Pediatric and Congenital Rhythm Congress VII

4 - 7 February 2017

Thessaloniki/GREECE

PEDIRHYTHM VII

Inherited Arrhythmia Syndromes

When to perform Genetic testing?

Arthur AM Wilde

February 4, 2017

Which pts should undergo genetic testing?

- SCD victims with a likely diagnosis
- Pts diagnosed with an inherited AS and their family members

Which pts should undergo genetic testing?

- SCD victims without a diagnosis?

Not addressed in this talk

(molecular autopsy)

Familial arrhythmia syndromes

Arrhythmogenic substrate

- in the electrical characteristics of the heart (primary)
- in the structural characteristics of the heart (secondary)

Secondary arrhythmia syndromes

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Arrhythmogenic RV cardiomyopathy
- Congenital anomalies (i.e.Holt-Oram)
- Muscular dystrophies

Primary arrhythmia syndromes (1995)

	Nº of genes
♥ Long QT syndrome(s)	2
♥ Short QT syndrome	-
♥ Brugada syndrome	-
♥ Catecholamine-induced PMVT/VF	-
♥ Short-coupled Torsades de Pointes	-
♥ Isolated conduction disorders (AVN, BB)	-
♥ Atrial fibrillation	-
♥ Sinus node disease, atrial standstill	-
♥ Idiopathic ventricular fibrillation	-

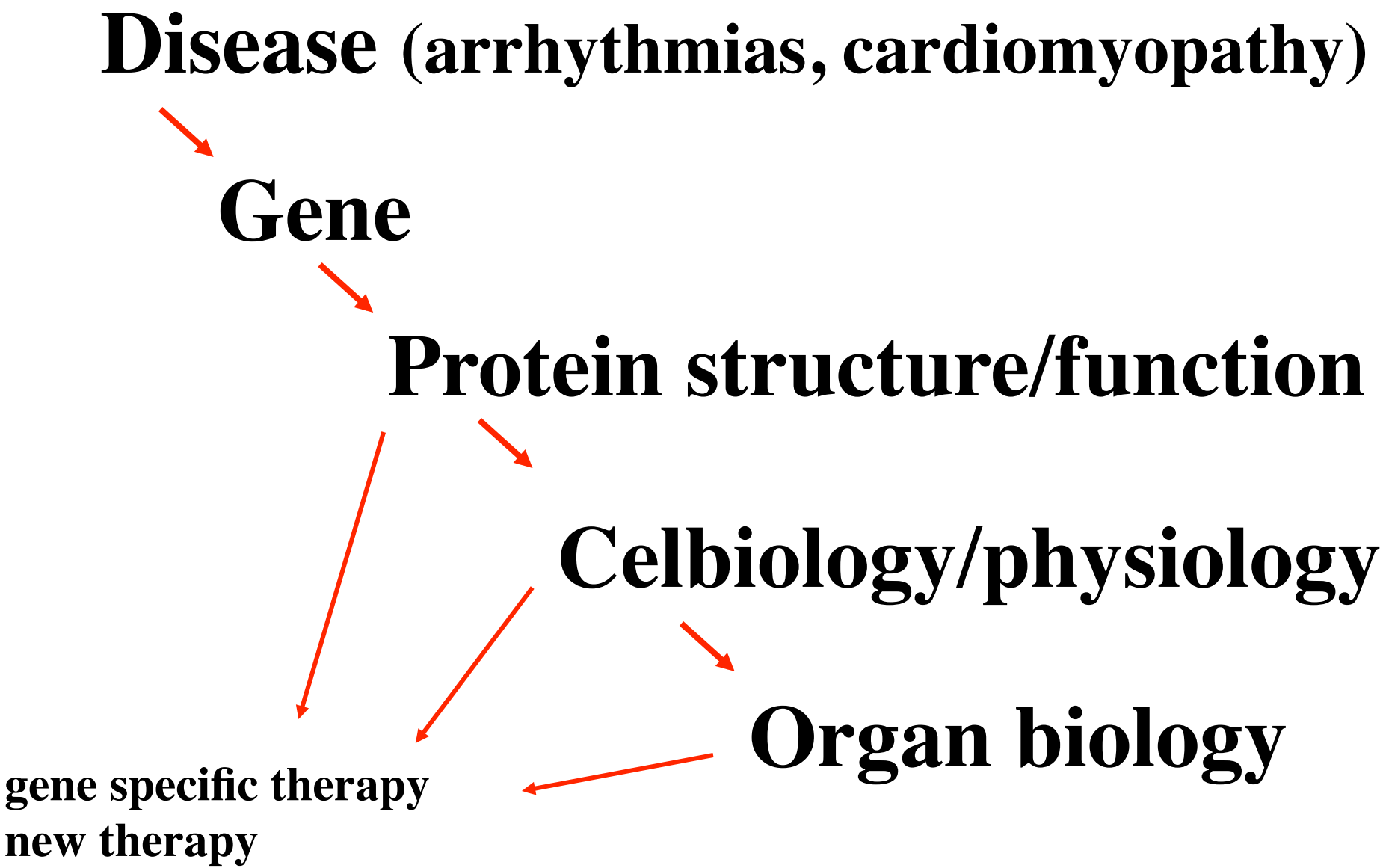
Primary arrhythmia syndromes (2016)

	Nº of genes
♥ Long QT syndrome(s)	16
♥ Short QT syndrome	3
♥ Brugada syndrome	>20
♥ Catecholamine-induced PMVT/VF	5
♥ Short-coupled Torsades de Pointes	1
♥ Isolated conduction disorders (AVN, BB)	3
♥ Atrial fibrillation	15
♥ Sinus node disease, atrial standstill	2
♥ Idiopathic ventricular fibrillation	1

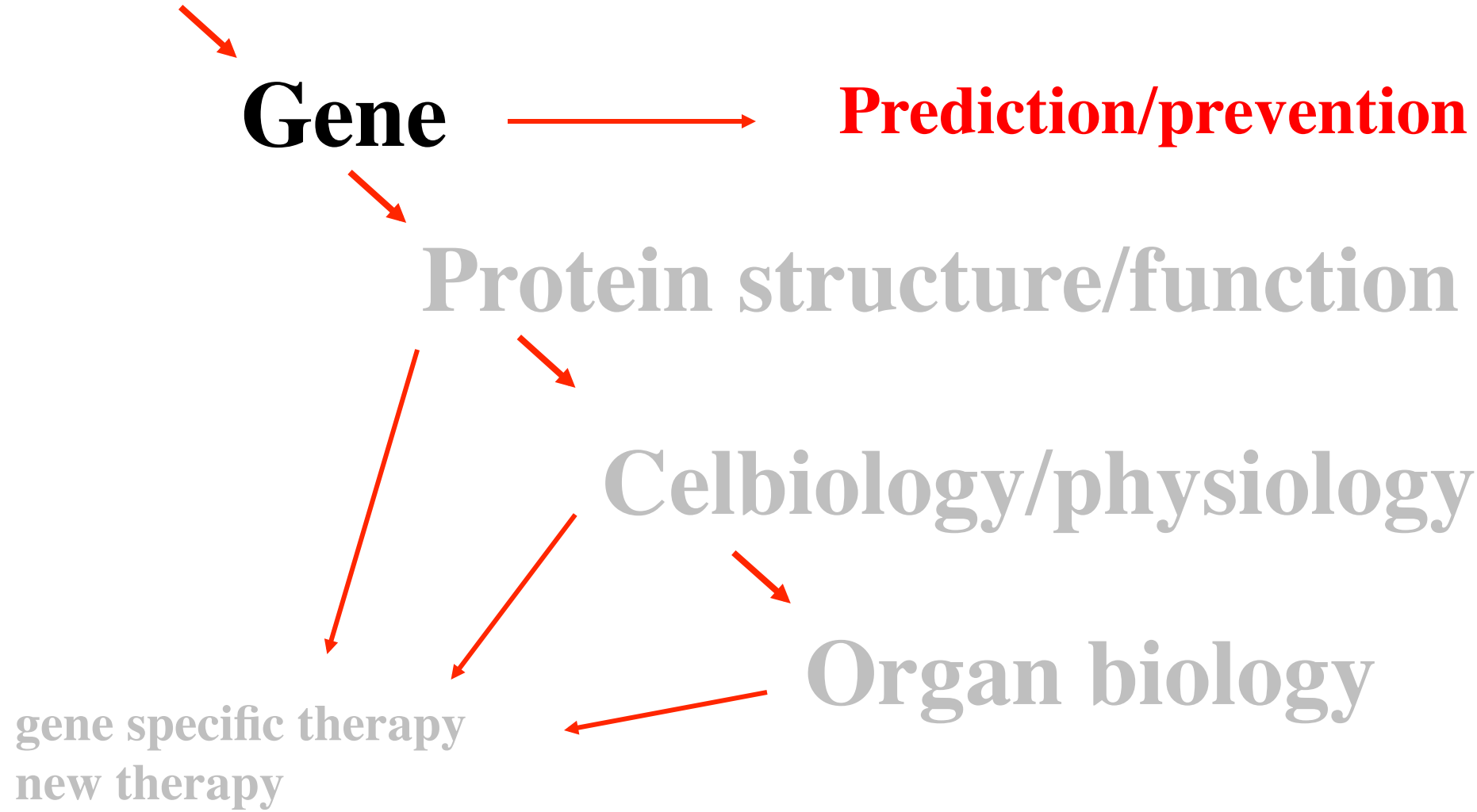
Disease (arrhythmias, cardiomyopathy)

↘

Gene


Disease (arrhythmias, cardiomyopathy)
Gene
Protein structure/function
Celbiology/physiology
Organ biology
gene specific therapy
new therapy

Disease (arrhythmias, cardiomyopathy)



HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

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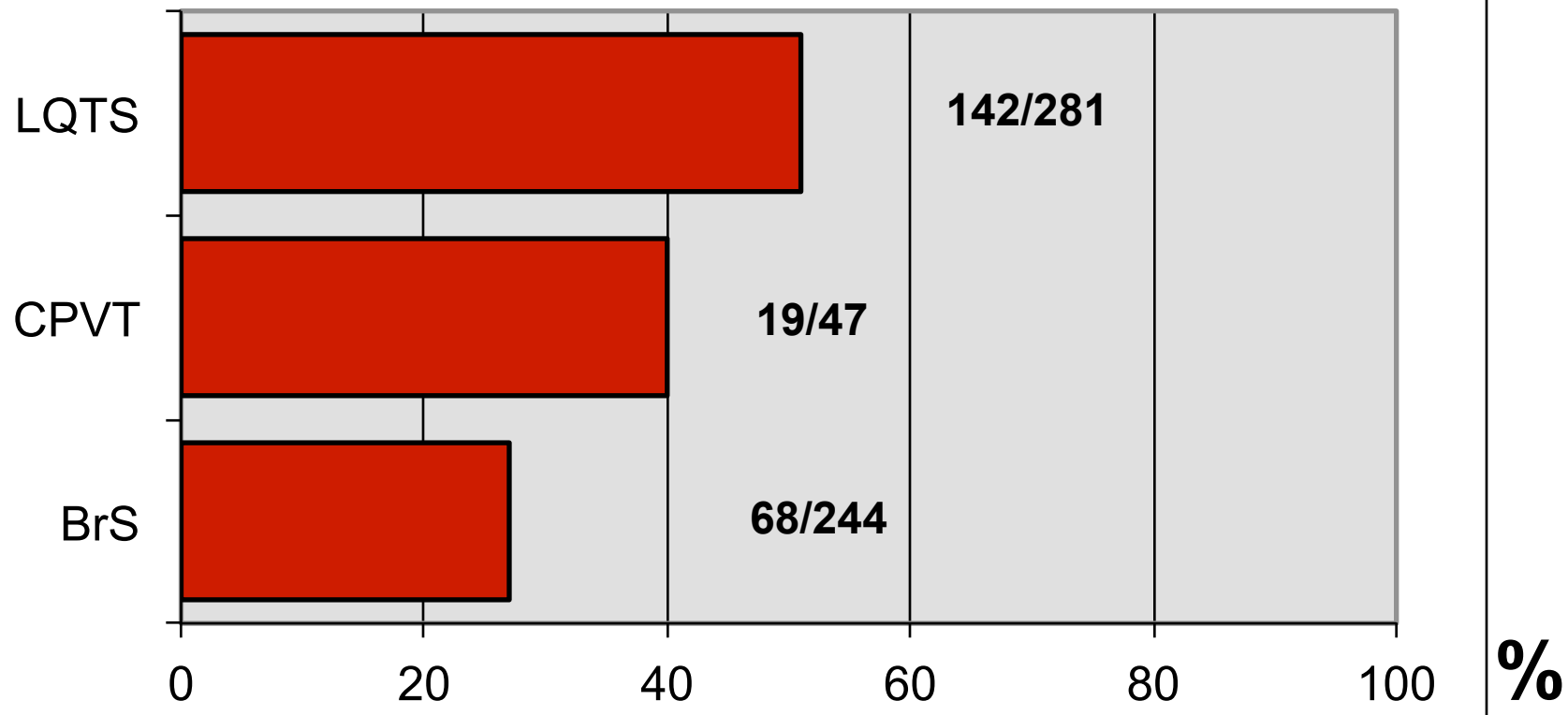
Heart Rhythm 2011;8:1308-1339

Section # – Disease	Diagnostic	Prognostic	Therapeutic
Section I – LQTS	+++	+++	++
Section II – CPVT	+++	+	-
Section III – BrS	+	+	-
Section IV – CCD	+	+	+
Section V – SQTS	+/-	-	-
Section VI – AF	-	-	-
Section VII – HCM	+++	++	+
Section VIII – ACM/ARVC	+	+/-	-
Section IX – DCM	+/-	-	-
Section IX – DCM + CCD	++	++	+
Section X – LVNC	+	-	-
Section XI – RCM	+	+	+
Idiopathic VF	+++	+++	++

Yield of molecular diagnosis in primary electrical heart disease

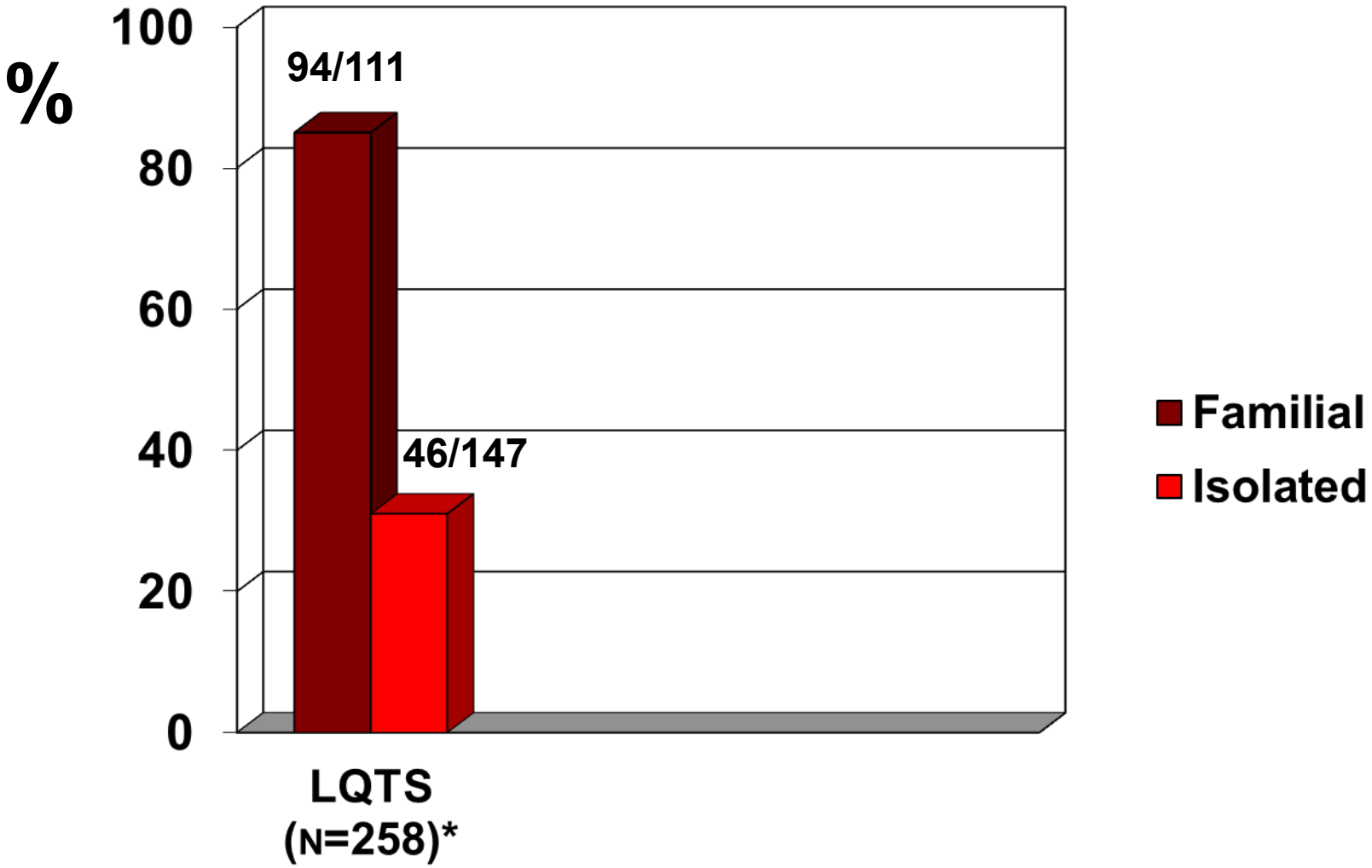


Yield of molecular diagnosis

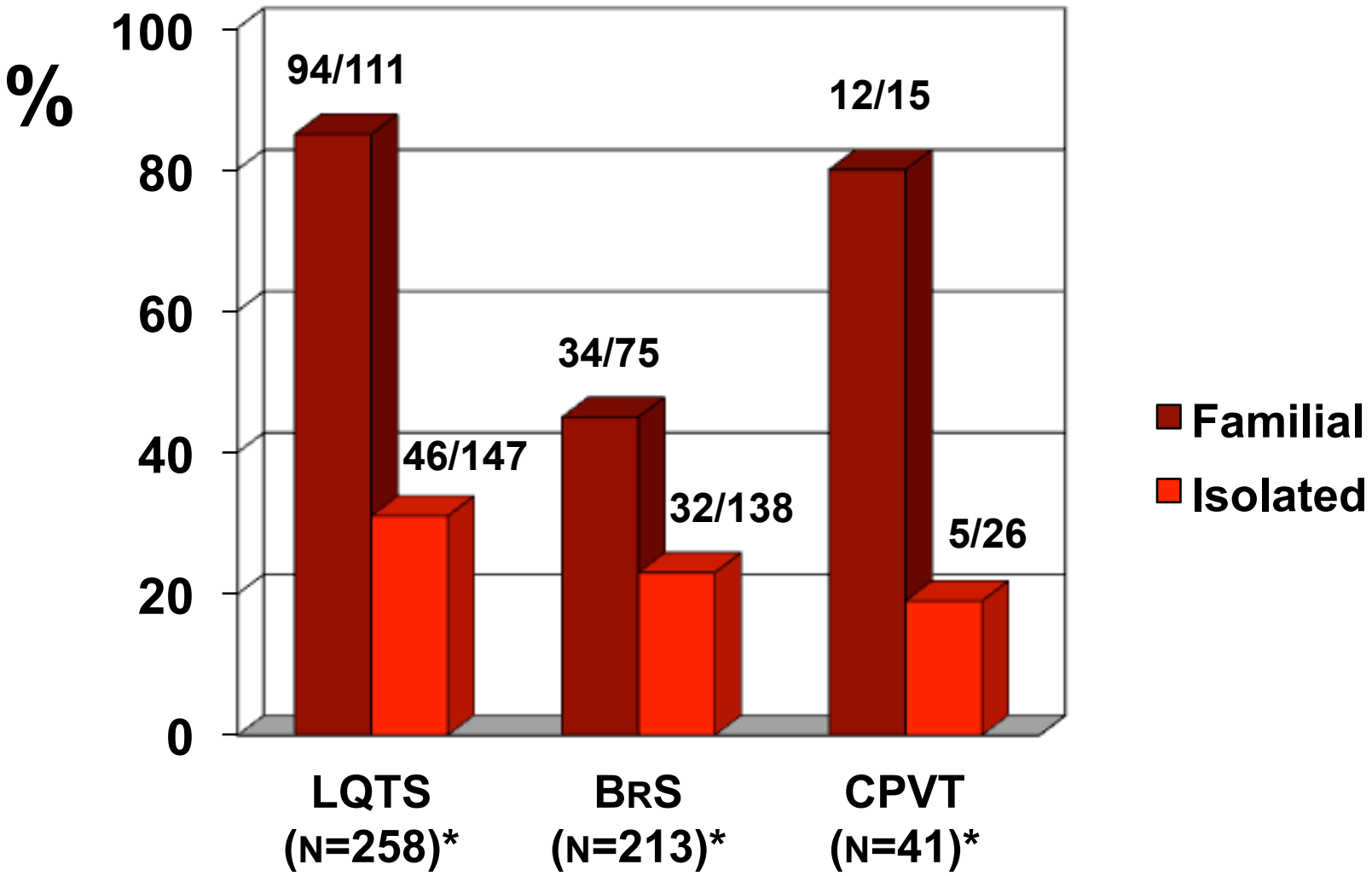
Depending on family history (defined as:)

- More than one person in the family is clearly affected, or has typical complaints of the same disease;
- sudden cardiac death under the age of 40

  of a first, second or third degree relative.



* Nrs of analyzed families (complete pedigree available)



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Active Cascade Screening in Primary Inherited Arrhythmia Syndromes

Does It Lead to Prophylactic Treatment?

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Irene M. van Langen, MD, PhD,* Arthur A. M. Wilde, MD, PhD†

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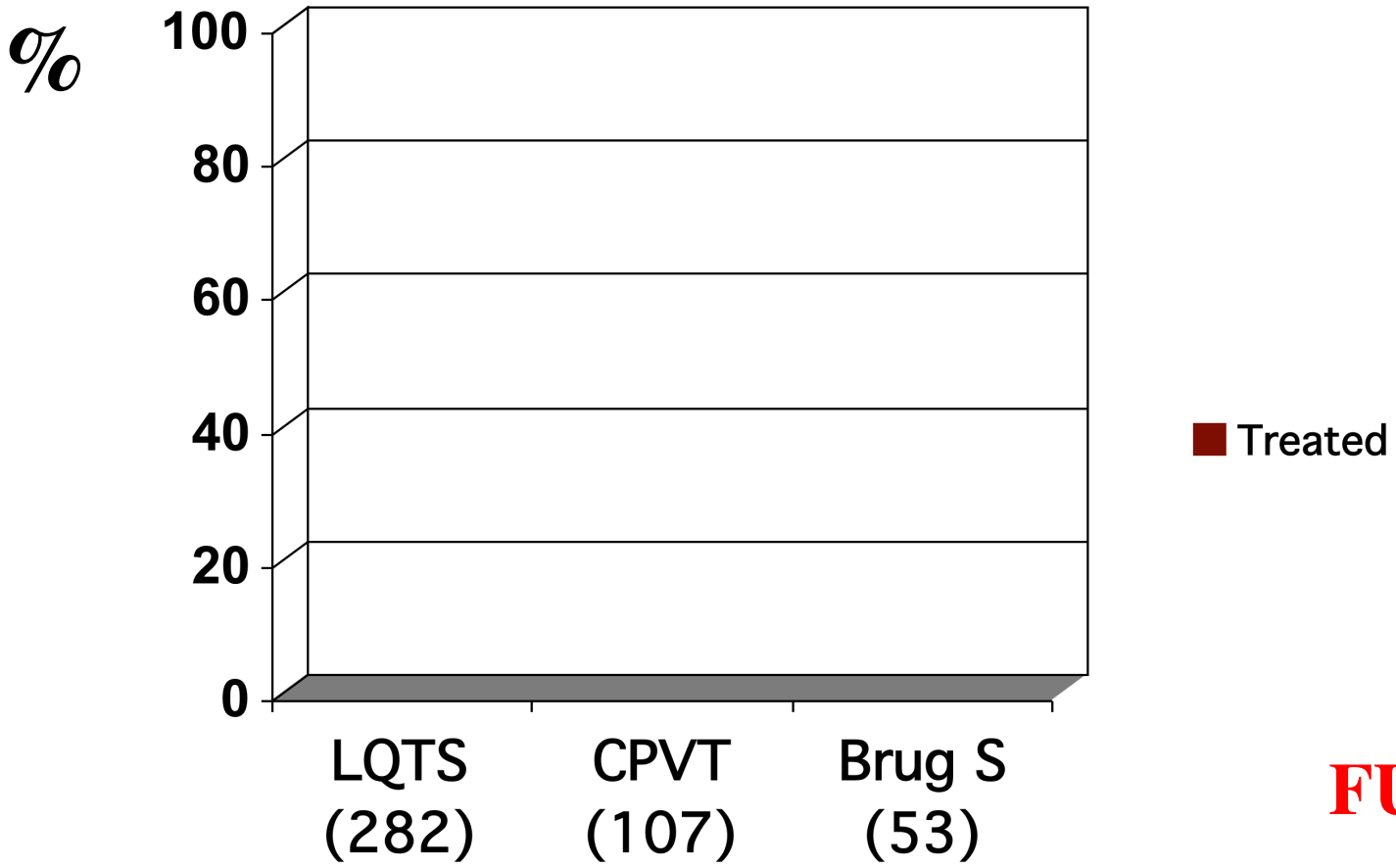
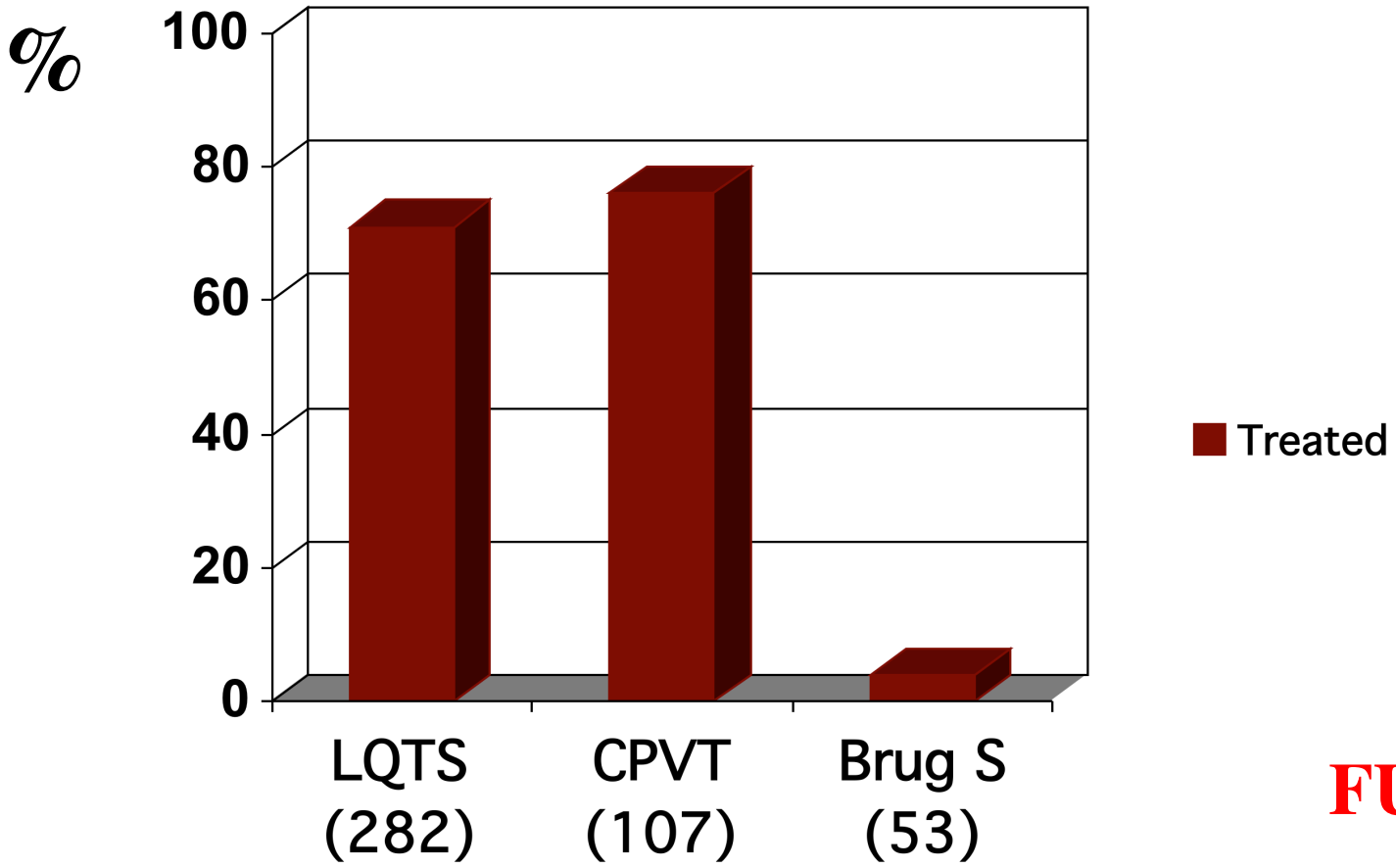
Does cascade screening lead to treatment?
A follow-up study in 442 presympt. screened family members



FU: 3-4 y

Hofman et al, JACC 2010;55:2579-6.

Does cascade screening lead to treatment?
A follow-up study in 442 presympt. screened family members



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Section V – SQTS	+/-	-	-
Section VI – AF	-	-	-
Section VII – HCM	+++	++	+
Section VIII – ACM/ARVC	+	+/-	-
Section IX – DCM	+/-	-	-
Section IX – DCM + CCD	++	++	+
Section X – LVNC	+	-	-
Section XI – RCM	+	+	+
Idiopathic VF	+++	+++	++

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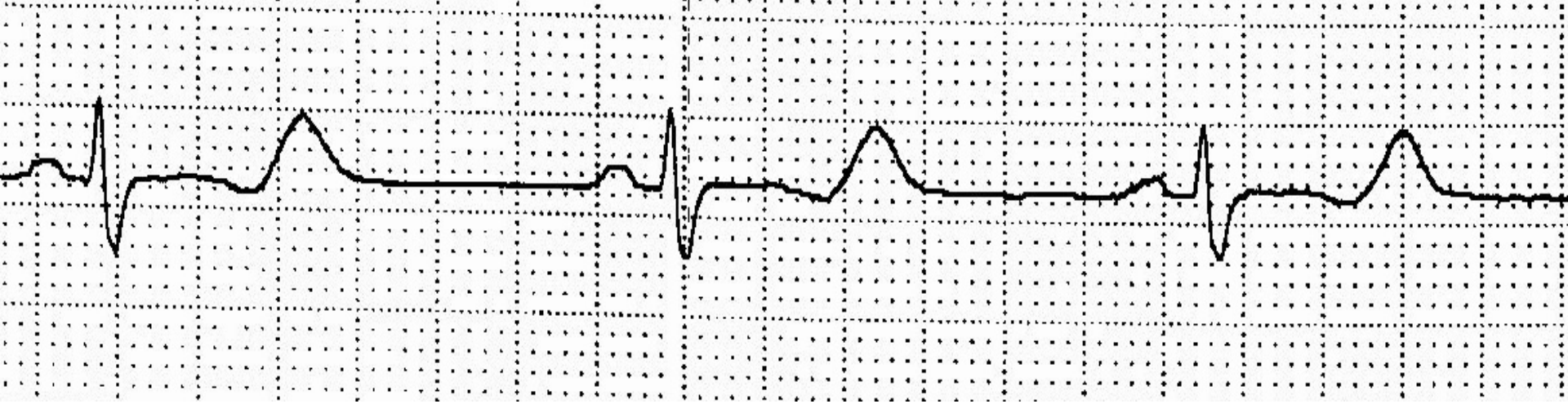
Section XI – RCM	+	+	+
Idiopathic VF	+++	+++	++

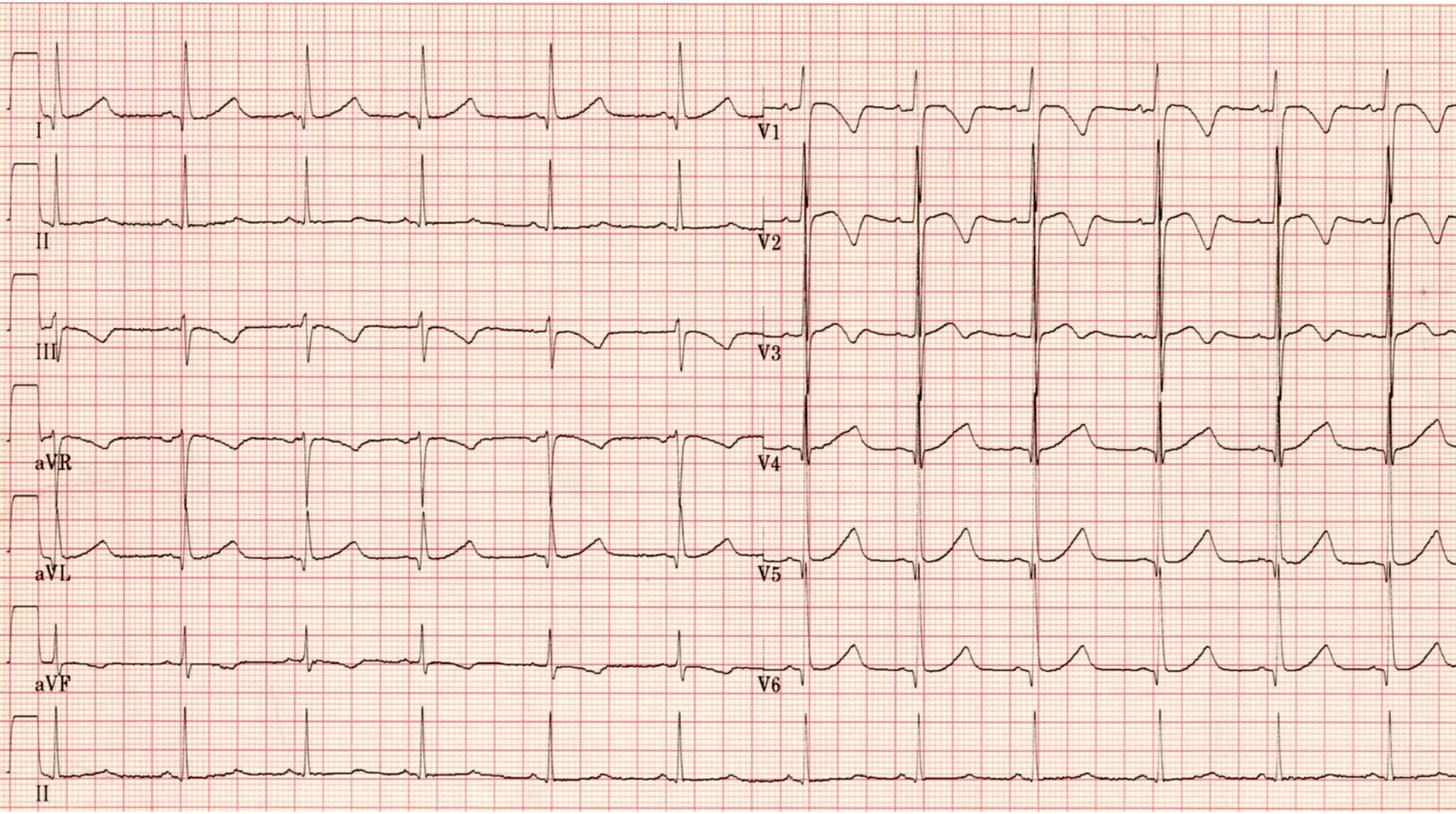


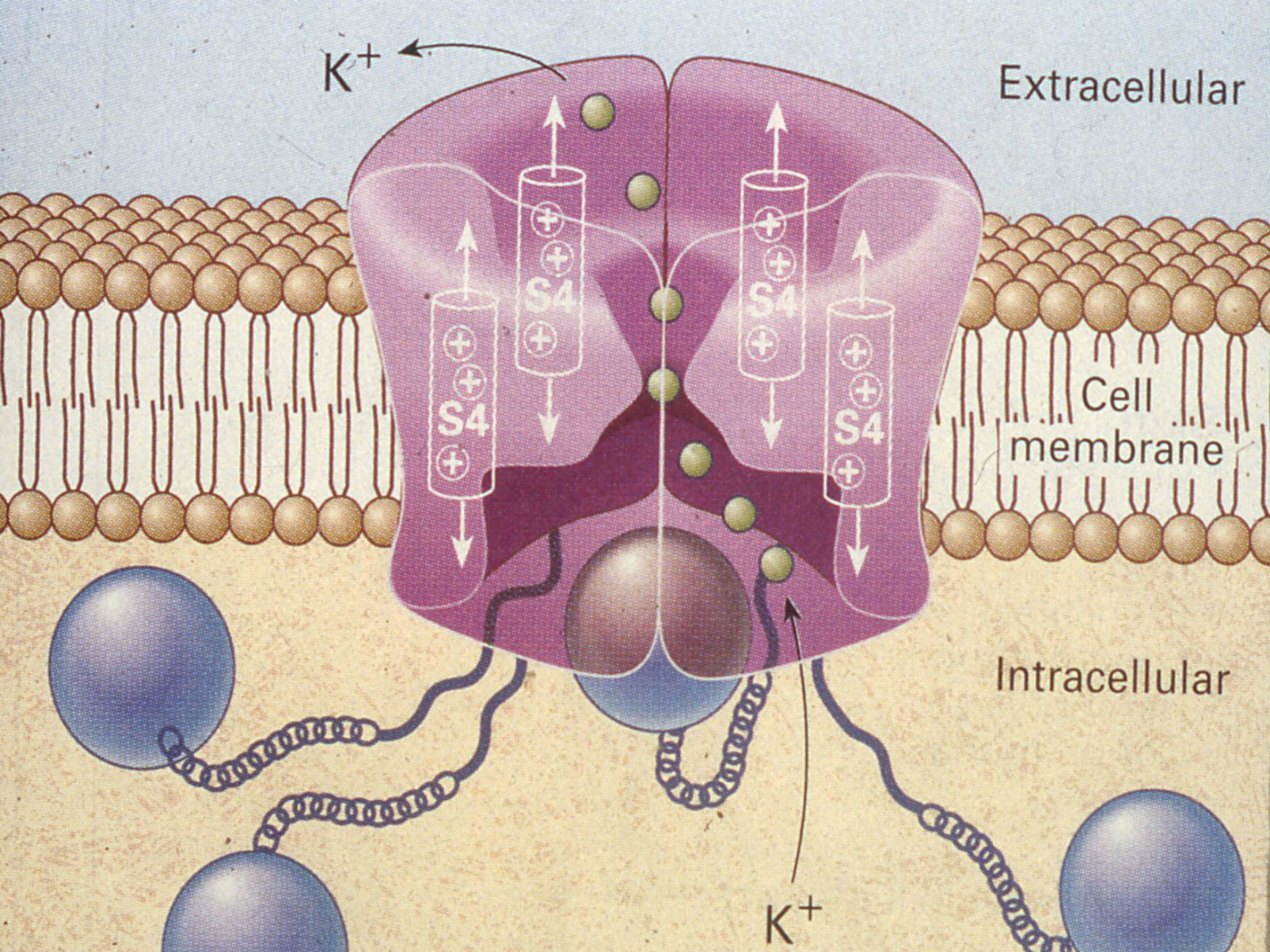
Long QT Syndrome(s)

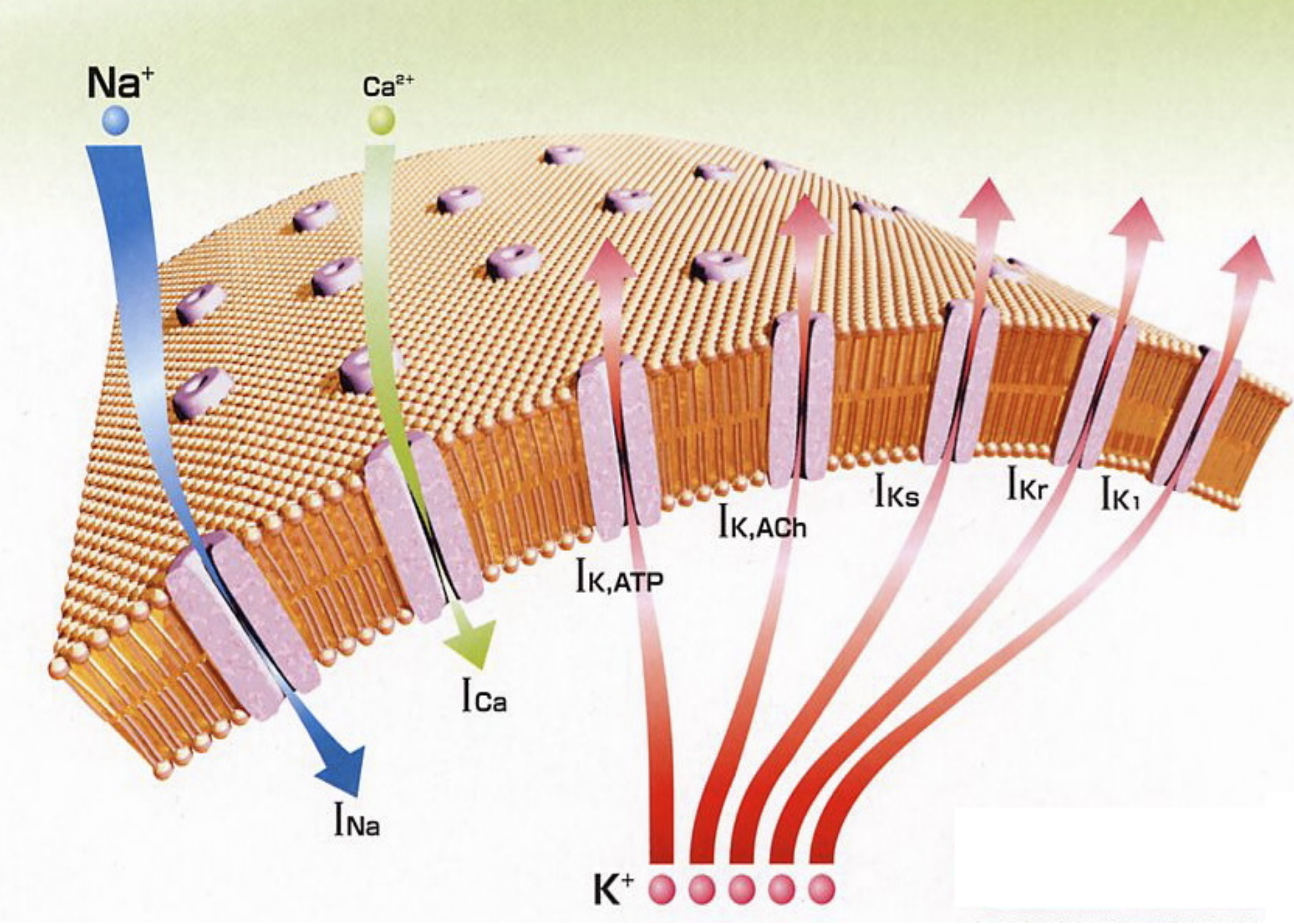
- Autosomal dominant/autosomal rec.
- genetically heterogeneous
- 16 genes (LQTS1-16)
- ≥ 60% genotyped (≥ 90% in families)
- gene-specific features

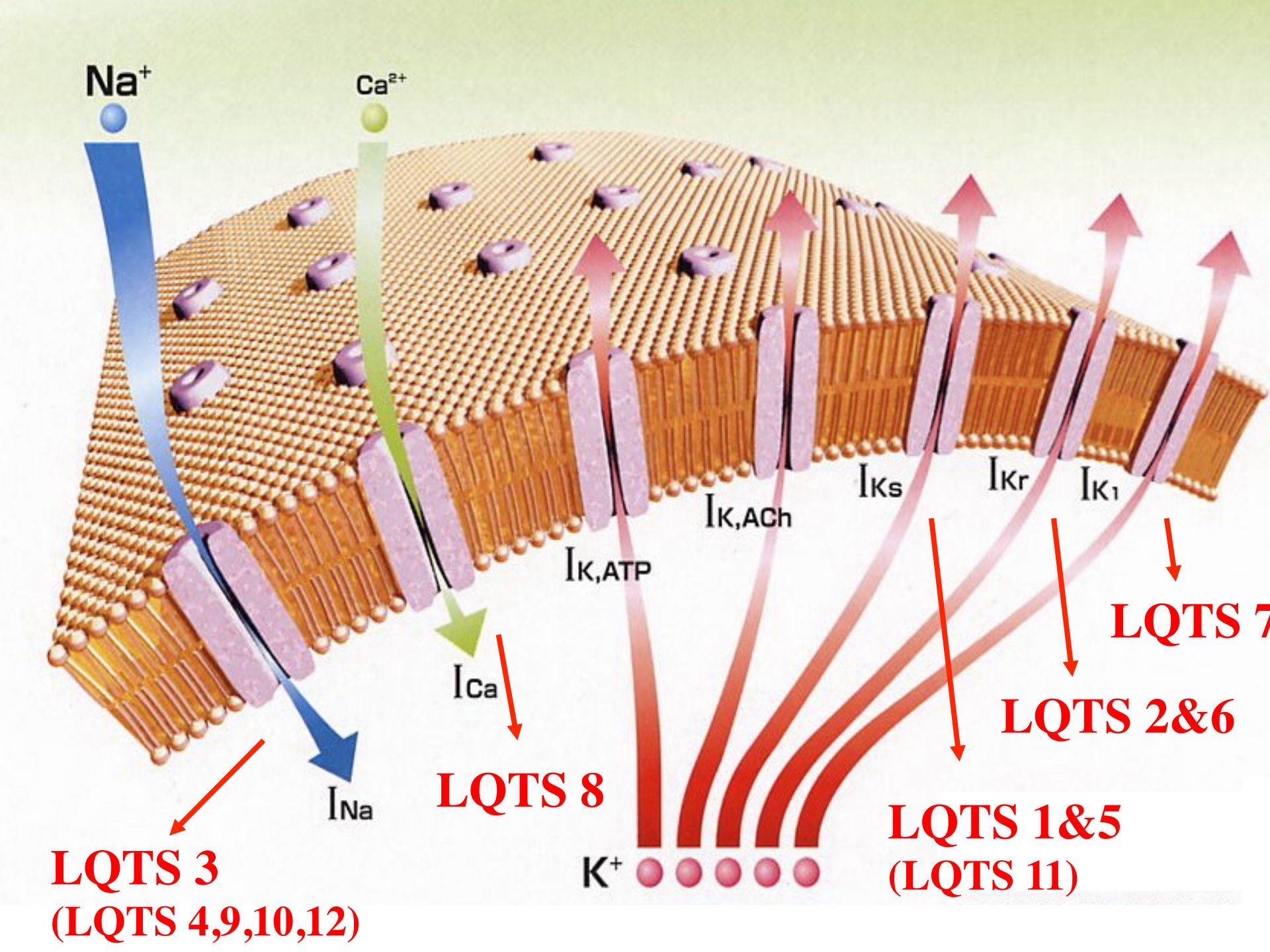
Male, 12 y, mother died suddenly age 32

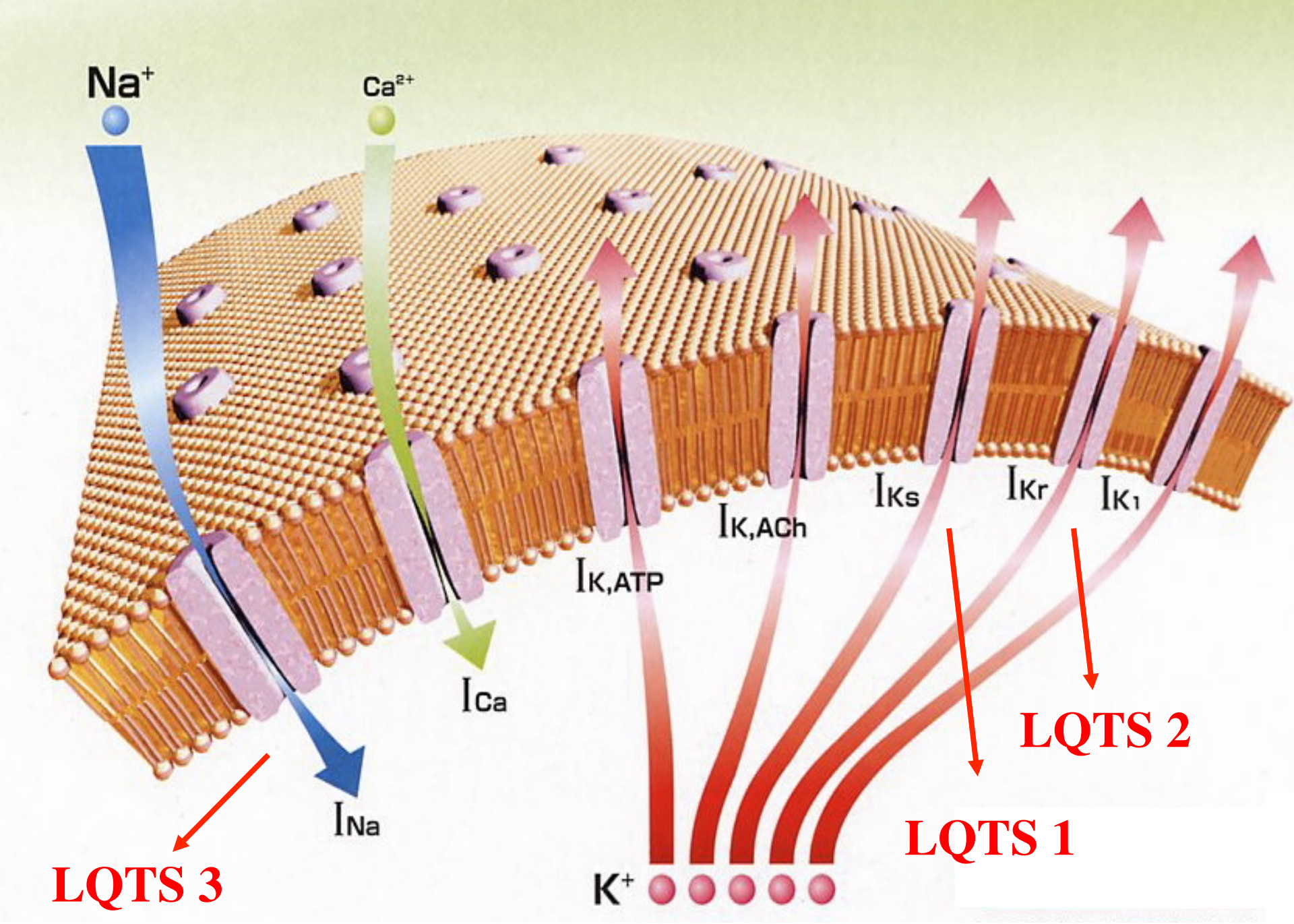
LQTS




K+
Extracellular
S4
S4
S4
S4
Cell membrane
Intracellular
K+


Na+
Ca2+
IK,ATP
IK,ACh
IKs
IKr
IK1
ICa
INa
K+


Na+
Ca2+
IK,ATP
IK,ACh
IKs
IKr
IK1
ICa
INa
K+
LQTS 8
LQTS 2&6
LQTS 7
LQTS 1&5
(LQTS 11)
LQTS 3
(LQTS 4,9,10,12)

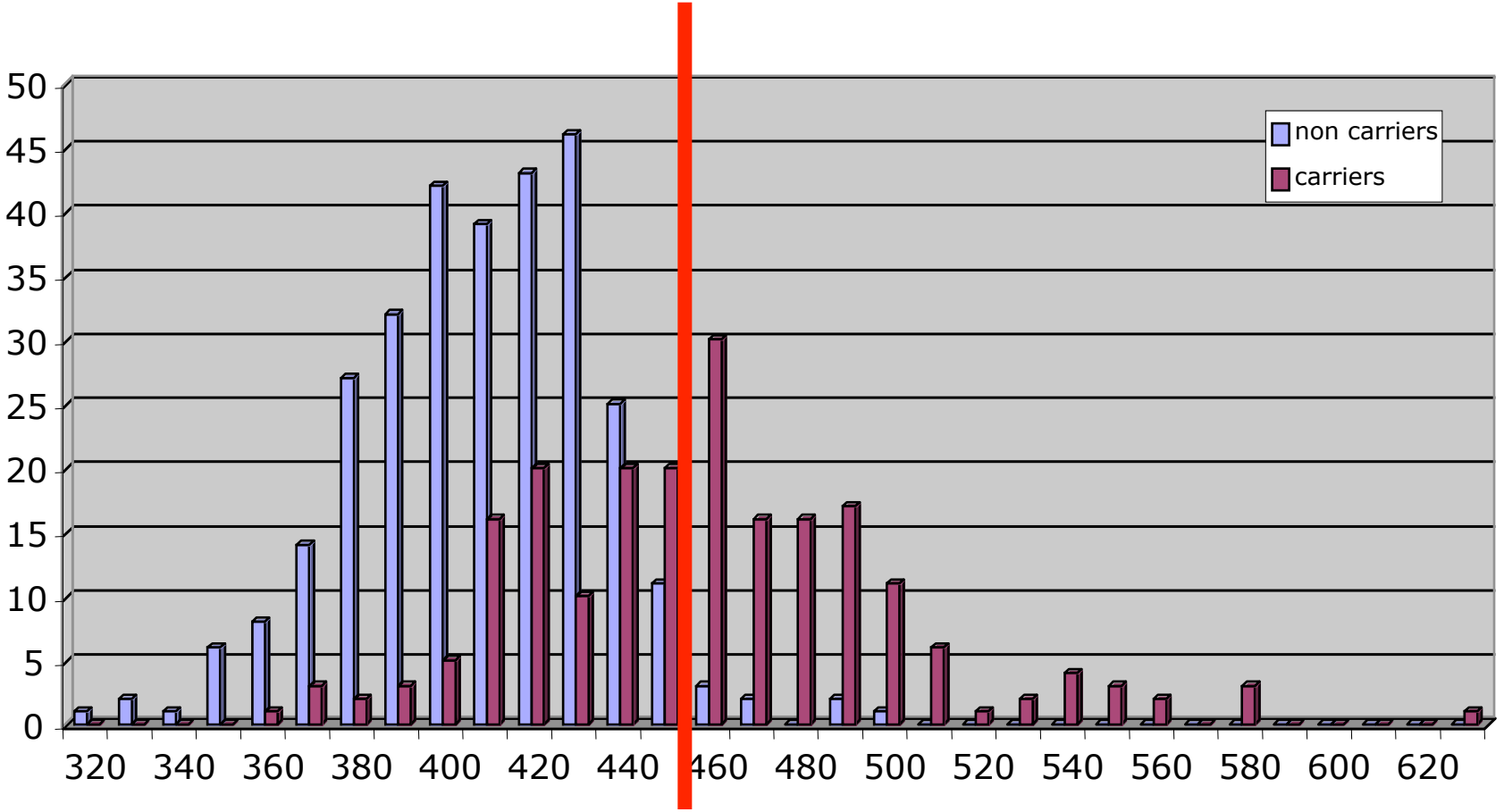

Na+
Ca2+
IK,ATP
IK,ACh
IKs
IKr
IK1
ICa
INa
K+
LQTS 3
LQTS 1
LQTS 2

LQTS, Genetic testing

Genetic testing is needed:

- **to reach the diagnosis**
- **to start presymptomatic treatment**

QT_C in genotyped family members
n=517



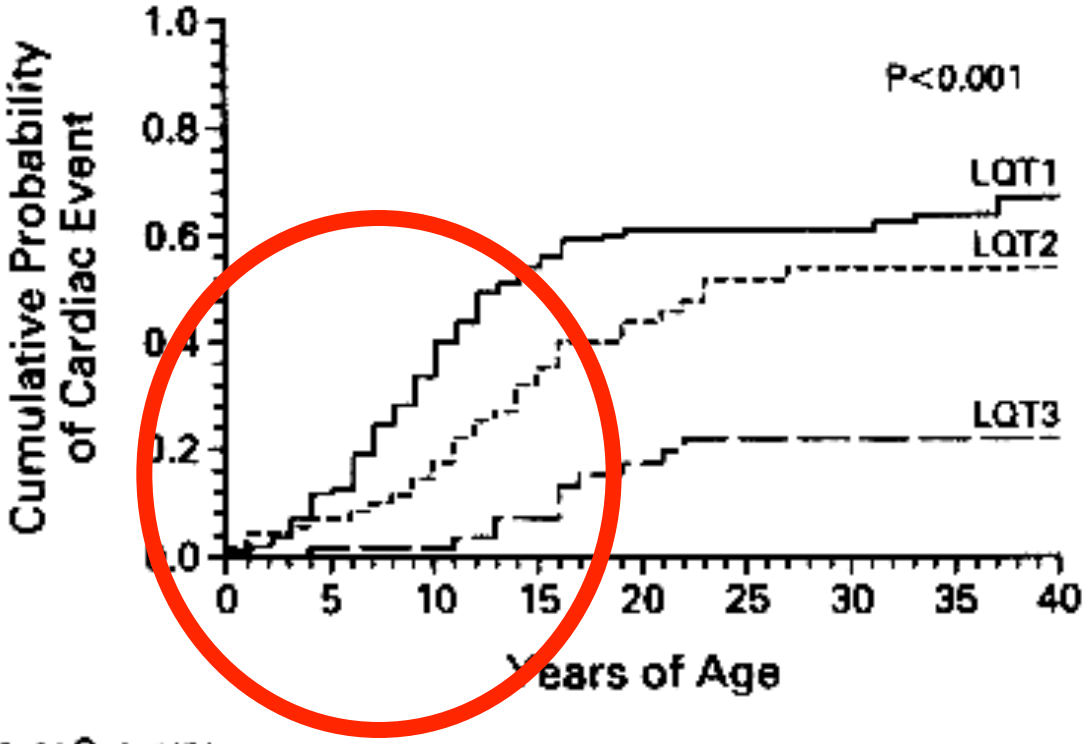
Data after Hofman et al. EHJ 2007.

LQTS, Genetic testing

Genetic testing is needed:

- **to reach the diagnosis**
- **to start presymptomatic treatment**
- **to decide on treatment choices**
- **and for risk stratification**

LQTS, Genotype-phenotype



No. of Subjects					
LQT1 group	112	72	36	27	19
LQT2 group	72	56	29	16	11
LQT3 group	62	56	36	24	16

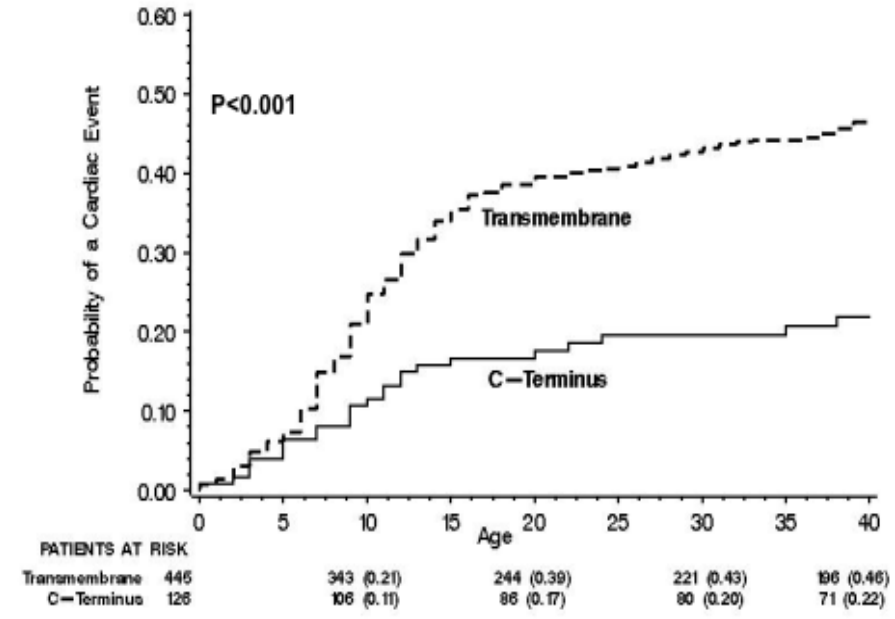
The LQT registry

Zareba et al. NEJM 1998; 339: 960-5.

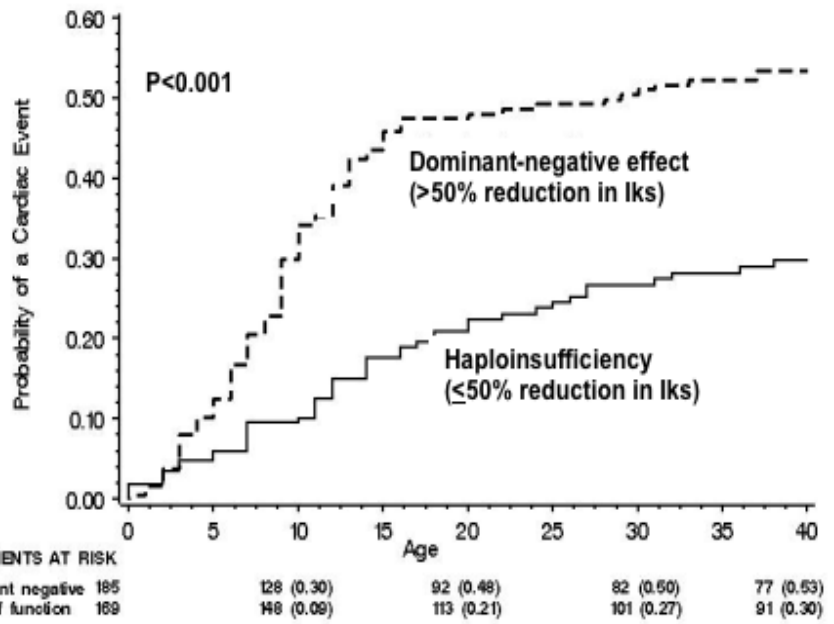
LQTS, Genotype-phenotype

LQTS1

A. Location of Mutation

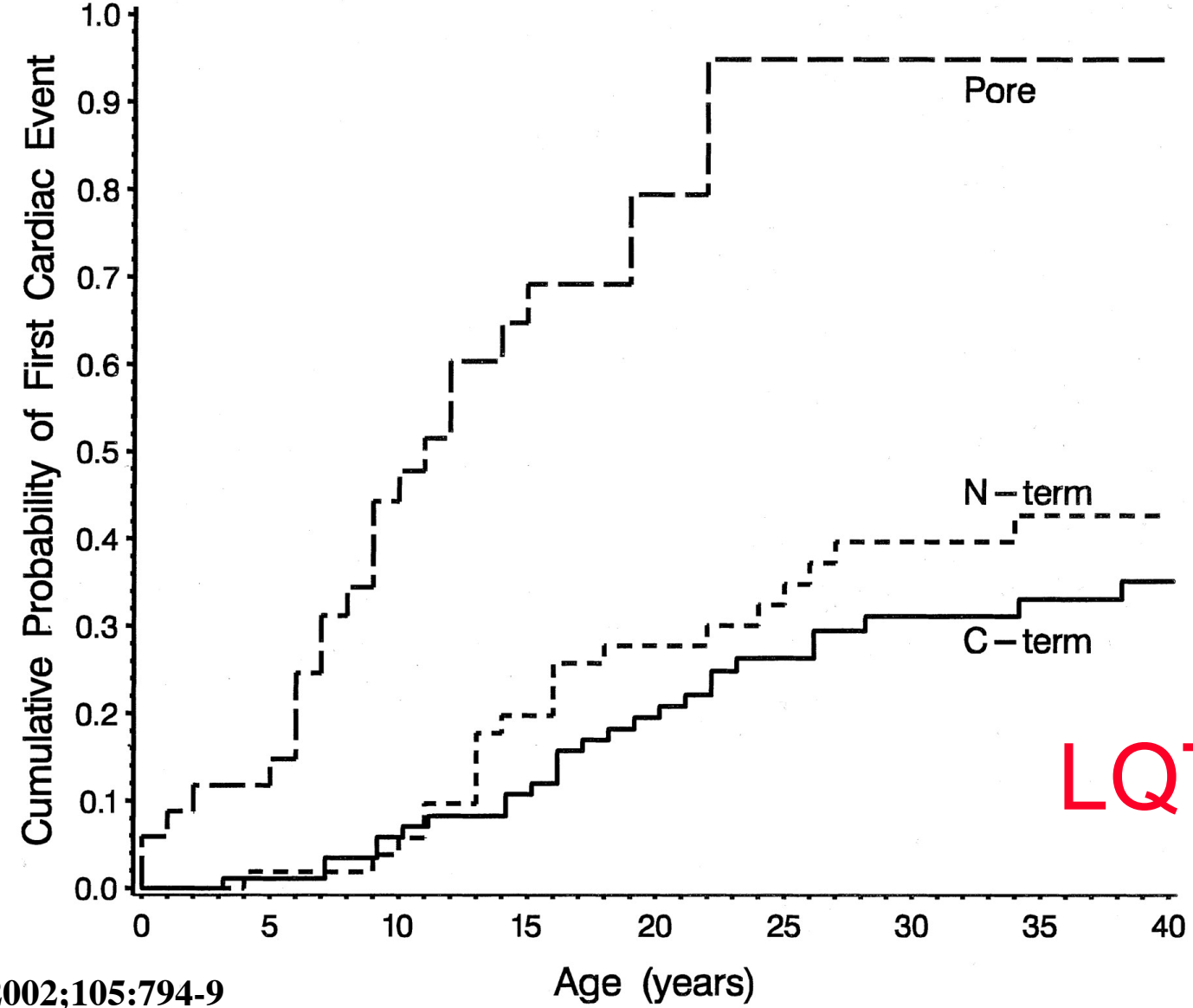


C. Biophysical Function



Moss, Shimizu, Wilde et al. Circulation 2007

LQTS, Genotype-phenotype



LQTS2

Circulation 2002;105:794-9

Brugada syndrome, Genetic testing

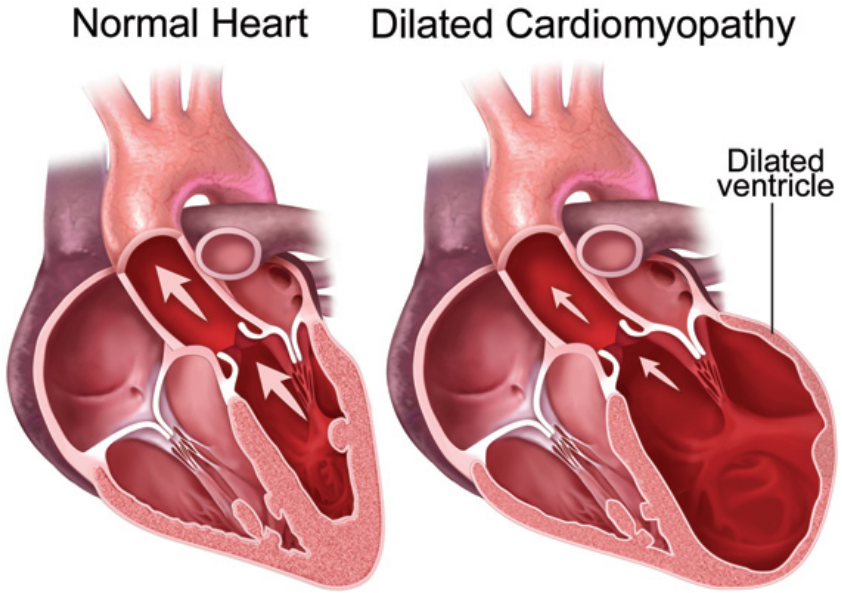
Genetic testing is not needed:

- **to reach the diagnosis**
- **to start presymptomatic treatment**
- **to decide on treatment choices**
- **and for risk stratification?**

Dilated cardiomyopathy

Major criteria:

- LV-dilatation
- systolic LV-dysfunction



Guidelines for the study of familial dilated cardiomyopathy,
Mestroni, Eur Heart J 1999

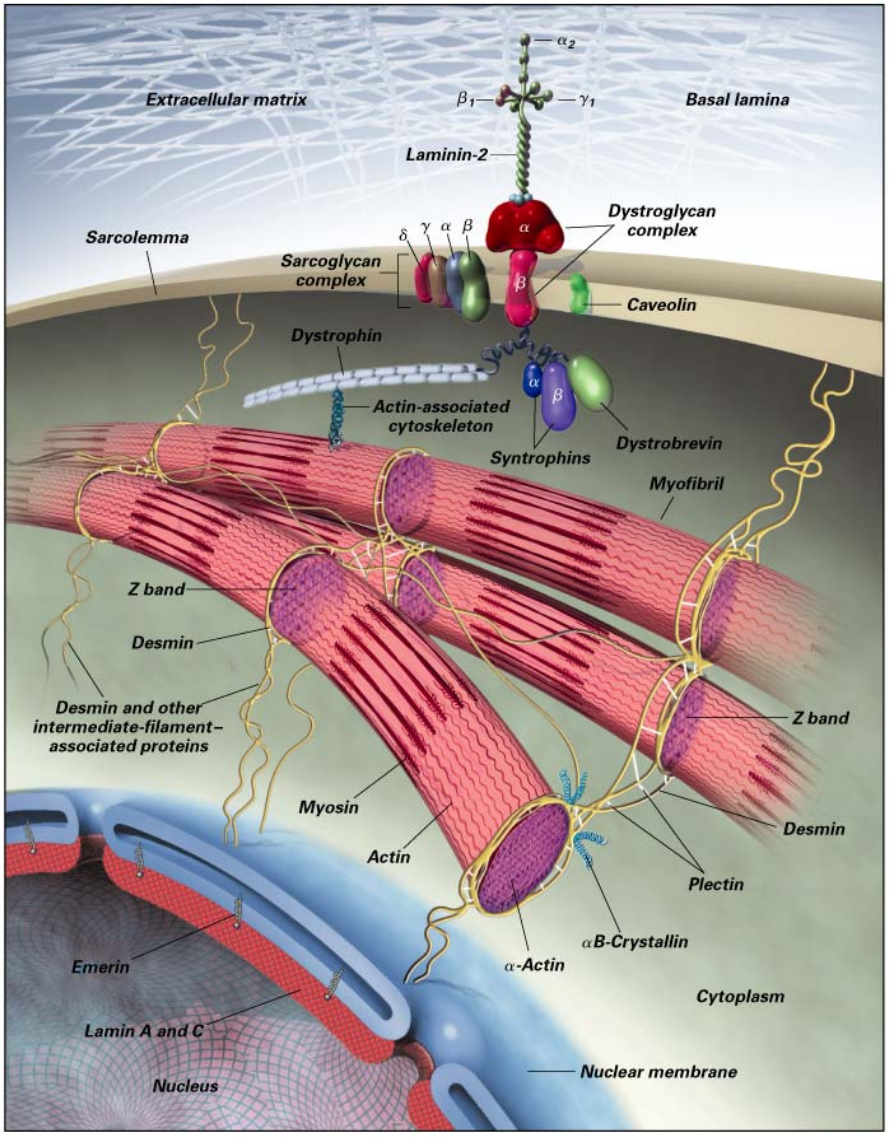
Dilatation:	LVEDD>117% (=2SD +5%, corrected for age and BSA)
Dysfunction:	Fractional shortening <25%; LV ejection fraction <45%

Familial dilated cardiomyopathy

1p32	NEXN	10q25	RBM20
1q21	lamin A/C	10q26	PDLIM
1q31	PSEN2	11p11.2	MyBPC3
1q32	TNNT2	11p15	CSRP3
1q42	ACTN2	11p15	ILK
2q31	t		YAB
2q35	c		CC9
3p14	T		IPO
3p21	S		′H6
5p15	S		′H7
5q33	δ		ΕN1
6q21	LAMA4	15q14	ACTC1
6q22	phospholamban	15q22	TPM1
6q23	EYA4	17q12	Tcap/telethonin
9q31	FKTN	19q13	TNNI3
10p13	Nebulette	Xq28	TAZ
10q21	MYPN	Xq28	emerin
10q22	metavinculin	Xp21	dystrophin
10q22	LDB3		
10q23	ANKRD1		

2012 > 40 genes!

Familial DCM: genetic heterogeneity



Involved structures/functions:

Cytoskeleton

Sarcomere

Nuclear envelope

Ion-channels

Calcium handling

Familial dilated cardiomyopathy

1p32	NEXN	<1%
1q21	**lamin A/C**	**2-21%**
1q31	PSEN2	<1%
1q32	TNNT2	1%
1q42	ACTN2	<1%
2q31	**titin**	**3% (25%)**
2q35	desmin	1%
3p14	TNNC1	
3p21	**SCN5A**	
5p15	SDHA	
5q33	δ- sarcoglyc	
6q21	LAMA4	
6q22	phospholam	
6q23	EYA4	
9q31	FKTN	<1%
10p13	Nebulette	1%
10q21	MYPN	<1%
10q22	metavinculin	<1%
10q22	**LDB3**	**2%**
10q23	**ANKRD1**	**2%**
10q25	**RBM20**	**2%**
10q26	PDLIM	<1%
11p11.2	MyBPC3	1%
11p15	CSRP3	<1%
11p15	ILK	<1%
11q22	CRYAB	<1%
12p12	ABCC9	<1%
	TMPO	1%
	MYH6	n=
	MYH7	**3%**
	PSEN1	<1%
	ACTC1	n=
	TPM1	<1%
	Tcap/telethonin	<1%
19q13	TNNI3	1%
Xq28	TAZ	n=
Xq28	emerin	n=
Xp21	**dystrophin**	**3%**

Total ± 25%

(+ Titin ± 50%)

LMNA – Lamin A/C

Neurologic phenotype:

Limb girdle muscular dystrophy e.g. Emery Dreifuss, CK ↑

Cardiac phenotype:

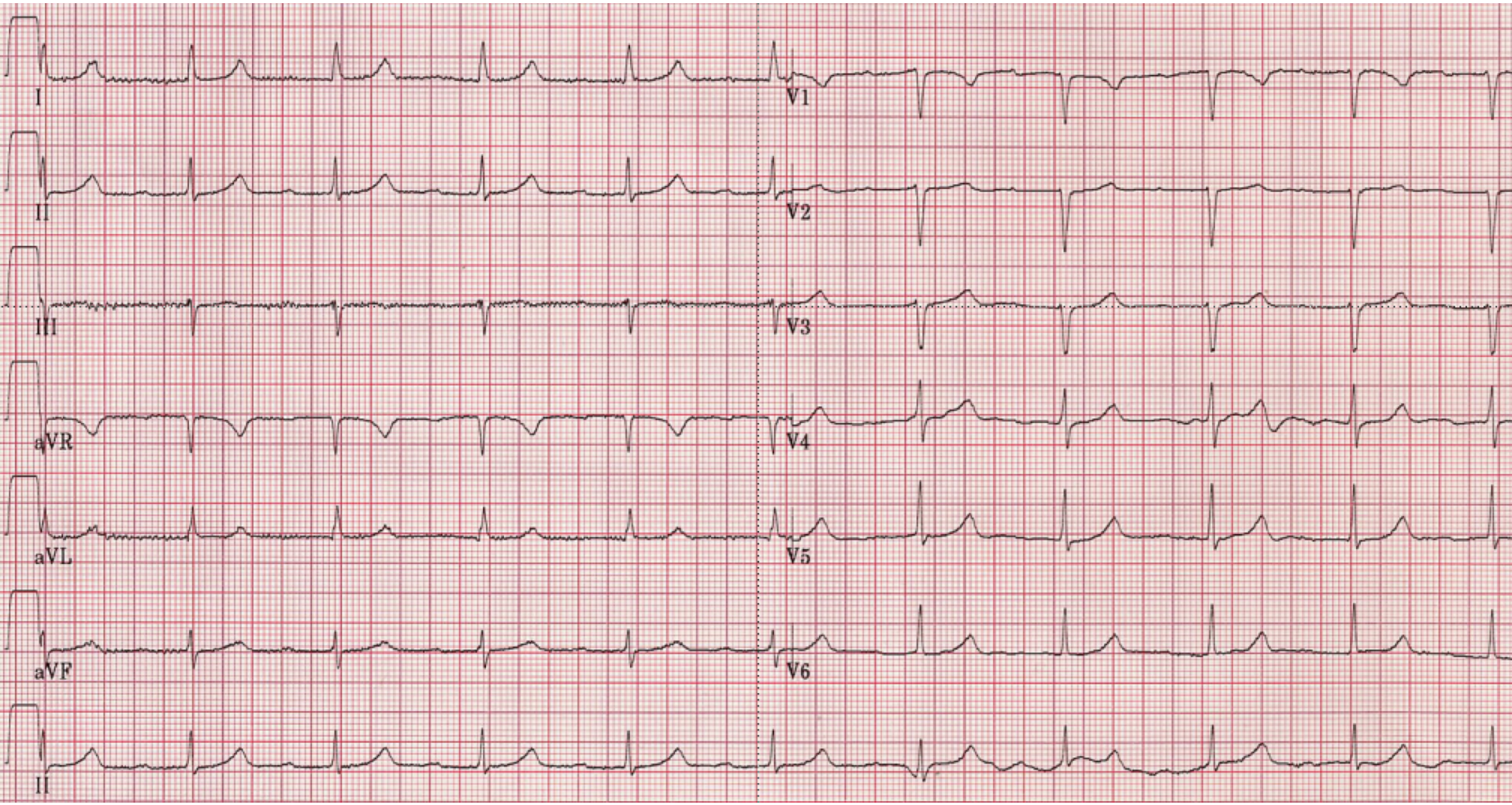
- first manifestation: AV-block, atrial fibrillation
- later LV dysfunction (DCM) – heart failure

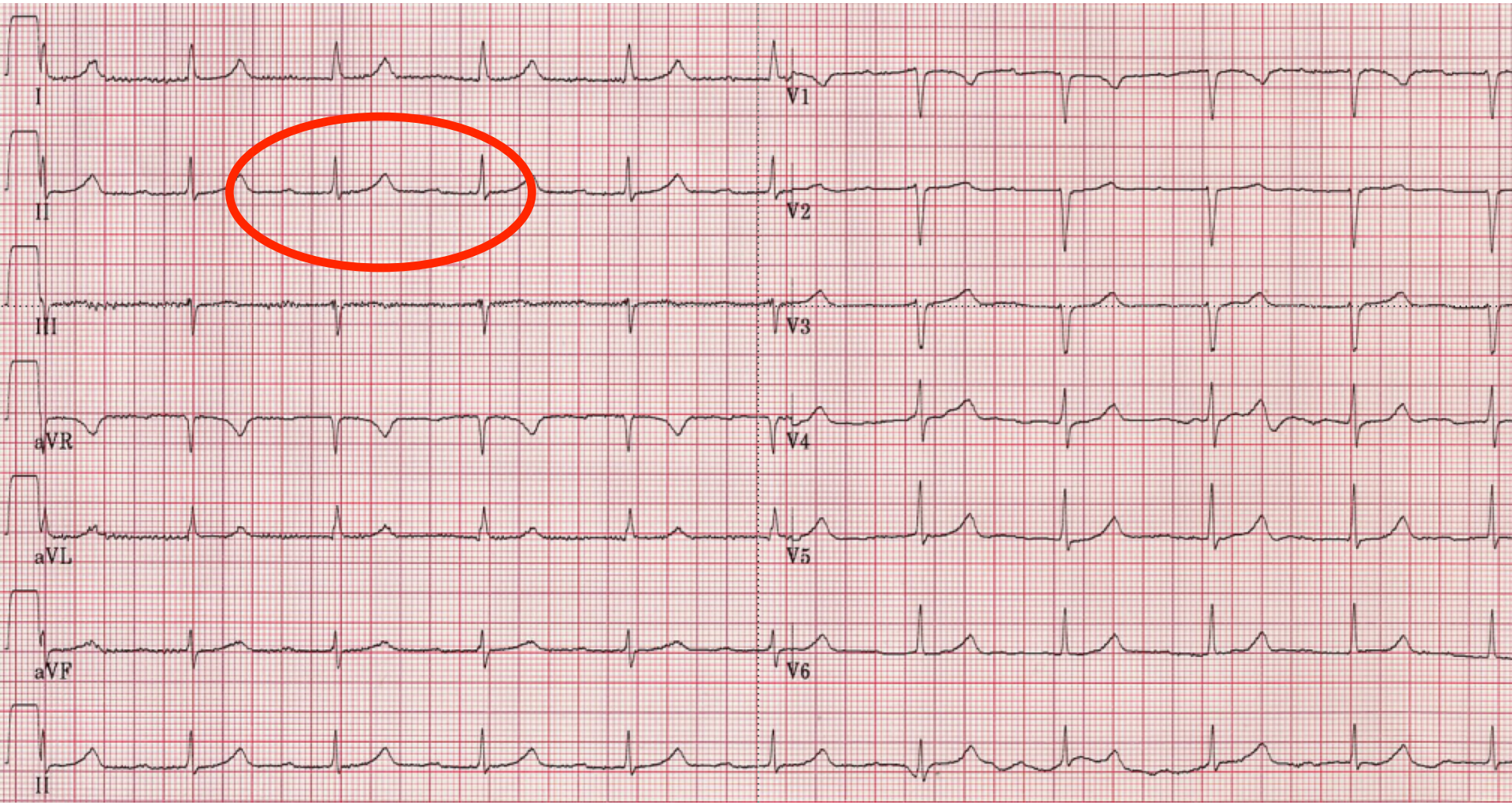
ECG:

- low amplitude p-wave
- first degree AV-block
- narrow QRS

32y old male

- father died age 42, HF
- uncle died age 38, PM age 35





Prolonged PR, normal QRS, low amplitude P-wave

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Genetic Disorders

Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

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Amsterdam, Utrecht, and Groningen, the Netherlands; Pavia, Italy; London, United Kingdom; Aarhus, Denmark; Paris, France; Berlin and Marburg, Germany

J Am Coll Cardiol 2012;59:493–500

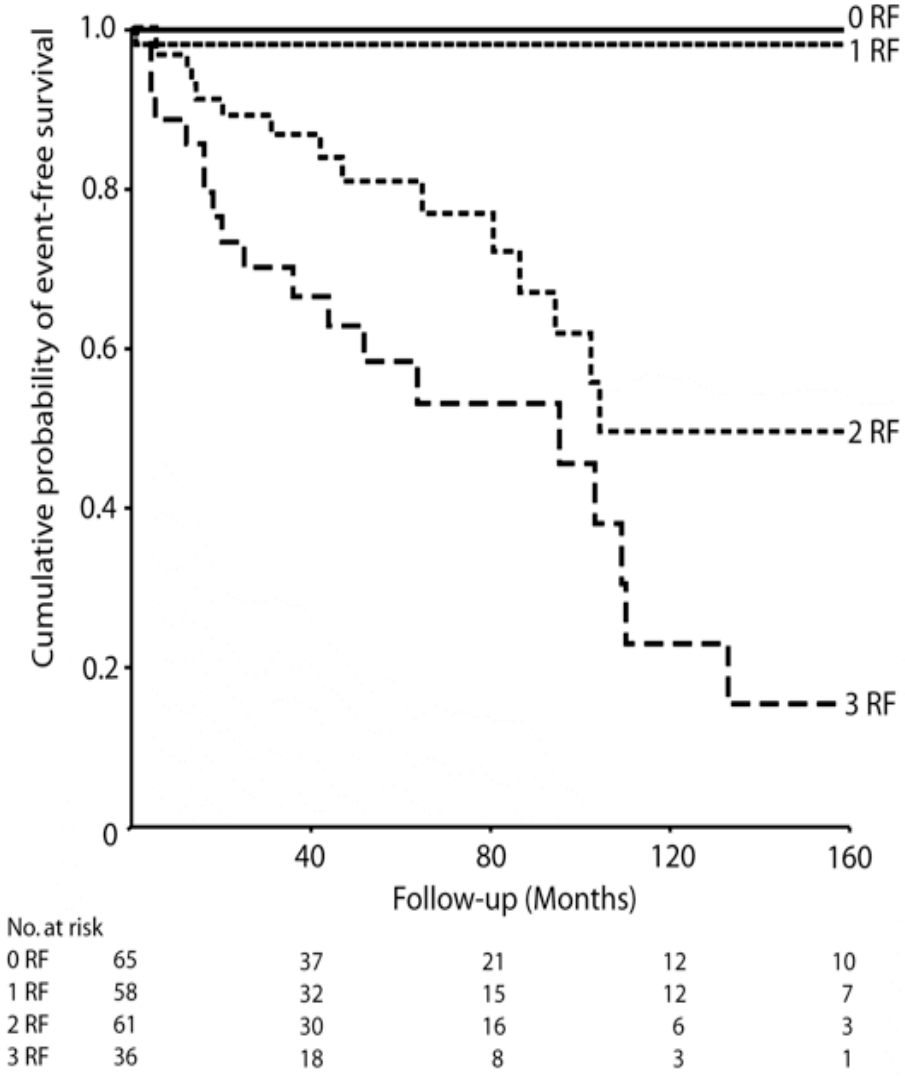
SCD-events

- **in 275 LMNA carries (multi centre (EU))**
- **Follow, multiple clinical + EP markers**

SCD events

- **SCD**
- **resuscitation**
- **appropriate ICD intervention**

LMNA Multicentre registry (n=275) risk factors for sudden cardiac death



KM curves stratified by 3
3 independent riskfactors

1.LVEF <45%

2.NSVT's on Holter

3.Male gender

van Rijsingen ea, JACC 2012

LMNA Multicentre registry (n=275) risk factors for sudden cardiac death

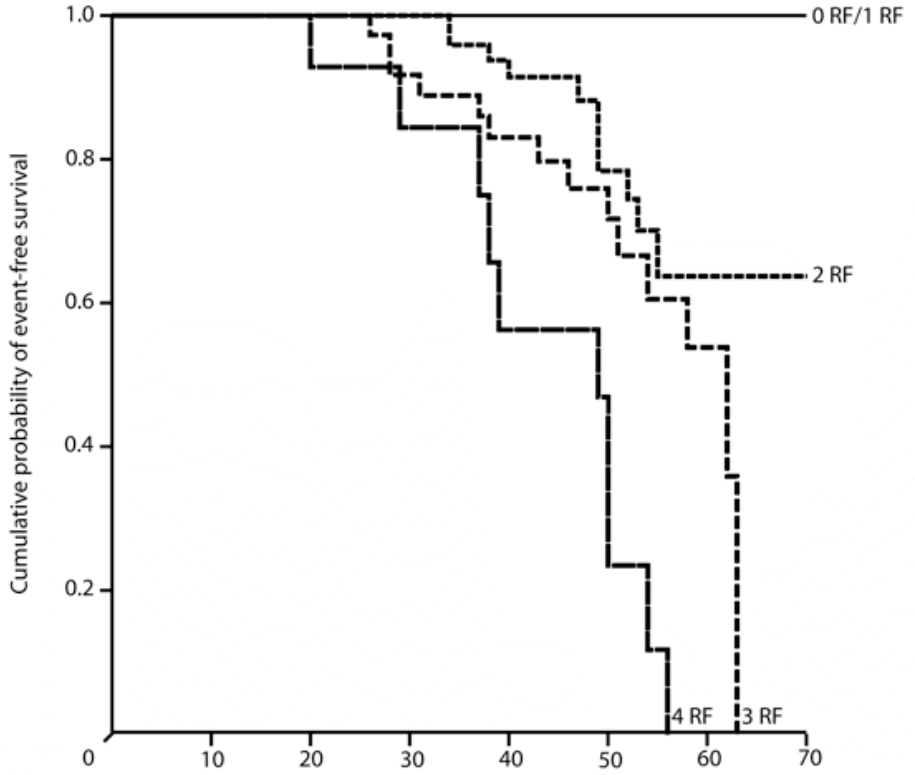
4 risk factors:

NSVTs

LVEF<45%

Male gender

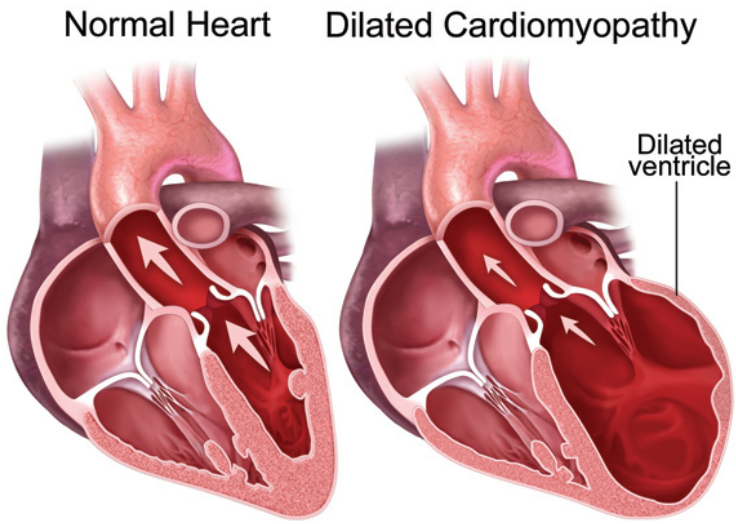
Non-missense mutation



No. at risk								
0 RF	33	33	31	27	17	12	4	1
1 RF	67	67	63	41	30	11	8	3
2 RF	66	66	63	56	40	24	5	2
3 RF	40	40	39	32	26	18	5	0
4 RF	14	14	14	10	6	4	0	0

van Rijsingen ea, JACC 2012

Dilated cardiomyopathy.



Genetic screening

- **many, many genes**
- **20-30% yield (+ Titin ≥ 50%)**
- **high yield in DCM/conduction disease**
- **usefullness for risk stratification**
- **useful for family screening**

Which pts should undergo genetic testing?

- SCD victims with a likely diagnosis
- Pts diagnosed with an inherited AS and their family members
- in some diseases it is mandatory
  - LQTS, DCM + conduction disease

In conclusion…

Genetic testing in CV disease:

- ♥ **becomes increasingly important**
- ♥ **has a high potential**
- ♥ **is important for risk stratification**
- ♥ **contributes to treatment choices**


Thank you