Pediatric and Congenital Rhythm Congress VII

4 - 7 February 2017

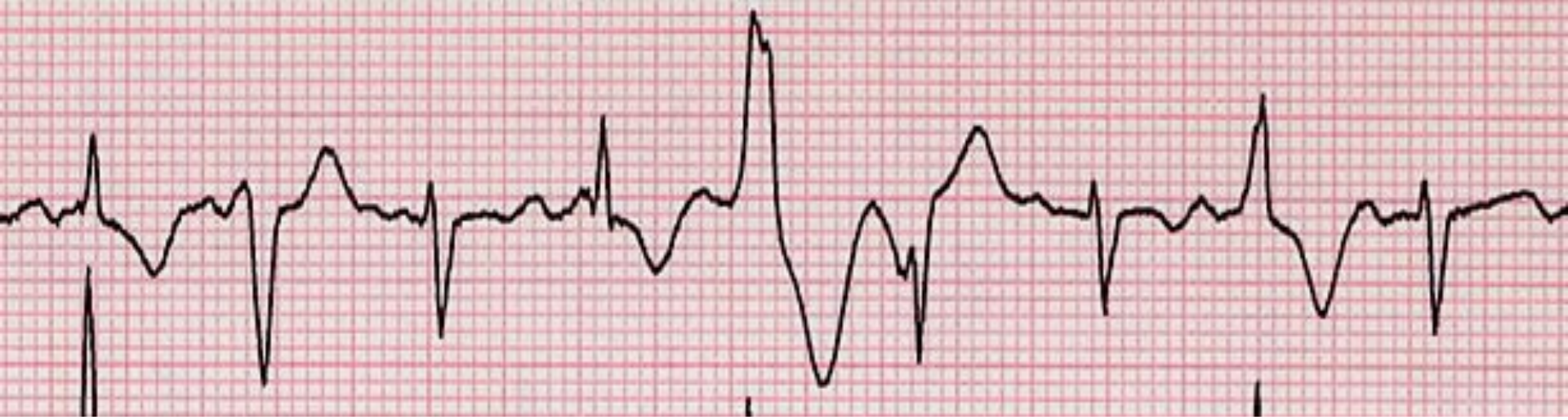
Thessaloniki/GREECE

PEDIRHYTHM VII

Genetic testing in CPVT

Arthur AM Wilde

February 4th 2017



Catecholamine-induced PMVT/VF 2017

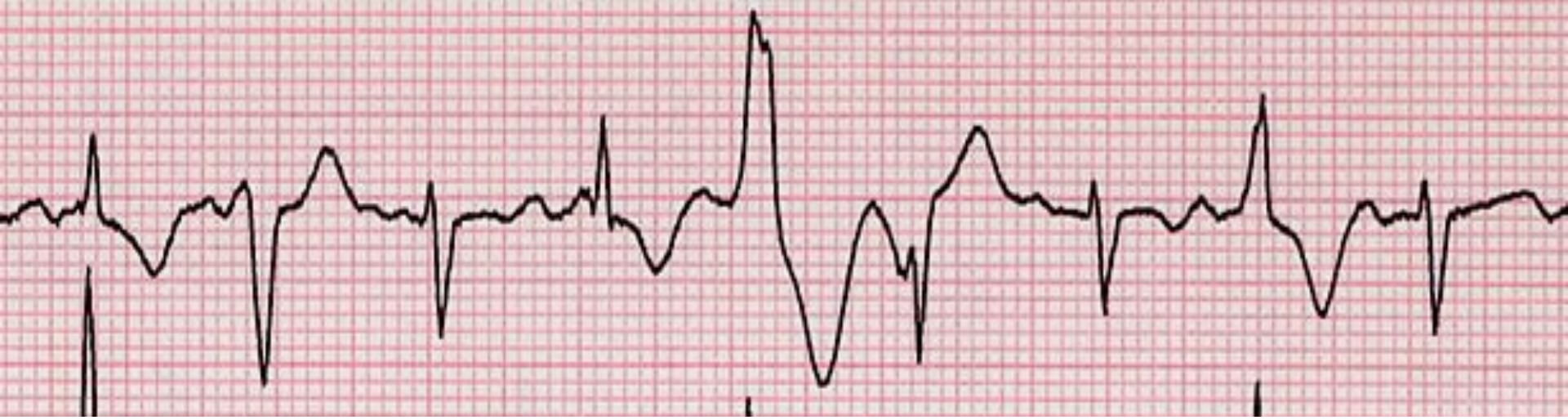
- Autosomal dominant/recessive
- genetic heterogeneous (6 genes)
- complaints during exercise, emotion, etc
- can start at young age
- baseline ECG = normal!

Catecholamine-induced PMVT/VF

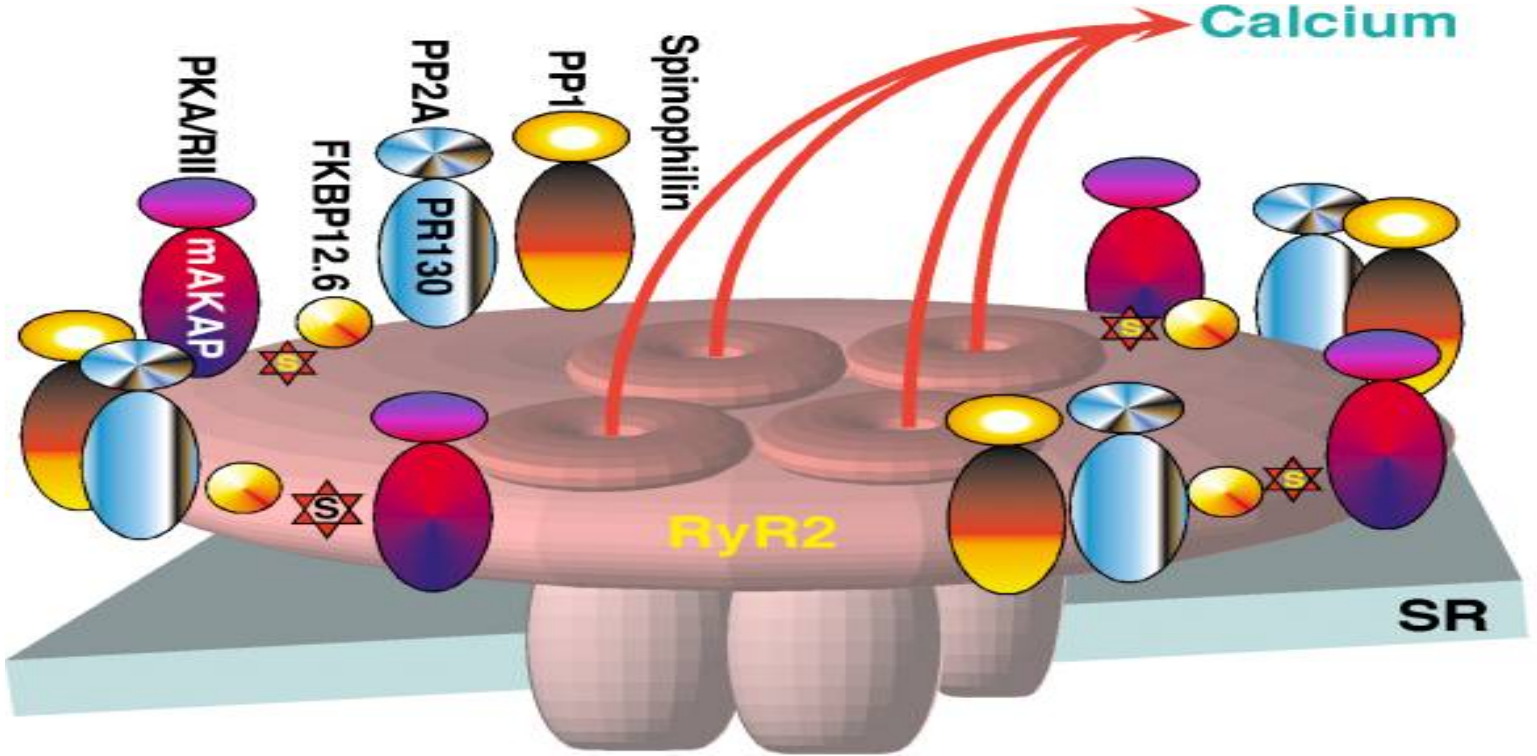
- **Berg, Am Heart J 60, 965-70, 1960**
  - **3 sisters (8-14 y)**
- **Coumel et al, Heart 40, 28-37, 1978**
  - **4 children (7-12 y)**
- **Leenhardt et al, Circulation 91, 1512-9, 1995**
  - **21 children (3.5-16.5 y)**

Catecholamine-induced PMVT/VF

- **Swan et al. JACC 34, 2035-42, 1999**
  - **familial stress-induced polymorphic VT**
  - **mapped to chromosome 1q42-q43**
- **Laitinen et al. Circulation 103, 45-490, 2001**
  - **in 3 families 3 hRyR2 mutations**
- **Priori et al. Circulation 102, r49-53, 2000**
  - **Catecholaminergic PMVT, 12 patients**
  - **in 4 fam. hRyR2 mutations (3 de novo)**



Catecholamine-induced PMVT/VF



CPVT, Genetic testing

Why genetic testing?:

- **Gene-specific treatment** -
- **Risk stratification** -
- **Reaching a diagnosis** ++
- **Presymptomatic treatment** ++

Catecholamine-induced PMVT/VF

hRyR mutations carriers

	Priori et al 2002	Bauce et al 2002	Postma et al 2005	Hayashi et al 2009
Number	23	43	50	81
Penetrance	83%	65%	78%	70%
Response to ß-blockade	63%	100%	98%	77%
FU (Months)	40±29	78±?	86±18	95±59

Catecholamine-induced PMVT/VF

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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)

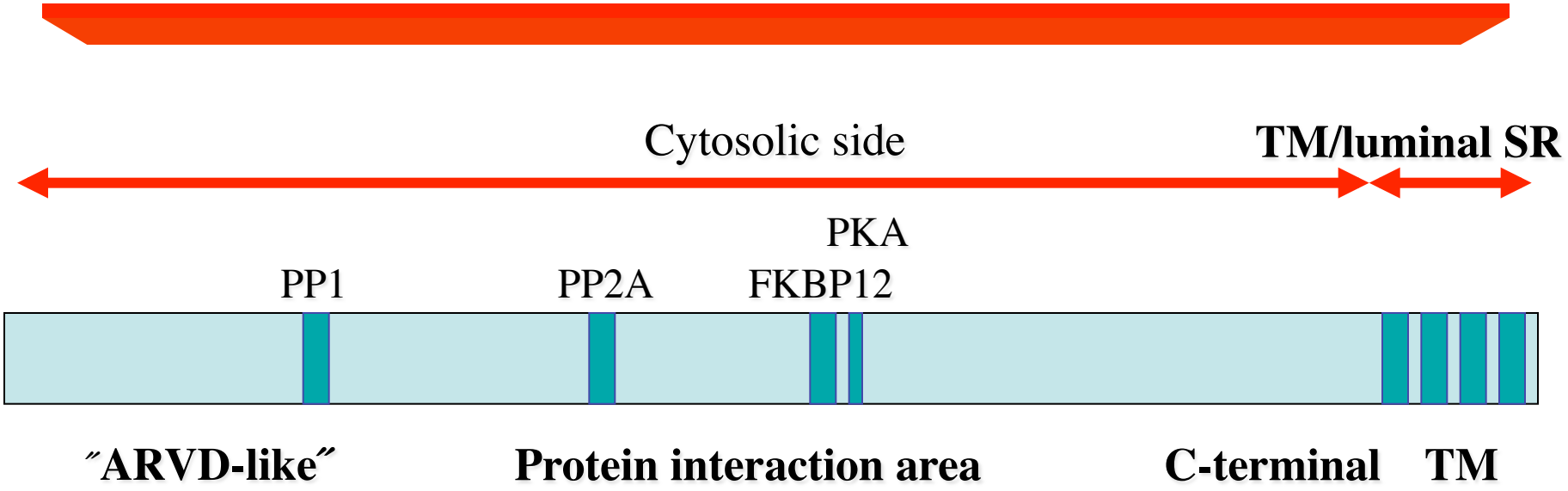
Heart Rhythm 2013, Europace 2013

*Expert Consensus Recommendations on **CPVT Diagnosis***

1. CPVT ***is diagnosed*** in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual <40 years of age.
2. CPVT ***is diagnosed*** in patients (index case or family member) who have a pathogenic mutation.
3. CPVT ***is diagnosed*** in family members of a CPVT index case with a normal heart who manifest exercise induced PVCs or bidirectional/polymorphic VT.
4. CPVT ***can be diagnosed*** in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual >40 years of age.

RyR2 mutation overview

105 exons, 15kb cDNA, homotetramer, largest known ion channel



Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 22, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.08.022

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

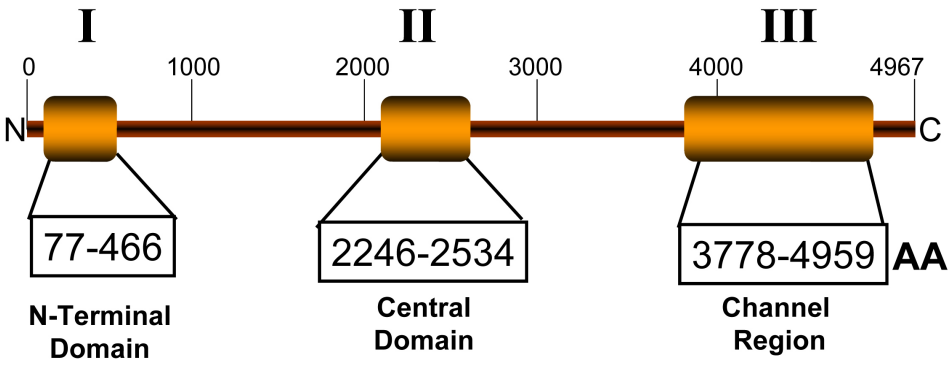
The *RYR2*-Encoded Ryanodine Receptor/Calcium Release Channel in Patients Diagnosed Previously With Either Catecholaminergic Polymorphic Ventricular Tachycardia or Genotype Negative, Exercise-Induced Long QT Syndrome

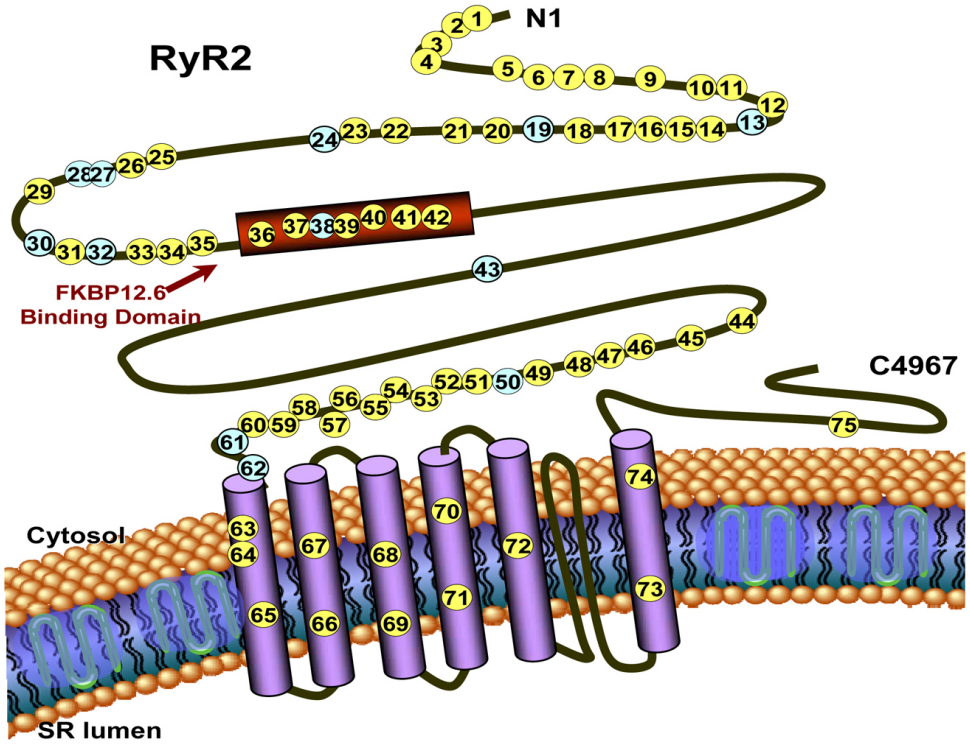
A Comprehensive Open Reading Frame Mutational Analysis

Argelia Medeiros-Domingo, MD, PHD,* Zahurul A. Bhuiyan, MD, PHD,§ David J. Tester, BS,* Nynke Hofman, MSC,§ Hennie Bikker, PHD,§ J. Peter van Tintelen, MD, PHD,¶ Marcel M. A. M. Mannens, PHD,§ Arthur A. M. Wilde, MD, PHD,§‖ Michael J. Ackerman, MD, PHD*†‡

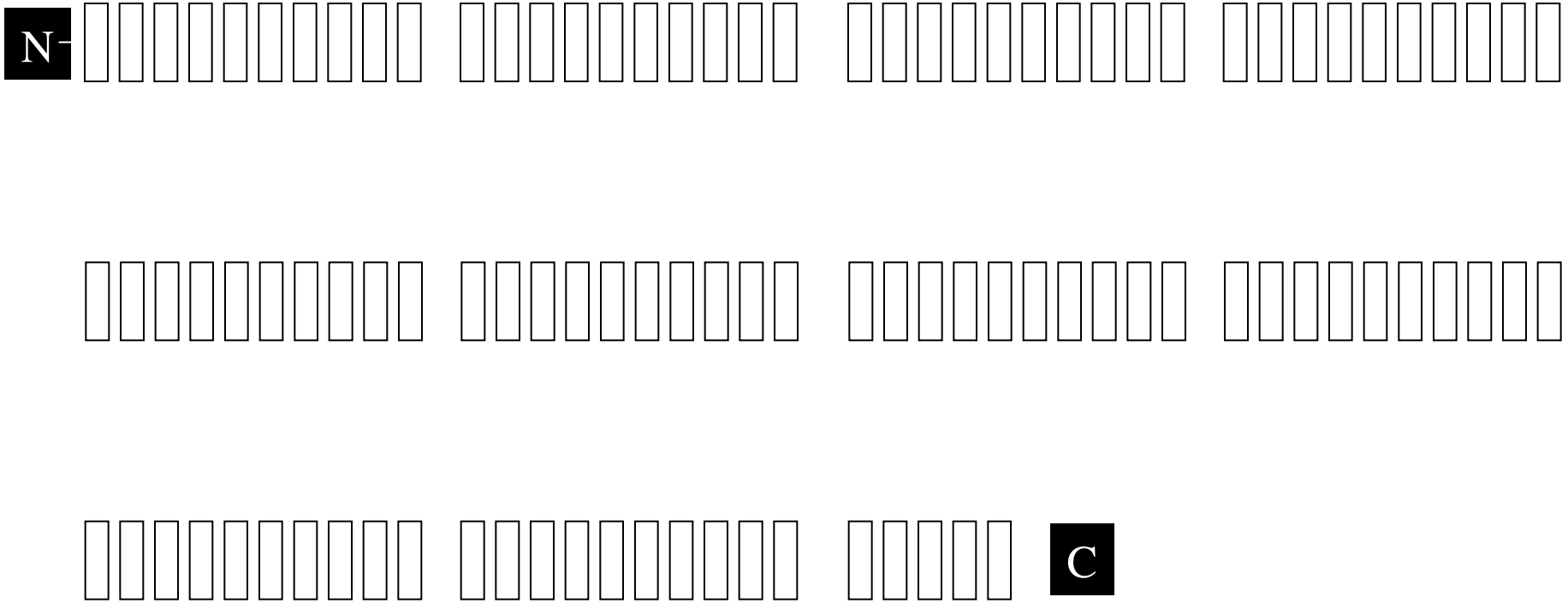
Rochester, Minnesota; and Amsterdam and Groningen, the Netherlands

Result of *RYR2* gene Screening

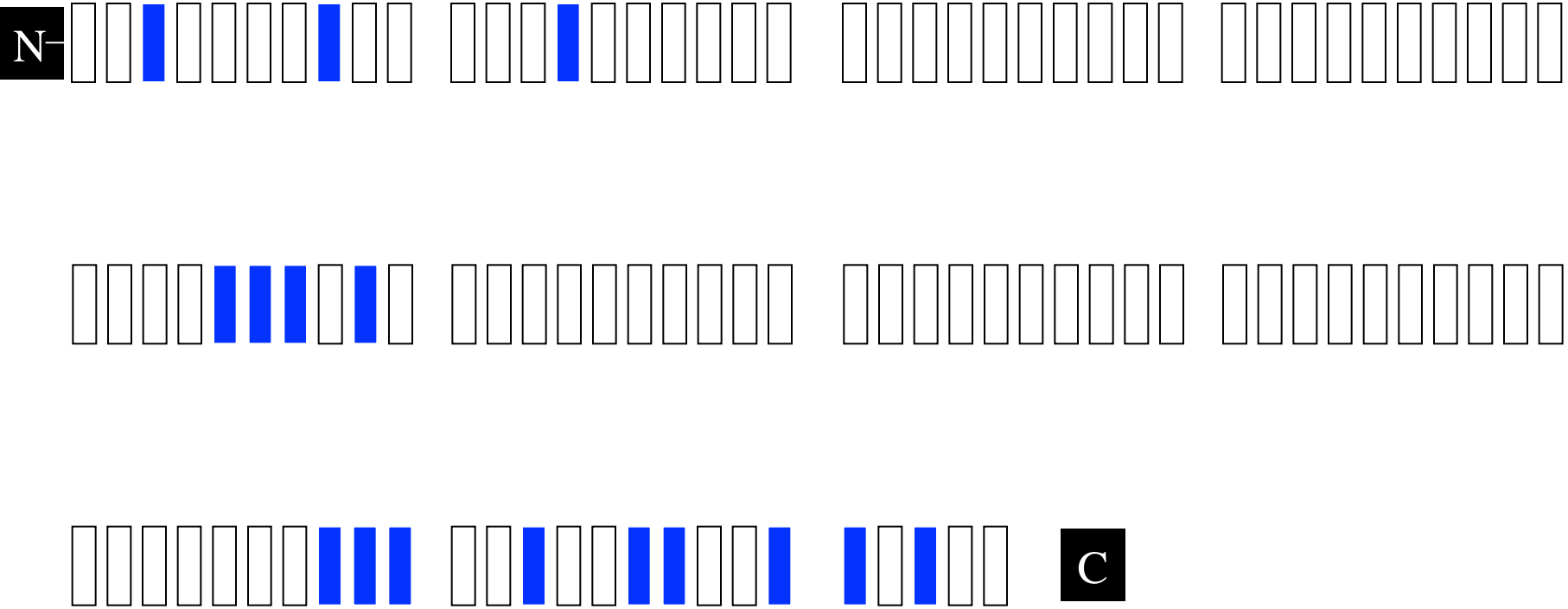




RYR2 gene is composed of 105 Exons

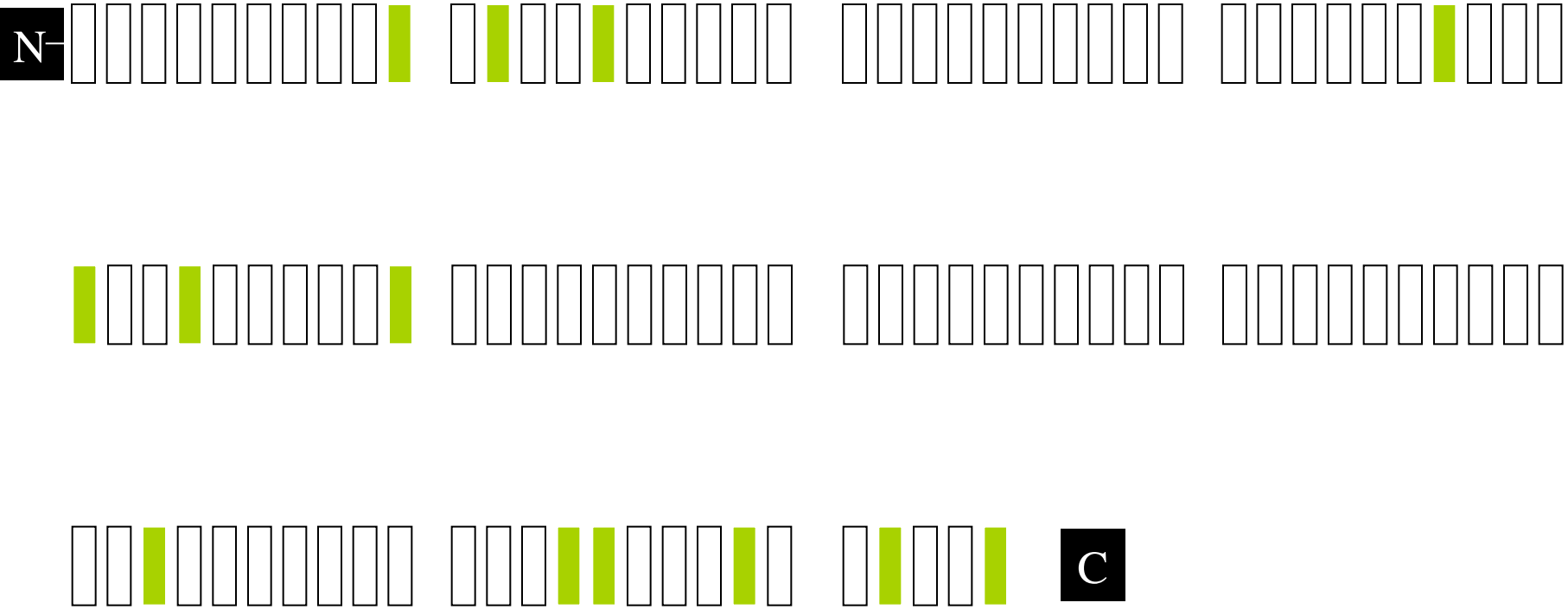


Result of *RYR2* gene Screening



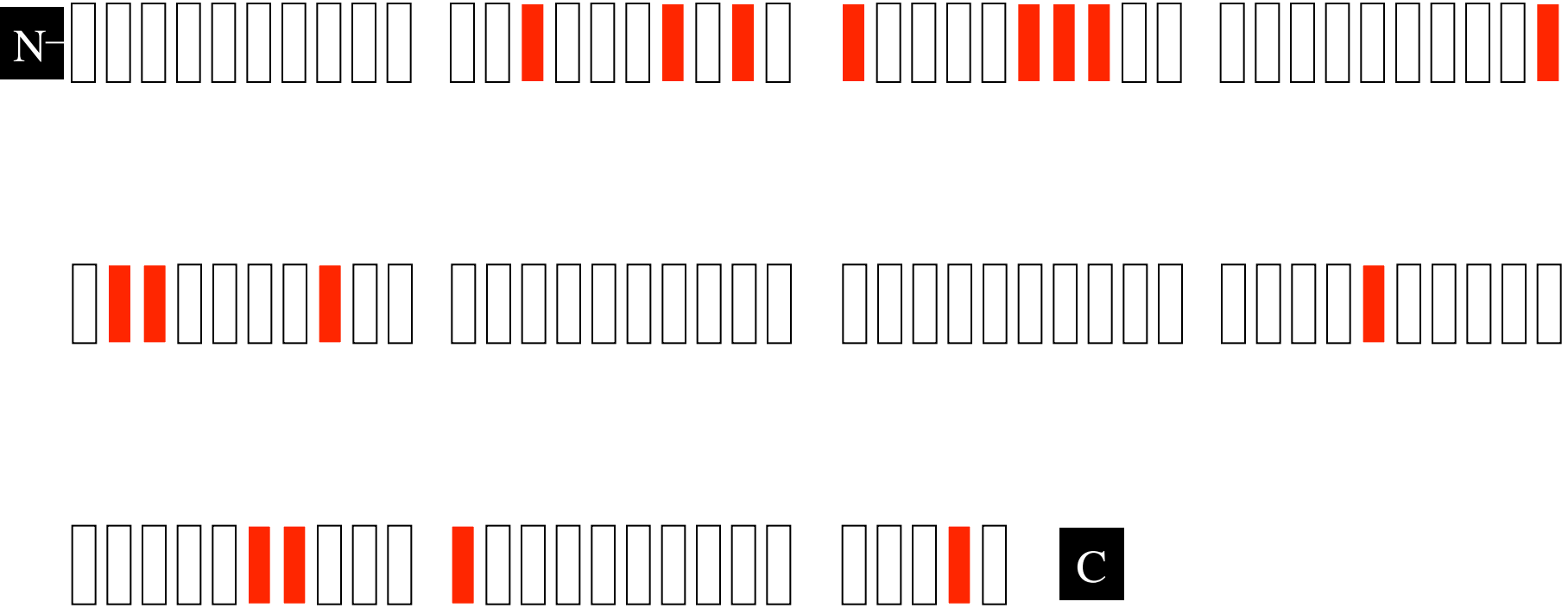
Exons with ≥ 3 mutations

Result of *RYR2* gene Screening



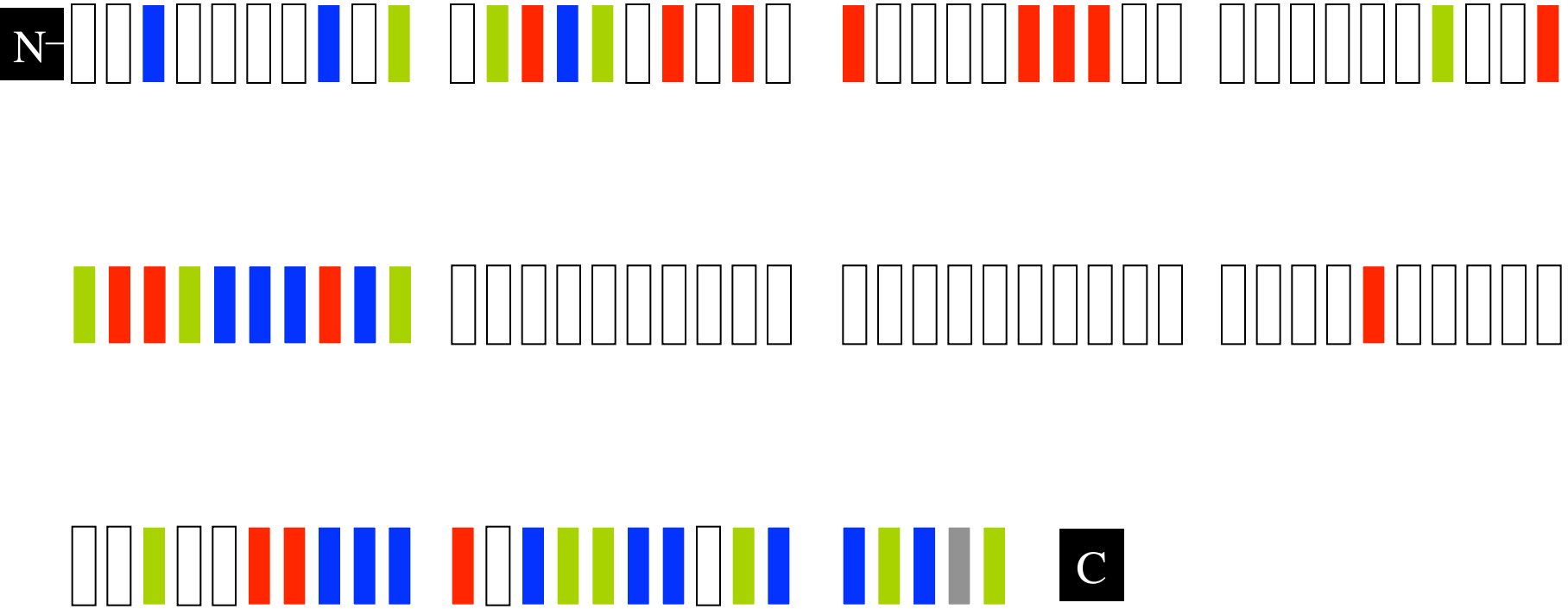
Exons with 2 mutations

Result of *RYR2* gene Screening



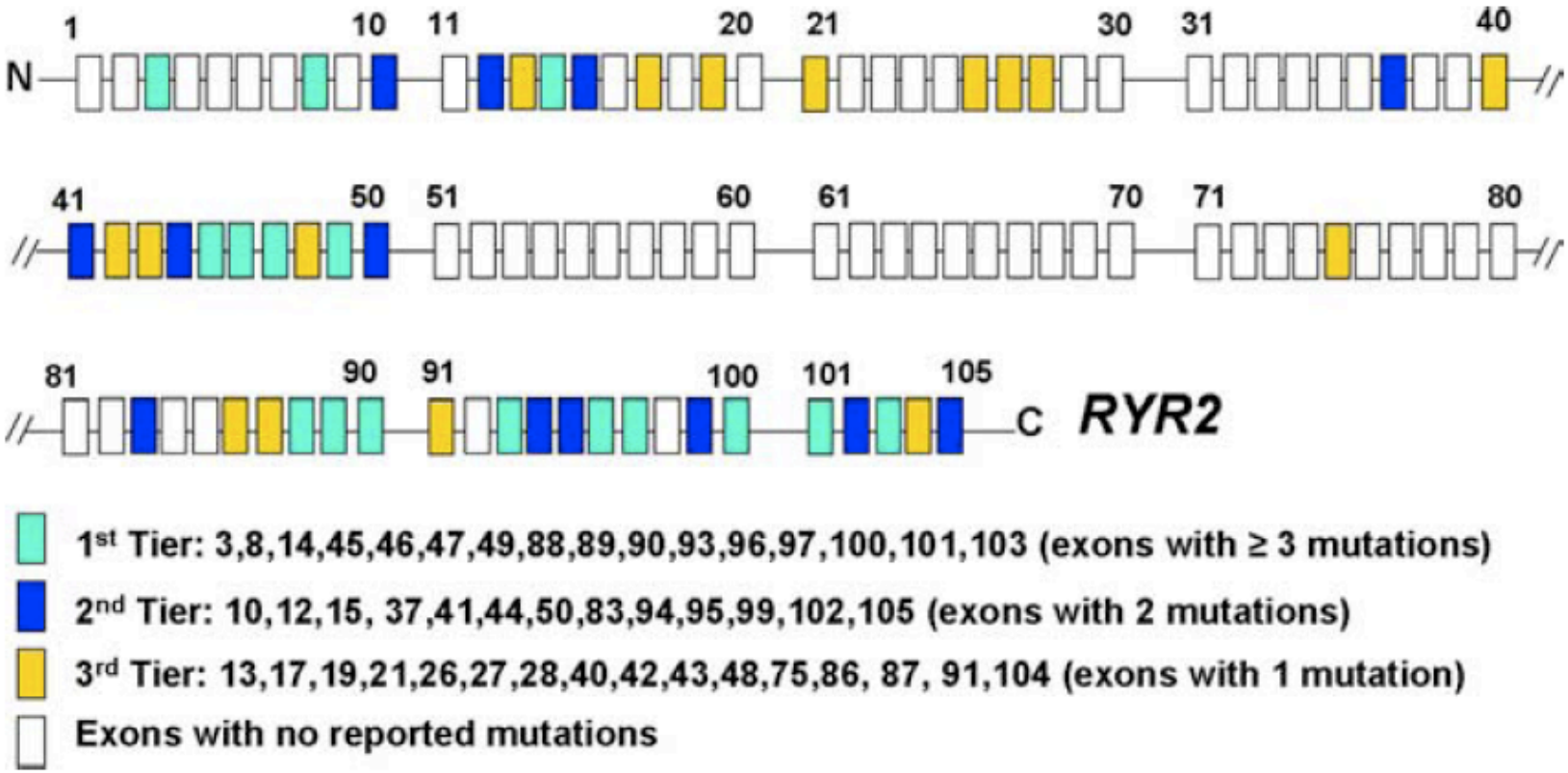
Exons with 1 mutation

Result of *RYR2* gene Screening



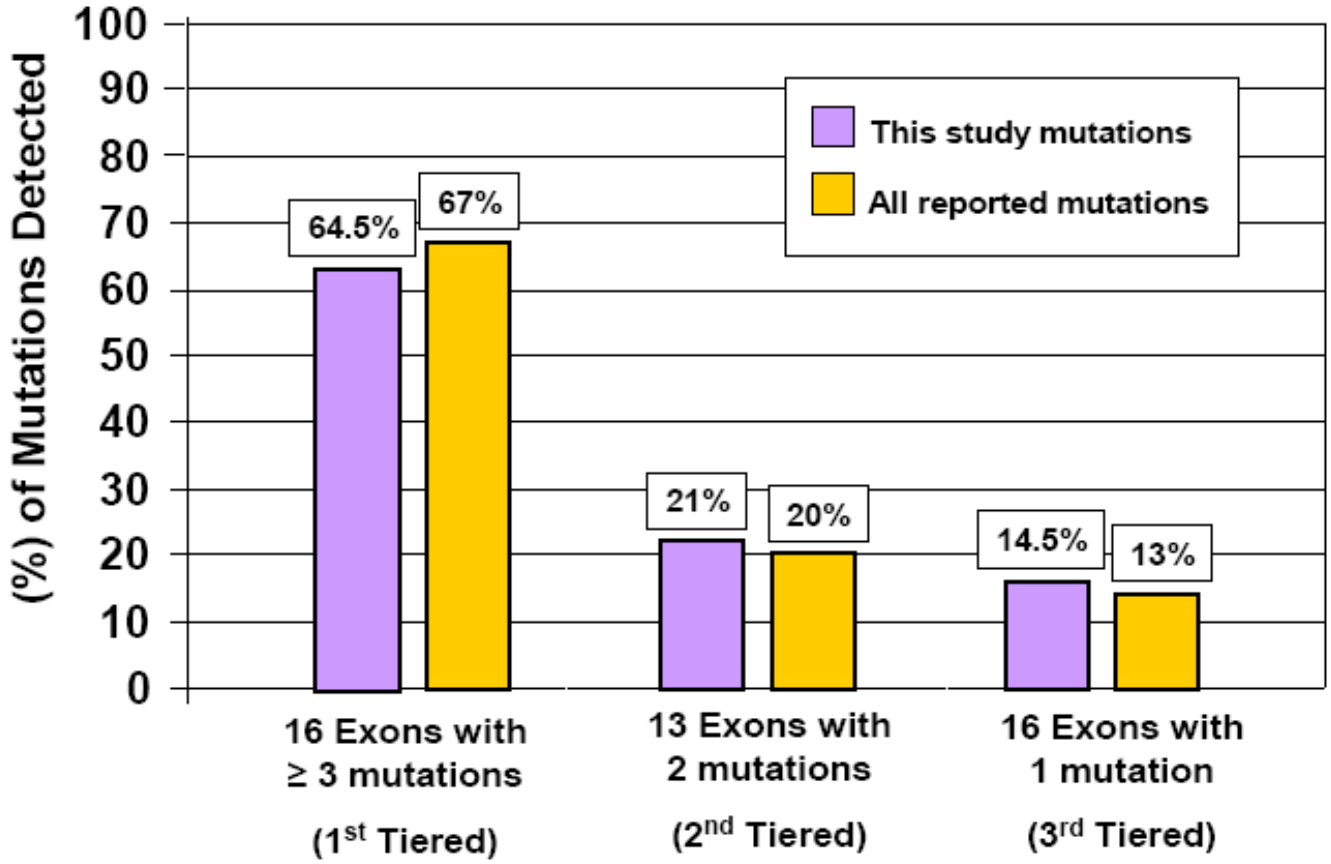
All exons with mutations

RyR2 mutation overview
proposed screening's strategy

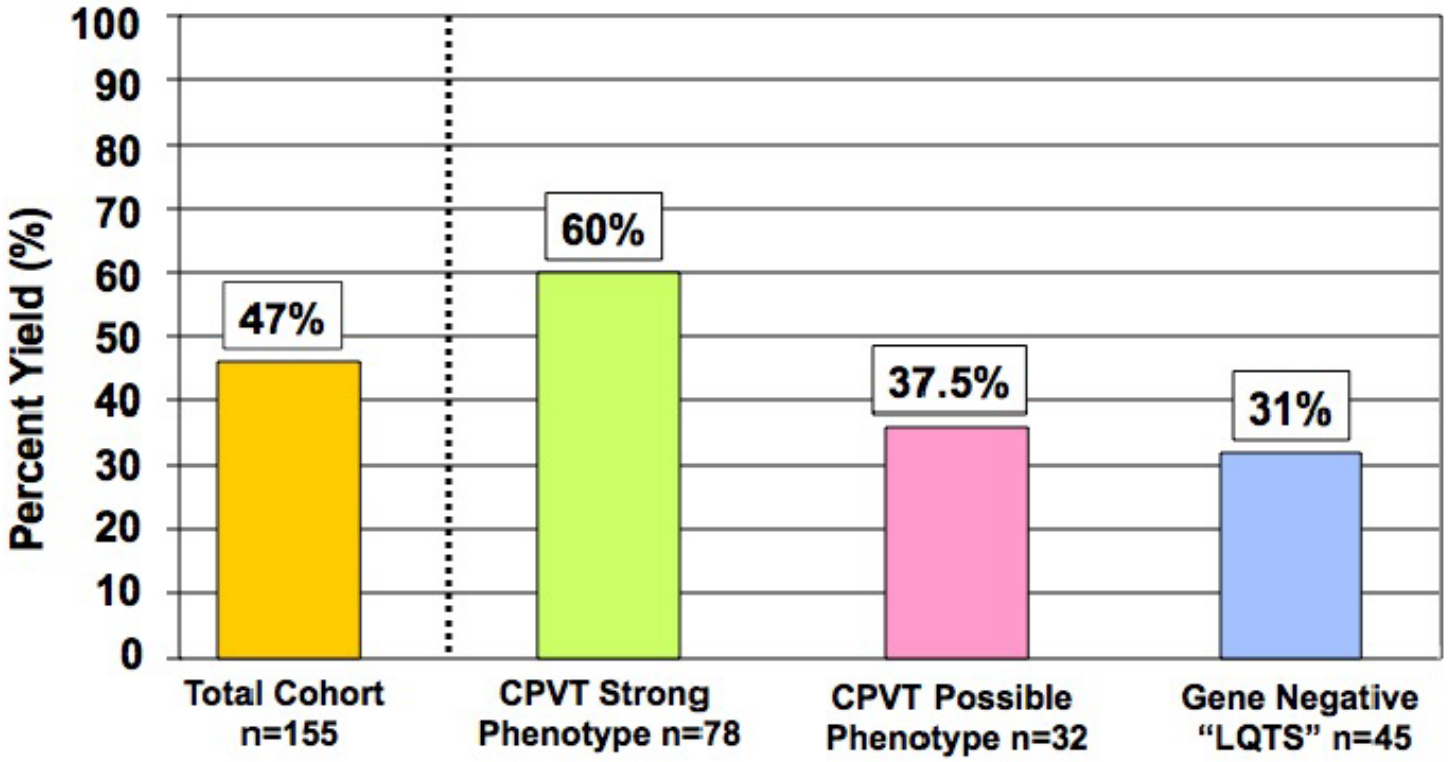


Medeiros-Domingo, Bhuiyan et al, JACC 2009

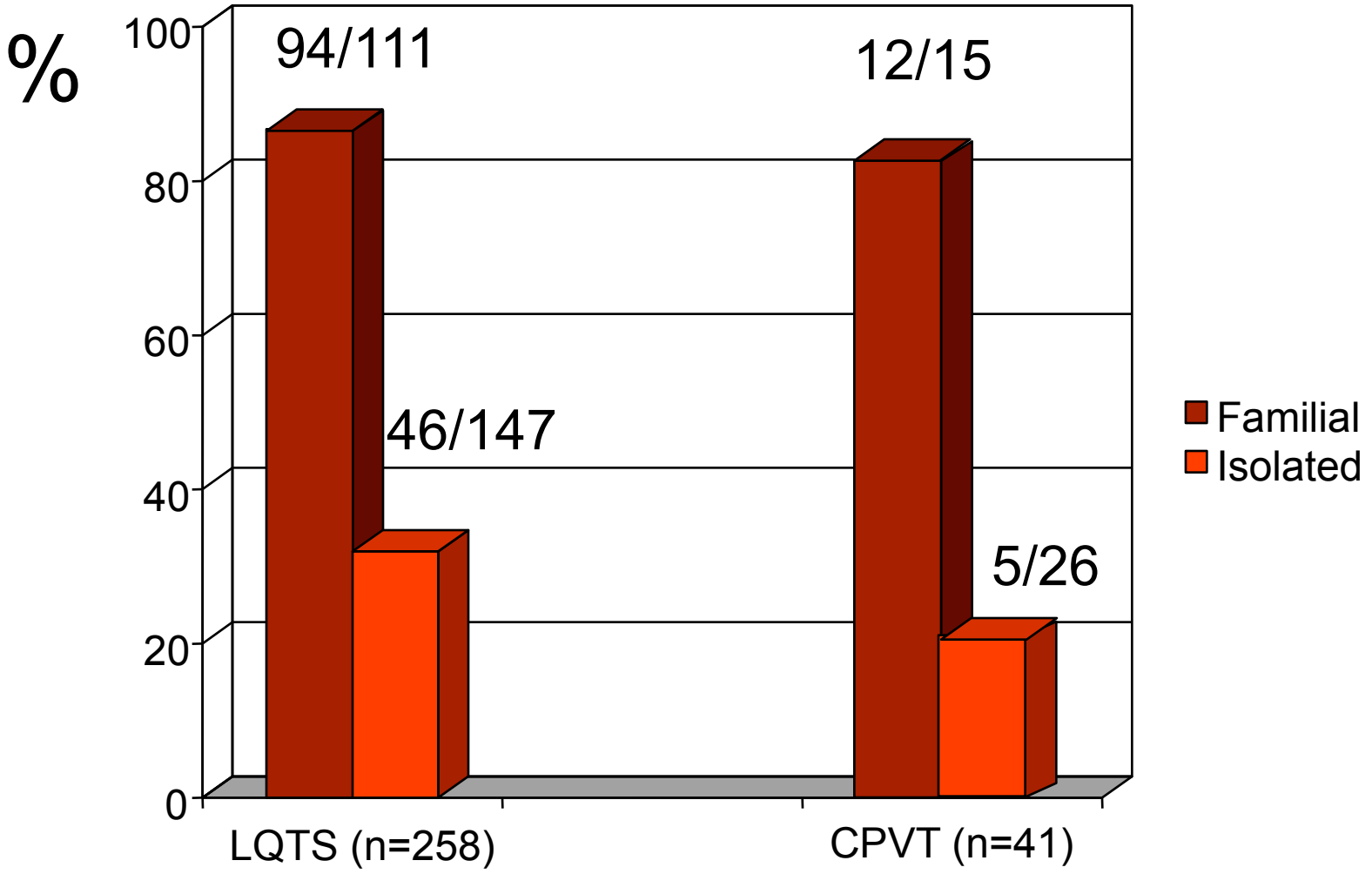
Result of *RYR2* gene Screening



Result of *RYR2* gene Screening



Yield of molecular genetic screening



Hofman ea. Circulation 2013

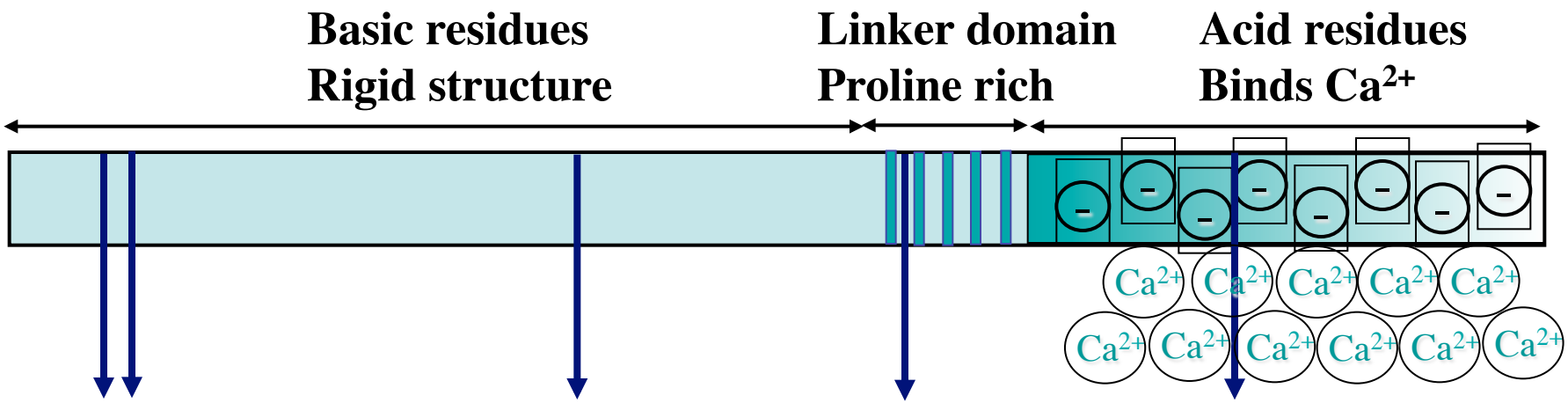
Catecholamine-induced PMVT/VF

Lahat et al. **Circulation 103, 2822-7, 2001**
Am J Hum Genet 69, 1378-84, 2001

- **One large Bedouin family**
- **Exercise-induced syncope, isoproterenol (PMVT)**
- **mean age 1st syncope 6.0 ± 3 (youngest 3.5 y.)**
- **Mean VPB treshold = 110 ± 10 bpm, bradycardia**
- **structural normal heart (?)**
- **linkage to 1p13-21, mutation in CASQ2 gene**

CASQ2 mutation overview

11 exons, 1.3kb cDNA, SR, Ca^{2+} binder



Exon 1
62delA ->STOP
R33 (STOP)*

Exon4
+1 G/A
splicesite

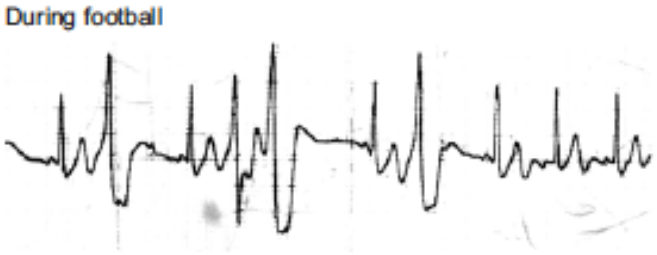
Exon6
K206N

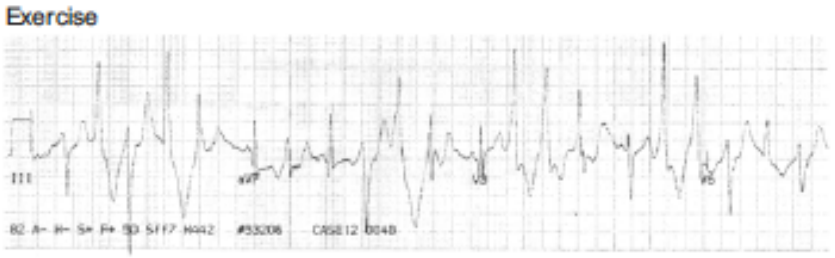
Exon9
D307H

Mutations in Calmodulin Cause Ventricular Tachycardia and Sudden Cardiac Death

Mette Nyegaard,[1,8,*] Michael T. Overgaard,[2,8] Mads T. Søndergaard,[2] Marta Vranas,[1] Elijah R. Behr,[3] Lasse L. Hildebrandt,[2] Jacob Lund,[2] Paula L. Hedley,[4,5] A. John Camm,[3] Göran Wettrell,[6] Inger Fosdal,[7] Michael Christiansen,[4] and Anders D. Børglum[1,*]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a devastating inherited disorder characterized by episodic syncope and/or sudden cardiac arrest during exercise or acute emotion in individuals without structural cardiac abnormalities. Although rare, CPVT is suspected to cause a substantial part of sudden cardiac deaths in young individuals. Mutations in *RYR2*, encoding the cardiac





Nyegaard *et al*, Am J Hum Genet 2012

Human Molecular Genetics, 2012, Vol. 21, No. 12 **2759–2767**
doi:10.1093/hmg/dds104
Advance Access published on March 14, 2012

Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human

Nathalie Roux-Buisson[1,2,3,4,†], Marine Cacheux[1,4,†], Anne Fourest-Lieuvin[1,4,5], Jeremy Fauconnier[6,7,8,9], Julie Brocard[1,4], Isabelle Denjoy[10], Philippe Durand[11], Pascale Guicheney[12,13], Florence Kyndt[14,15,16], Antoine Leenhardt[10], Hervé Le Marec[14,16,17], Vincent Lucet[18], Philippe Mabo[19], Vincent Probst[14,16,17], Nicole Monnier[1,2], Pierre F. Ray[2,3,4], Elodie Santoni[2], Pauline Trémeaux[2], Alain Lacampagne[6,7,8,9], Julien Fauré[1,2,4], Joël Lunardi[1,2,4] and Isabelle Marty[1,4,*]

Roux-Buisson *et al*, Hum Molec Genet 2012

A Novel Early Onset Lethal Form of Catecholaminergic Polymorphic Ventricular Tachycardia Maps to Chromosome 7p14-p22

ZAHURUL A. BHUIYAN, M.D., PH.D.,*,† MOHAMED A. HAMDAN, M.D., F.A.C.C.,‡
EMAN T.A. SHAMSI, M.D.,§ ALEX V. POSTMA, PH.D.,† MARCEL M.A.M. MANNENS, PH.D.,*
ARTHUR A. M. WILDE, M.D., PH.D.,† and LIHADH AL-GAZALI, M.D., F.R.C.P.§

From the *Department of Clinical Genetics; †Experimental and Molecular Cardiology Group, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; ‡Department of Pediatrics, Tawam Hospital; and §Faculty of Medicine, United Arab Emirates University, Al-Ain, UAE

J Cardiovascular Electrophysiology 2007

Published online: October 24, 2016

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

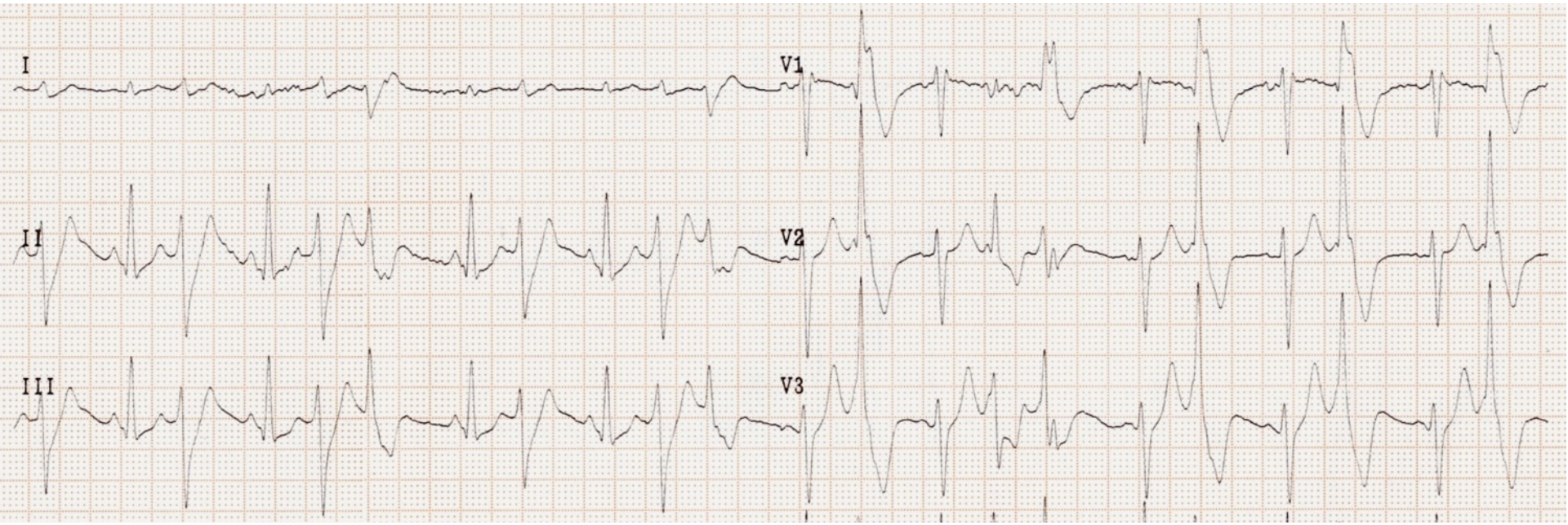
TECRL, a new life-threatening inherited arrhythmia gene associated with overlapping clinical features of both LQTS and CPVT

Harsha D Devalla[1,*,†], Roselle Gélinas[2,3,†], Elhadi H Aburawi[4,†], Abdelaziz Beqqali[5,†], Philippe Goyette[2], Christian Freund[1,6], Marie-A Chaix[2,3], Rafik Tadros[2,3,5], Hui Jiang[7,8,9], Antony Le Béchec[10], Jantine J Monshouwer-Kloots[1], Tom Zwetsloot[1], Georgios Kosmidis[1], Frédéric Latour[2], Azadeh Alikashani[2], Maaike Hoekstra[5], Jurg Schlaepfer[11], Christine L Mummery[1], Brian Stevenson[10], Zoltan Kutalik[10,12], Antoine AF de Vries[13,14], Léna Rivard[2,3], Arthur AM Wilde[15,16], Mario Talajic[2,3], Arie O Verkerk[5,‡], Lihadh Al-Gazali[4,‡], John D Rioux[2,3,**,†,‡], Zahurul A Bhuiyan[17,***,‡] & Robert Passier[1,18,****,‡]

- 3 families, autosomal recessive transmission
- trans-2,3-enoyl-CoA reductase-like (TECRL) gene
- Chromosome 4q13, 12 exons

KCNJ2 mutations

Andersen Tawil Syndrome

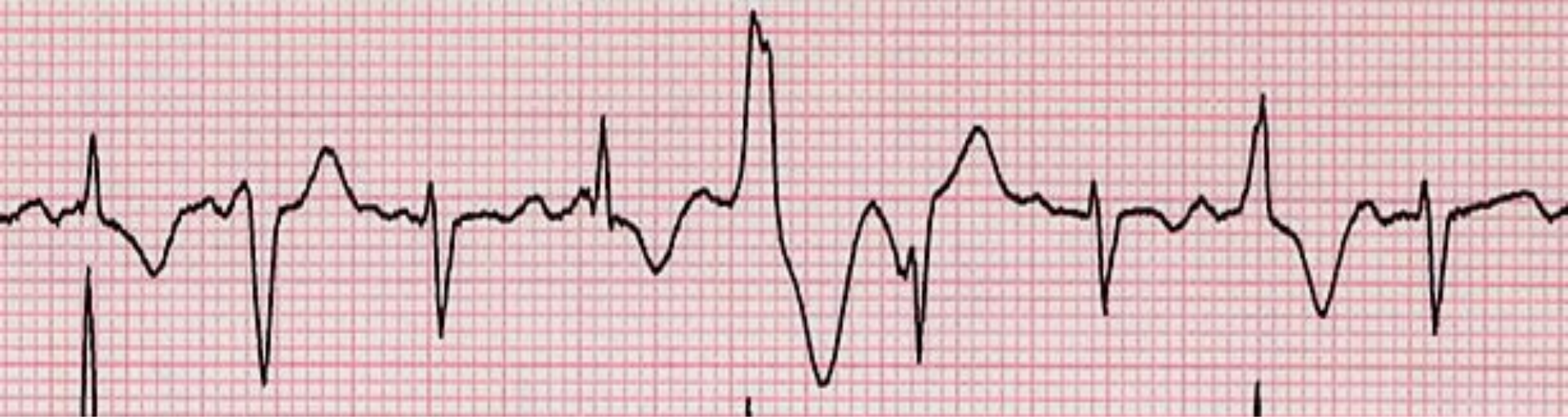


- significant arrhythmia burden, also at rest
- exercise related bidirectional VT
- significant U-wave

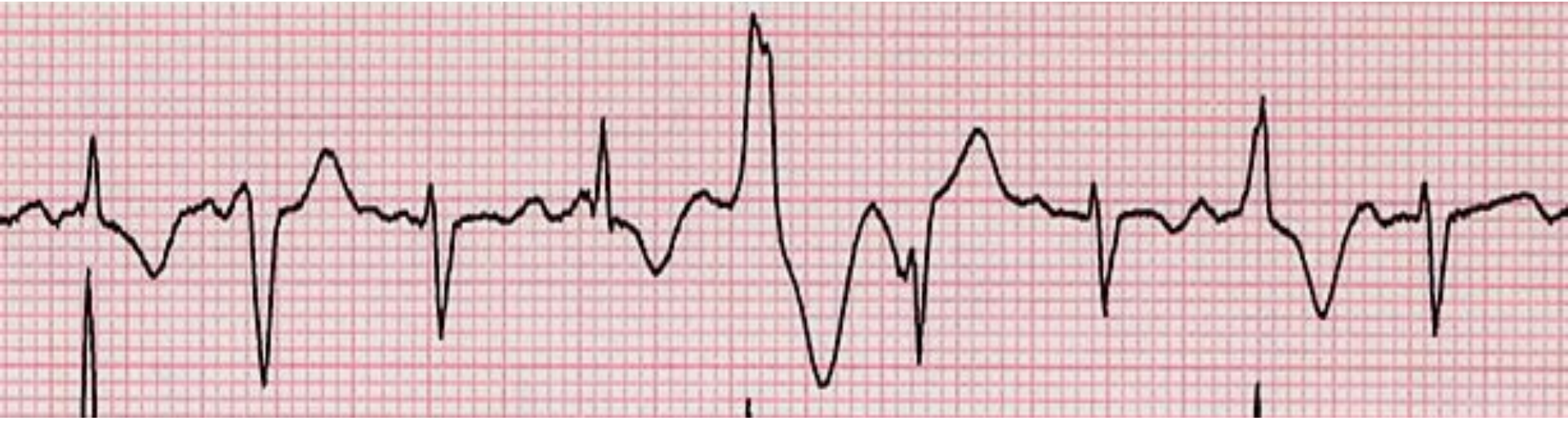
CPVT, Conclusions

Why genetic testing?:

- **Gene-specific treatment** -
- **Risk stratification** -
- **Reaching a diagnosis** ++
- **Presymptomatic treatment** ++



Risk stratification



Catecholamine-induced PMVT/VF

Risk factors

- ♥ cardiac arrest prior to therapy
- ♥ complexicity of ectopy (≥ doublets)
- ♥ syncopal events

Catecholaminergic Polymorphic VT

Role of genetics

- **C-terminal channel forming domain carry a higher risk on VT's.**

Circ Arrhythm Electrophysiol. 2012;5:748-756.

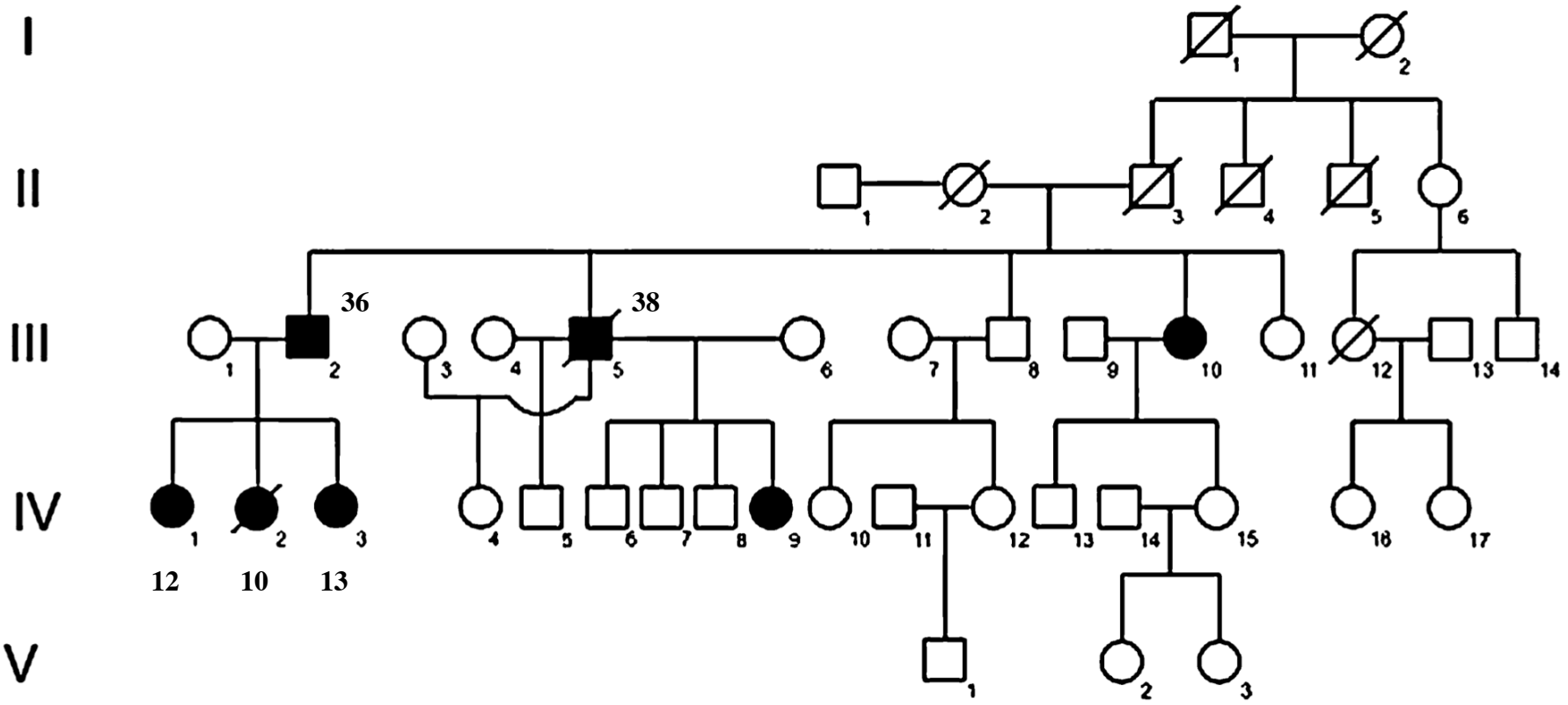
Pediatr Cardiol
DOI 10.1007/s00246-014-0950-2

ORIGINAL ARTICLE

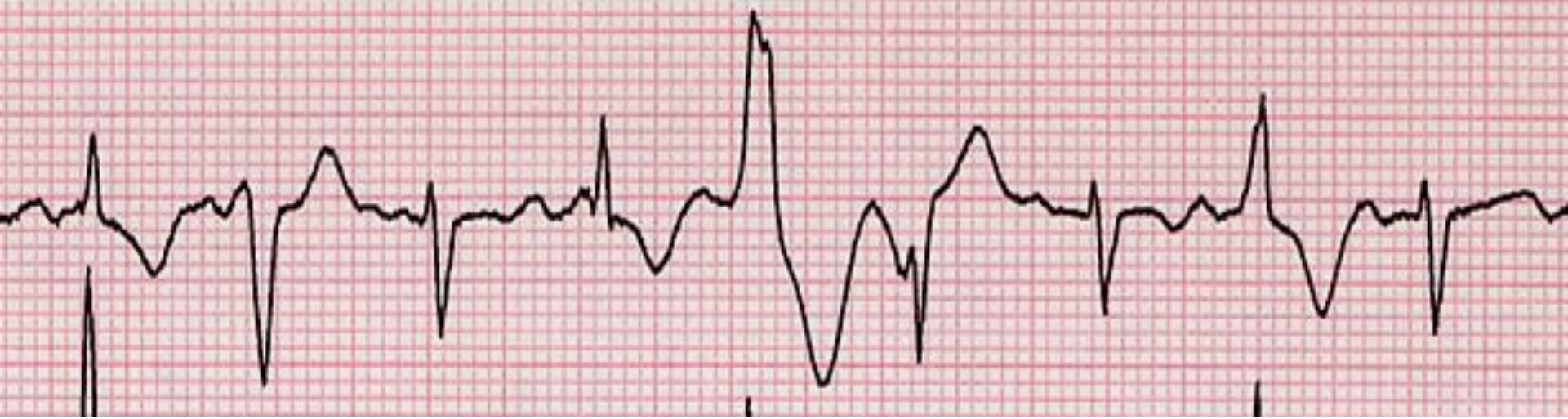
Ryanodine Receptor Mutations Presenting as Idiopathic Ventricular Fibrillation: A Report on Two Novel Familial Compound Mutations, c.6224T>C and c.13781A>G, With the Clinical Presentation of Idiopathic Ventricular Fibrillation

Christian Paech · Roman Antonin Gebauer · Jens Karstedt · Christoph Marschall · Andreas Bollmann · Daniela Husser

Received: 15 February 2014 / Accepted: 3 June 2014



- DNA: RyR2 + : p.Ile2075Thr & Lys4594Arg
- 7 mutation carriers, 4 aSCD, 2 SCD.
- adrenergic trigger in 5; 7 more SCD (no data)



CPVT, Genetic testing

- genetic heterogeneous (6 genes)
- vast majority is RyR2 related
- Important to identify ‘silent’ gene carriers
- role in risk stratification?
- role in IVF (adrenergically triggered)


Thank you

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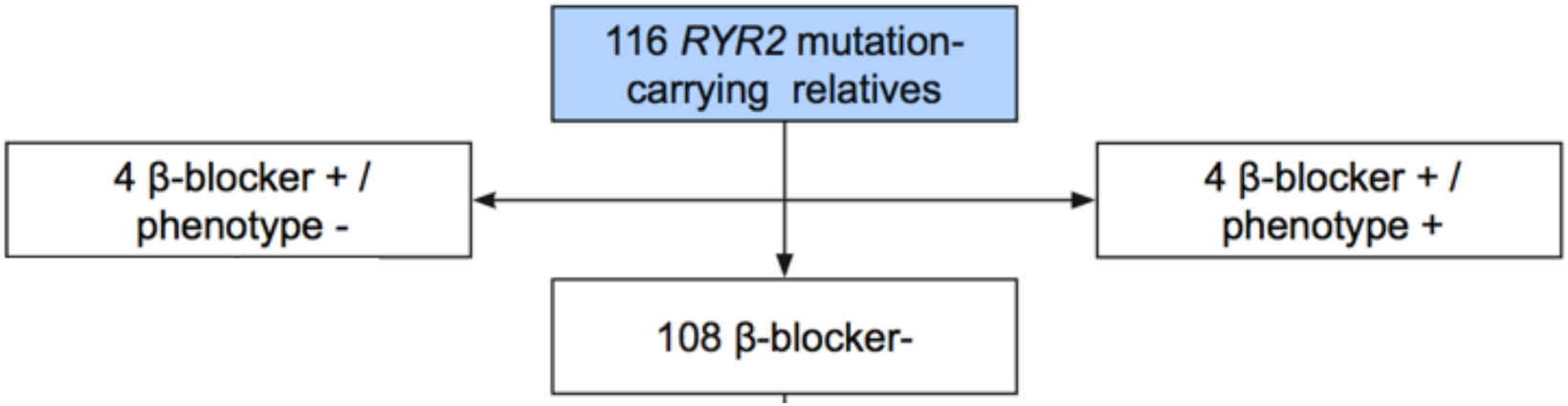
Circulation: Arrhythmia & Electrophysiology

Familial Evaluation in Catecholaminergic Polymorphic Ventricular Tachycardia

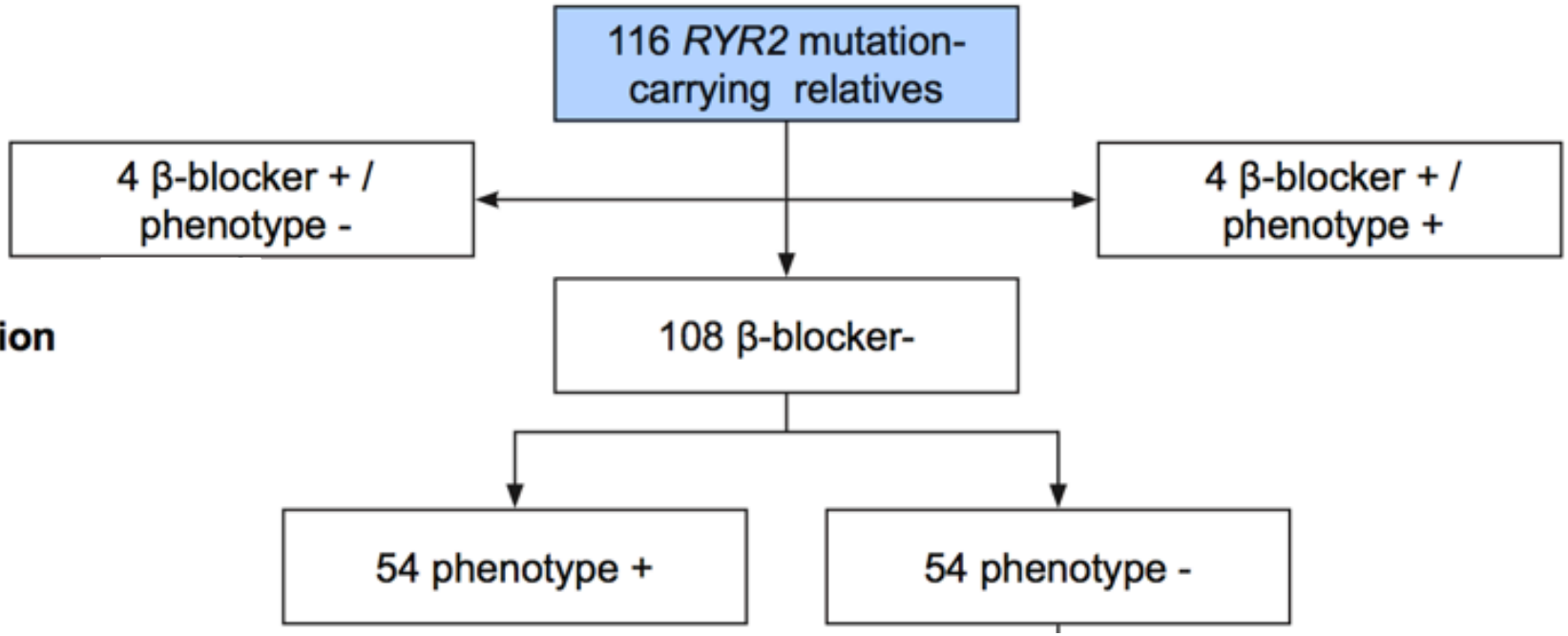
Disease Penetrance and Expression in Cardiac Ryanodine Receptor Mutation–Carrying Relatives

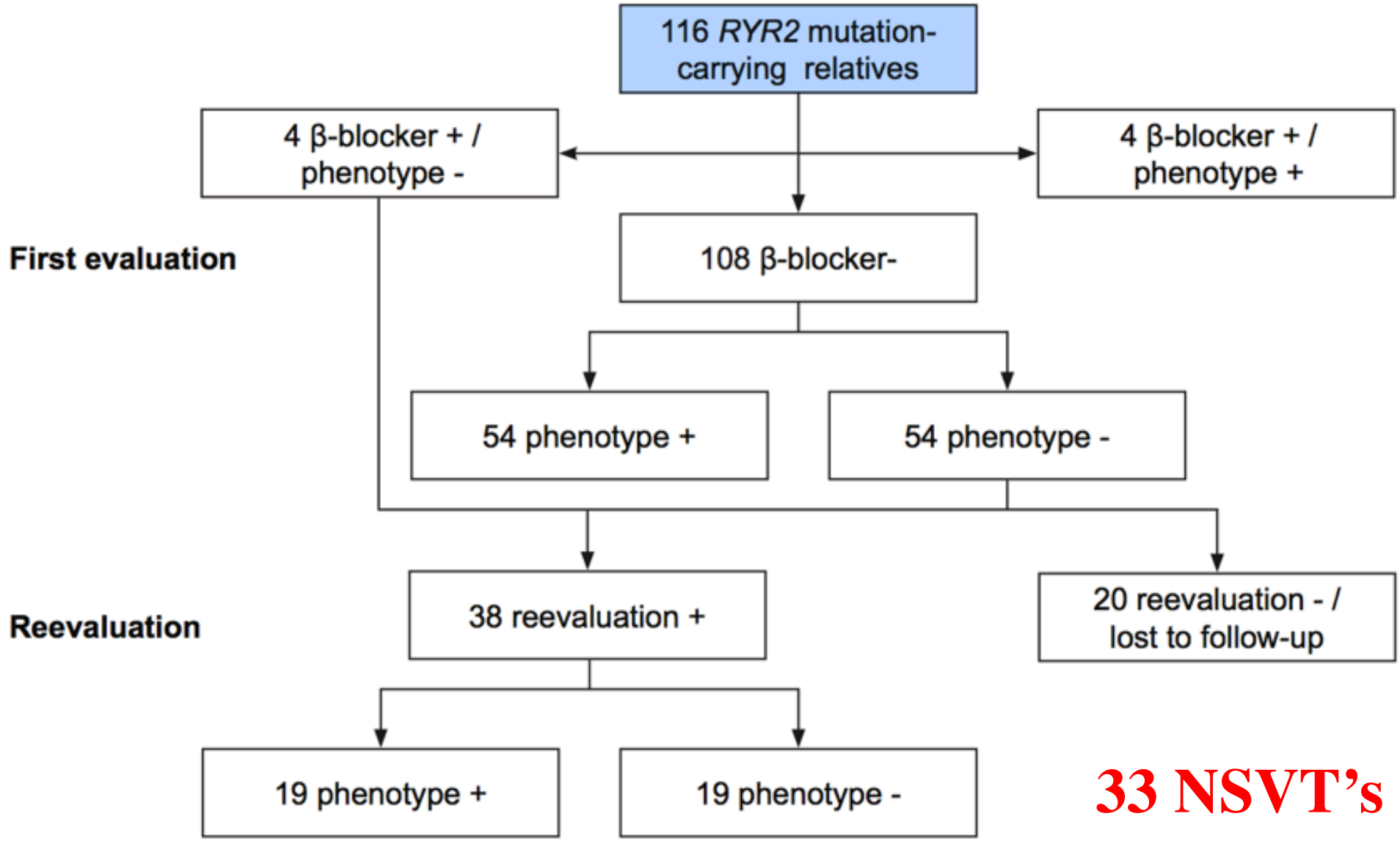
Christian van der Werf, MD; Ineke Nederend, MSc; Nynke Hofman, MSc; Nan van Geloven, MSc; Corné Ebink, MD; Ingrid M.E. Frohn-Mulder, MD; A. Marco W. Alings, MD, PhD; Hans A. Bosker, MD, PhD; Frank A. Bracke, MD, PhD; Freek van den Heuvel, MD, PhD; Reinier A. Waalewijn, MD, PhD; Hennie Bikker, PhD; J. Peter van Tintelen, MD, PhD; Zahurul A. Bhuiyan, MD, PhD; Maarten P. van den Berg, MD, PhD; Arthur A.M. Wilde, MD, PhD

Circ Arrhythm Electrophysiol. 2012;5:748-756

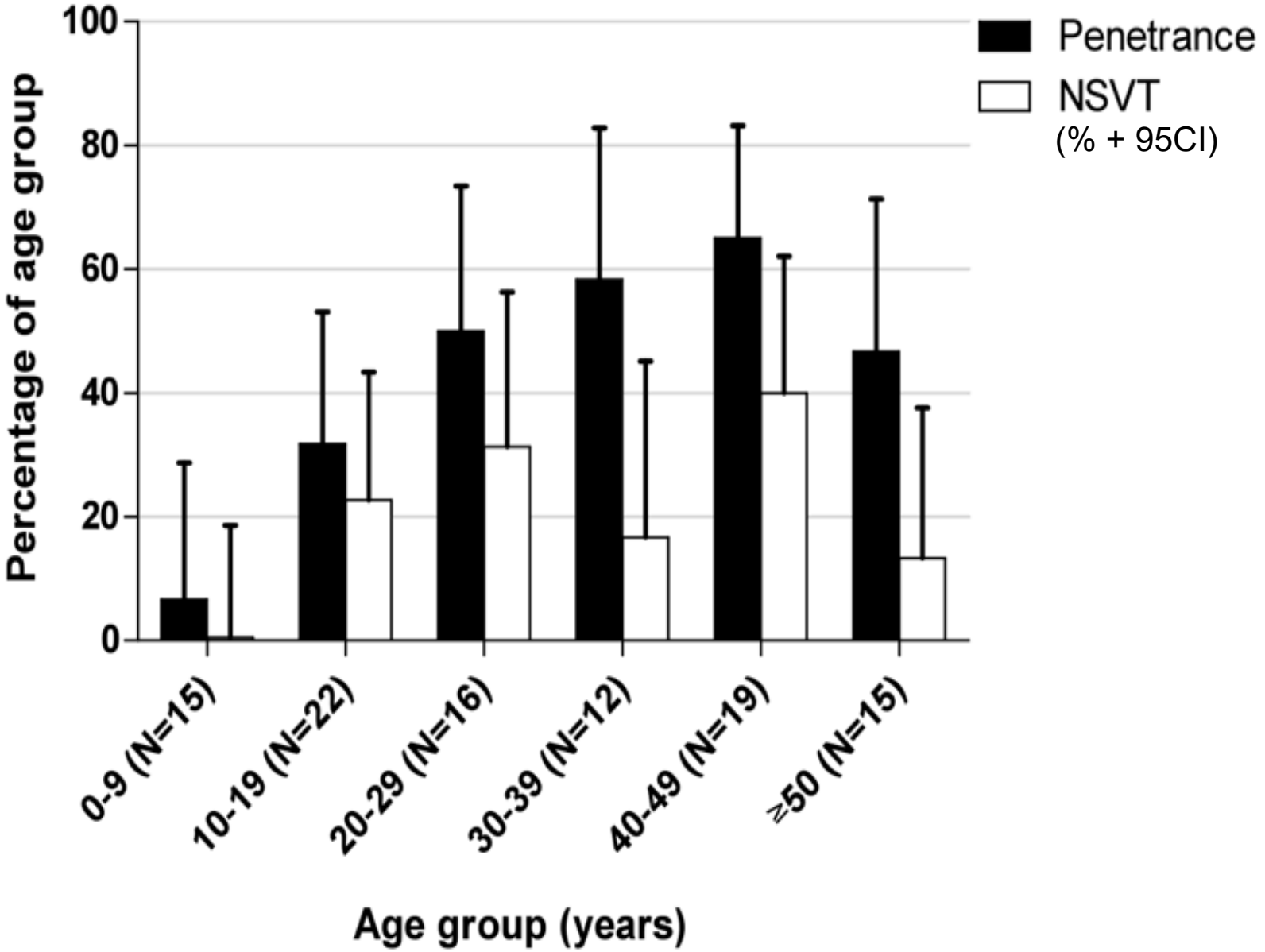

116 RYR2 mutation-carrying relatives
4 β-blocker + / phenotype -
4 β-blocker + / phenotype +
108 β-blocker-

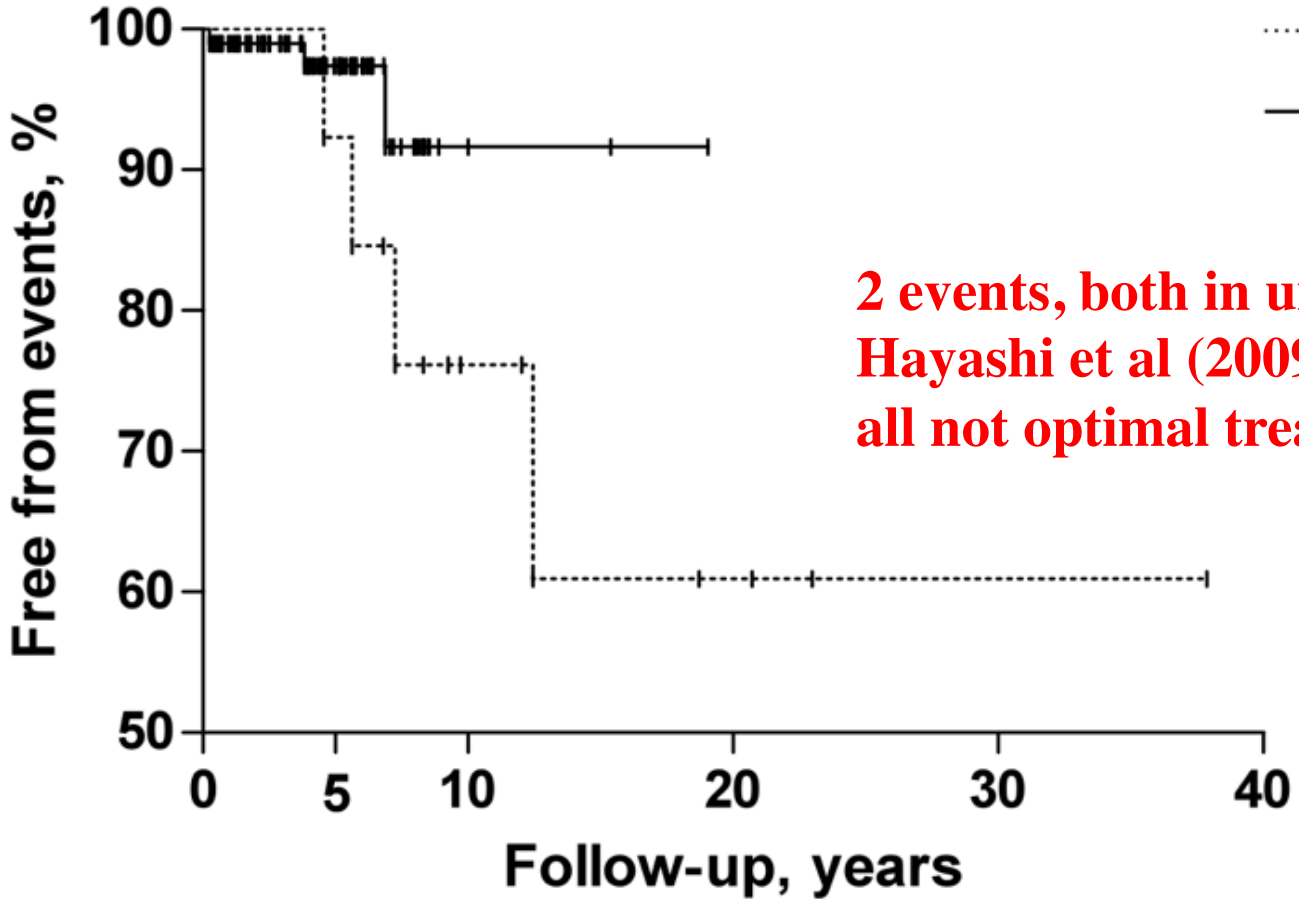
First evaluation




116 RYR2 mutation-carrying relatives
4 β-blocker + / phenotype -
4 β-blocker + / phenotype +
First evaluation
108 β-blocker-
54 phenotype +
54 phenotype -
Reevaluation
38 reevaluation +
20 reevaluation - / lost to follow-up
19 phenotype +
19 phenotype -

33 NSVT's


Penetrance
NSVT
(% + 95CI)
Percentage of age group
100
80
60
40
20
0
0-9 (N=15)
10-19 (N=22)
20-29 (N=16)
30-39 (N=12)
40-49 (N=19)
≥50 (N=15)
Age group (years)



2 events, both in untreated pts
Hayashi et al (2009): 8y FU: 12/51, all not optimal treated

No. at risk	0	5	10	20	30
Probands	12	11	5	2	1
Relatives	98	45	2	-	-