Pediatric and Congenital Rhythm Congress VII

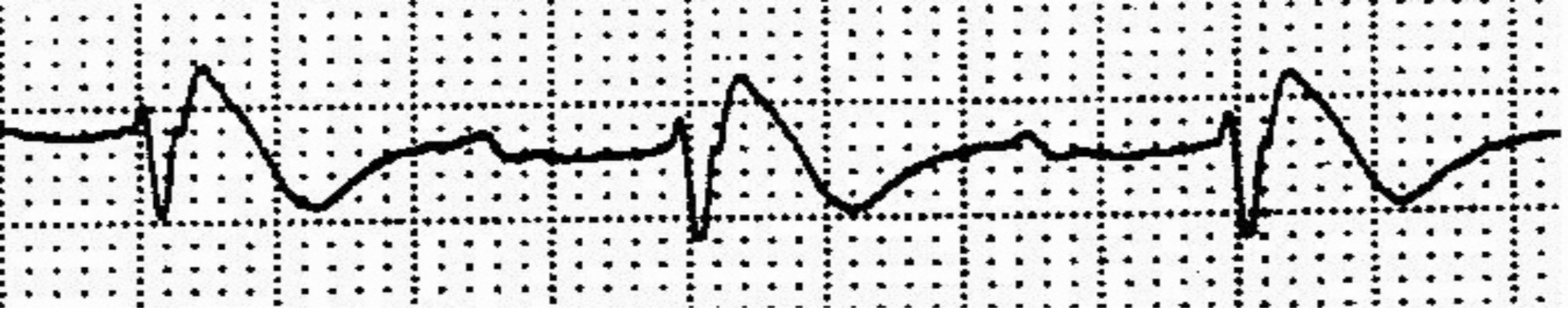
4 - 7 February 2017

Thessaloniki/GREECE

PEDIRHYTHM VII

The Genetics of Brugada syndrome

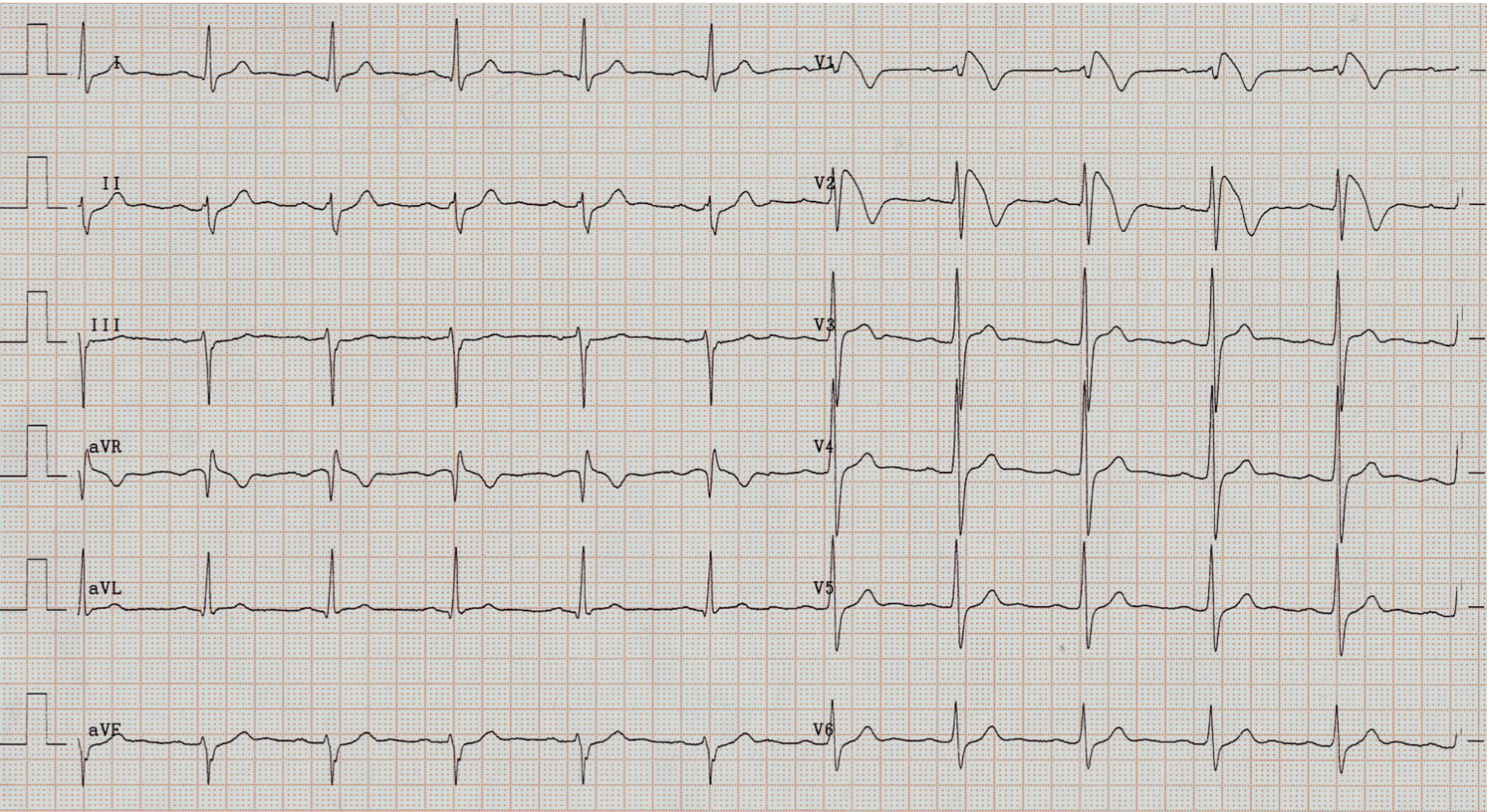
Arthur A.M. Wilde

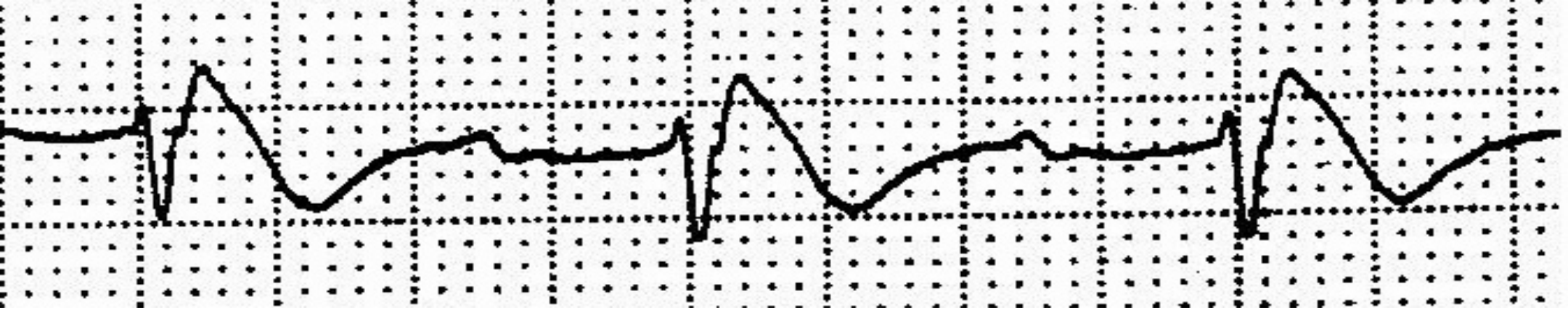


Brugada syndrome

The diagnosis

Male 39 years (resuscitated)





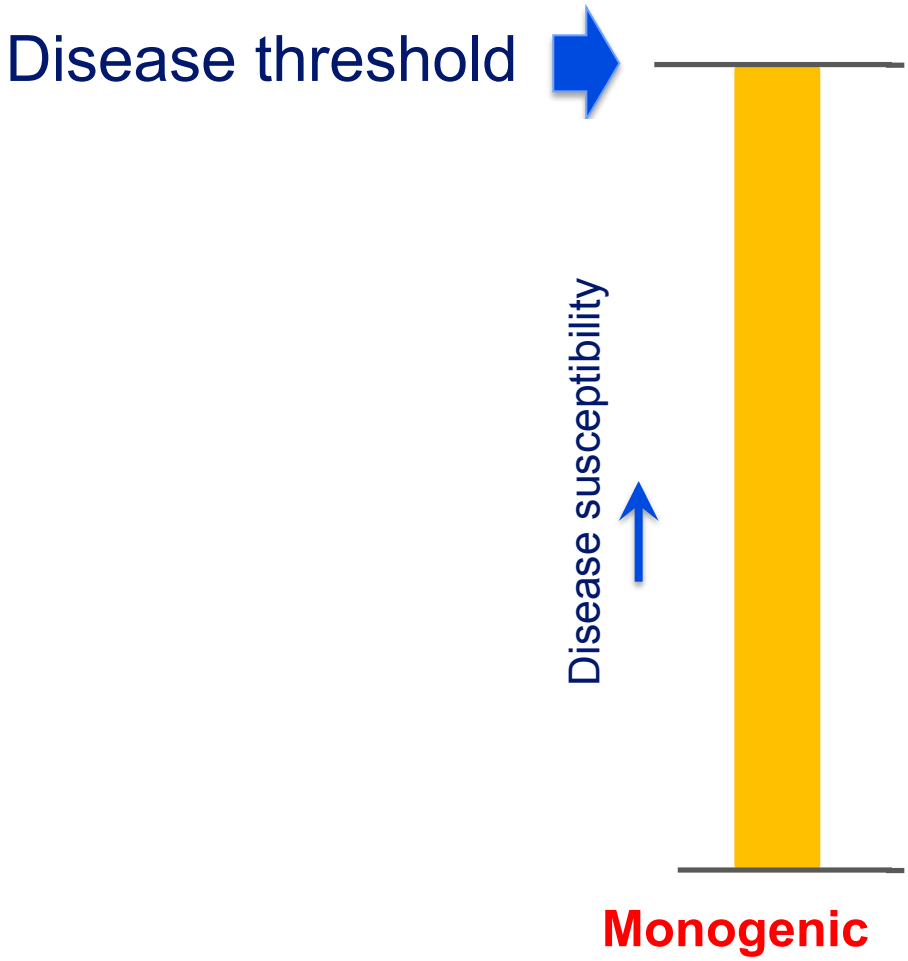
Brugada syndrome

Genetics

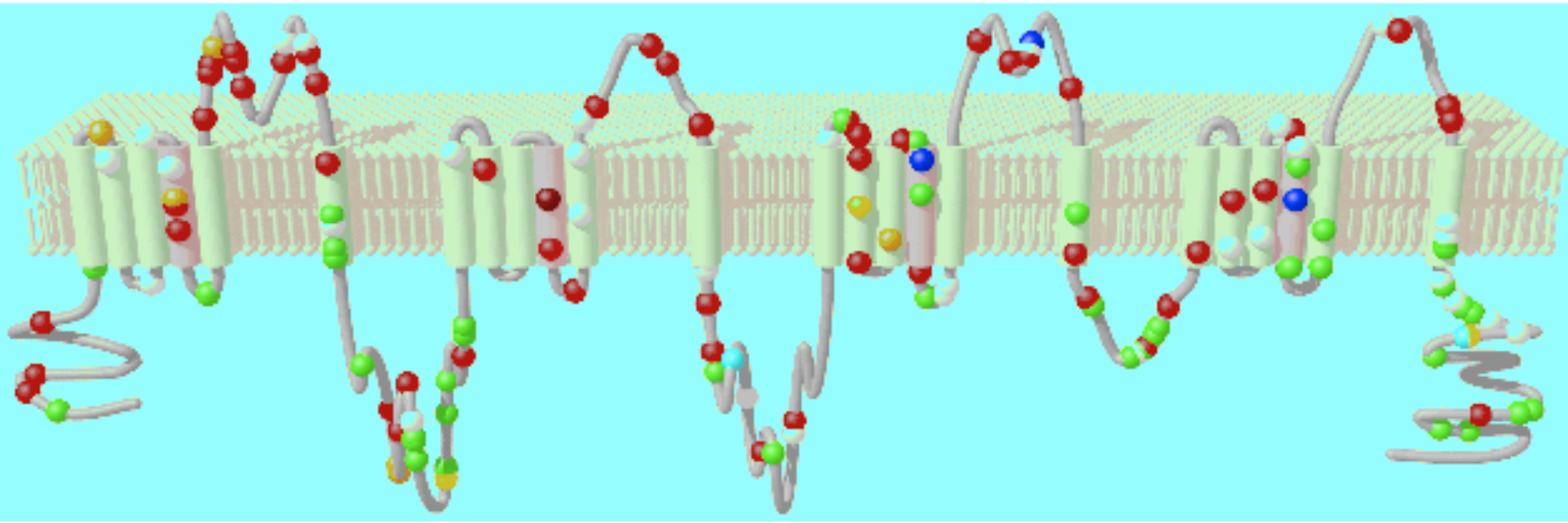
Brugada syndrome, genetics

- Genetically heterogeneous

BrS a monogenetic disorder?



SCN5A (3p21) mutations



● : Brugada syndrome

● : (P)CCD

● : LQTS

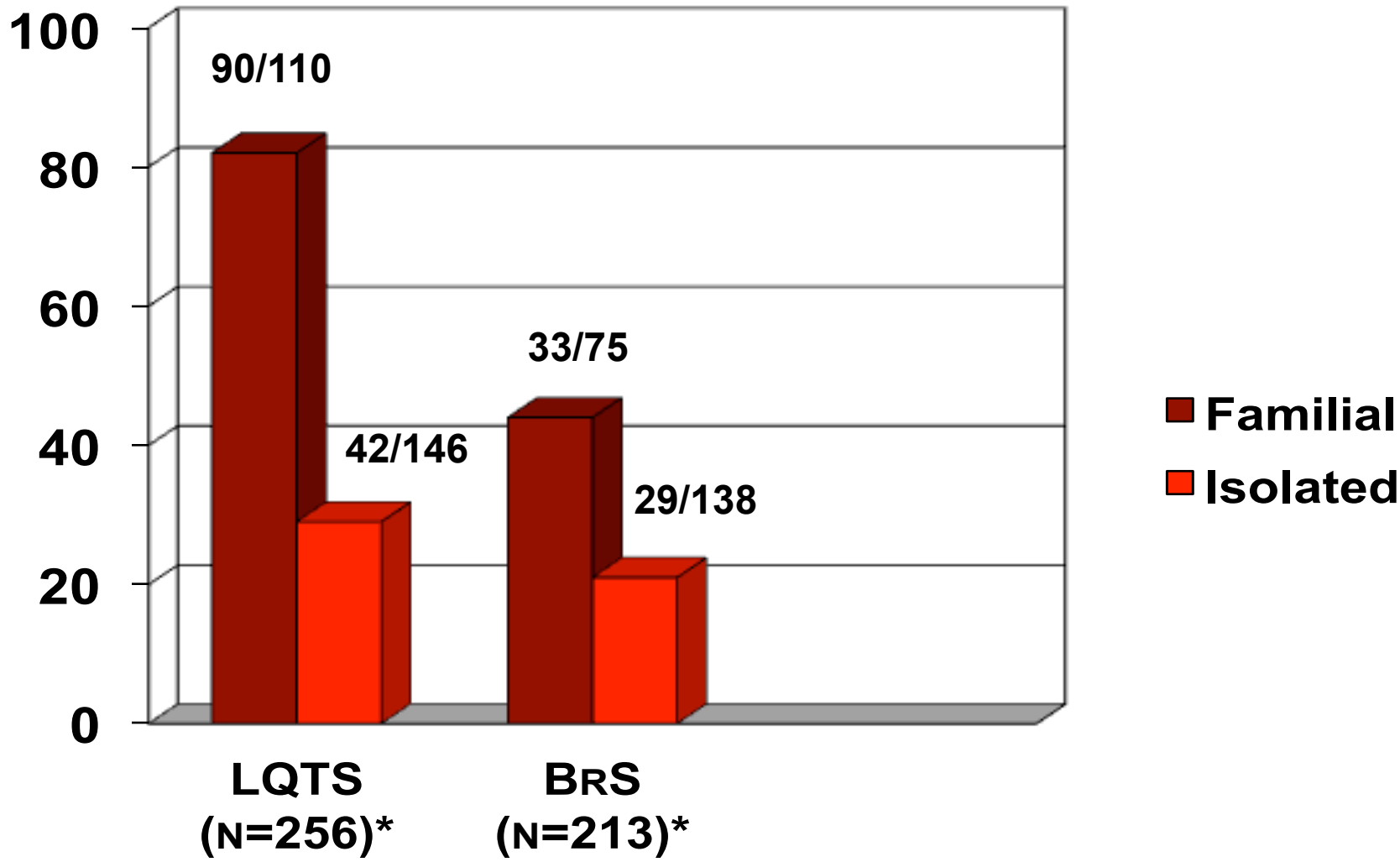
Brugada syndrome, genetics

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

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

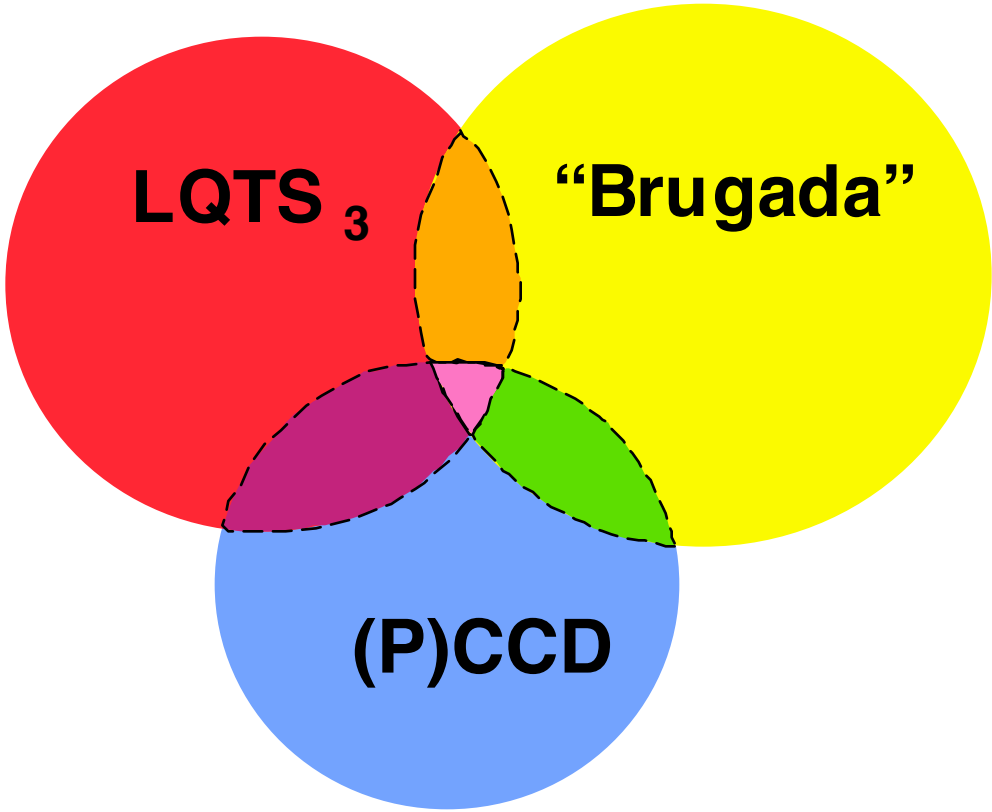
3/10 (30%) : Vatta et al., 2002 (Japan, Thailand)

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



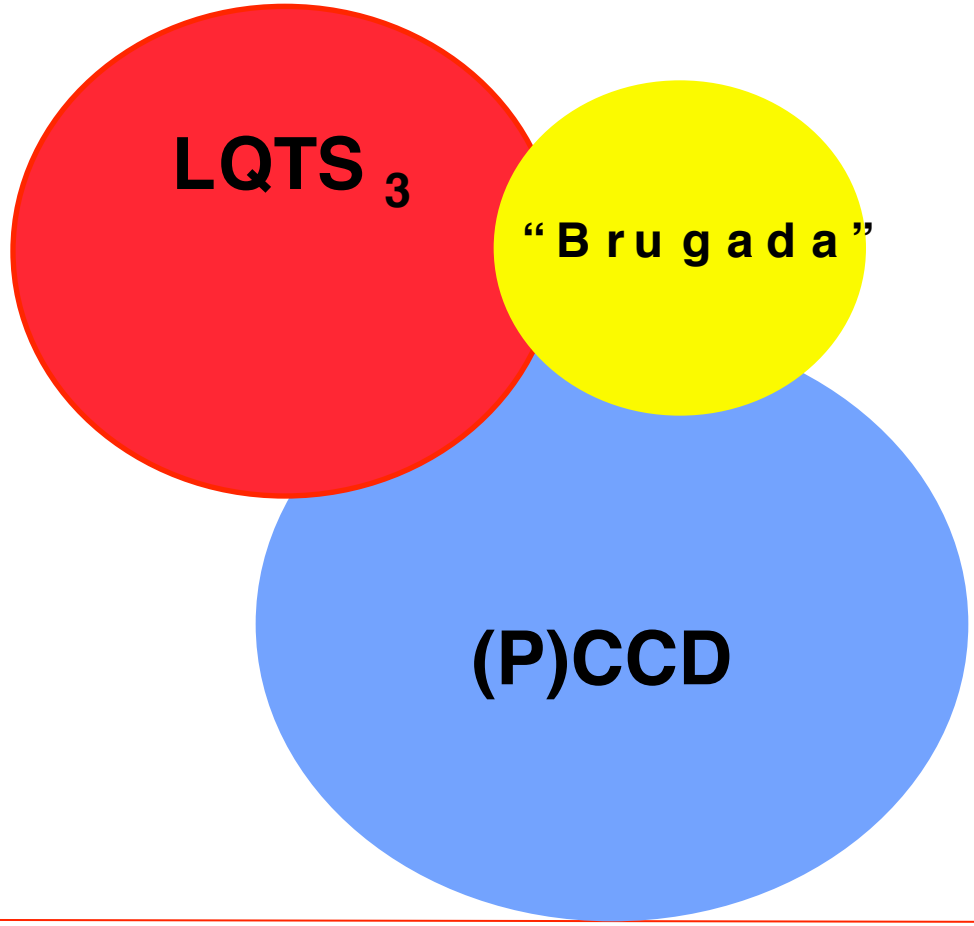
Hofman et al., Circulation 2013

SCN5A: cardiac sodium channel mutations



SCN5A: cardiac sodium channel mutations

In Pediatric patients?



OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

PEDIATRICS

Fever-Induced Life-Threatening Arrhythmias in Children Harboring an *SCN5A* Mutation

AUTHORS: Priya Chockalingam, MBBS,[a] Lukas A. Rammeloo, MD,[b] Pieter G. Postema, MD,[a] Jarda Hruda, MD,[b] Sally-Ann B. Clur, MD,[c] Nico A. Blom, MD, PhD[c] and Arthur A. Wilde, MD, PhD[a]

[a]Department of Cardiology, Heart Failure Research Centre, and [c]Department of Pediatric Cardiology, Academic Medical Centre, Amsterdam, Netherlands; and [b]Department of Pediatric Cardiology, VU University Medical Centre, Amsterdam, Netherlands

KEY WORDS
arrhythmia, children, childhood immunization, fever, *SCN5A* sodium-channel mutation

ABBREVIATIONS
BrS—Brugada syndrome
bpm—beats per minute
ECG—electrocardiogram
VT—ventricular tachycardia

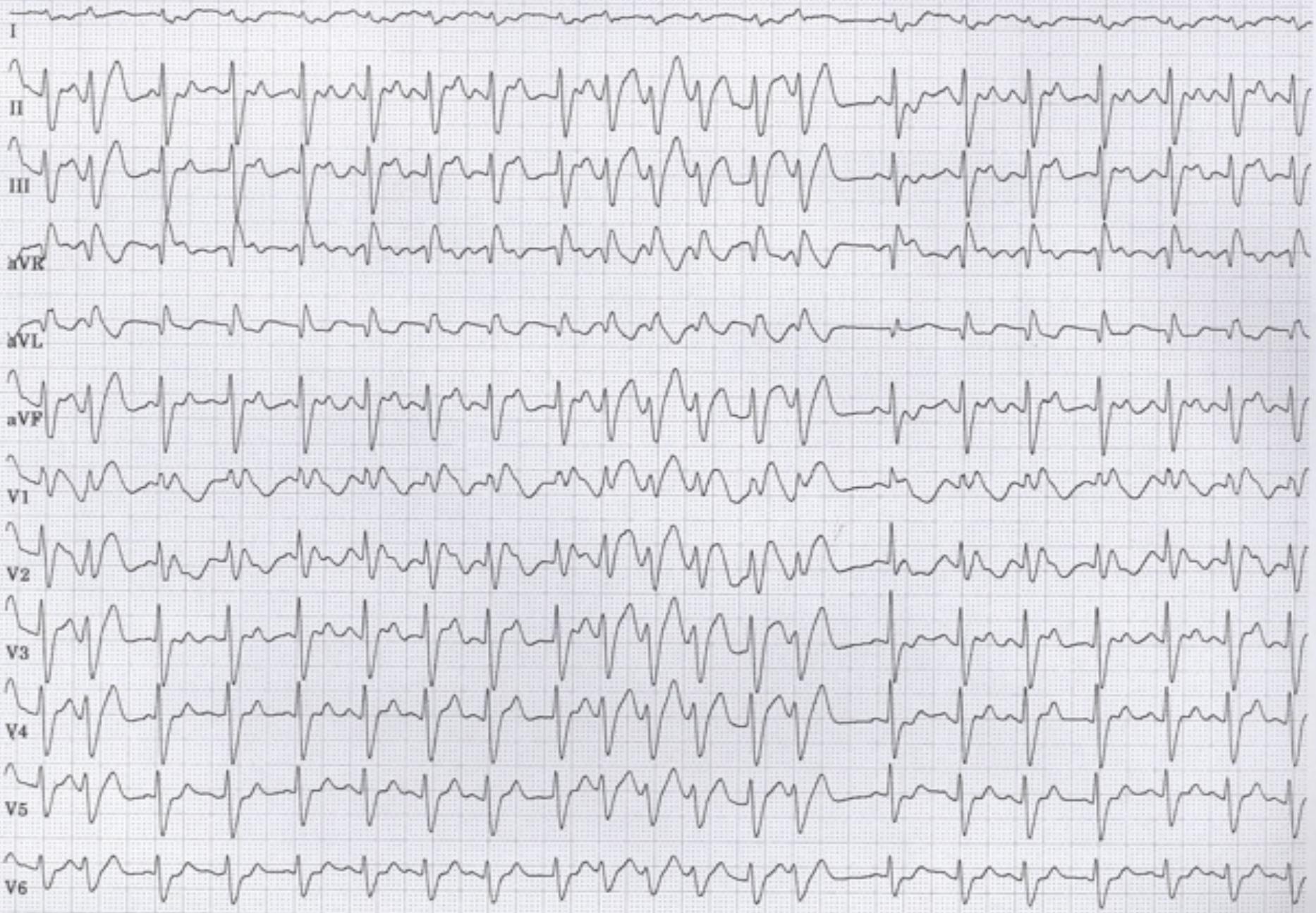
www.pediatrics.org/cgi/doi/10.1542/peds.2010-1688

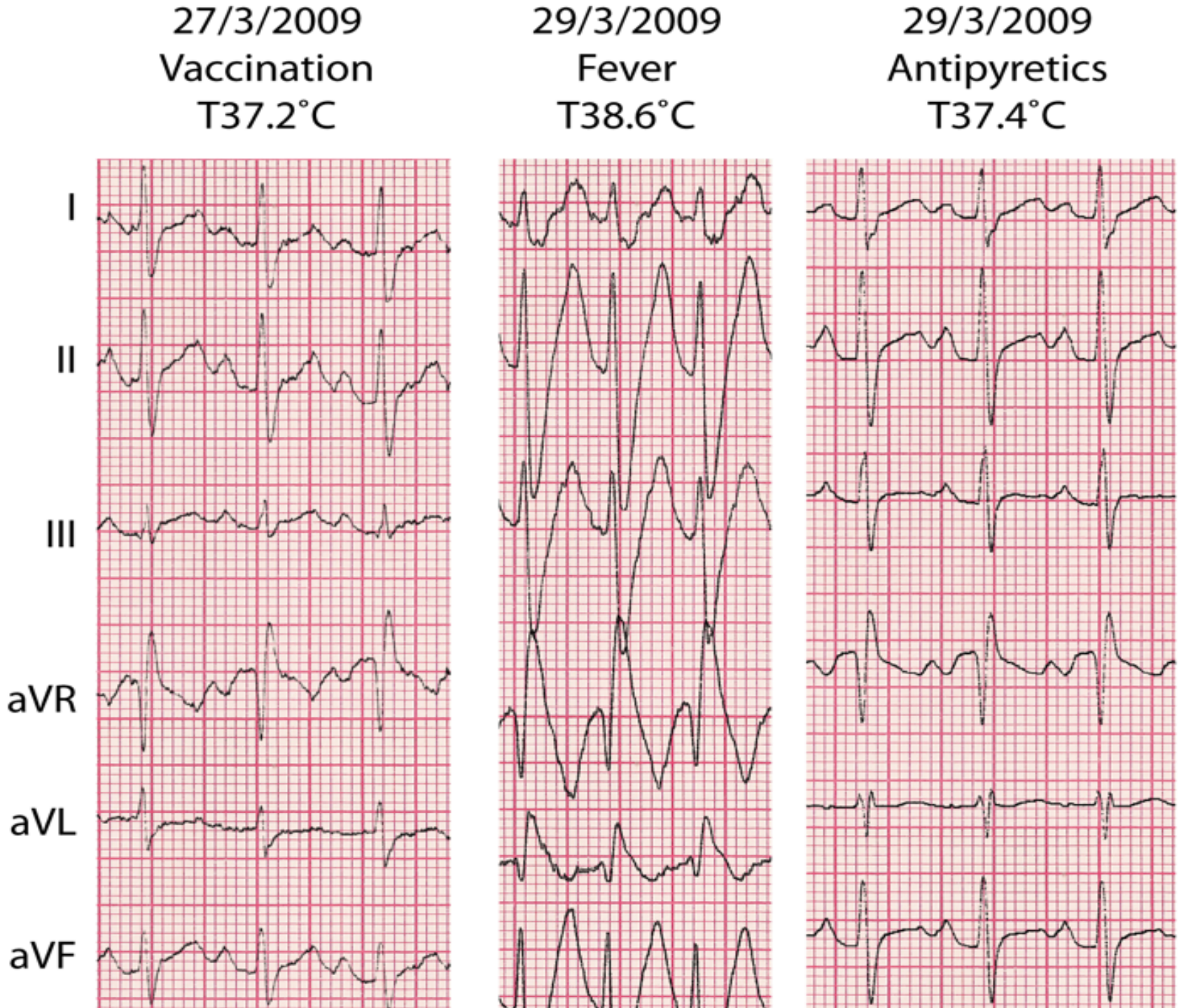
abstract

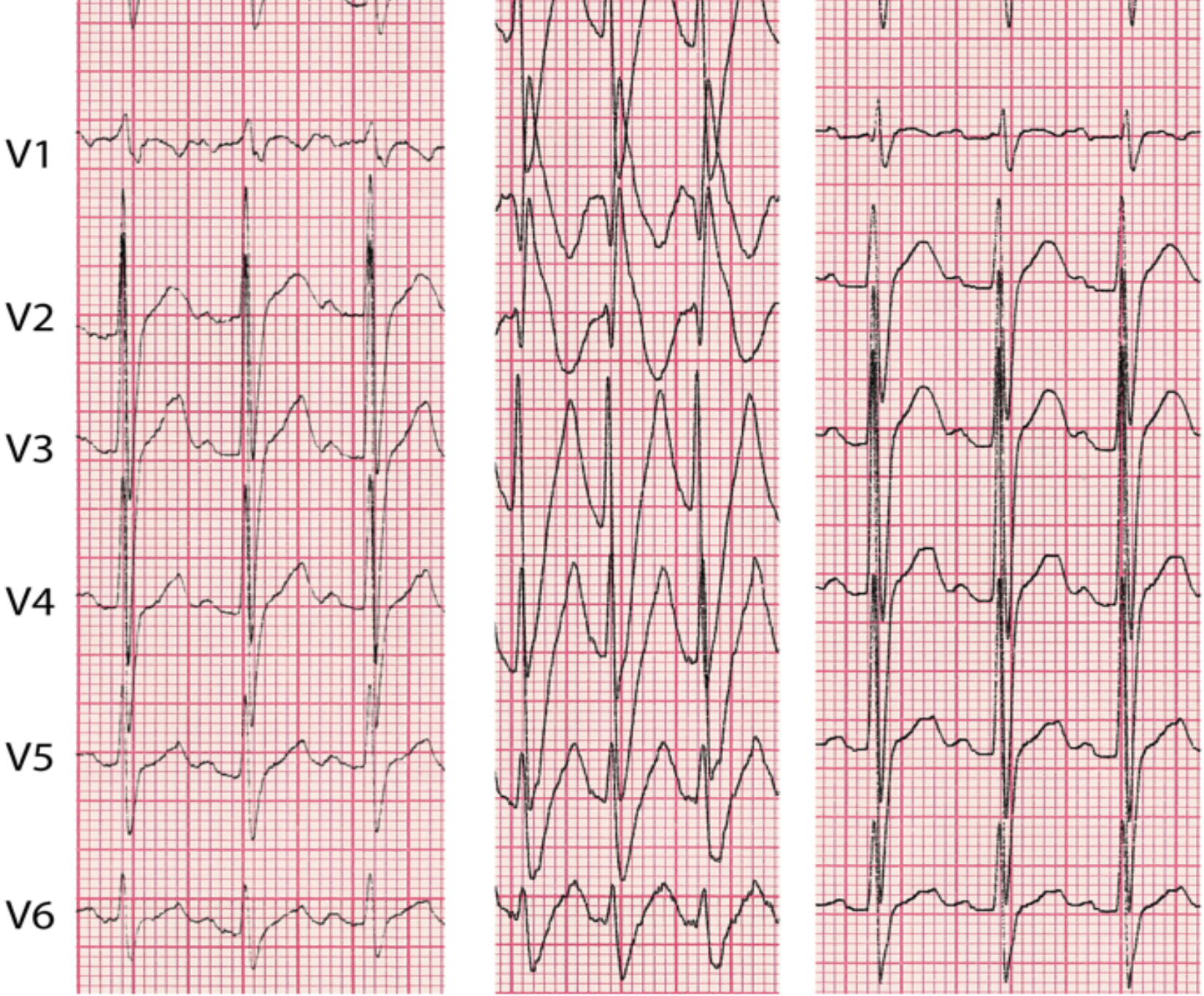
Cardiac channelopathies caused by *SCN5A* mutation are well tolerated by most patients. However, the dramatic presentation of a previously healthy 4-month-old girl with life-threatening arrhythmias and the subsequent findings in the child and her family provide evidence that loss-of-function sodium-channel mutations can present very early in life. An *SCN5A* mutation was detected in the infant, her brother, and their father. Both the siblings manifested recurrent serious arrhythmias during febrile episodes, which followed immunization, as well as fever of nonspecific origin. Management consisted of prompt antipyretic measures, hospitalization with vigorous monitoring during immunization and febrile episodes, and prevention of tachycardia-induced conduction disturbance with β-blockers. *Pediatrics* 2011;127:e000

RITMERAPPORT

ID: 6-[illegible]-2008 20:16:10 VUmc Amsterdam IC-8D




27/3/2009
Vaccination
T37.2°C
29/3/2009
Fever
T38.6°C
29/3/2009
Antipyretics
T37.4°C
I
II
III
aVR
aVL
aVF


V1
V2
V3
V4
V5
V6

Brugada syndrome, genetics

	Locus	Ion channel	Gene/Protein
BrS 1	3p21	I_{Na} ↓	SCN5A, $Na_v1.5$
BrS 2	3p24	I_{Na} ↓	GPD1L
BrS 3	12p13.3	I_{Ca} ↓	CACNA1C, $Ca_v1.2$
BrS 4	10p12.33	I_{Ca} ↓	CACNB2b, Ca_vb2b
BrS 5	19q13.1	I_{Na} ↓	SCN1B, $Na_v\beta1$
BrS 6	11q13-q14	I_{to} ↑	KCNE3, MiRP2
BrS 7	11q23.3	I_{Na} ↓	SCN3B, $Na_v\beta3$
BrS 8	12p11.23	$I_{K.ATP}$ ↑	KCNJ8
BrS 9	7q21-q22	I_{Ca} ↓	CACNA2D1, Cavα2δ
BrS 10	1p13.3	I_{to} ↑	KCND3
BrS 11	17p13.1	I_{Na} ↓	MOG1
BrS 12	3p21.2-p14.3	I_{Na} ↓	SLMAP
BrS 13	12p12.1	$I_{K.ATP}$ ↑	ABCC9, SUR2A
BrS 14	11q23	I_{Na} ↓	SCN2B

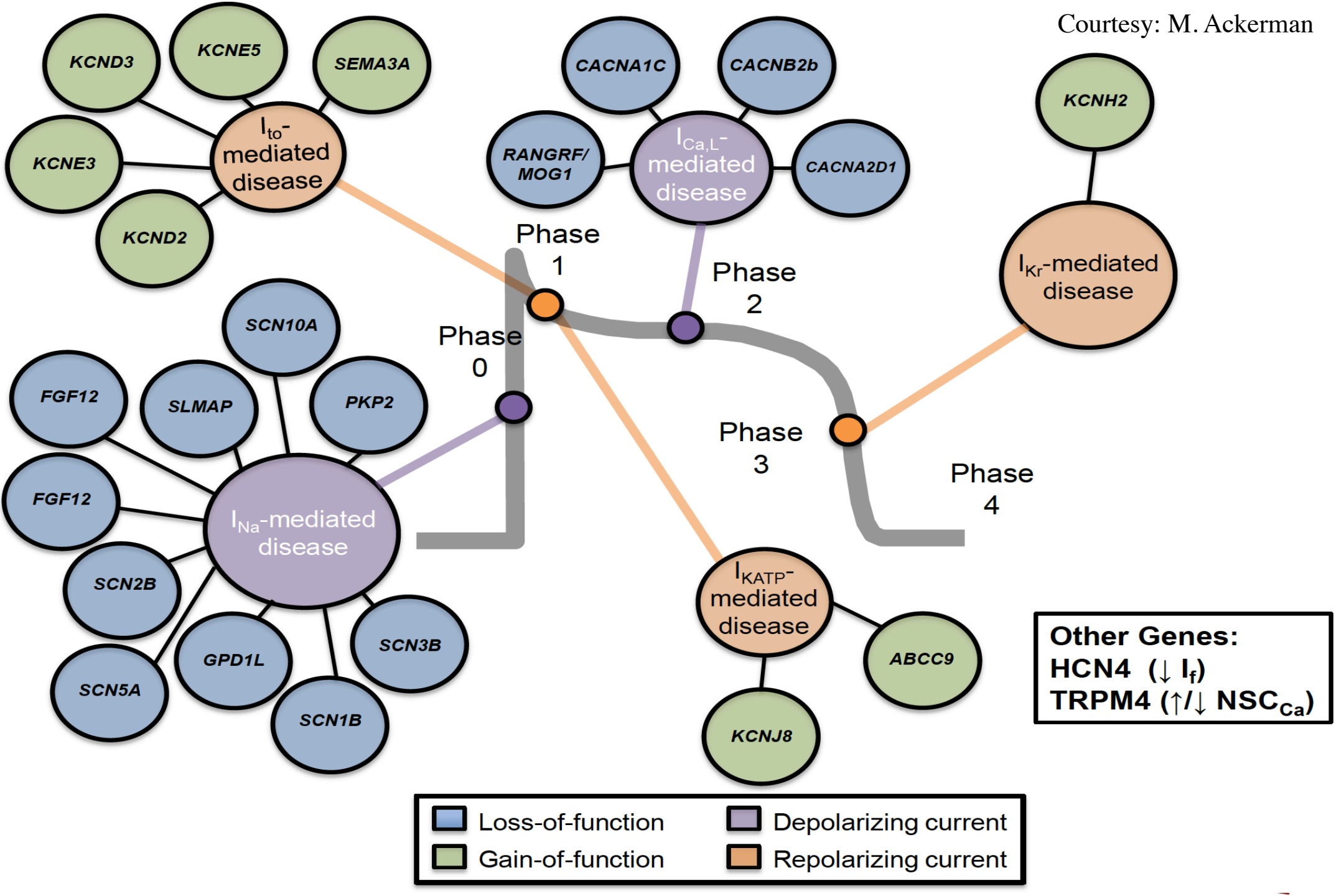
Brugada syndrome, genetics

	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

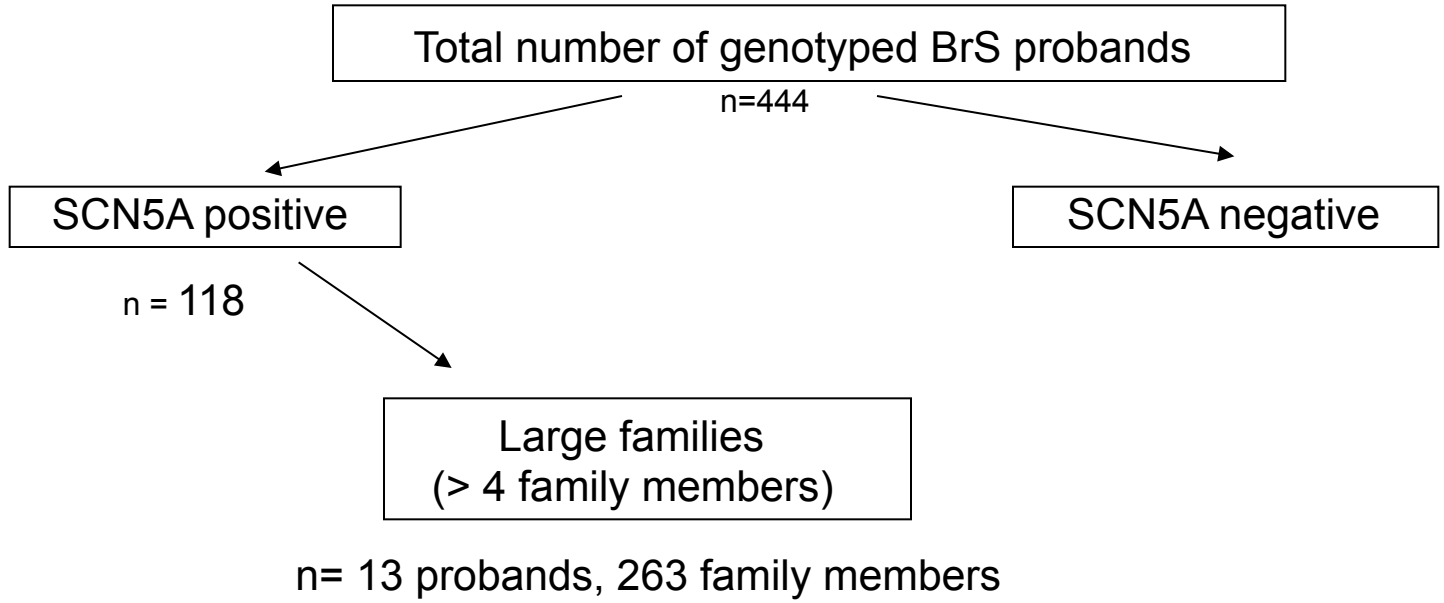


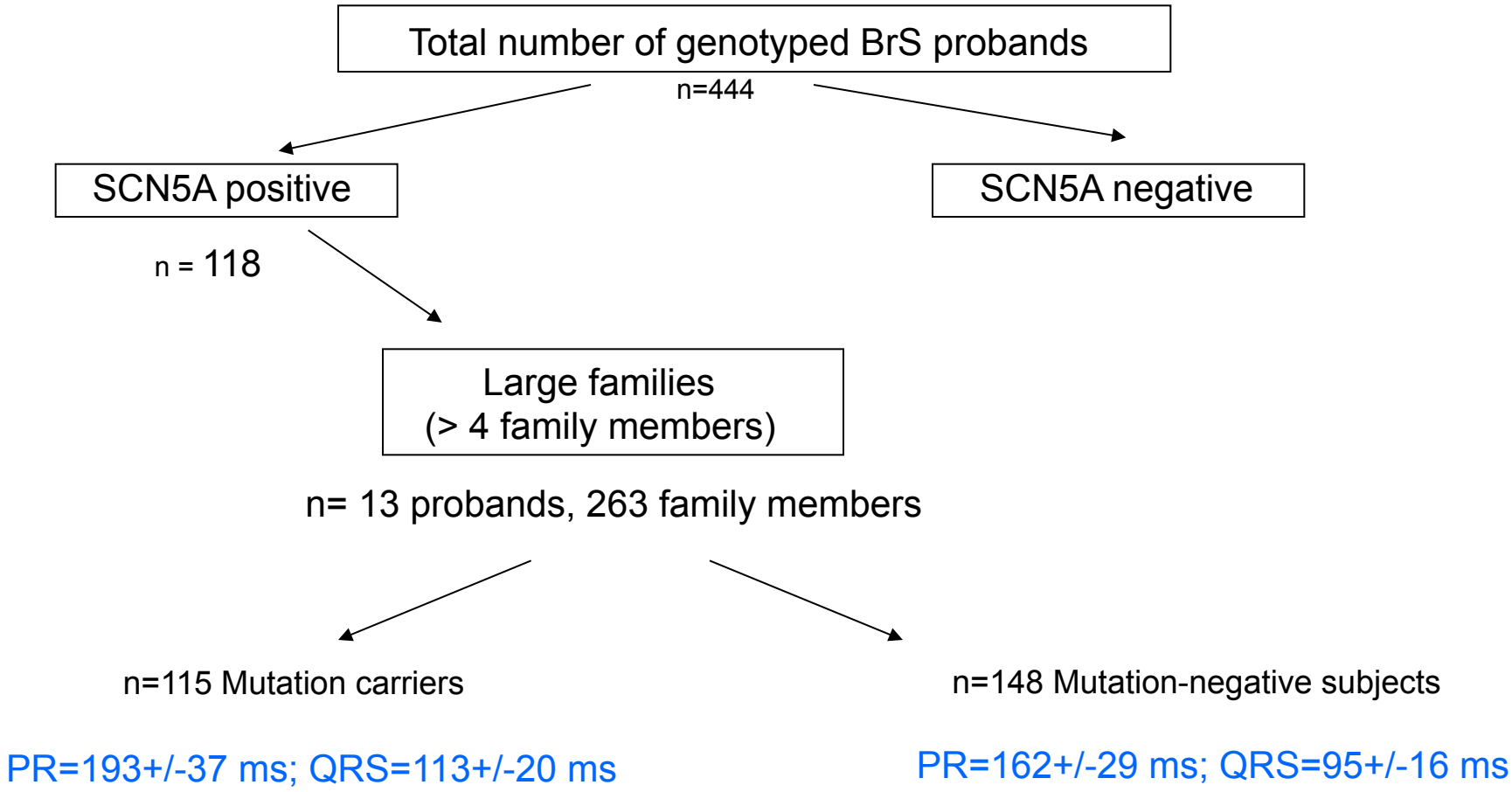
Circulation
Cardiovascular Genetics
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association
Learn and Live

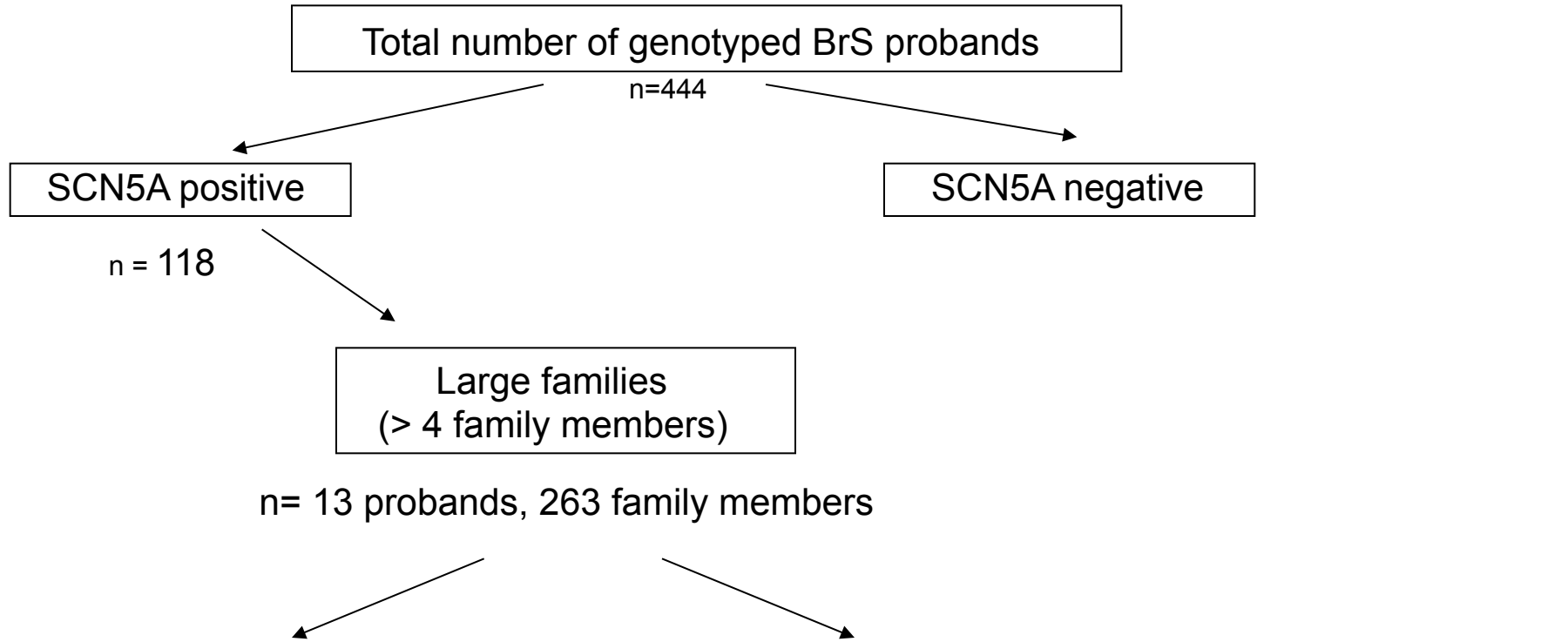
SCN5A Mutations and the Role of Genetic Background in the Pathophysiology of Brugada Syndrome

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

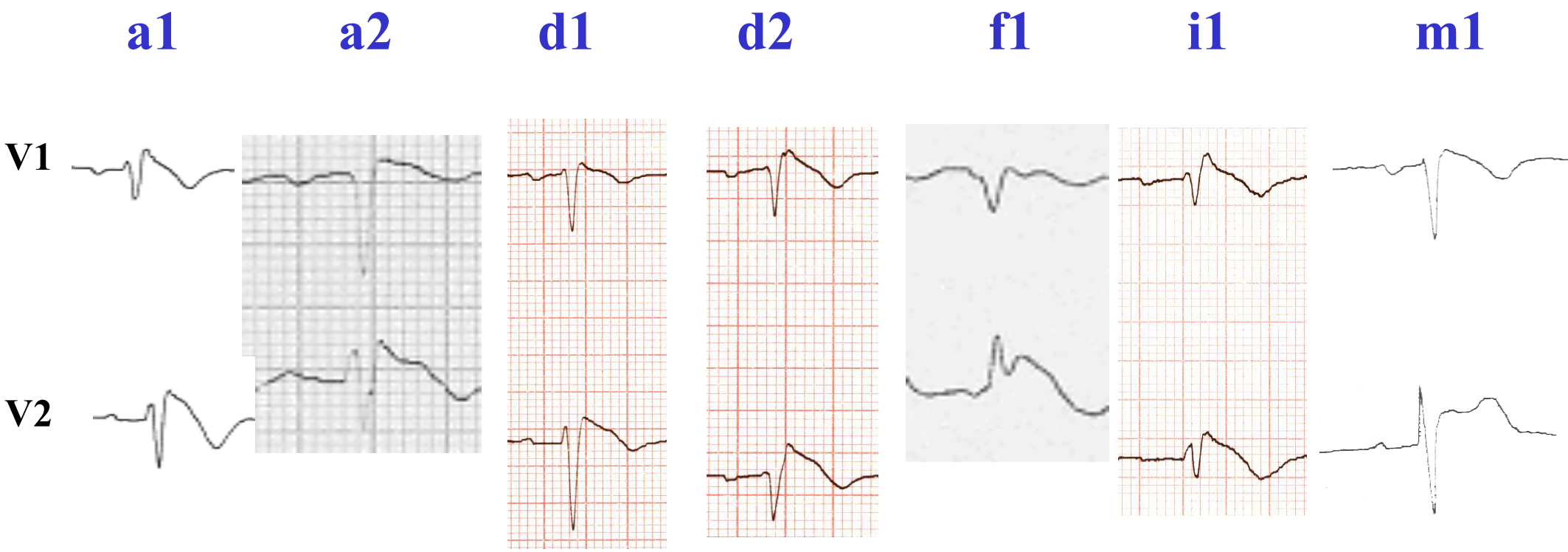
Circ Cardiovasc Genet 2009;2;552-557; originally published online Sep 29, 2009;
DOI: 10.1161/CIRCGENETICS.109.853374


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


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
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



BrS-ECG + N=54	BrS-ECG – N=61	BrS-ECG + N=7	BrS-ECG – N=141
PR=194+/-37 ms; QRS= 113+/-18 ms	PR=193+/-37 ms; QRS=113+/-21 ms	PR=170+/-14 ms; QRS= 99+/-14 ms	PR=162+/-30 ms; QRS= 94+/-14 ms


a1
a2
d1
d2
f1
i1
m1
V1
V2

Brugada syndrome, 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…

Brugada syndrome
Genotype-phenotype relation

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

Paola G. Meregalli, MD,* Hanno L. Tan, MD, PhD,*† Vincent Probst, MD, PhD,‡§‖¶
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,‡§‖¶
Arthur A. M. Wilde, MD, PhD*

*From the *Department of Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; †Heart Failure Research Centre, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; ‡INSERM, UMR915, l'institut du thorax, Nantes, F-44000 France; §CNRS, ERL3147, Nantes, F-44000 France; ‖CHU Nantes, l'Institut du Thorax, Service de Cardiologie, Nantes, F-44000 France; ¶Université de Nantes, Nantes, F-44000 France; #Department of Clinical Epidemiology Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; **Department of Clinical Genetics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, ††CHU de Bordeaux, University of Bordeaux, France; ‡‡CHU Nantes, Service de Génétique Médicale, Nantes, F-44000 France; §§Service de Cardiologie, CHU de Rennes, France.*

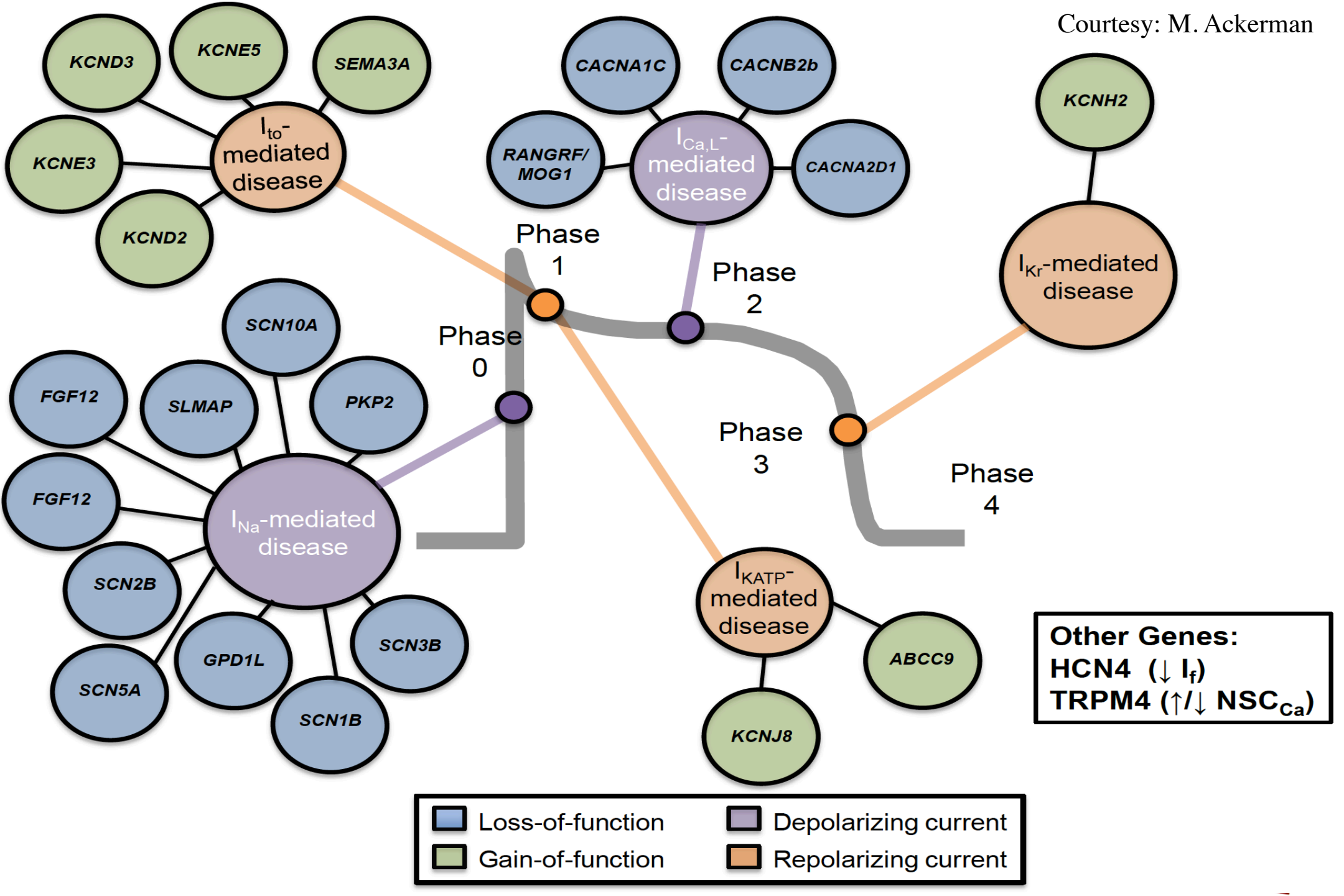
***: Meregalli et al. Heart Rhythm 6, 341-348 , 2009**

Brugada syndrome
Genotype-phenotype relation

With more severe Na-channel ↓

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

Courtesy: M. Ackerman



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^{-7}[a]	2.4% (21)	1.7×10^{-15}[a]
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

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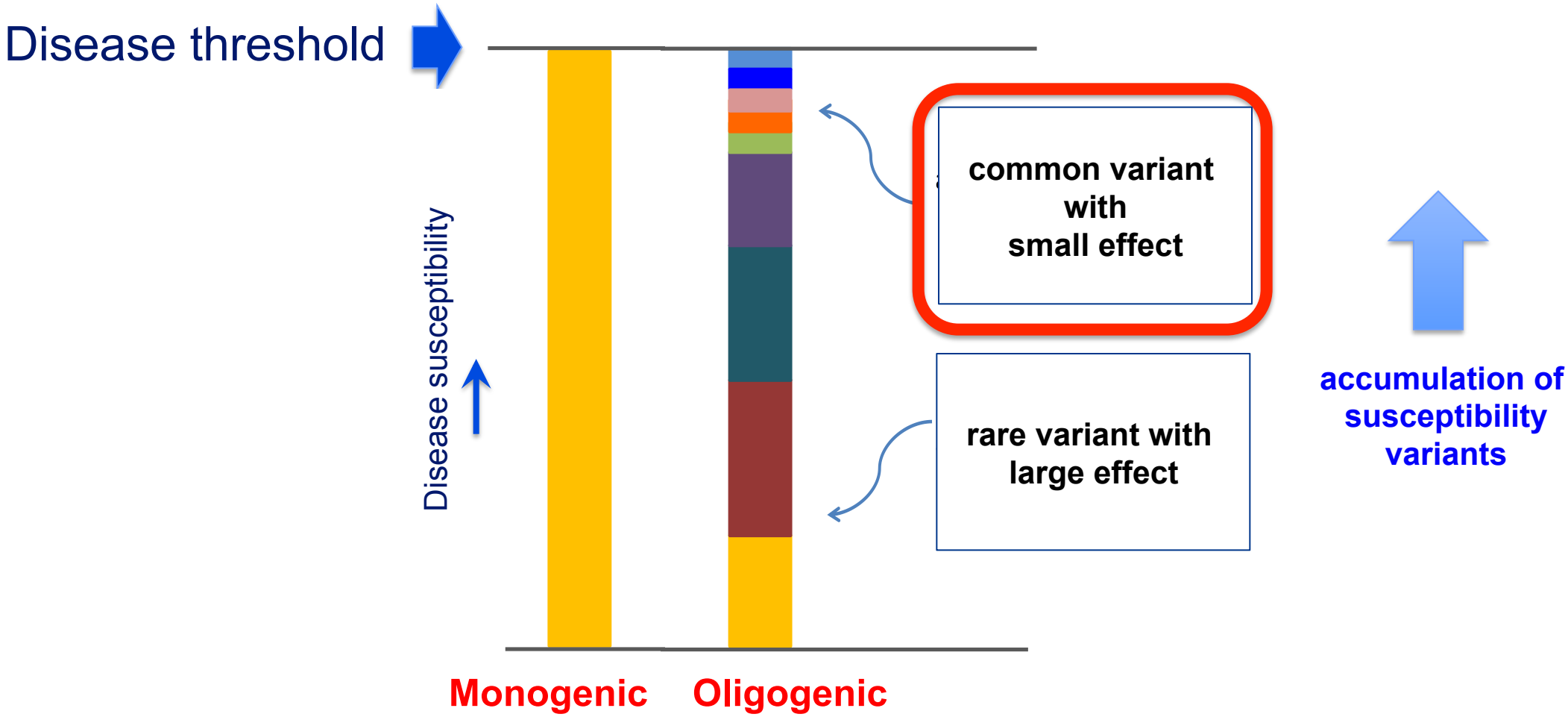
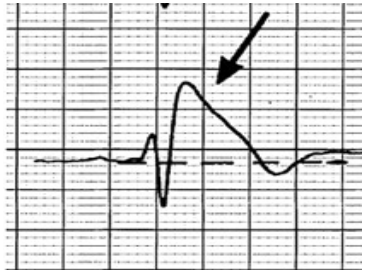
KCNE3	—	—	—	0.1% (1)	1
KCNJ8	—	—	—	0.5% (4)	1

More complex genetic architecture?

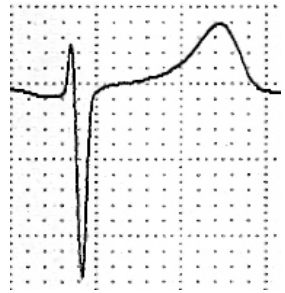


Genetics of Brugada Syndrome: new strategy

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%)

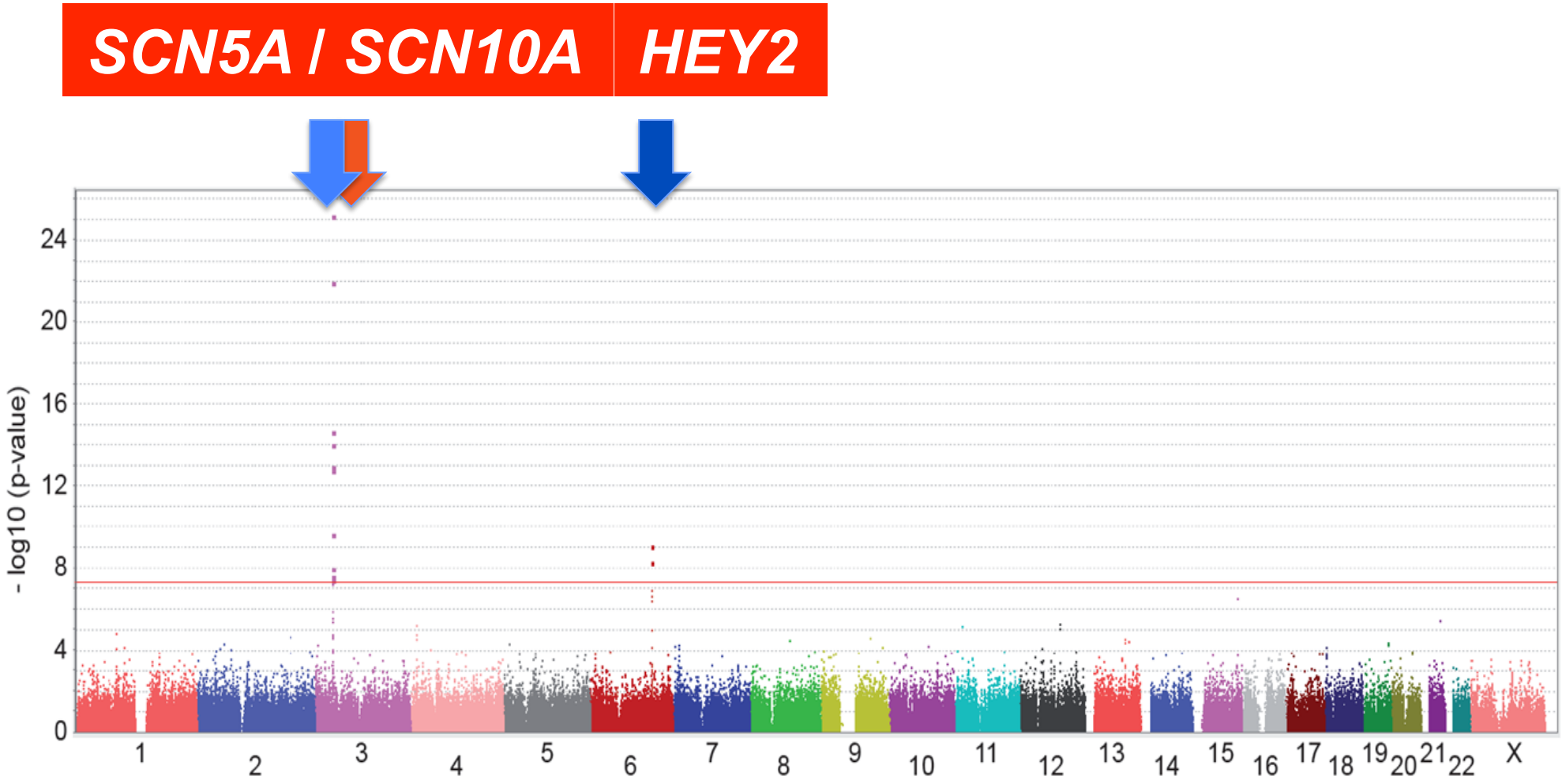
[1] Ventricular tachycardia, ventricular fibrillation, syncope and near syncope

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

[3] Osaka, Nagasaki, Shiga

Genome Wide Association Study in Brugada Syndrome

‘GWAS #1’

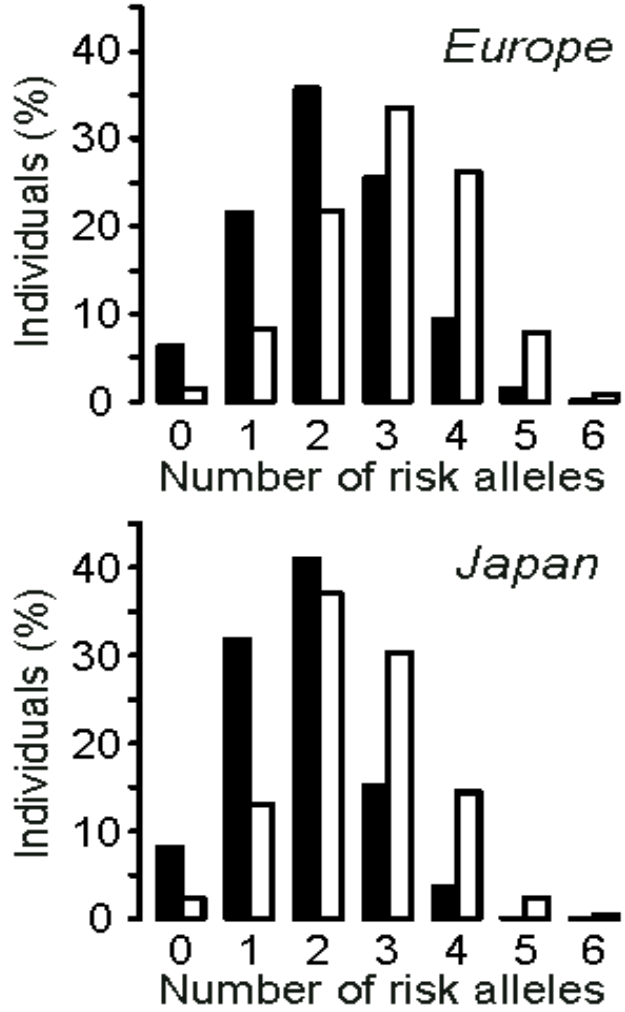


Bezzina et al., Nat Genet 2013

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

Controls

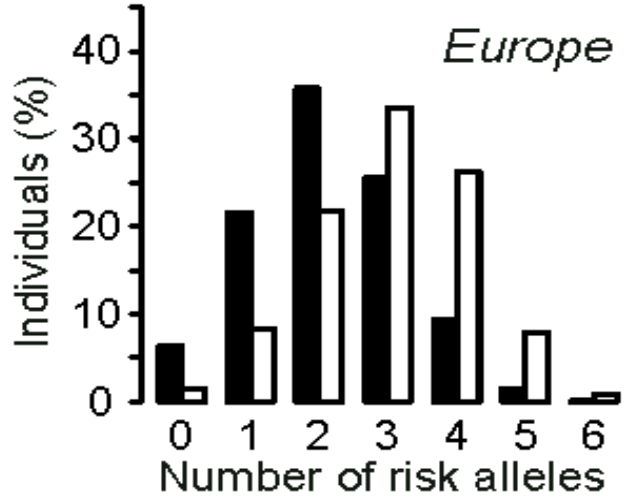
BrS cases

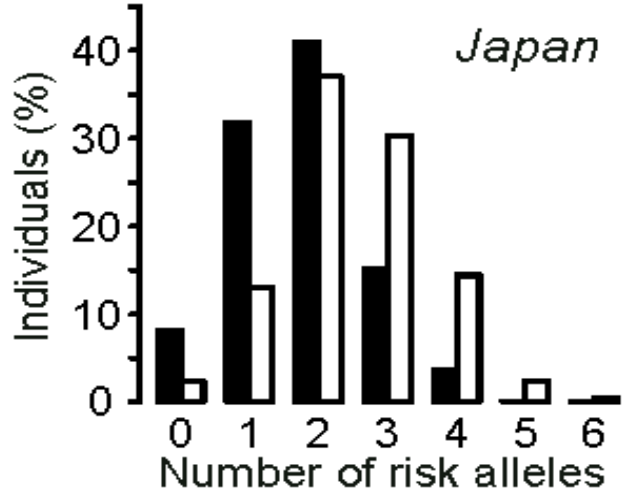


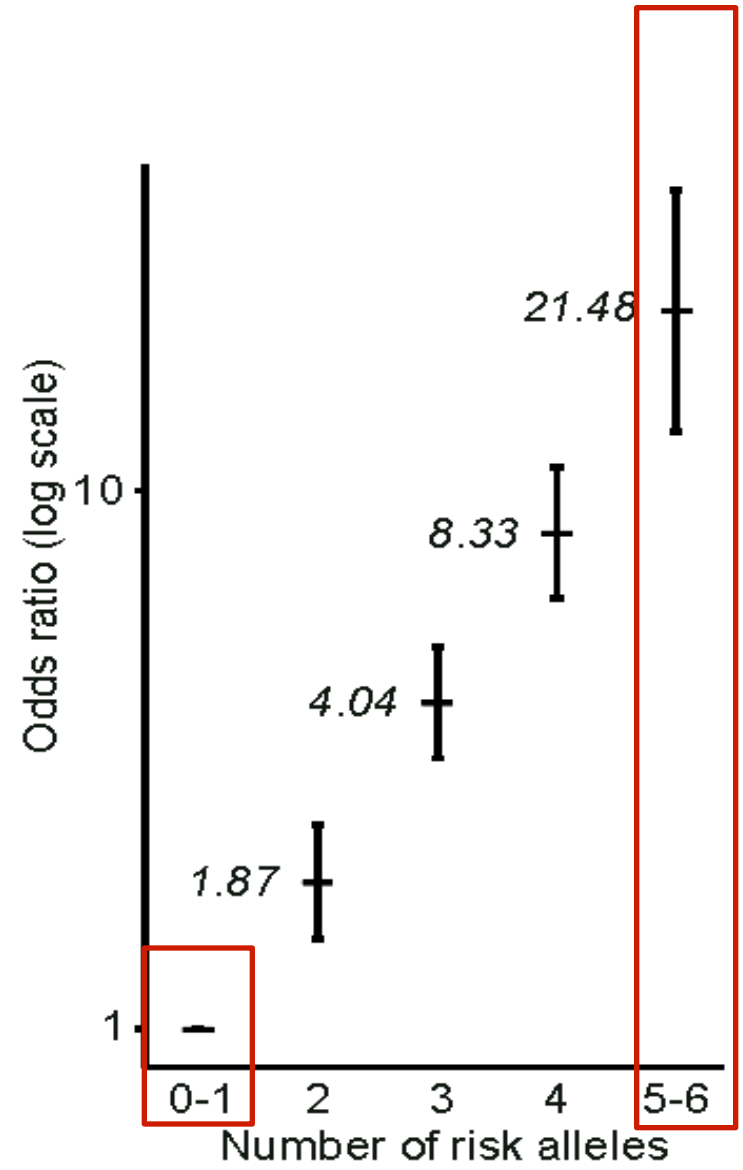
Cumulative effect of alleles at the three loci on susceptibility to BrS

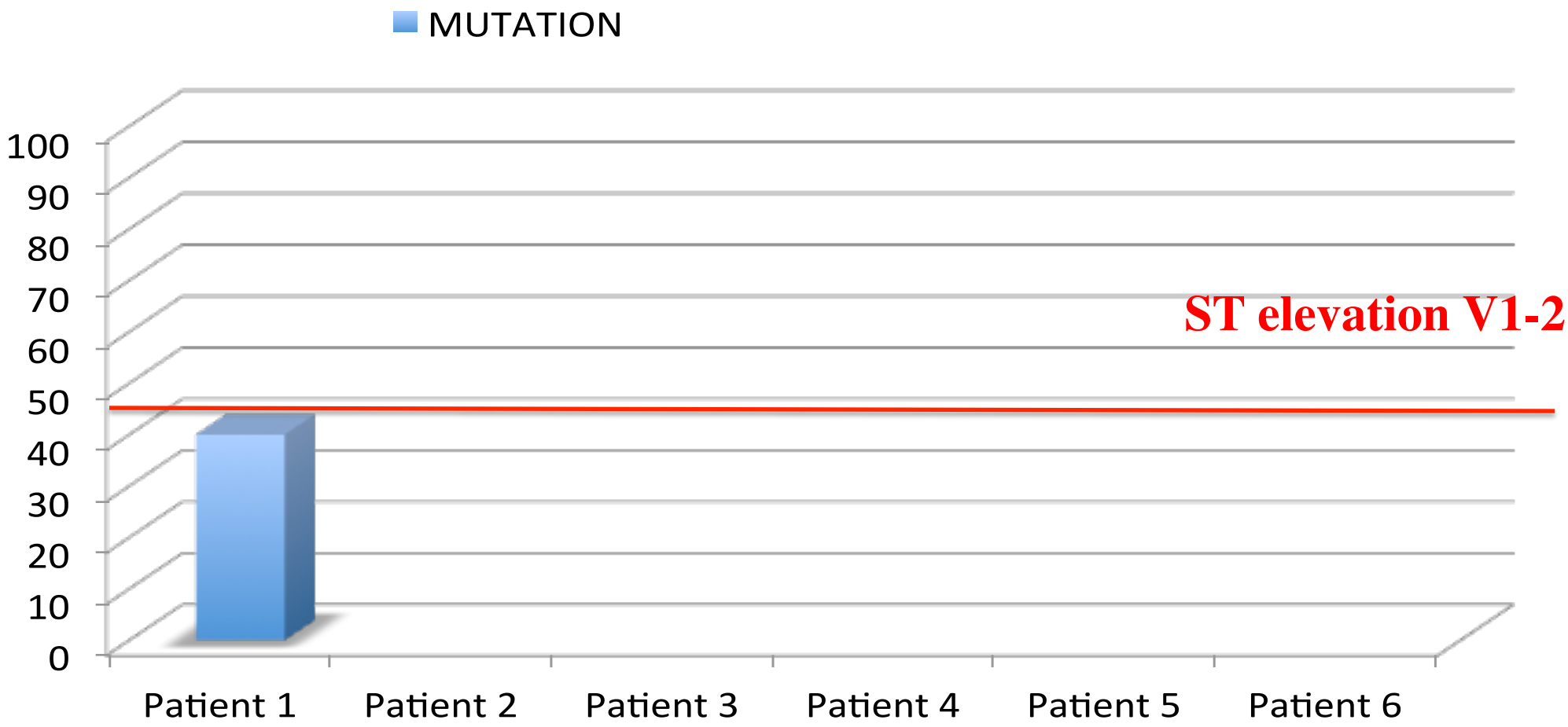
Controls

BrS cases





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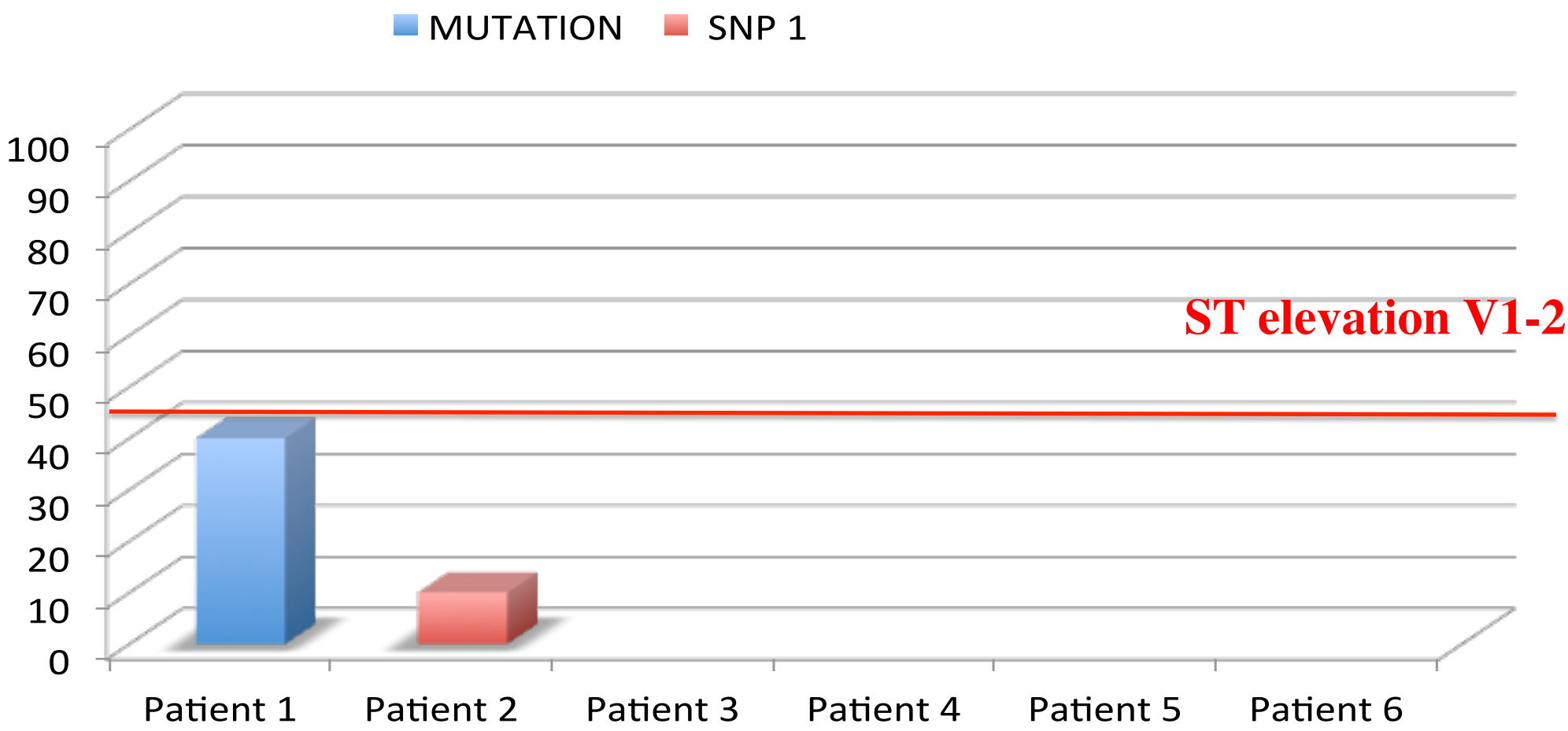
ST elevation V1-2
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6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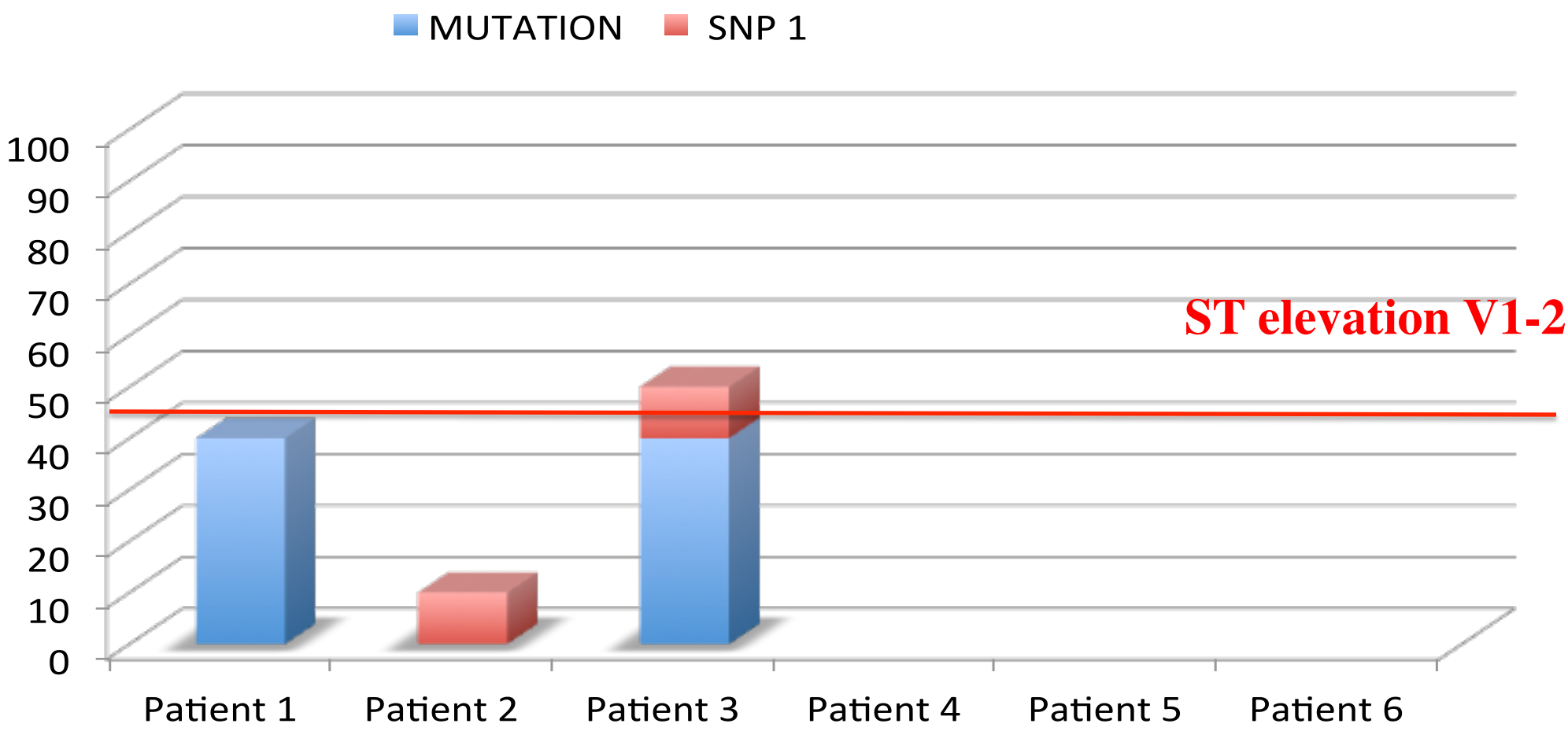
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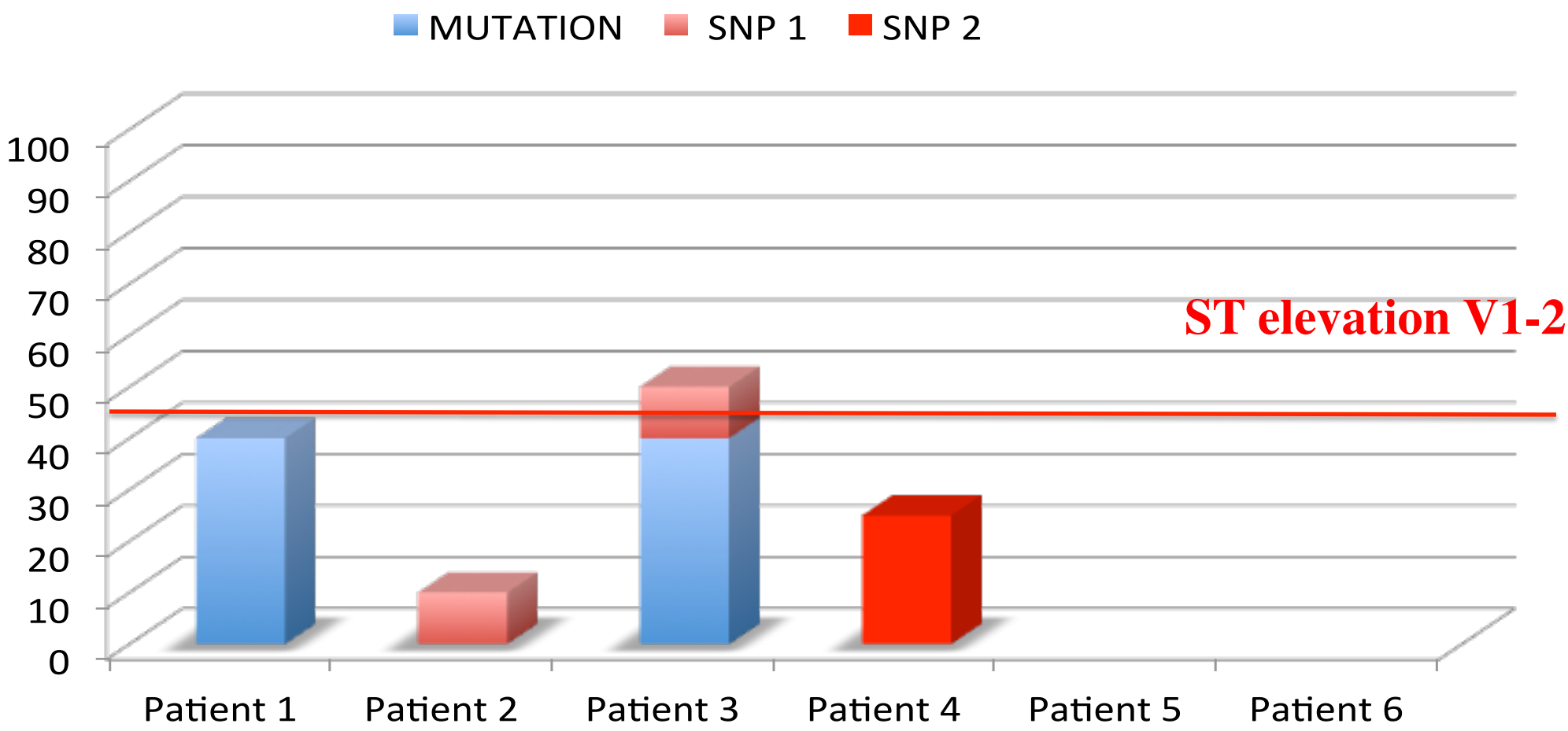
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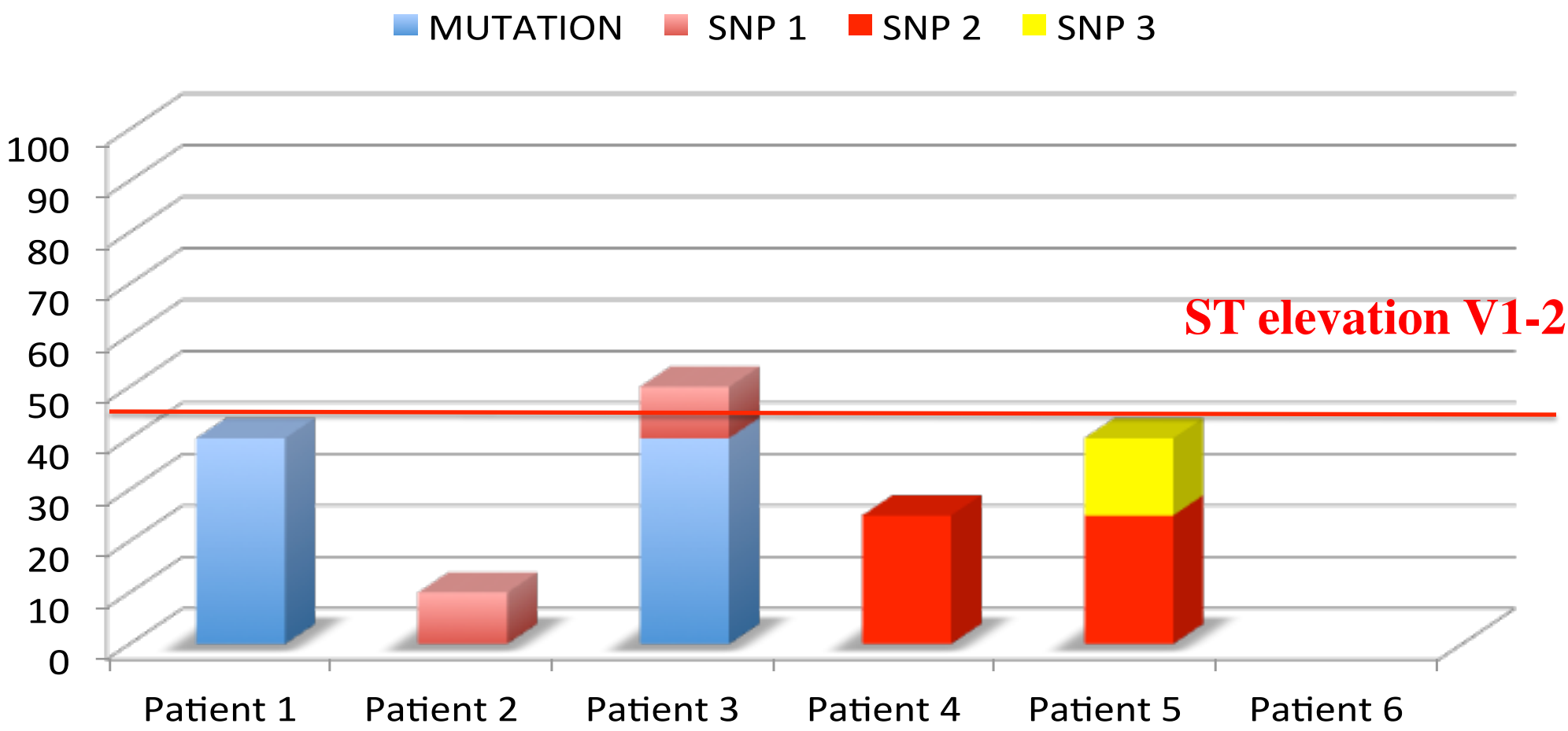
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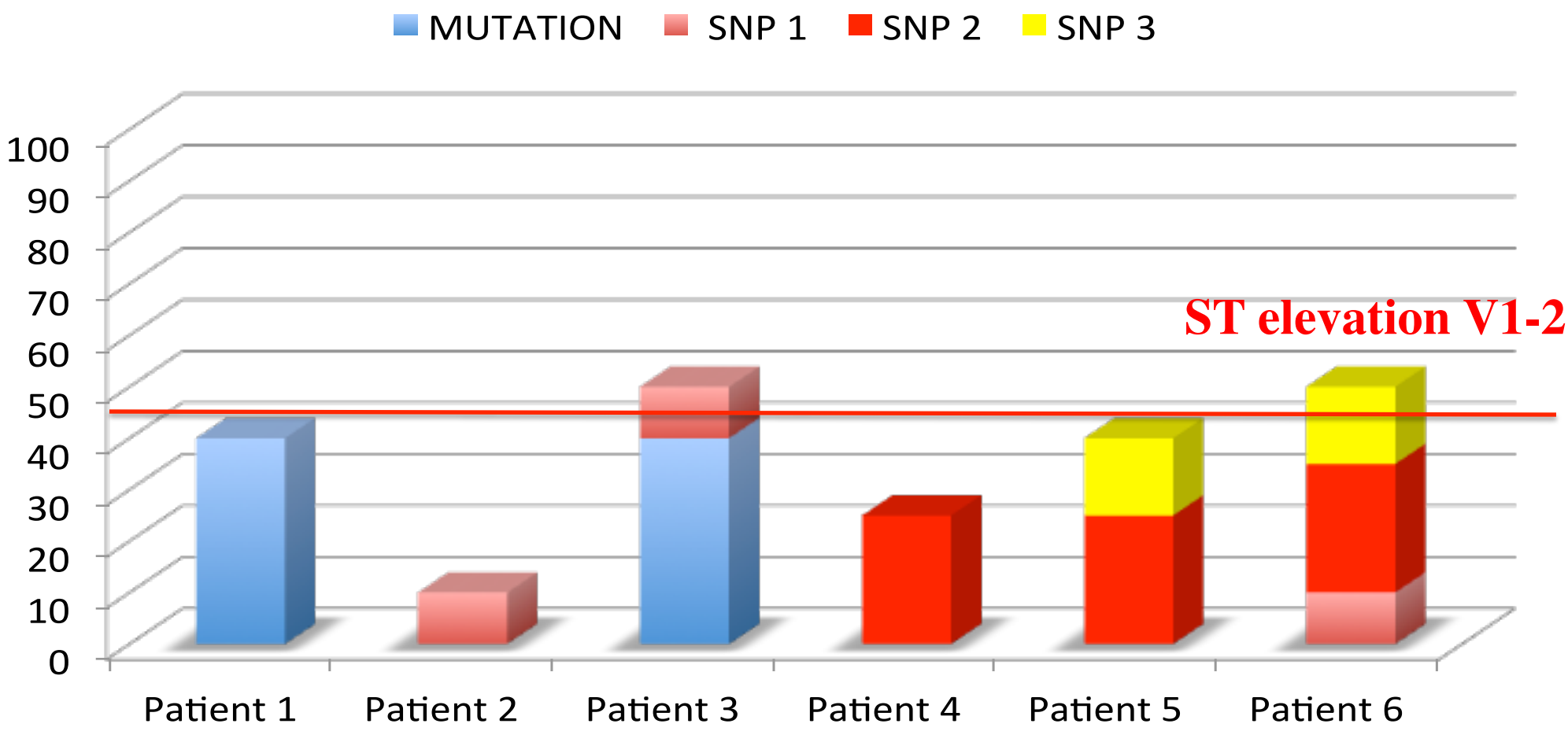
MUTATION
SNP 1
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SNP 3
100
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0
ST elevation V1-2
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6

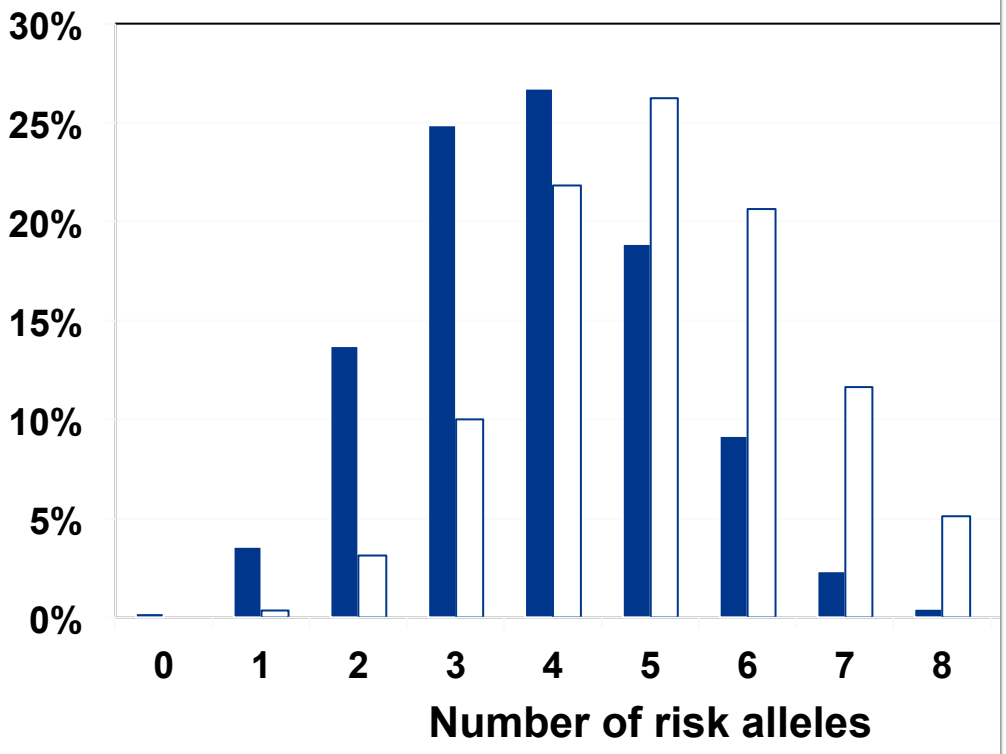
Brugada syndrome, genetics

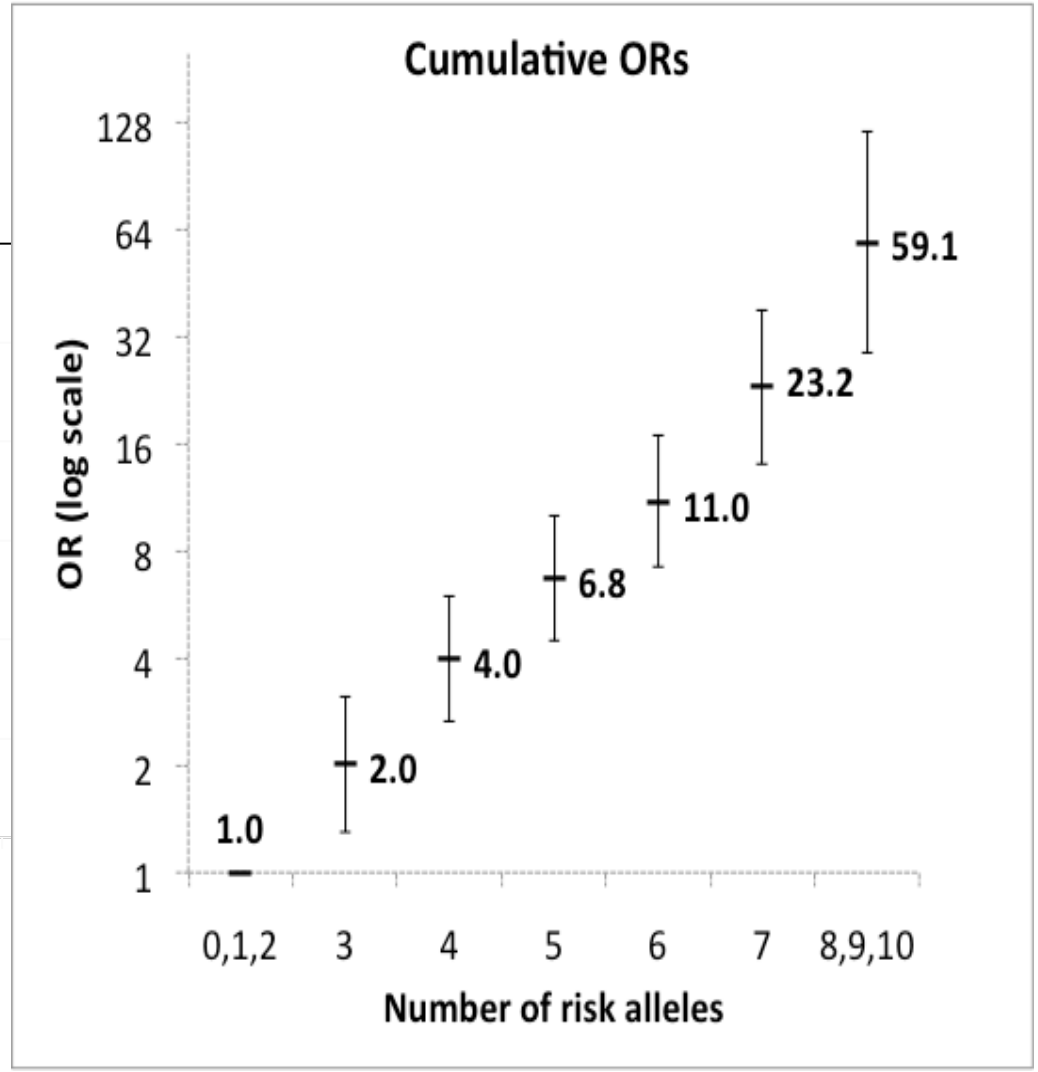
Conclusions:

- Genetically heterogeneous
- SCN5a 15-30% of patients
- likely oligogenetic
- no major impact on prognosis

Cumulative risk for Brugada Syndrome ECG

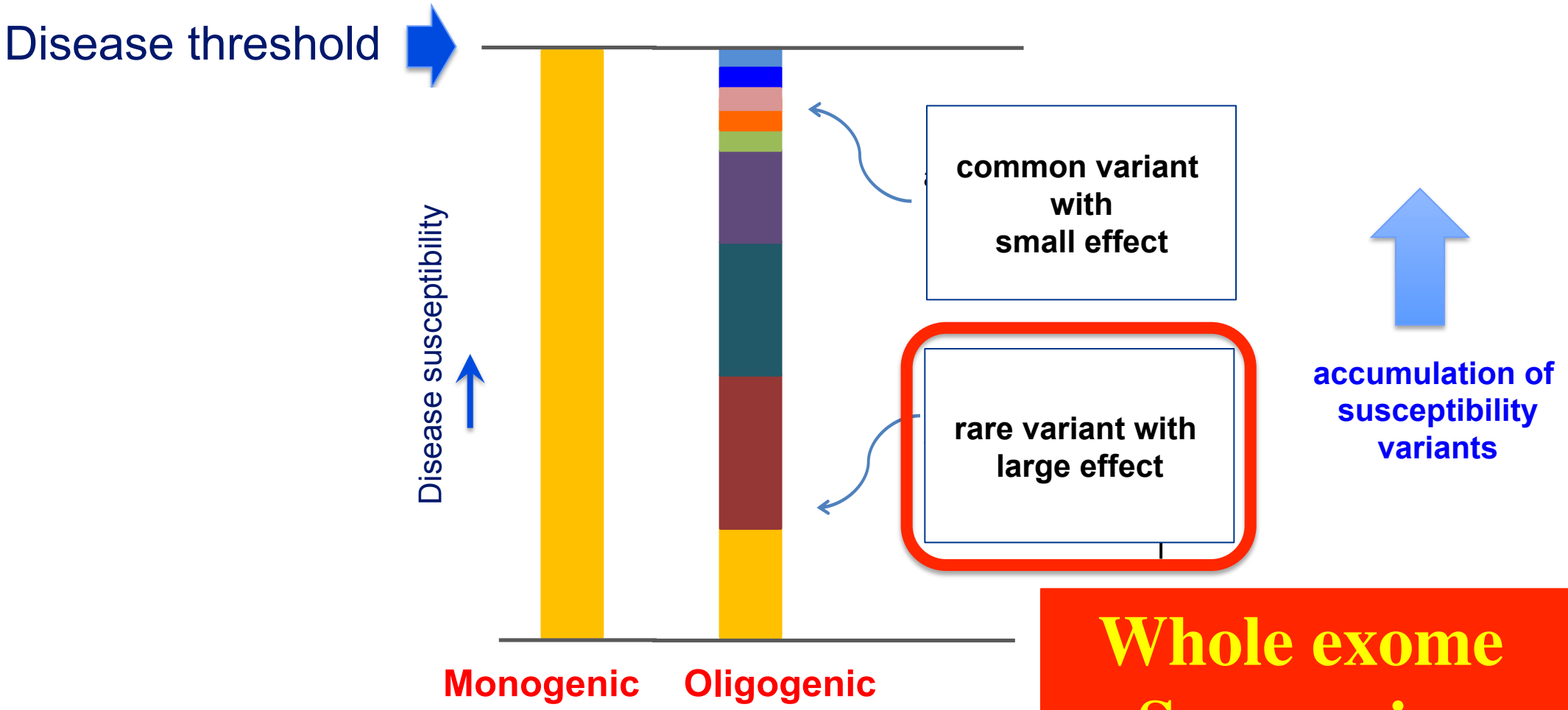
2nd GWAS, 876 pts
5 loci identified





unpublished

More complex genetic architecture?



Whole exome Sequencing

Conclusions

- ♥ Brugada syndrome is an oligogenetic dis.
- ♥ SCN5a is the most important gene
- ♥ In children most often conduction disease
- ♥ Genetic Risk Sc. relates to the phenotype
- ♥ GRS cannot be used as riskfactor (yet)

Conclusions & consequences

- If anything only ‘act’ on SCN5a mutations
- ‘act’ = life style measurements/drugs
- Also investigate gene negative individuals in SCN5a positive families

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NOSTALGIA
Thank you