

Screening families for inherited cardiac conditions.... when to start and when to stop

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Key Questions

- Who should be screened?
- Why is it important to screen?
- Clinical vs genetic cascade screening
- Frequency of screening & when to stop

Who should be screened?

1. FHx of an inherited arrhythmia disorder or cardiomyopathy:

- A. HCM
- B. DCM
- C. ARVC

2. FHx Sudden death under age 50 years.

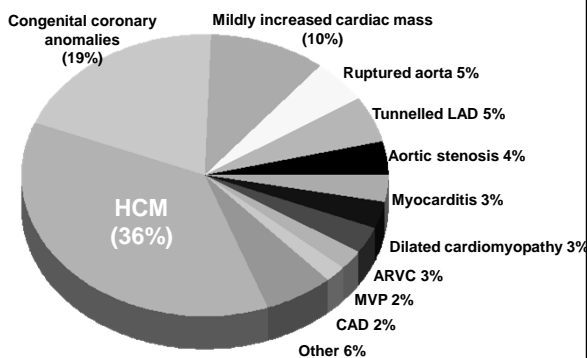
3. Unexplained syncope/seizures-exercise induced



Epidemiology

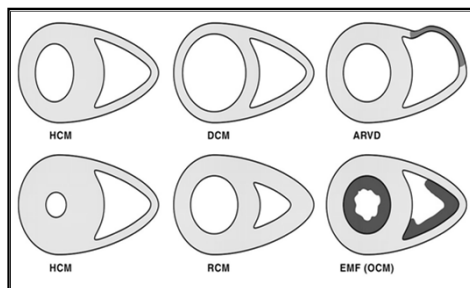
	Prevalence	Estimated UK Affected
HCM	1:500	120,000
ARVC	1:1,000 - 5,000	60,000
DCM	1:1,000 - 5,000	60,000
Long QT	1:5,000-10,000	45,000
Brugada	1:10,000	30,000

Causes of SCD in Young People

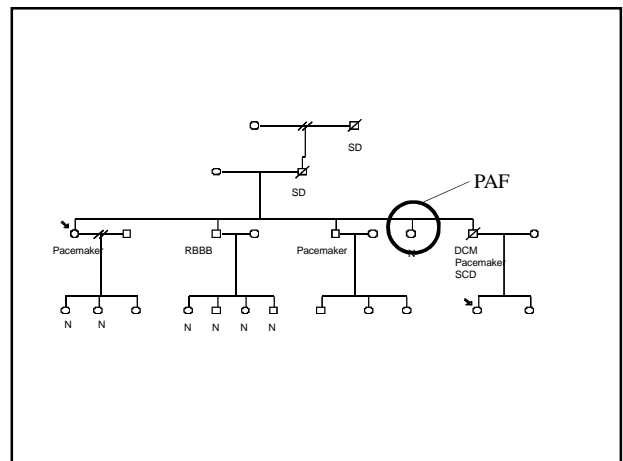
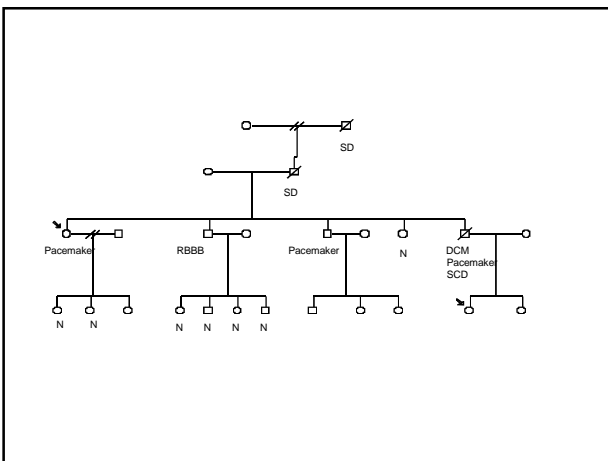
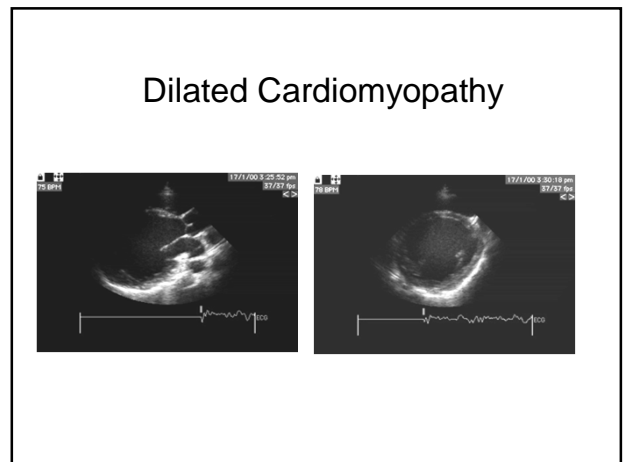
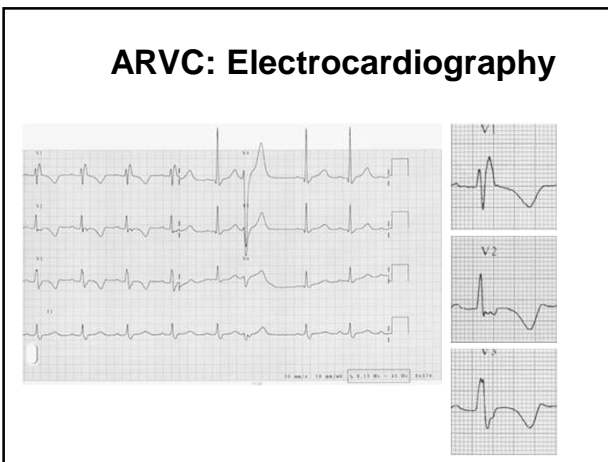
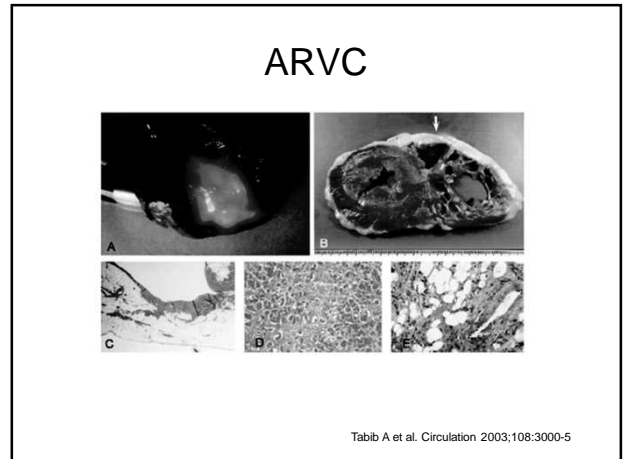
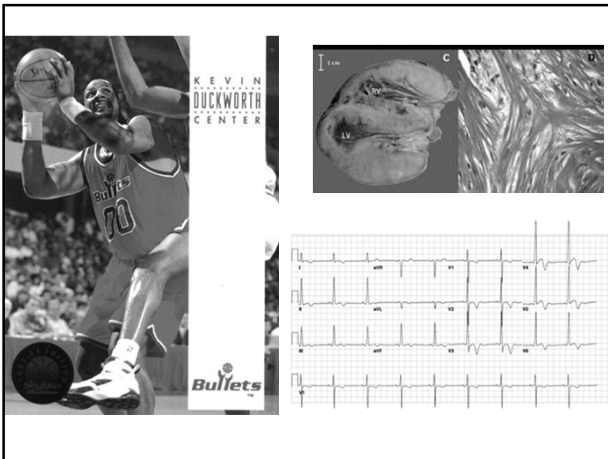


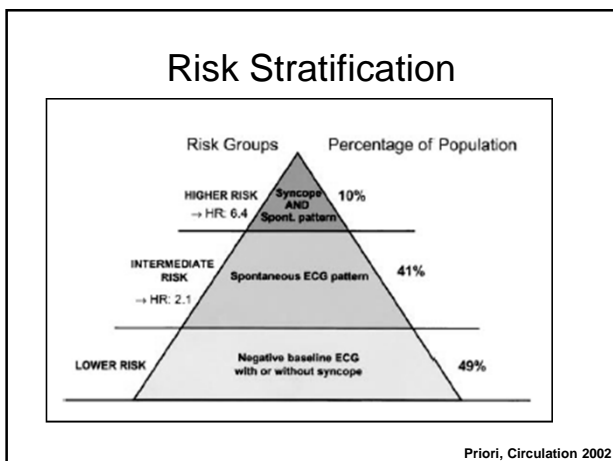
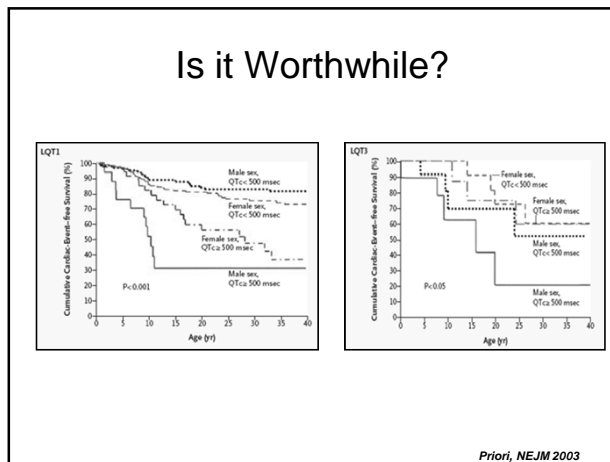
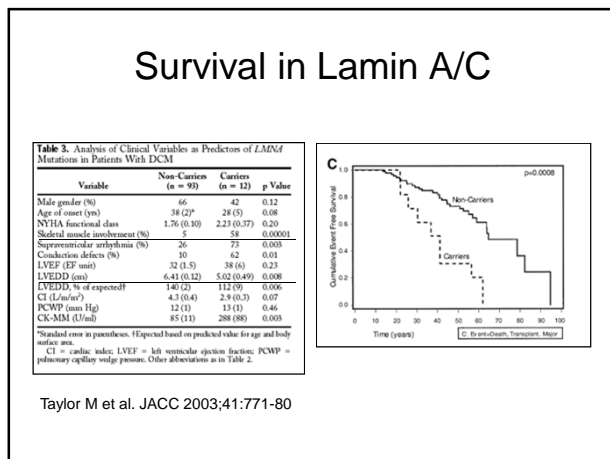
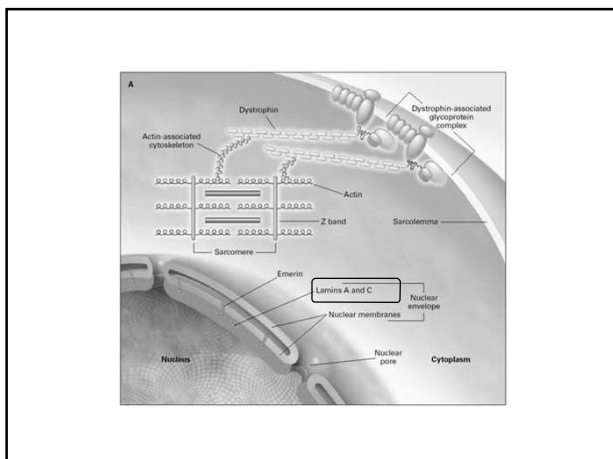
Maron BJ et al. *Circulation*. 1996;94:850-56.

Classification of Cardiomyopathies



Davies M. *Heart* 2000;83:469-474

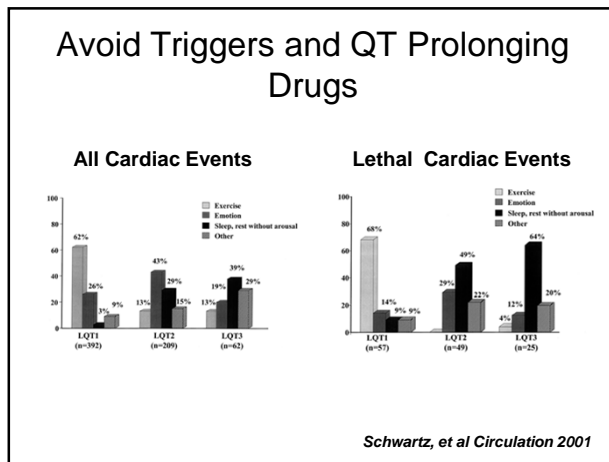
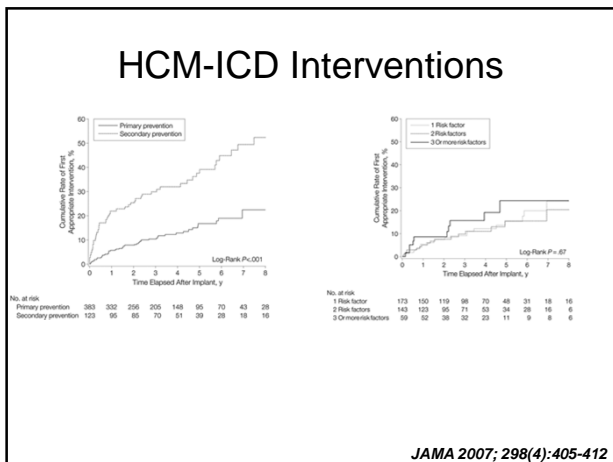
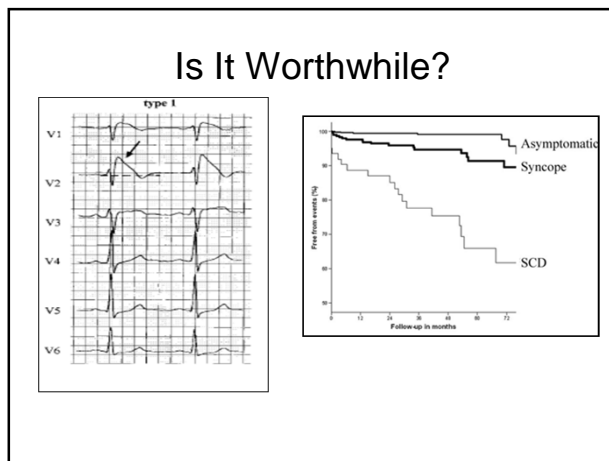
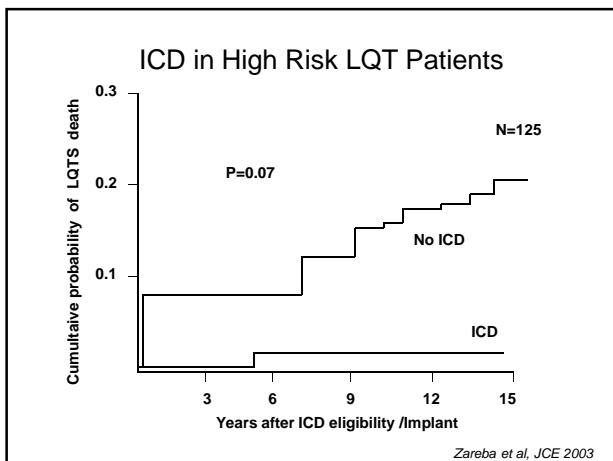




Efficacy of Beta Blockers

Genotype	Recurrences Syncope/VF (% Patients)	VF/SCD (%)
LQT1	19	4
LQT2	41	4
LQT3	50	17

Schwartz et al. Circulation 103 (1): 89. (2001)

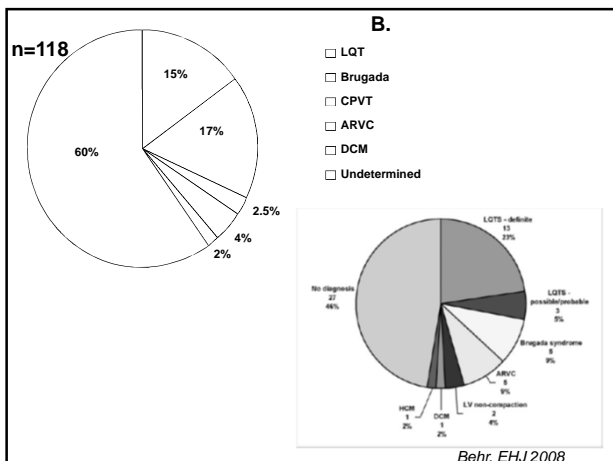


SADS Definition

- Age 1–35 years
- No cardiac history
- Seen alive in the 12h before death
- Normal coroner's autopsy and cardiac pathologist's confirmation of normal heart
- Negative toxicological screen

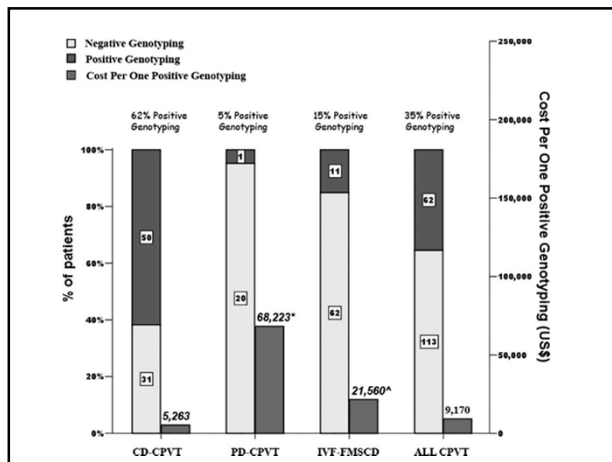
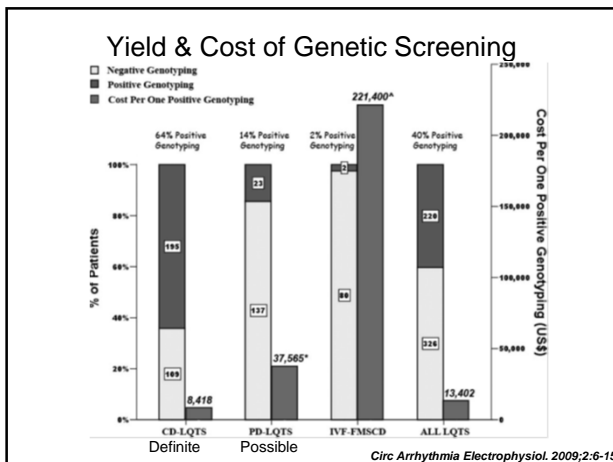
SADS Family Screening

- SADS
 - >450 deaths/ya in UK
 - >1000 deaths /pa USA
- *Clinical family screening* 22% diagnostic yield (*Behr, et al Lancet 2003*).
- *Molecular autopsy*-Over 1/3 cases ion channelopathy-RyR or LQT mutations (*Tester, Ackerman JACC 2007*)
- *Integrated*: 40% diagnostic yield with confirmatory genetic testing. (*Tan, et al Circulation 2005*)



Indications for Genetic Testing

Indication	HCM	LQTS	CPVT	BrS
Evaluation – Clinically Suspected	+	+	+	+
Unexplained LVH	+	-	-	-
QTc ≥ 500 ms	-	+	-	-
Drug-Induced TdP	-	+	-	-
Postmortem for Autopsy Neg. SUD	-	+	+	+
Pre-sports Participation	-	-	-	-
Universal Screening	-	-	-	-
Family Testing	+	+	+	+



Genetic Cascade Screening

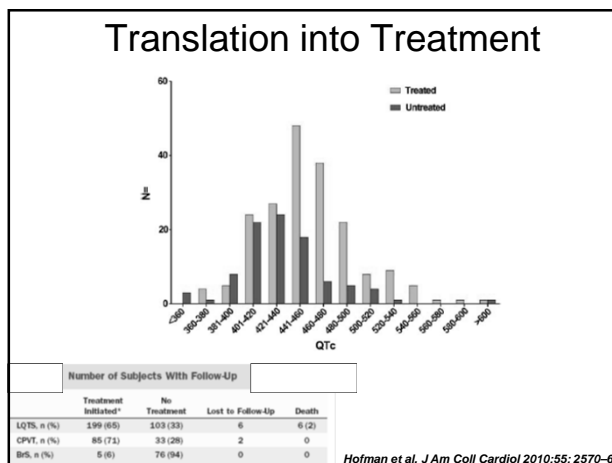
Sociodemographic Characteristics

	LQTS	BrS	CPVT	Total
Probands, n	66	24	10	100
Relatives, n	308	81	120*	509
Mean age, yrs (SD)	34 (22)	48 (20)	31 (22)	36 (22)
Male/female, n	150/158	36/45	50/70	236/273

Initiation of Therapy in Subtypes of LQTS*

Treatment	Symptomatic/Asymptomatic	LQTS1	LQTS2	LQTS3
β-blocker, n	Symptomatic: 10 Asymptomatic: 36	10 93	23 93	0 1
Pacemaker, n	Symptomatic: 0 Asymptomatic: 0	0 1	1 51	51 51
ICD, n	Symptomatic: 1 (+ β-blocker) Asymptomatic: 0	1 (+ β-blocker) 0	3 (+ β-blocker) 0	1 5
Totally treated, n		47	121	31

Hofman et al. J Am Coll Cardiol 2010;55:2570-6



Specific Conditions

- HCM-10-60 years-5 yearly
- ARVC-Annual screening with ECG and Holter
- DCM
- Inherited arrhythmia syndromes-
 FHx SCD
 Familial disease-children
 strongest case in LQT and CPVT
 Brugada Syndrome

Summary

- Detailed FHx can be very informative
- Circumstances of syncope: Triggers, frequency.
- Refer for further Ix
 Abnormal ECG- QTc, LVH, T wave inversion
 Abn. Echo: Think about inherited disorders

Long QT Syndrome

Clinical

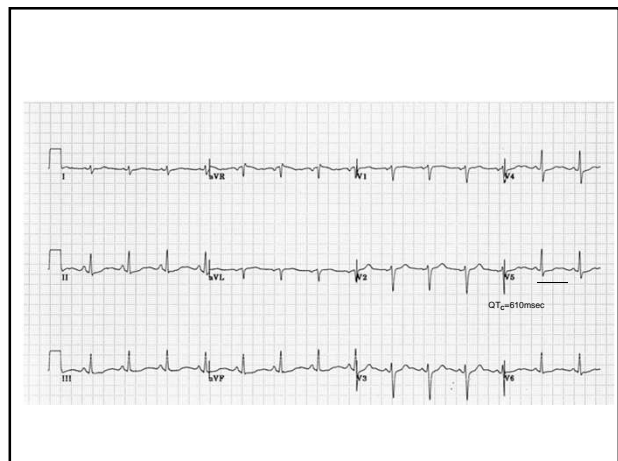
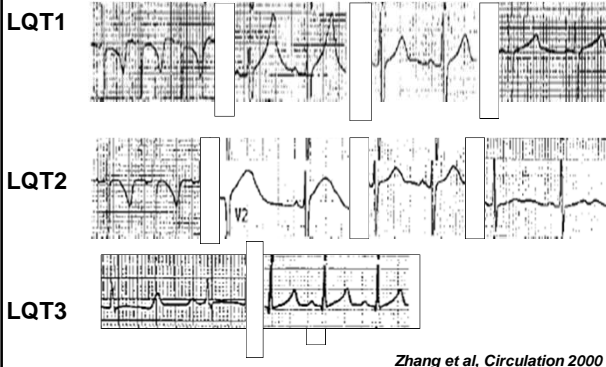
QTc = 600 ms

Normal QT interval
Prolonged QT

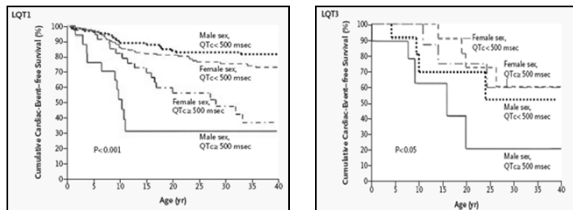
1. Syncope
2. Seizures
3. Sudden death

Torsade de pointes

Comparison of LQT ECG Phenotypes

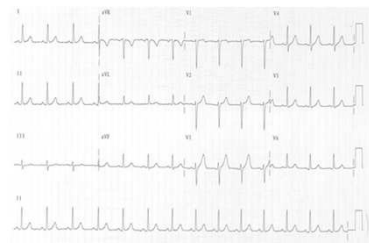


LQT Genotype and Prognosis



Priori et al, NEJM 2003

Father



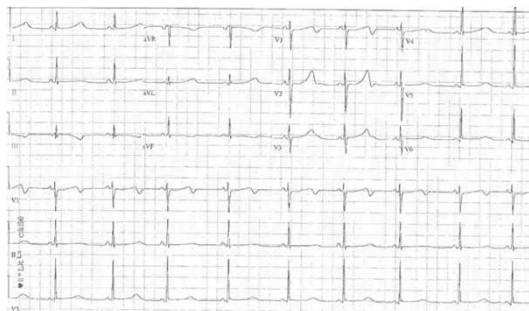
QTc 384msec

Mother

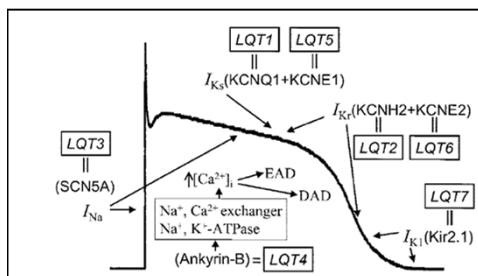


QTc 450msec

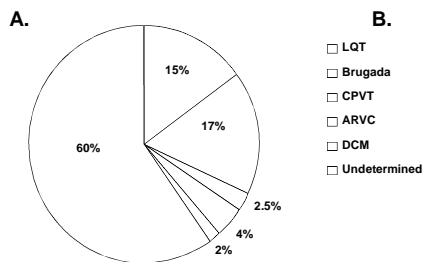
Gene Interactions



“Repolarisation reserve”



Proportion of Families with Diagnosis Made by Clinical Screening



Factors Influencing Probability of a Clinical Diagnosis

	With Diagnosis (n=48)	Without Diagnosis (n=70)	P
Relatives examined, n	3.9 (±2.9)	3.1 (±5.9)	ns
SADS cases per family,	1.47 (±3.2)	1 (±0.64)	ns
Youngest age range of SADS, y	4-34	1-35	
Families with 2 SADS, n	9	6	0.2
Families with 3 SADS, n	5	0	<0.01
Families with 4 SADS, n	4	0	<0.05

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Families with 4 SADS, n	4	0	<0.05
Families with SADS at < 30 y of age, n	30	48	1
Families with SADS at < 20 y of age, n	13	27	0.2

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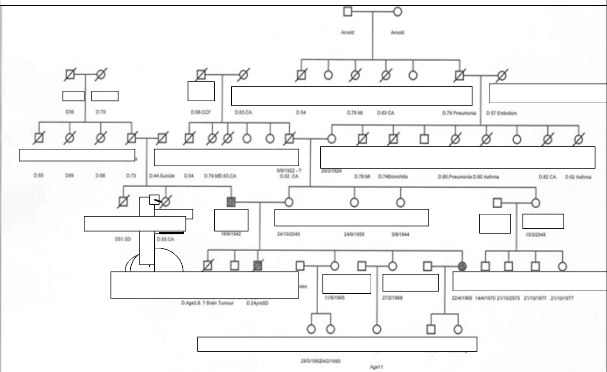
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SADS during exercise or stress,* n	10	20	1
SADS at rest,* n	23	39	1

*Index SAD victim.

Case Hx

Proband-22 male rugby player
 No prior medical history
 No palpitations, pre-syncope, syncope
 Post mortem- Heart weight 500g (ULN)
 Structurally normal heart

Family tree



Mother's ECG



Father's ECG



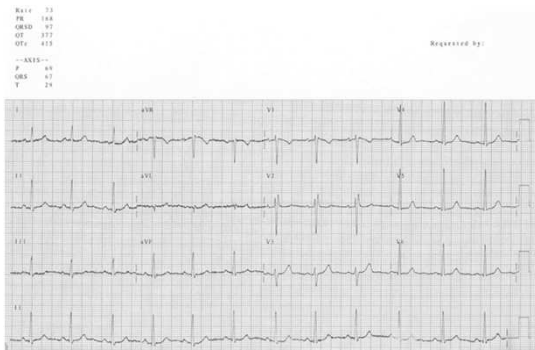
Sibling's ECG 1



Sibling's ECG 2



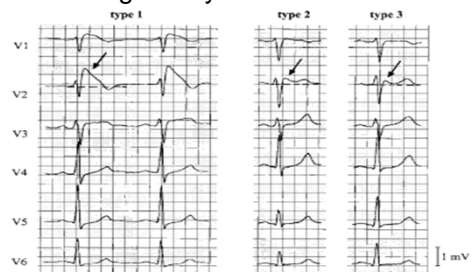
Sibling's ECG 3



Diagnostic Testing



Brugada Syndrome ECG



	ST-Segment Abnormalities in Leads V ₁ to V ₃		
	Type 1	Type 2	Type 3
J wave amplitude	≥2 mm	≥2 mm	≥2 mm
T wave	negative	positive or biphasic	positive
ST-T configuration	coved type	saddleback	saddleback
ST segment (terminal portion)	gradually descending	elevated ≥1 mm	elevated <1 mm

1 mm=0.1 mV. The terminal portion of the ST segment refers to the latter half of the ST segment.

Brugada –Cardiomyopathy or Channelopathy?

