,**
Frederic Sacher, MD,†† Florence Kyndt, PharmD, PhD,‡§¶‡‡ Jean-Jacques Schott, PhD,‡§‖¶
J. Albuisson, MD,‡§¶‡‡ Philippe Mabo, MD,§§ Connie R. Bezzina, PhD,†** Herve Le Marec, MD, PhD,‡§‖¶
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*: Meregalli et al. Heart Rhythm 6, 341-348 , 2009

Brugada syndrome
Genotype-phenotype relation

With more severe Na-channel 

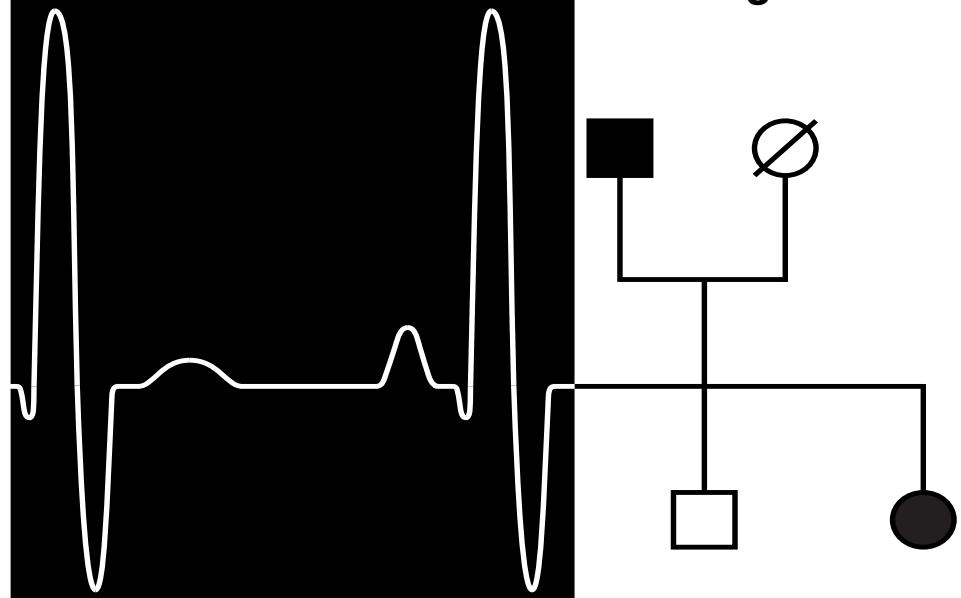
- there are more symptoms
- wider PR-interval
- Wider PR and QRS after class 1a

*: Meregalli et al. Heart Rhythm 6, 341-348 , 2009

20 years cardiogenetics in the Netherlands

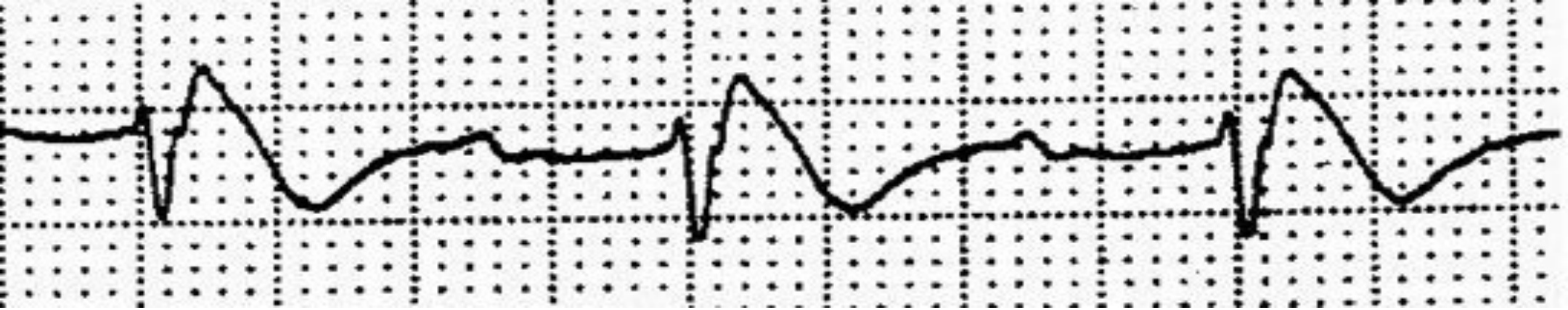
Amsterdam, the Netherlands
December 4th 2015

For information and registration see www.20yrsCG.nl



Organising committee:
Karin Y. van Spaendonck
J. Peter van Tintelen
Arthur Wilde


NOSTALGIA
Thank you



Conclusions:

- still much to learn!
- expanding genetics (pathophysiol.), role SCN5a

- symptomatic patients are at risk, ICD treatment
- asymptomatic patients, risk ill defined.
- plea for large registries!!!!