Flecainide therapy suppresses exercise-induced ventricular arrhythmias in patients with CASQ2 associated catecholaminergic polymorphic ventricular tachycardia

Asaad Khoury[2,3] MD, Monther Boulos[1,3] MD, Mahmoud Suleiman[1,3] MD, Miry Blich[1,3] MD , Michael Eldar[4] MD, Ibrahim Marai[1,3] MD ,

[1] The division of Pacing and Electrophysiology. Rambam Health Care Campus
[2] The Department of Pediatric Cardiology. Rambam Health Care Campus
[3]Bruce Rappaport Faculty of Medicine, Haifa, Israel
[4]Sheba, Medical Center, Tel Ha Shomer

Introduction

Catecholamine sensitive polymorphic ventricular tachycardia (CPVT) is a rare disease that occurs in subjects without organic heart disease

It is characterized by episodes of syncope, seizures or SCD in response to physiological or emotional stress

First described by Reid *et al*. in 1975 and defined as a distinct clinical entity by Leenhardt *et al*. in 1995

CPVT is a genetic disorder

Autosomal dominant and recessive inheritance have been described. The causative genes have been mapped to chromosome 1

Mutations of the RYR2 gene cause AD CPVT, while CASQ2 gene mutation may cause AR and AD CPVT

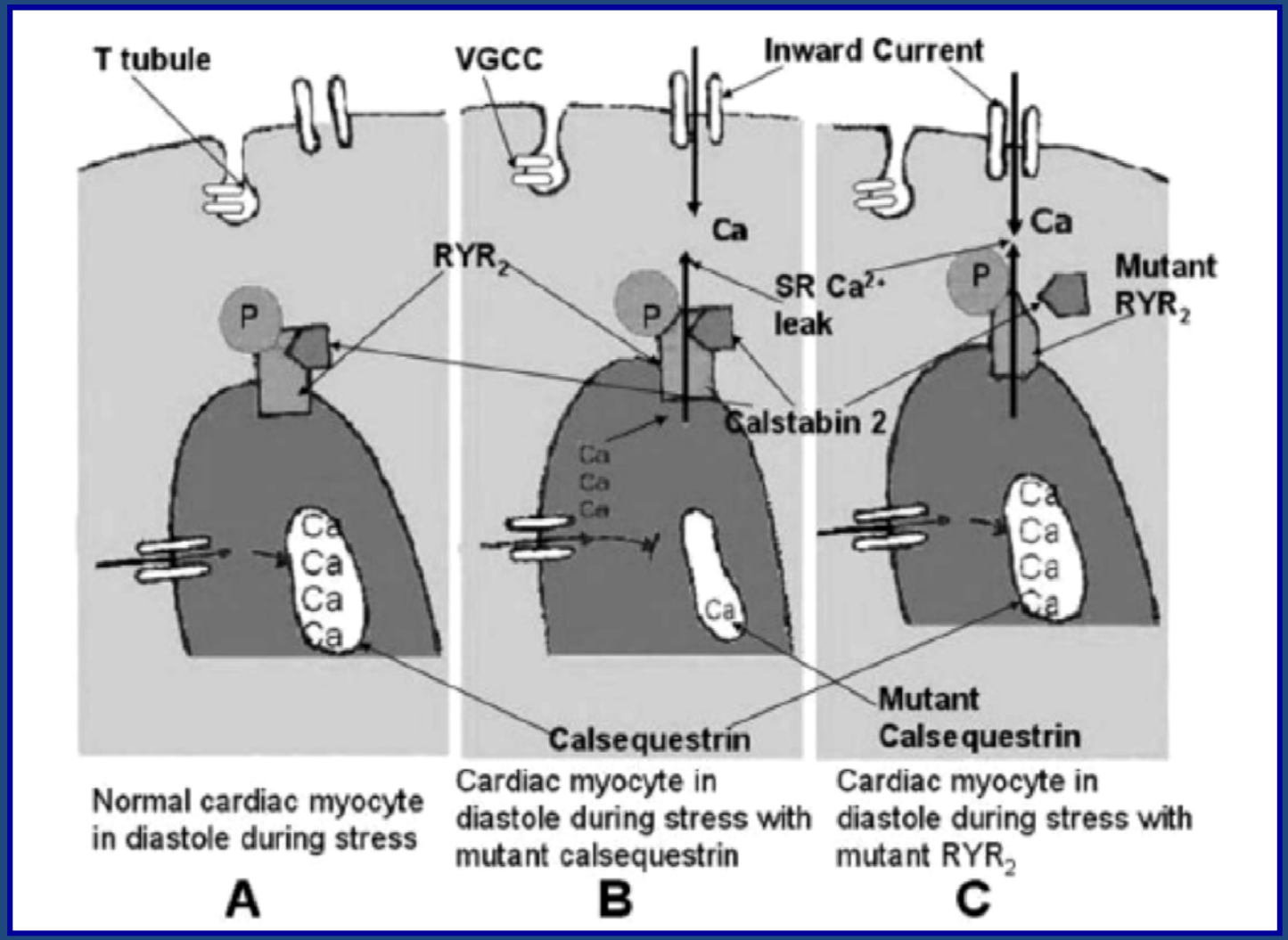
~ 50 RYR2 mutations (CPVT1), 6 CASQ2 mutations (CPVT2).

The CASQ2 protein

- Localized to the terminal cisternae of the SR
- Binds Ca^{+2} with high capacity & moderate affinity
- Ca^{+2} buffer and a Ca^{+2} storage reservoir inside the SR, lowering free Ca^{+2} concentrations

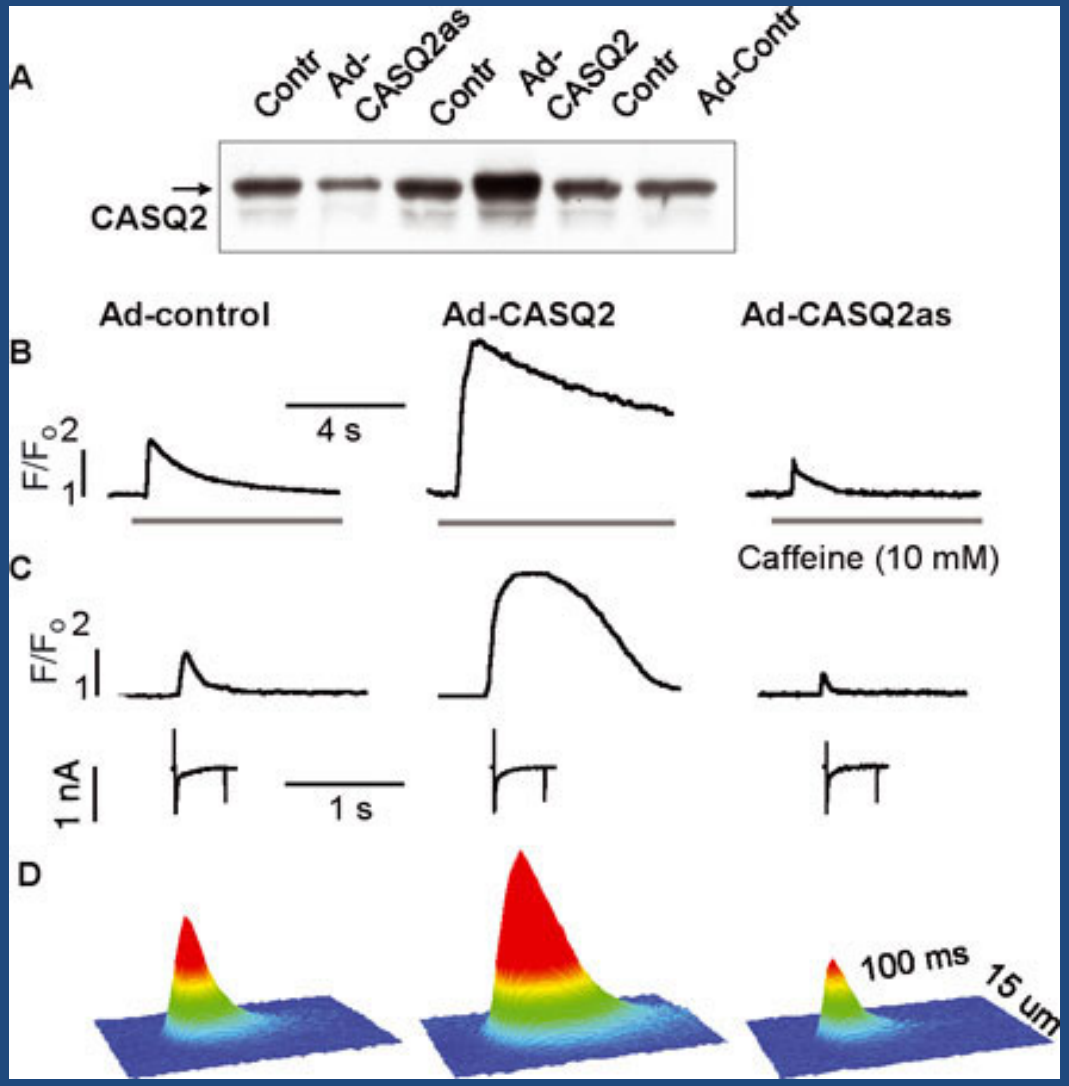
A quaternary protein complex that anchors calsequestrin to the ryanodine receptor, junctin1 & triadin

Molecular Pathogenesis: DADs that may trigger arrhythmia in CPVT



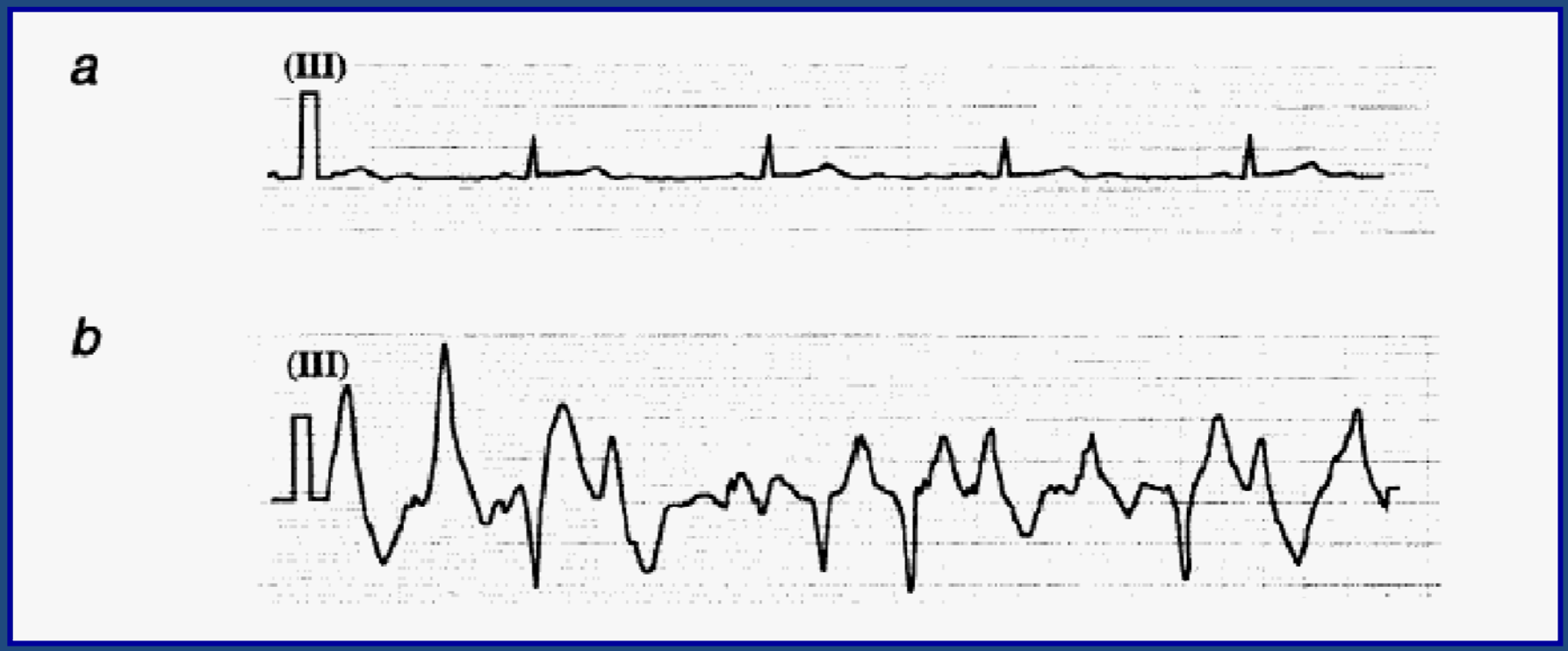
Francis *et al*. Heart Rhythm 2005;2:550–554

Averaged Spontaneous Ca^{2+} Sparks



Biol Res 37: 603-607, 2004

Our Cohort of Patients



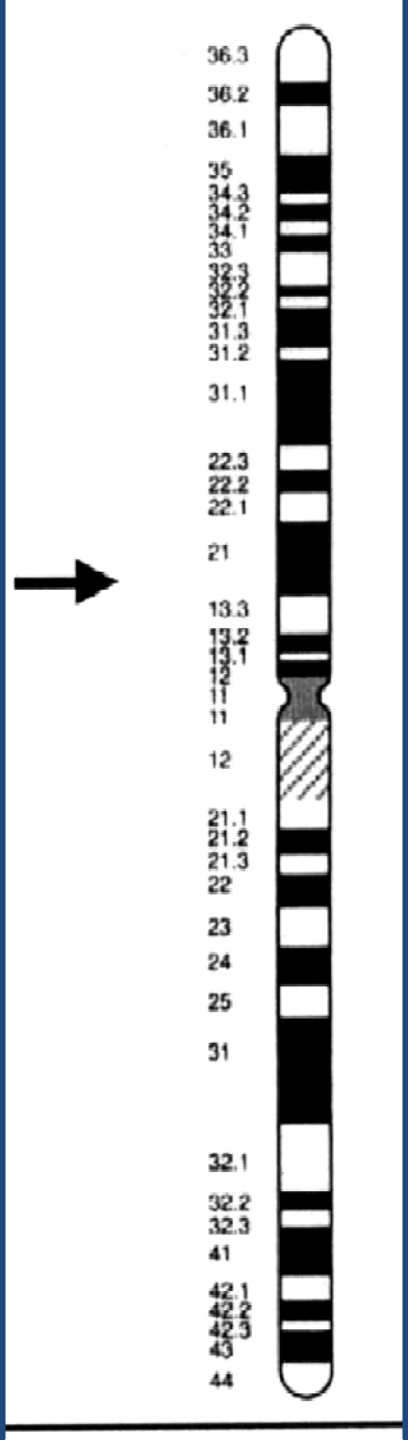
A Missense Mutation in a Highly Conserved Region of *CASQ2* Is Associated with Autosomal Recessive Catecholamine-Induced Polymorphic Ventricular Tachycardia in Bedouin Families from Israel

Lahat *et al. Am J Hum Genet* 2001; 69:1378–1384

Linkage to Chromosome 1P

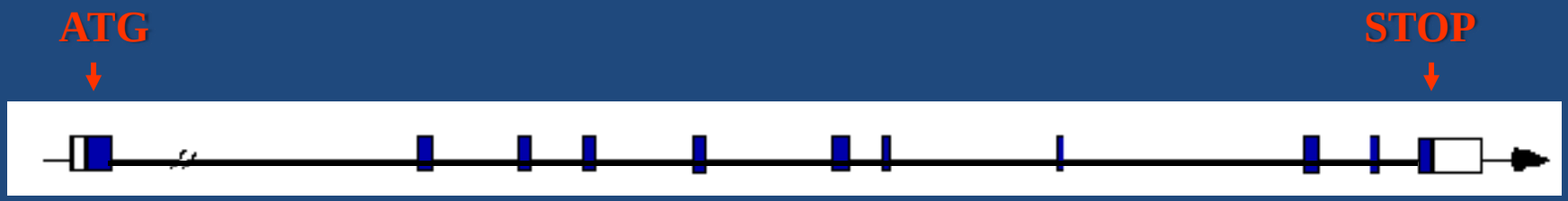
- We mapped the disease locus to chromosome 1p 13-21

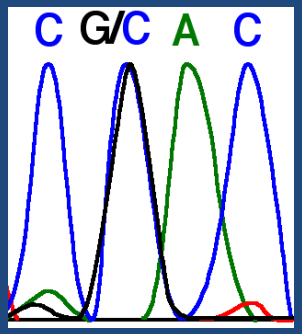
- A new CPVT linkage area



Calsequestrin 2 (CASQ2)

Composed of 11 exons; encodes 399 amino acid protein

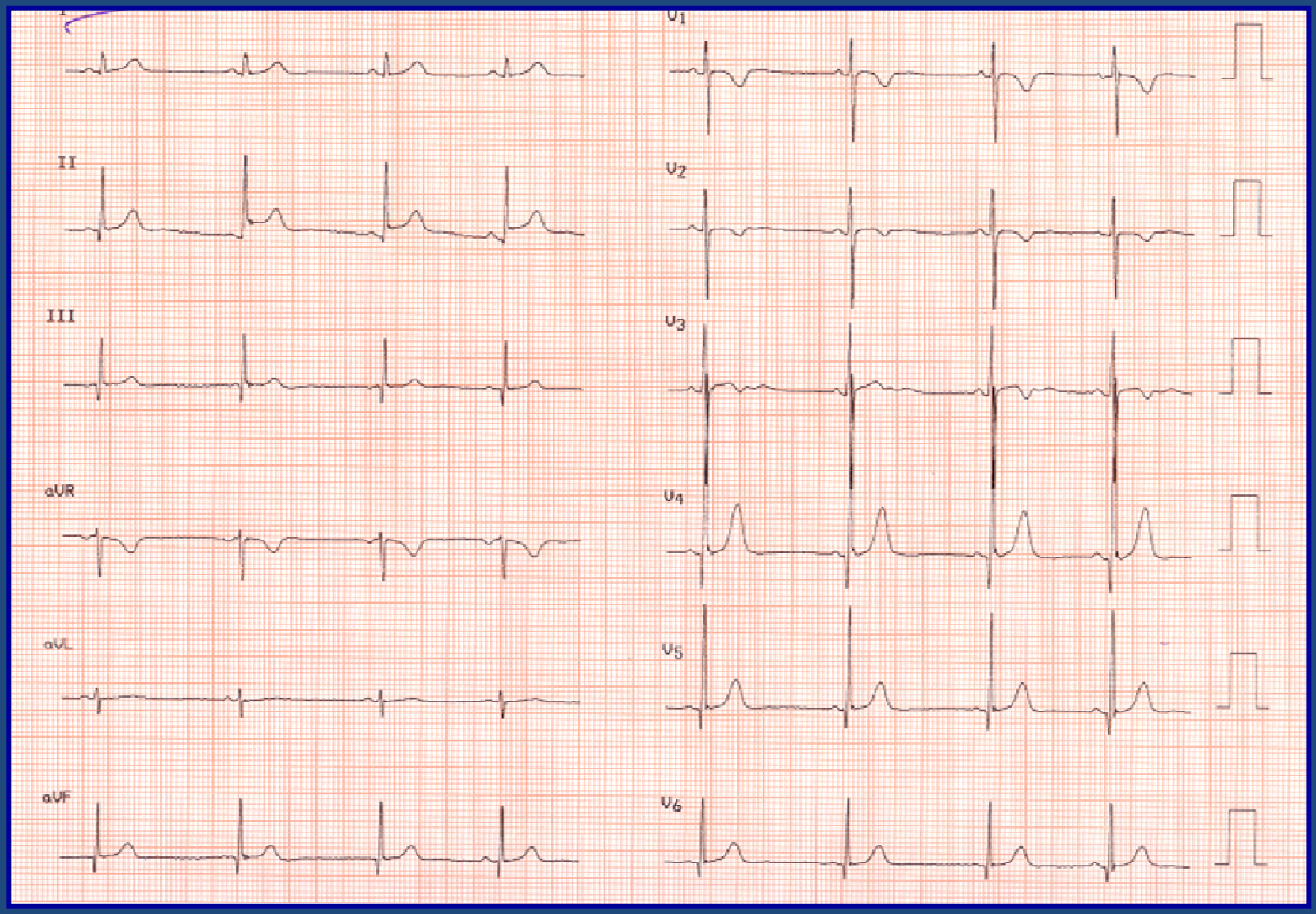




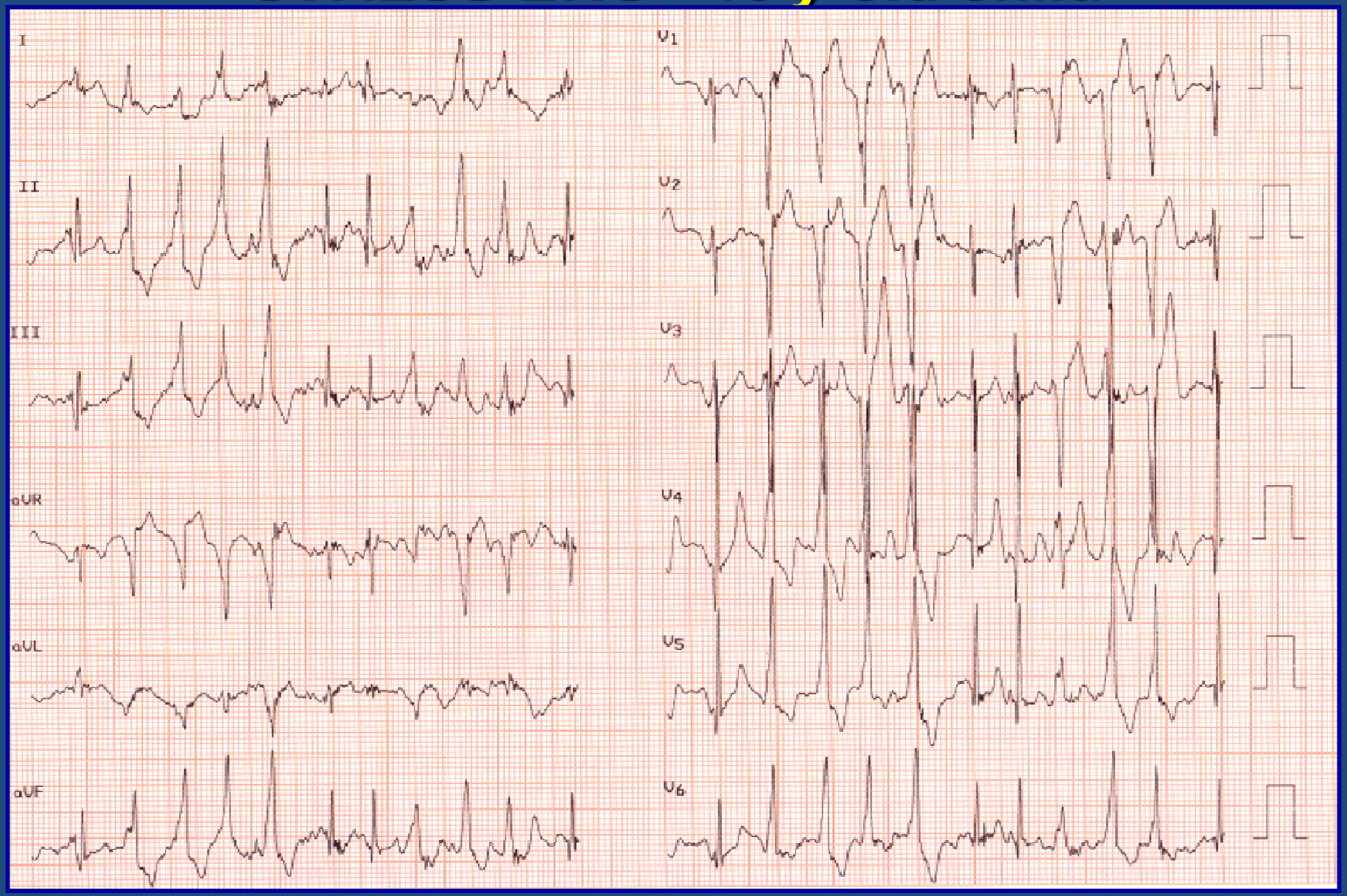
g → C (1038)

Aspartic Acid → Histidine (307)

Rest EKG –10 y old child



STRESS EKG –10 y old child



Clinical Data

27 Patients (16 F,11 M), 12 Families. Age 0-22 (mean 8±7) years

20 were **symptomatic** (13 syncope,7 seizures)

Age at first symptom**: 2-10** (**6** ±**4)** years.

Resting **HR = 66** ± **14, 47-93** bpm

VPCs/ VT Threshold = **117** ± **12** bpm

QTc, interval (Bazzett's) = 0.36-0.43 sec

All had normal hearts by Echo, 10 Pts normal cardiac MRI

One girl underwent successful BPV at two years of age with minimal residual PS and PR

All had positive stress test (treadmill/ isoproternol)

All were homozygous for CASQ2-D307H mutation

None of the heterozygous carriers had symptoms or positive stress test

Response to Medical treatment

6 asymptomatic Pts remained symptom-free for f/u of 8±2.5 (0-13) years. They were younger in age. Propranolol mean dose 2.3 mg/kg/d.

12 symptomatic Pts (60%) remained symptom-free for 6.1±4 (2-11) years. Propranolol mean dose 3.5 mg/kg/d.

6 Pts continued to have syncope despite high dose Propranolol of 5.1 mg/kg/d thereby AICD was implanted.

6 sudden deaths (4F,2 M) . (Age 15,10,15,17,17,16 yrs).
4 have refused AICD due to social/cultural constrains.

β-blockers and CCB versus β-blockers alone

Results:

- 5/10 – No response ,2 pts had NSVT in repeated test.
- 1/10 – mild response, had repeated syncope - AICD.
- 4/10- had significant response in repeated test. All kept on both drugs.(one died 6 month later on both drugs).
- 2/4 responders had increased number and lower threshold for VPBs after 6 months.
- Combined therapy was well tolerated.
- One child had typical NM- Syncope.

Flecainide-1

- Flecainide , an approved antiarrhythmic drug was reported to reduce exercise-induced ventricular arrhythmias (EIVA) in patients with CPVT, mainly ryanodine receptor (RyR2) associated CPVT (CPVT1) (van der Werf C et al . J Am Coll Cardiol 2011;57:2244–54).
- The **role of flecainide in CASQ2 associated CPVT (CPVT2)is not known.**

Flecainide-2

- Flecainide has **dual mode of an action in CPVT:** suppression of spontaneous sarcoplasmic reticulum Ca2+ release events via RyR2 inhibition and suppression of triggered beats via Na+ channel block (**Watanabe H et al** *Nat Med*. 2009 April ; 15(4): 380–383).
- Flecainide can also reduce ventricular arrhythmia during exercise by keeping the heart rate below the threshold of VPBS.

Study protocol-1

- ✓ 7 high features CPVT2 with AICD
  (5 syncope, 1ab. SCD,1 prim. Prevention)
- ✓ All had EIVA,4 had app. Shocks,
- ✓ All receiving high dose BB or BB and CCB
- ✓ Stress test (Bruce protocol), 2-3 hours after last dose of BB .
- ✓ Flecainide was titrated to a dose of 3-4 mg/kg bid and CCB was discontinued
- ✓ 2-3 weeks later stress test was repeated 2-3 hours after last dose of medication .

Study protocol -2

- ✓ Pts were followed and stress test was repeated every 4-6 months .
- ✓ All pts had CBC, KFT,LFT,Ca,Mg and TSH
- ✓ The study was approved by the RMC and ministry of heath ethical committees . Pts or their parents gave written informed consent.
- ✓ Statistics: Data presented as mean ±**SD** or median. Student T test was used to compare exercise test parameters.

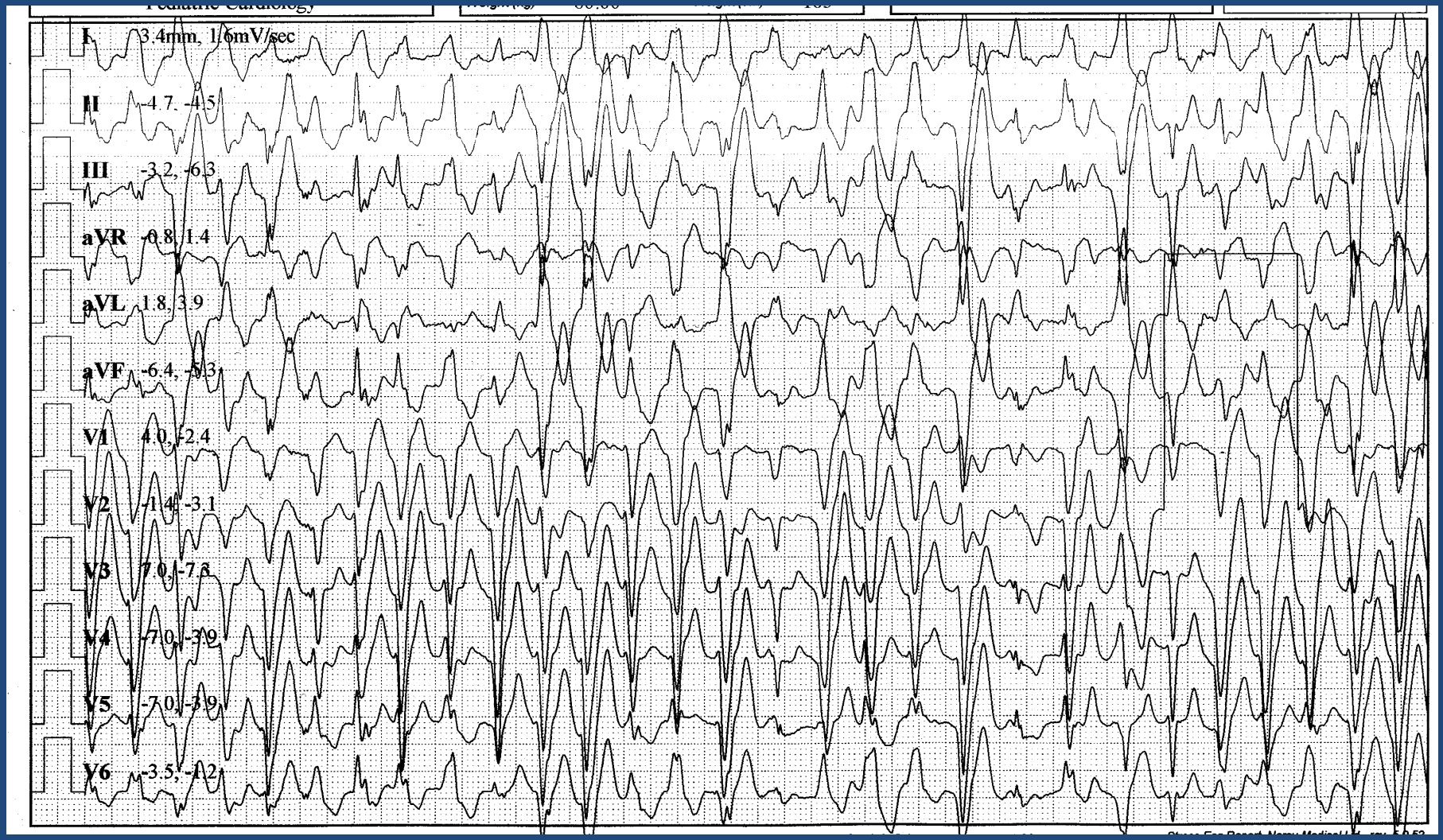
P. Data

Patient	sex	age	Indication of ICD	Drug therapy at baseline	Indication for flecaibide	Flecainide dose	ET at baseline	ET after flecainide	Side effects	F/U months	Arrhythmia during F/U
	F	16	Cardiac arrest	Propranolol+ verapamil	Multiple ICD+ EIVA	100mg x2	Frequent VPBS +bigeminy	non	no	7	no
	m	16	syncope	Propranolol+ verapamil	EIVA	100mg x2	Frequent VPBS +bigeminy	non	no	24	1 VT storm at 16 mo
	m	16	syncope	Deralin	EIVA	100mgx3	Frequent VPBS +bigeminy+VT	non	no	14	no
	m	17	primary	Deralin	Multiple ICD shocks+ EIVA	100mgx2	Frequent VPBS +bigeminy	non	no	20	no
	m	21	syncope	Deralin+verapamil	Multiple ICD shocks+ EIVA	100mgx2	Frequent VPBS +VT	non	no	26	no
	m	21	syncope	Deralin	EIVA	50mgx3	Frequent VPBS +bigeminy+VT	non	no	15	no
	m	14	syncope	Deralin+verapamil	EIVA	50mgx3	Frequent VPBS, couplets	VPB only	no	17	1 VT storm after ?

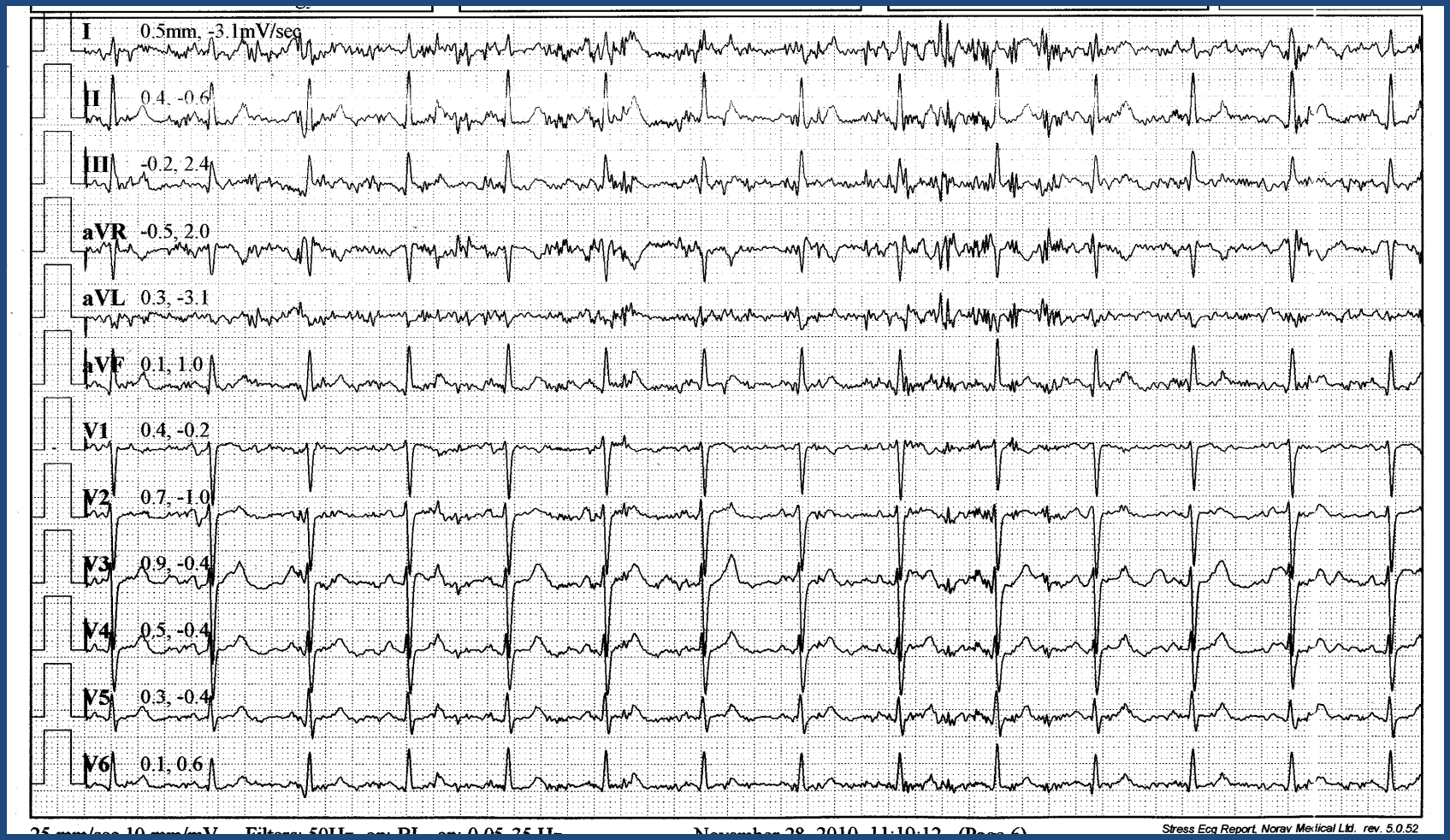
Table: parameters of exercise test before and after flecainide therapy

	Before flecainide	After flecainide	p
Duration (minutes)	13.1±1.6	12.9±2	0.23
stage	4.4±0.5	4.3±0.5	0.18
Workload (METs)	16.8±2.6	16.1±3.6	0.15
Maximal heart rate	117±10.4	116±12.5	0.4

END OF STAGE 3 - BB



END OF STAGE 4 – BB + flec.



Results-1

- Flecainide in combination with high dose BB completely suppressed EIVA in CALSQ H307D mutation CPVT pts.
- 5/7 pts. Were symptom free and free of arrhythmias according to ICD interrogation
- 2/7 had one episode of VT storm despite negative stress test . The VT storm was proceeded by AT in one and ST in the other. These pts were treated, one for VT during stress and app. DC shock for the other .

Results -2

- Treatment was well tolerated with no side effects.
- Mild increase of QRS duration without prolongation of QT interval was noticed

Study limitation

- This study included small number of patients with specific mutation. So, studies with large number of patients and with other types of CASQ2 mutations are needed.
- We did not measure the plasma level of flecainide. Thus we are not sure that all the patients received the optimal dosage (**or were non complaint**). It could be that the two patients who ICD shocks during follow up had low plasma levels as the case in the study of Werf van der et al.

CONCLUSION

- Flecainide can completely prevent ventricular arrhythmia during exercise test and partially prevent recurrent ICD shocks in high risk CASQ2 D307H associated CPVT patient


Thank you

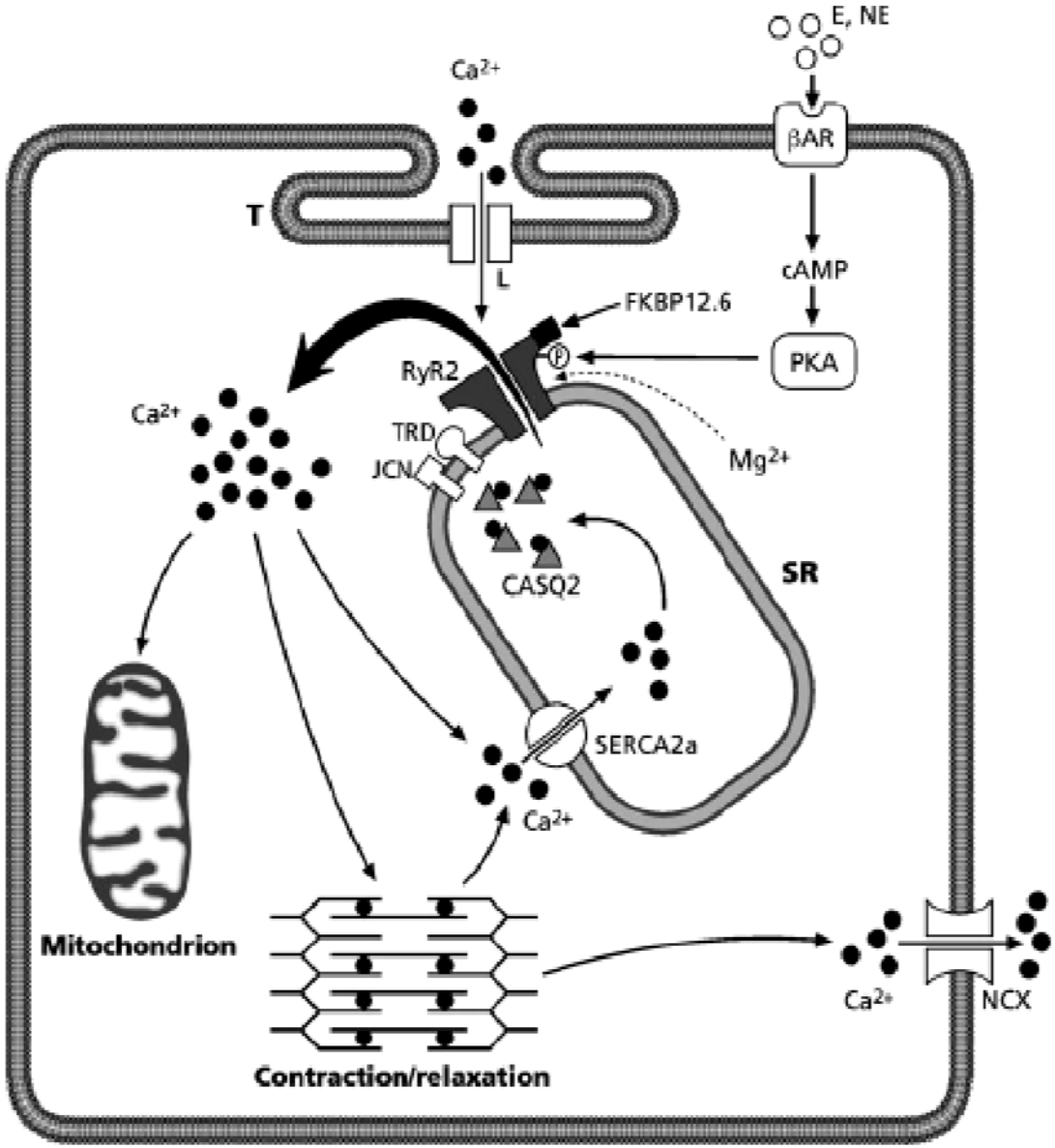


Fig. 2. Regulation of the RyR2 channel function in cardiac myocytes. Abbreviations: T—T-tubule, L—L-type of Ca^{2+} channel; E, NE—epinephrine, norepinephrine; βAR—beta-adrenergic receptor; cAMP—cyclic AMP; PKA—protein kinase A; FKBP12.6—calstabin2; TRD—triadin 1; JCN—junctin; CASQ2—calsequestrin 2; SR—sarcoplastic reticulum; SERCA2a—sarcoplastic reticulum Ca^{2+}-ATPase; NCX—Na^{+}/Ca^{+} exchanger.