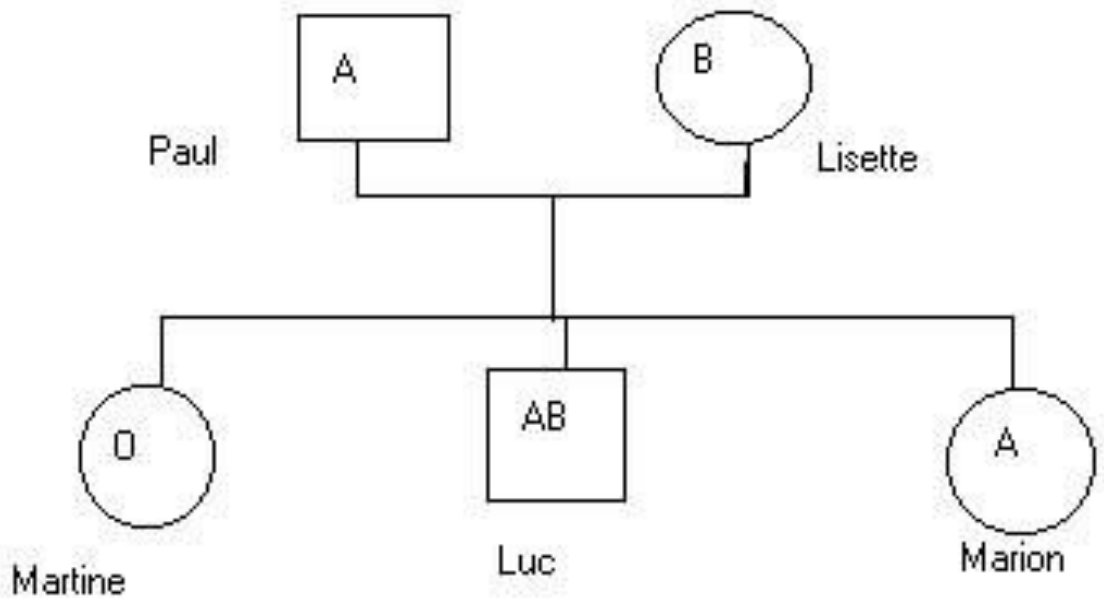
Genetic testing and arrhythmias :

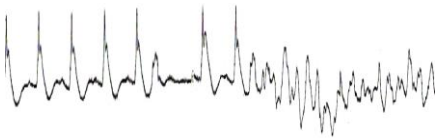
When? How? So what ?

Philippe Chevalier
Hôpital Louis Pradel
Lyon, France

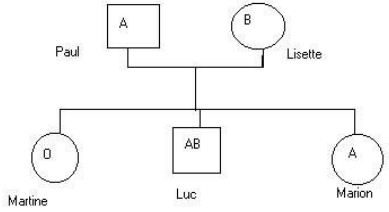
Enquête familiale



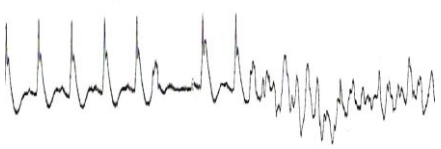
Génotypage: La démarche

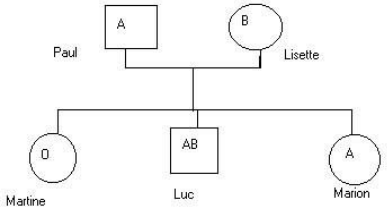


Mort subite



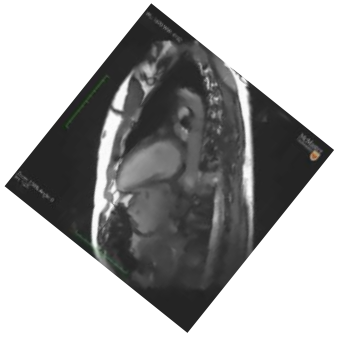
Génotypage: La démarche



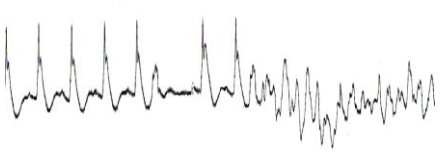


Mort subite

Enquête
Phénotypique

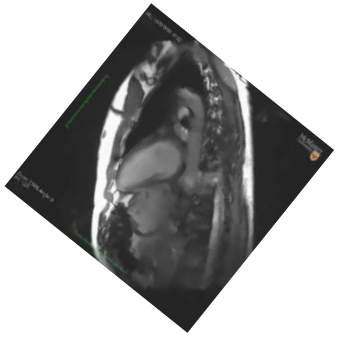


Génotypage: La démarche



Mort subite

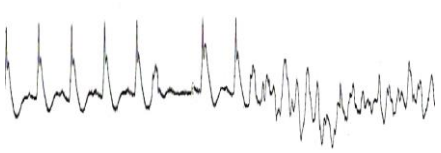
Enquête
Phénotypique



Investigation
génotypique

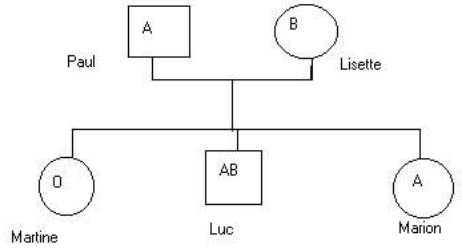
Traitement/
dépistage
personnalisé

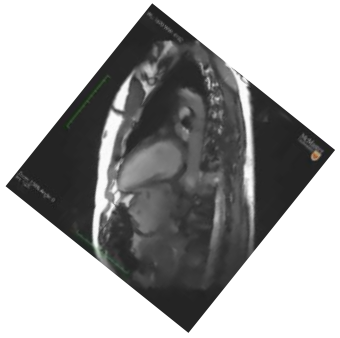
Génotypage: La démarche



Mort subite

Enquête
Phénotypique



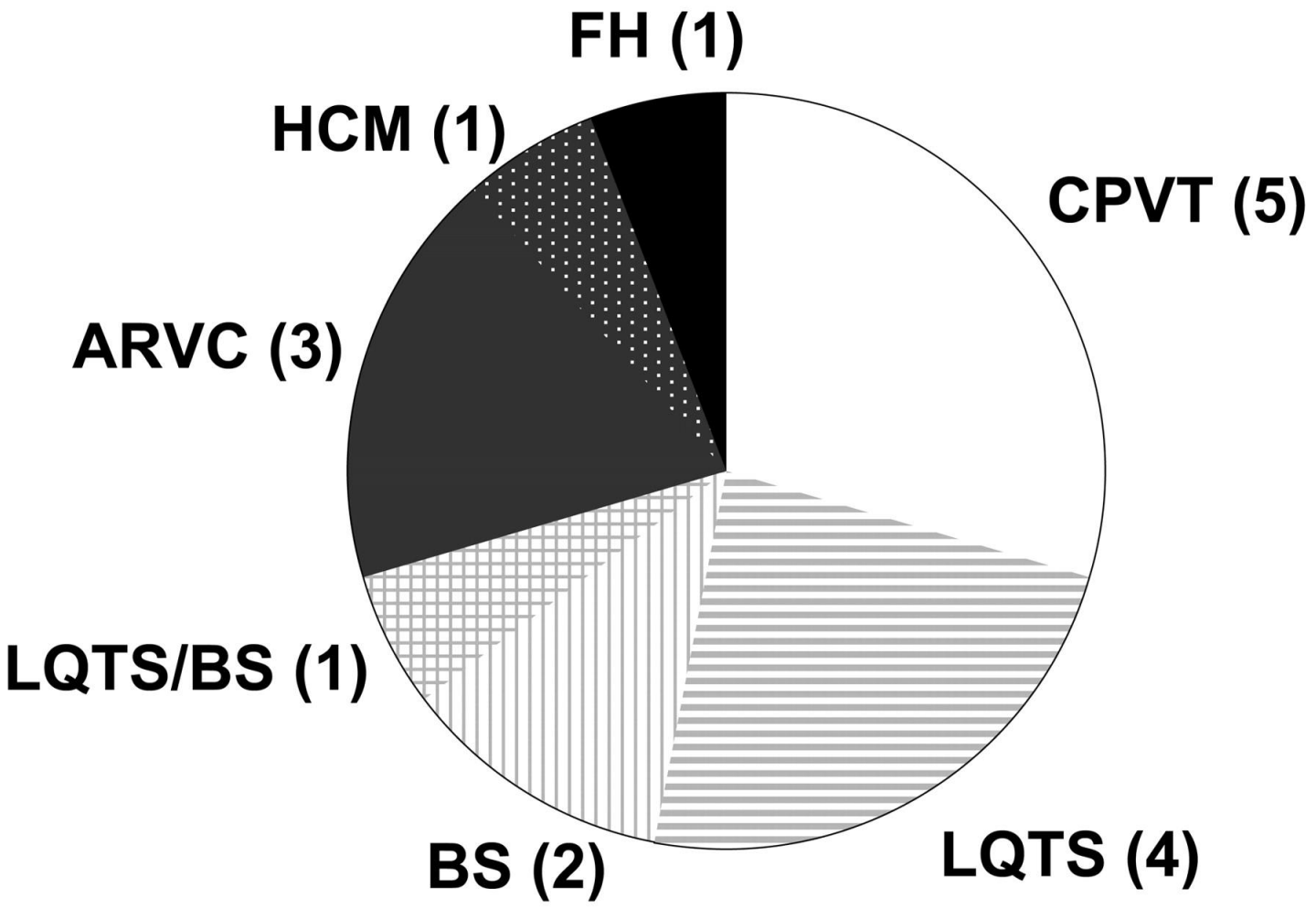


Investigation
génotypique

Enquête familiale

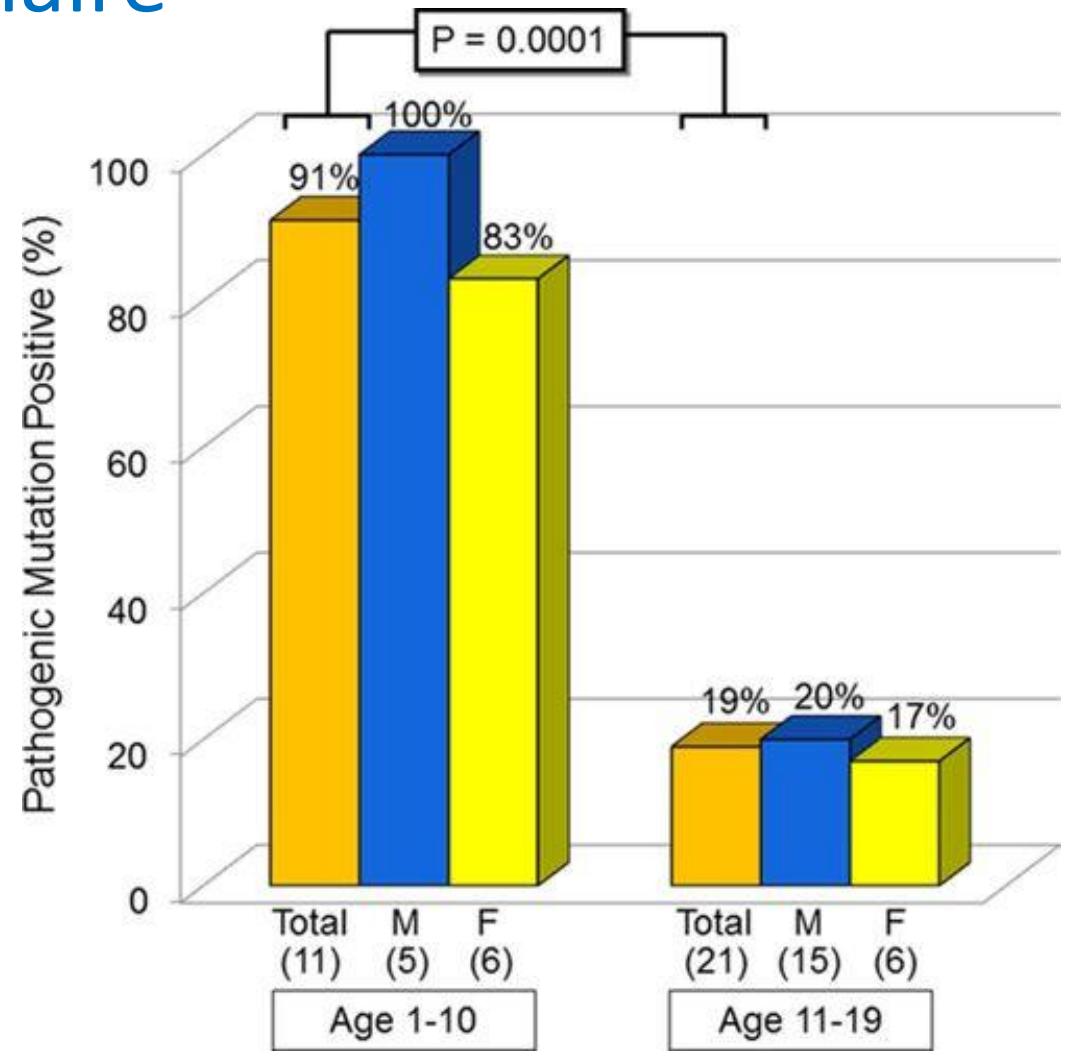
Traitement/
dépistage
personnalisé

Mort subite sur cœur sain
Enquête chez les apparentés

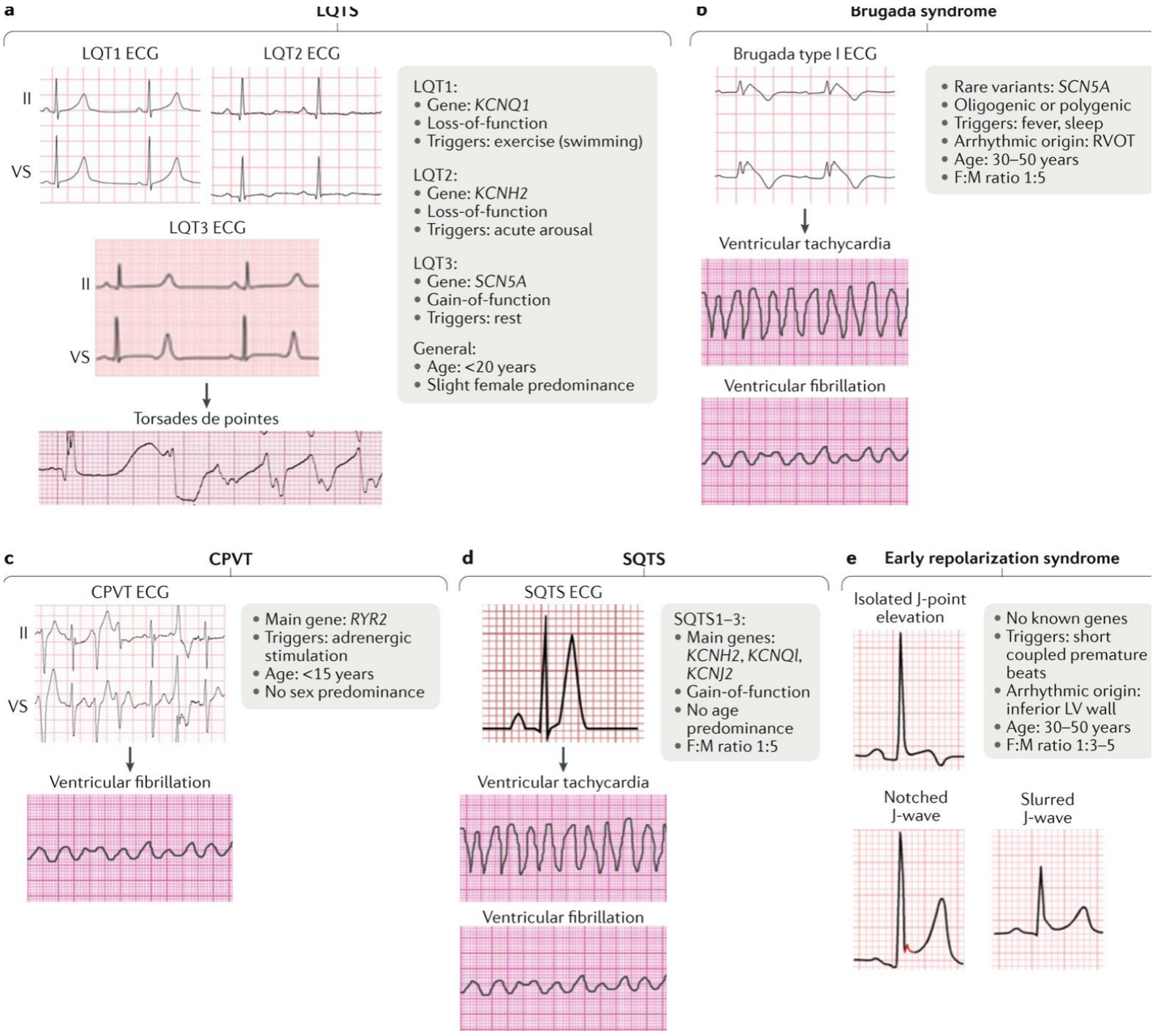


Tan, H. L. et al. Circulation 2005;112:207-213

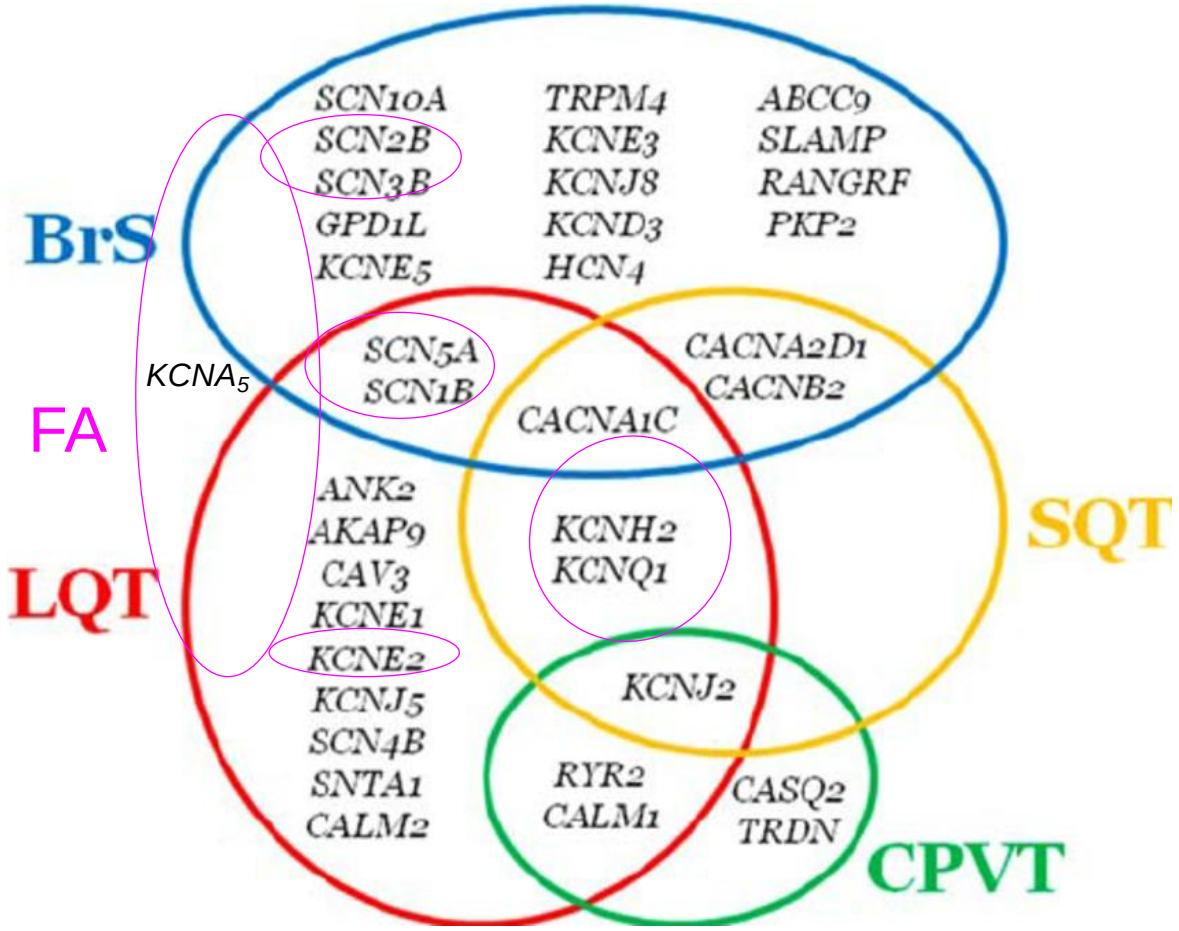
Autopsie moléculaire



Circulation: Cardiovascular Genetics. Whole-Exome Molecular Autopsy After Exertion-Related Sudden Unexplained Death in the Young 2016


a
LQTS
LQT1 ECG
LQT2 ECG
II
VS
LQT3 ECG
II
VS
Torsades de pointes
LQT1:
• Gene: KCNQ1
• Loss-of-function
• Triggers: exercise (swimming)
LQT2:
• Gene: KCNH2
• Loss-of-function
• Triggers: acute arousal
LQT3:
• Gene: SCN5A
• Gain-of-function
• Triggers: rest
General:
• Age: <20 years
• Slight female predominance
b
Brugada syndrome
Brugada type I ECG
Ventricular tachycardia
Ventricular fibrillation
• Rare variants: SCN5A
• Oligogenic or polygenic
• Triggers: fever, sleep
• Arrhythmic origin: RVOT
• Age: 30–50 years
• F:M ratio 1:5
c
CPVT
CPVT ECG
II
VS
Ventricular fibrillation
• Main gene: RYR2
• Triggers: adrenergic stimulation
• Age: <15 years
• No sex predominance
d
SQTS
SQTS ECG
Ventricular tachycardia
Ventricular fibrillation
SQTS1–3:
• Main genes: KCNH2, KCNQl, KCNJ2
• Gain-of-function
• No age predominance
• F:M ratio 1:5
e
Early repolarization syndrome
Isolated J-point elevation
Notched J-wave
Slurred J-wave
• No known genes
• Triggers: short coupled premature beats
• Arrhythmic origin: inferior LV wall
• Age: 30–50 years
• F:M ratio 1:3–5

Arrhythmias : Phenotypic and genotypic heterogeneity



The Promise and Peril of Precision Medicine…..

…*Phenotyping* Still Matters Most

….Don’t forget cascade screening

Jaeger P. Ackerman et al *Heart Rhythm* 2019

Indications for genetic testing

Indication	HCM	LQTS	CPVT	BrS
Evaluation – Clinically Suspected	+	+	+	+
Unexplained LVH	+	–	–	–
QTc ≥ 500 ms	–	+	–	–

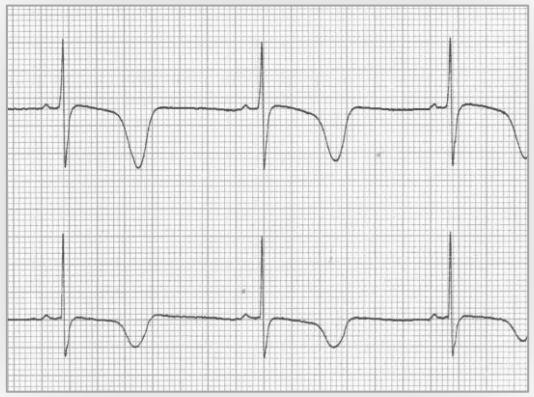
Tester, D. J. et al. Circulation 2011;123:1021-1037

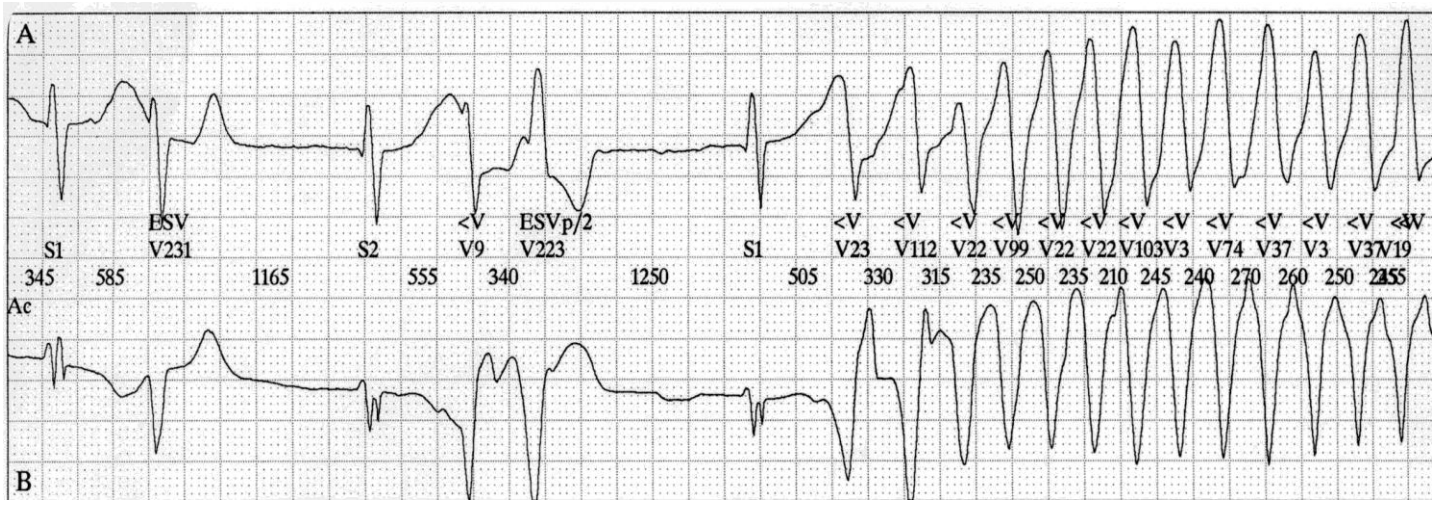
Indications for genetic testing

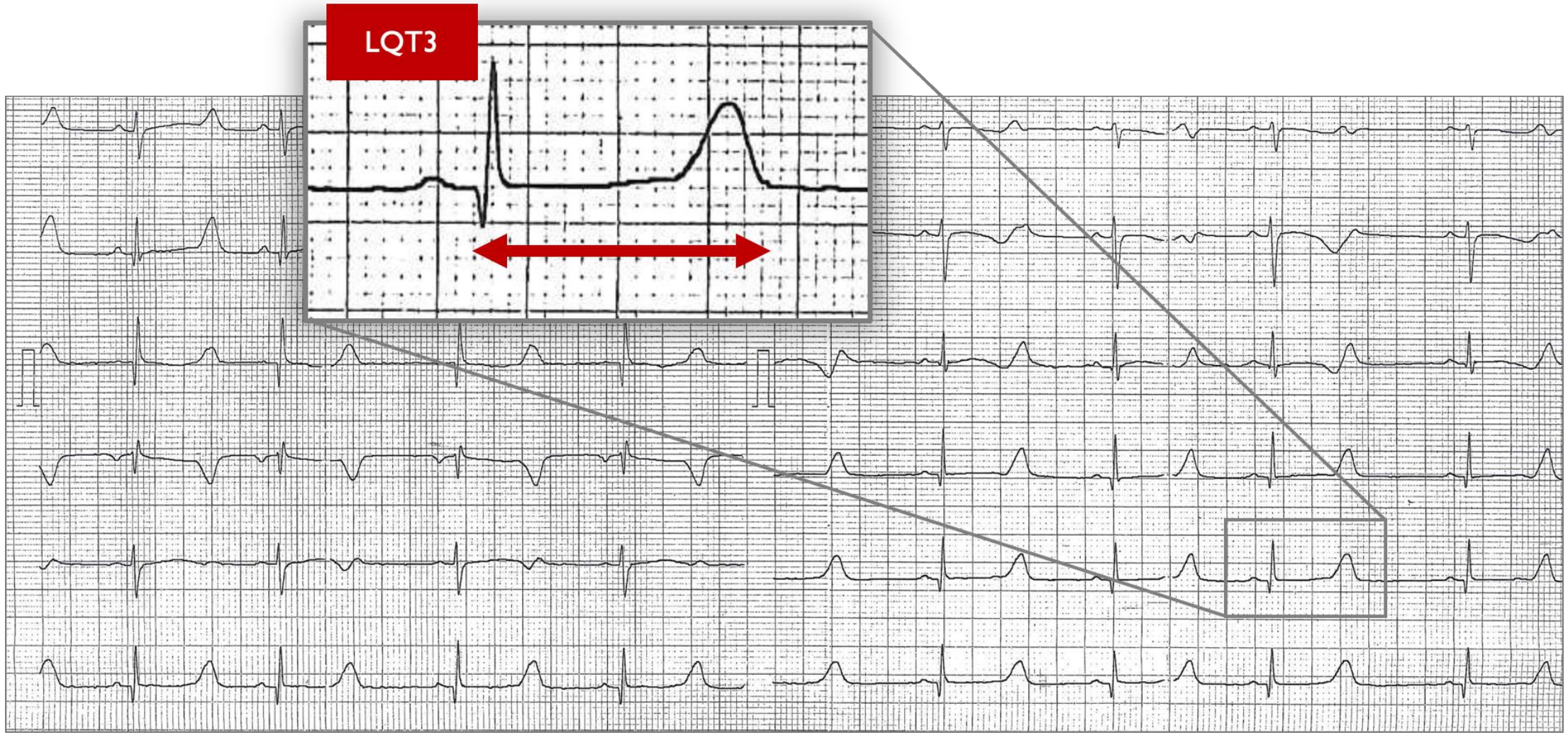
Indication	HCM	LQTS	CPVT	BrS
Evaluation – Clinically Suspected	+	+	+	+
Unexplained LVH	+	–	–	–
QTc ≥ 500 ms	–	+	–	–
Drug-Induced TdP	–	+/–	–	–
Postmortem for Autopsy Neg. SUD	–	+	+	+
Pre-sports Participation	–	–	–	–
Universal Screening	–	–	–	–
Family Testing	+	+	+	+

Tester, D. J. et al. Circulation 2011;123:1021-1037

Congenital and acquired long QT syndrome

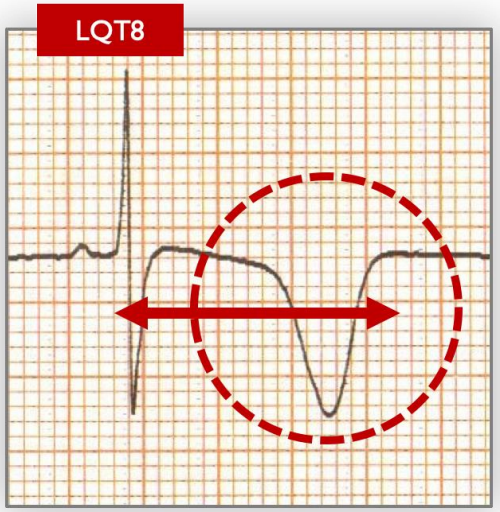


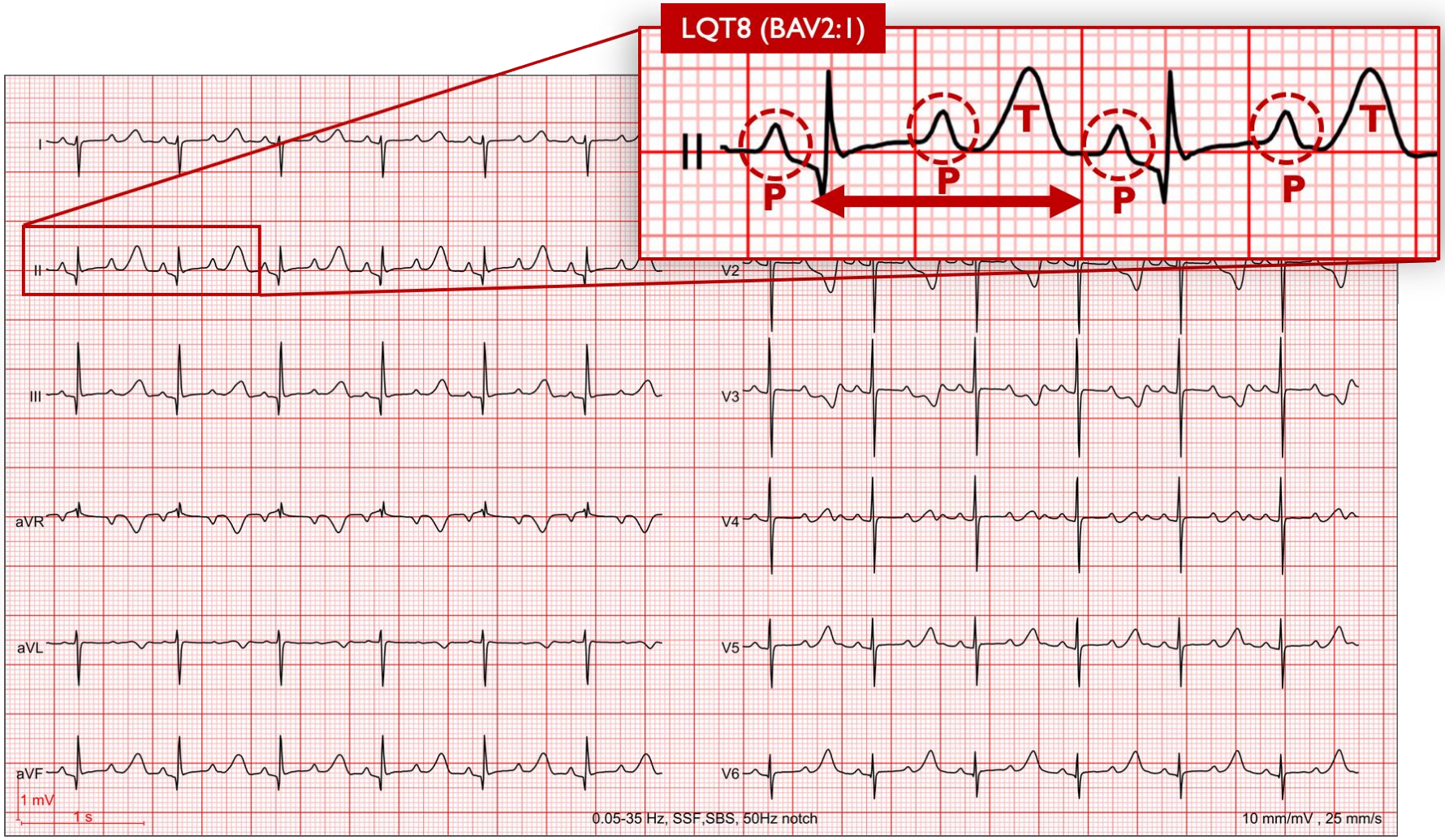



LQT3

FORMES CLINIQUES

TIMOTHY syndrome
LQT8, *CACNA1C*





Splawski I et al. Cell. 2004 Oct 1;119(1):19-31.

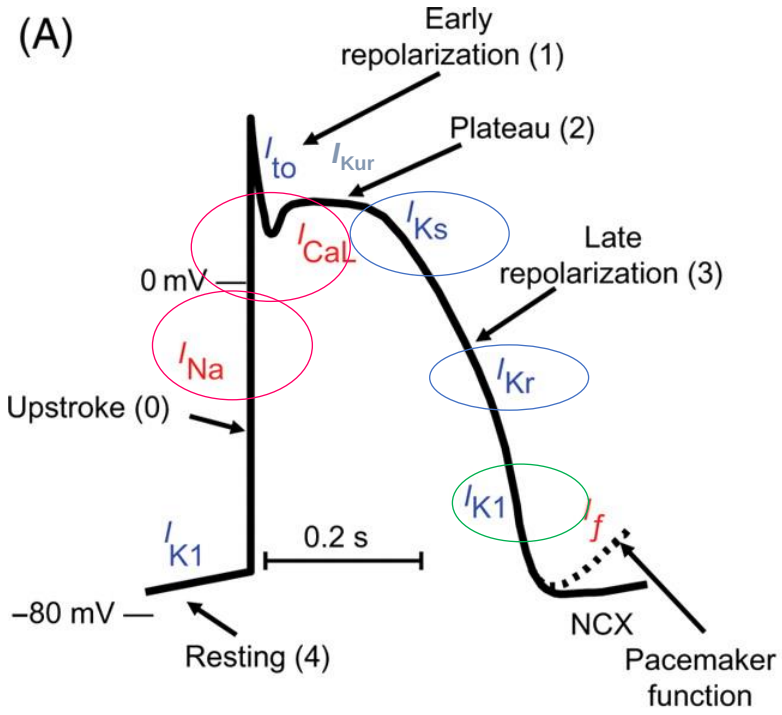
Long QT syndrome

Niveau 1

- KCNQ1, KCNE1 → I_{KS}
- KCNH2, KCNE2 → I_{KR}
- SCN5A → I_{Na}

Niveau2

- AKAP9 ancrage de KCNQ1
- ANK2/ANKB
- CACNA1C → I_{CaL}
- CALM1, CALM2, CALM3, CASQ2, RYR2, TRDN → Ca
- KCNJ2, KCNJ5 → I_{K1}
- SCN4B → I_{Na}
- CAV3, SNTA1 en lien avec SCN5A

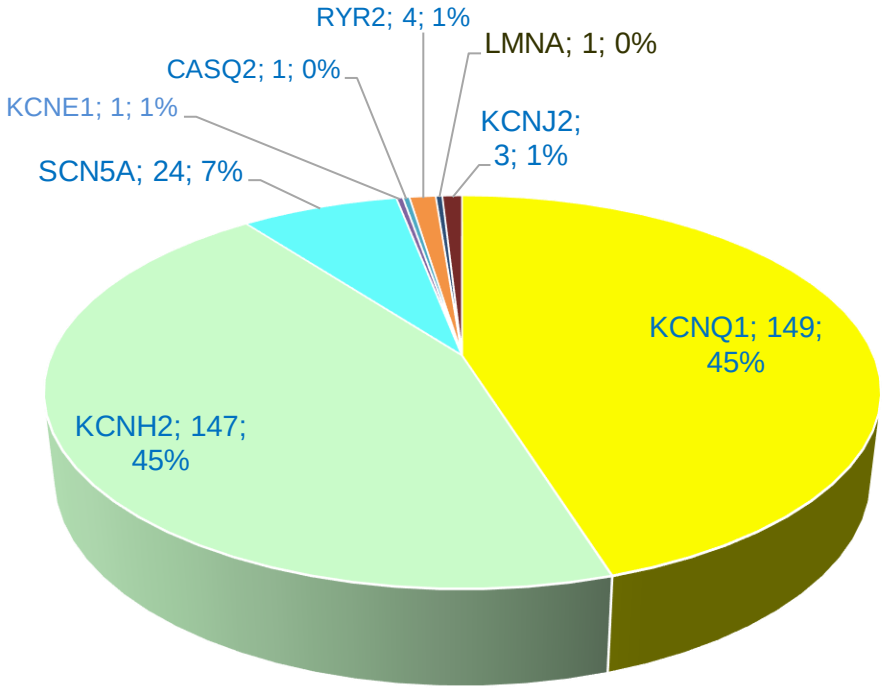


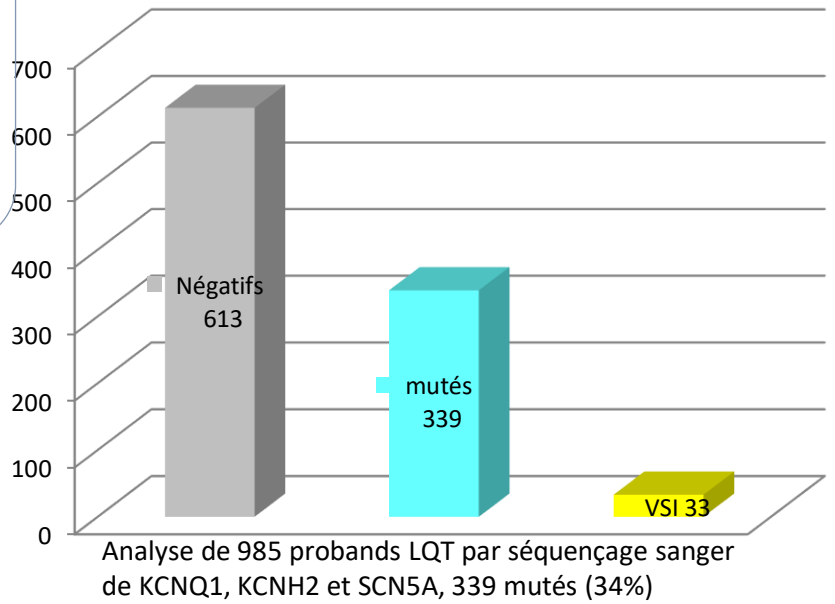
Long QT syndrome

SANGER
KCNQ1
KCNH2
SCN5A

NGS Niveau 1
KCNQ1
KCNH2
SCN5A
KCNE1
KCNE2

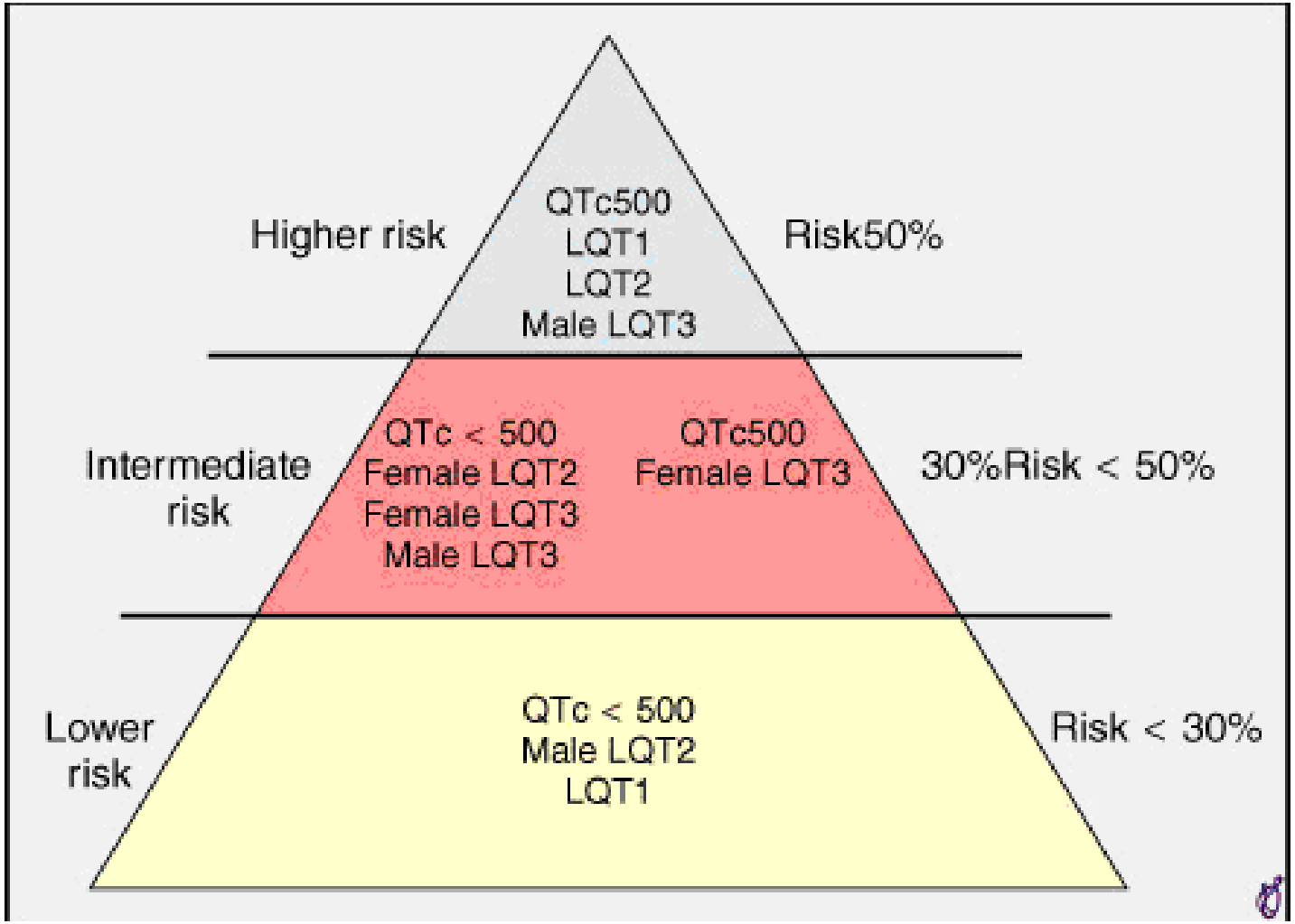
NGS Niveau2
AKAP9
ANK2/ANKB
CACNA1C
CALM1
CALM2
CASQ2
CAV3
KCNJ2
KCNJ5
RYR2
SCN4B
SNTA1
TRDN



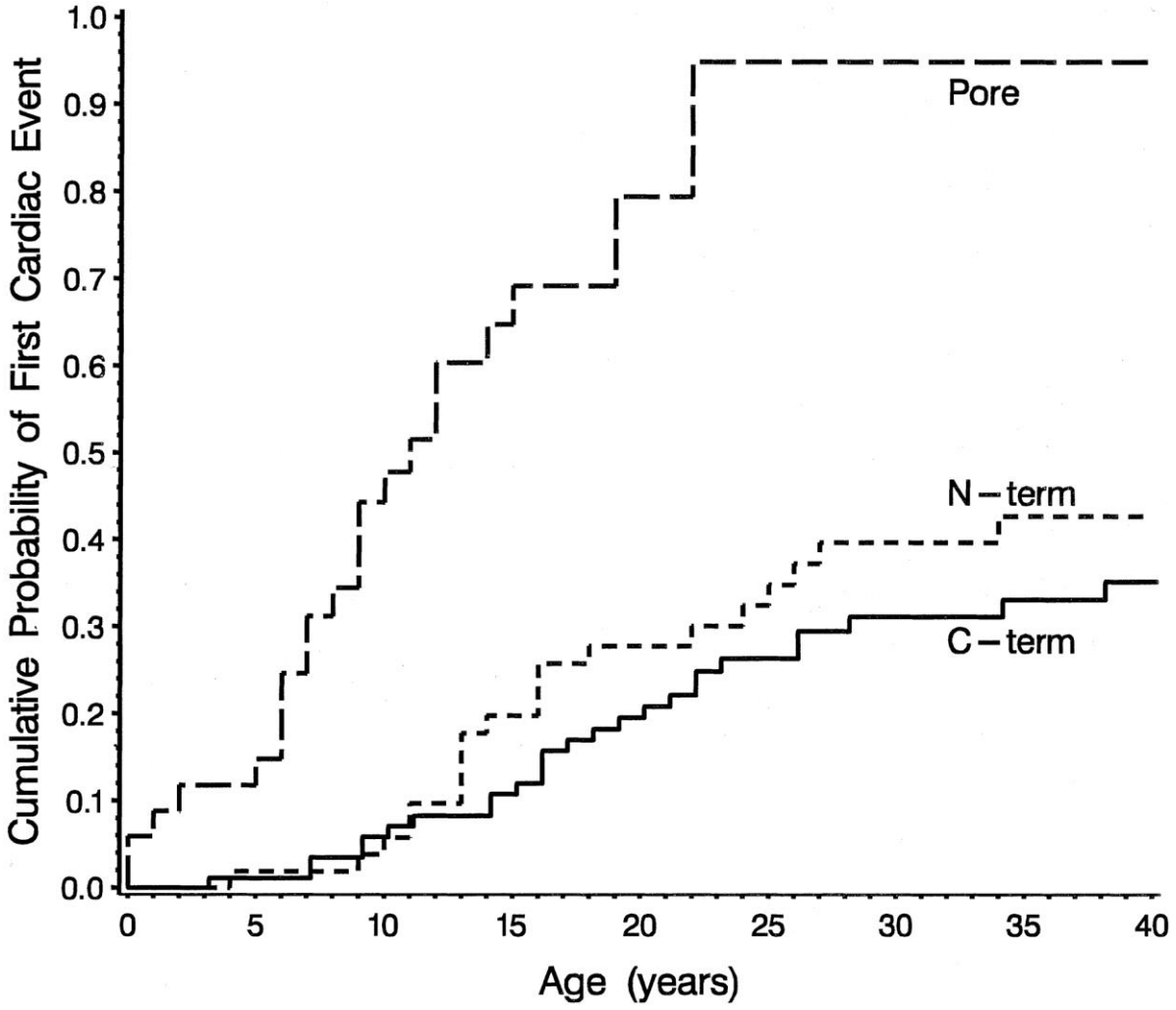


Analyse de 985 probands LQT par séquençage sanger de KCNQ1, KCNH2 et SCN5A, 339 mutés (34%)

Congenital long QT syndrome

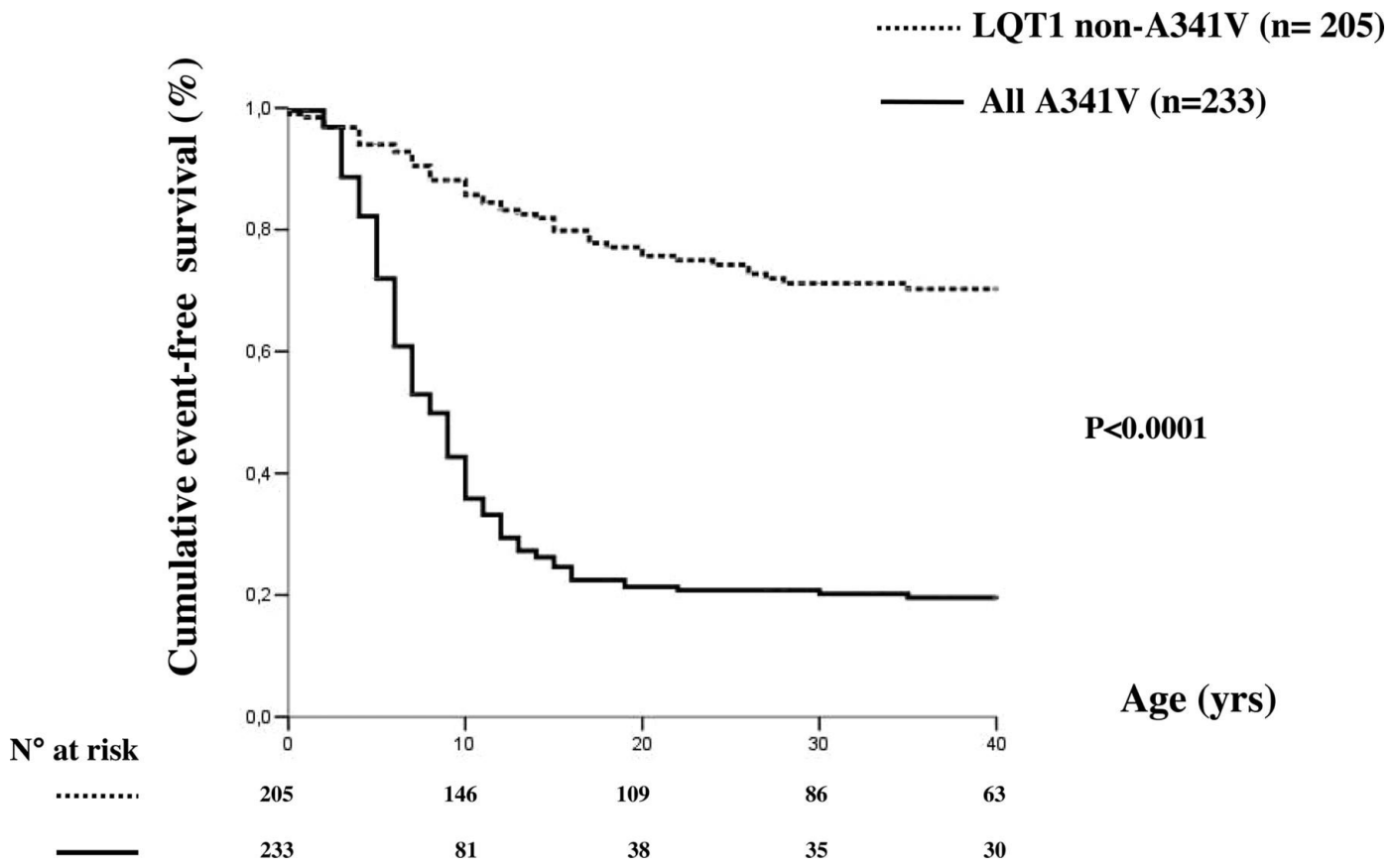


KCNH2 variant



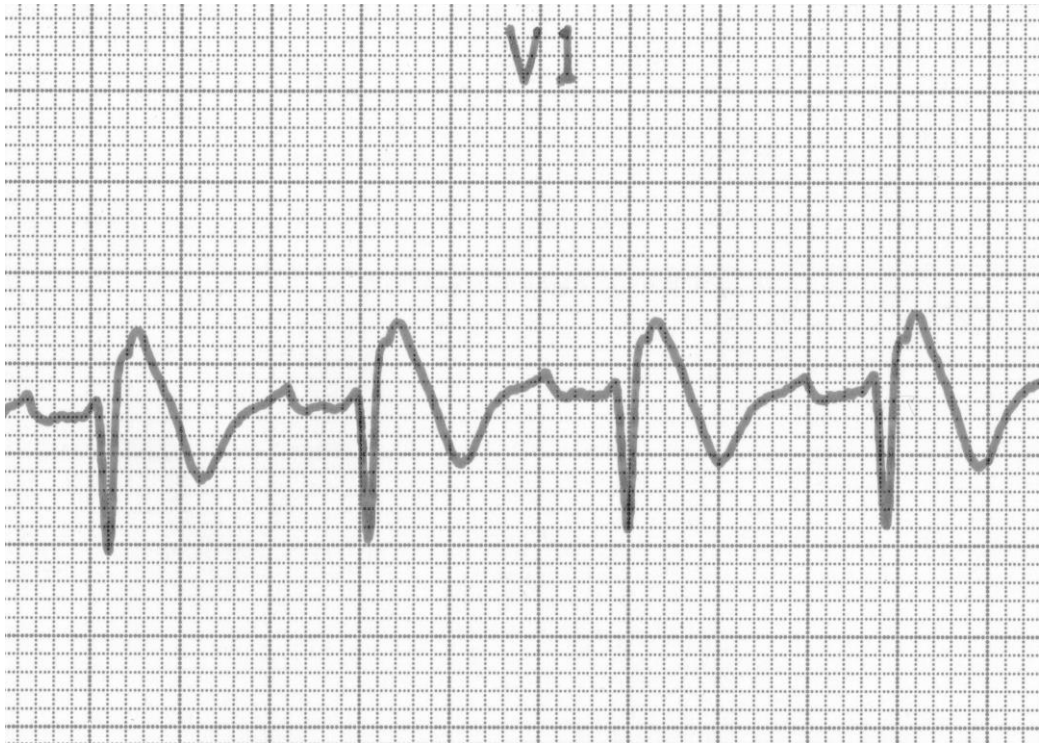
Moss, A. J. et al. Circulation 2002;105:794-799

KCNQ 1 variant

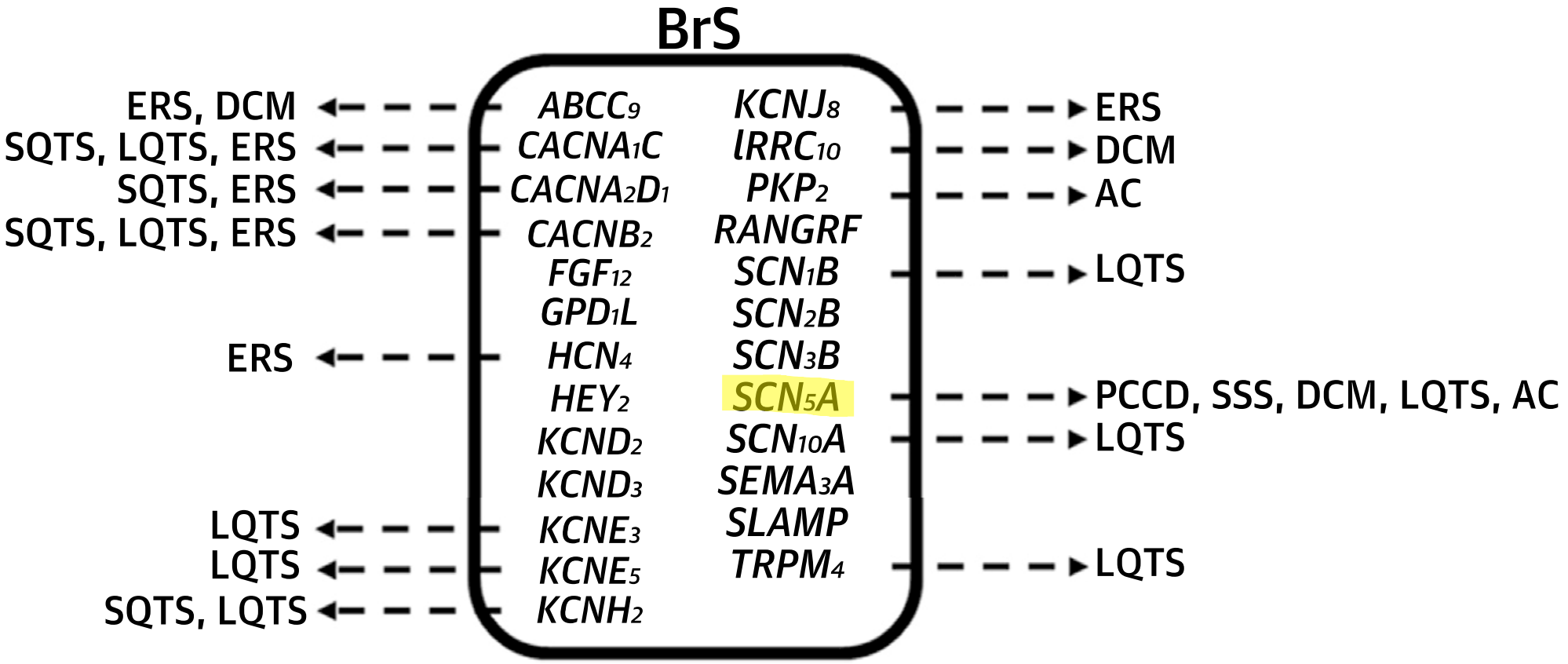


Crotti, L. et al. Circulation 2007;116:2366-2375

Brugada syndrome or *Brugada ECG pattern*

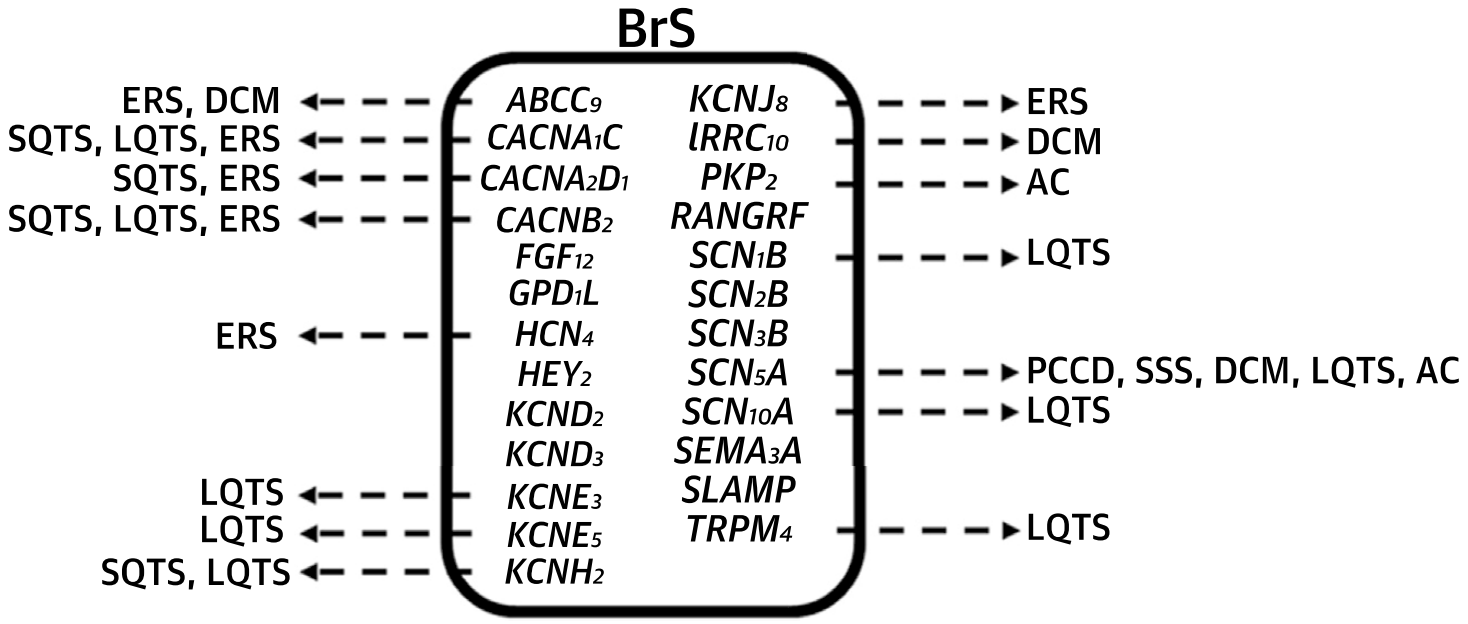


Pathogenic mutations or polygenic score?

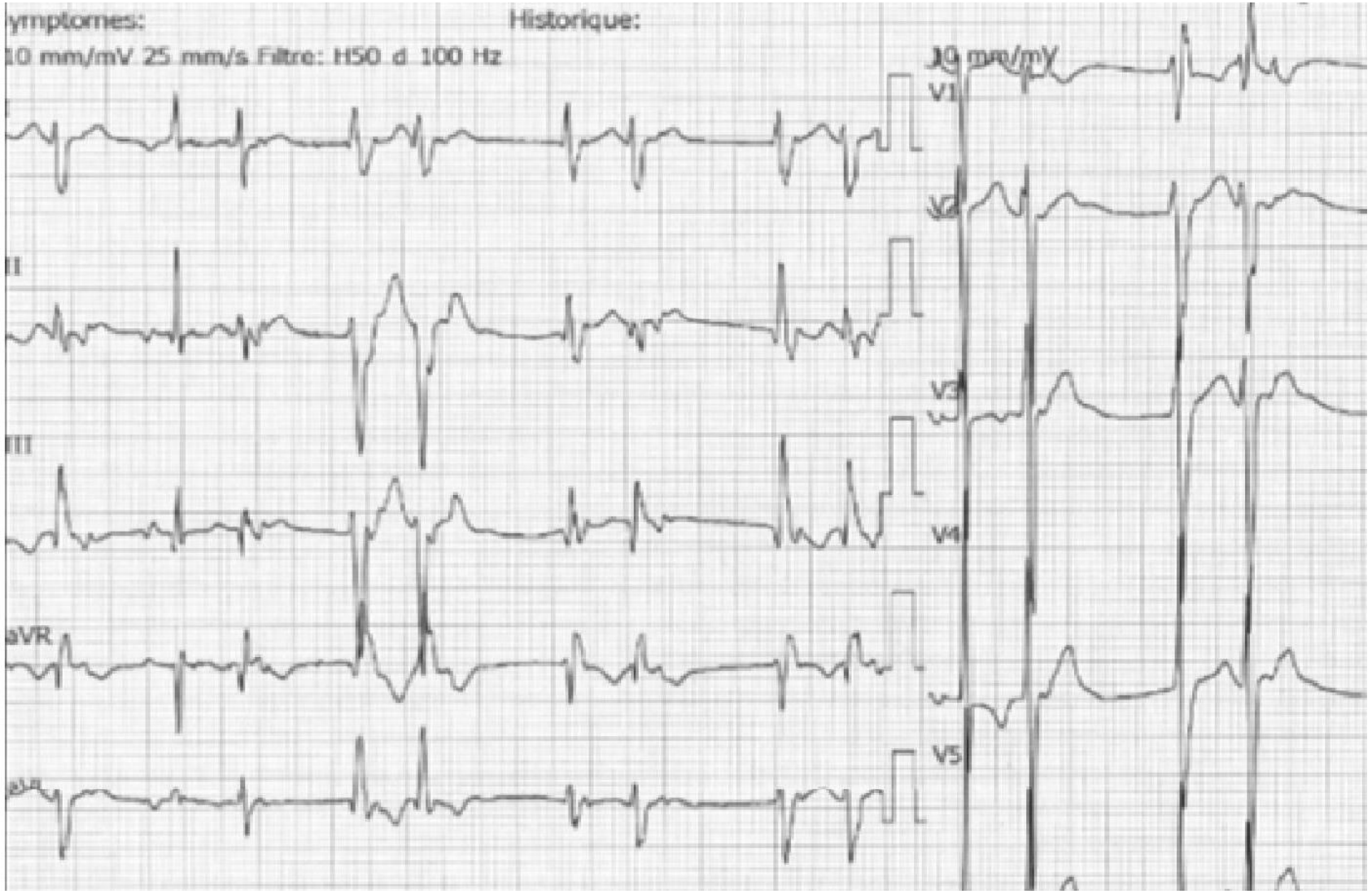


SCN5A variants in Brugada syndrome: True, true false, or false true?

Arthur A M Wilde

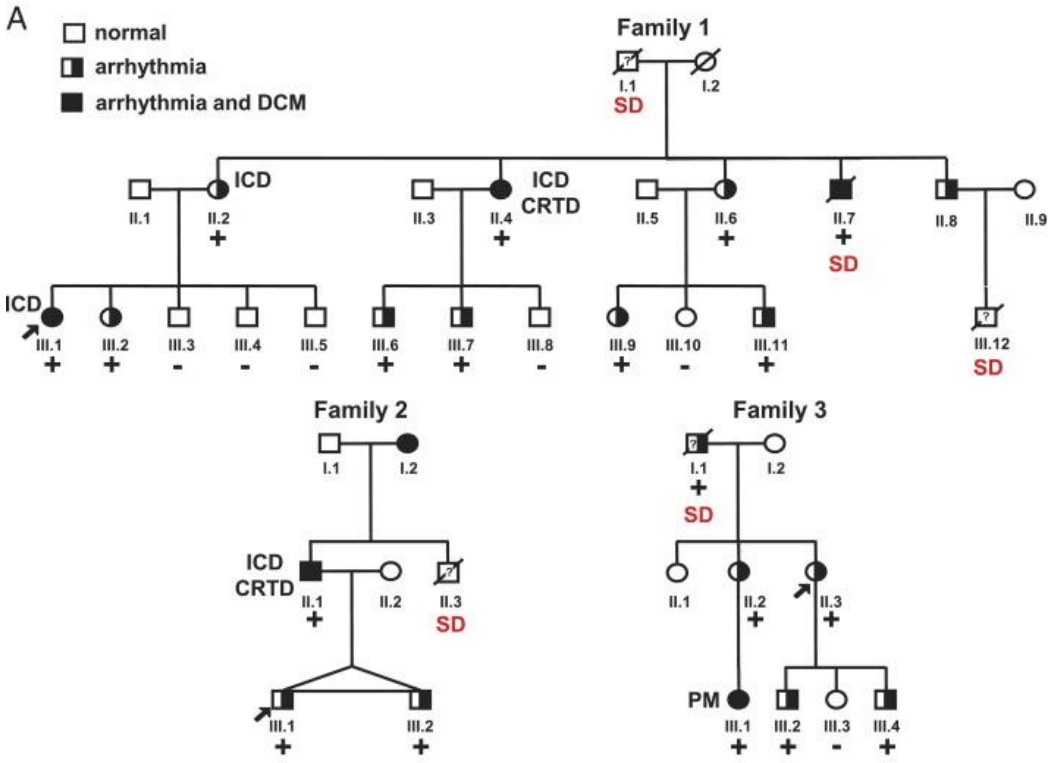


Multifocal Ectopic Purkinje-related Premature Contractions MEPPC

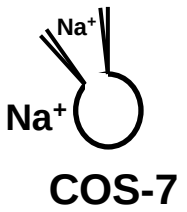


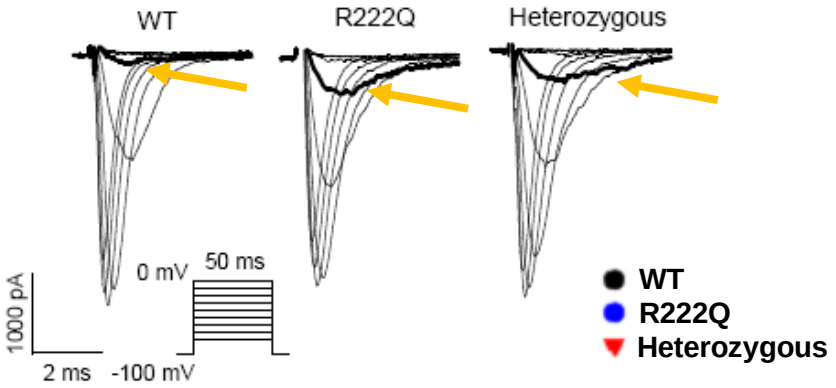
Laurent *et al. J Am Coll Cardiol* 2012;60:144–56.

SCN5A p.R222Q variant induces MEPPC



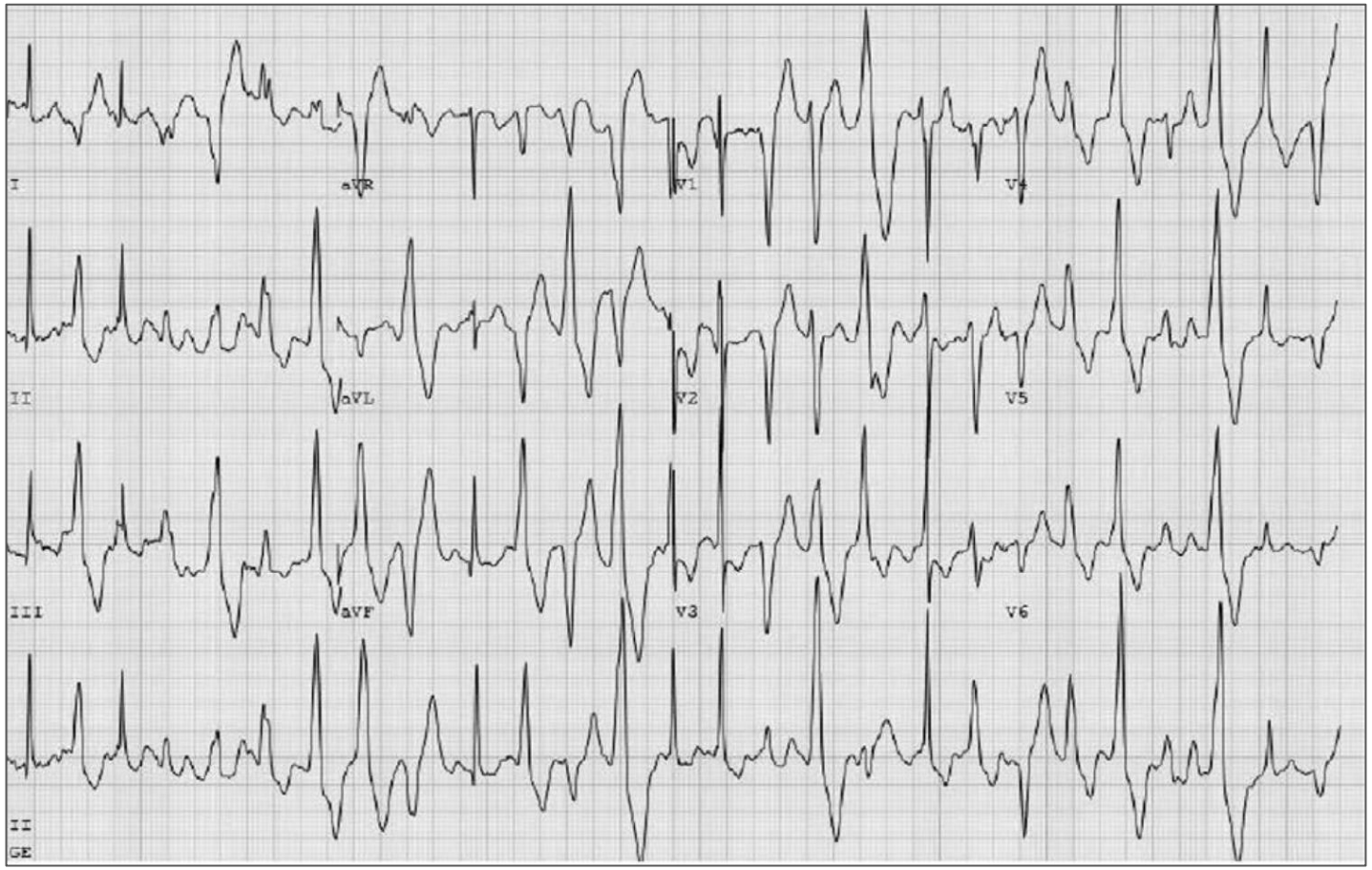
➔ $Na_V1.5$ gain of function



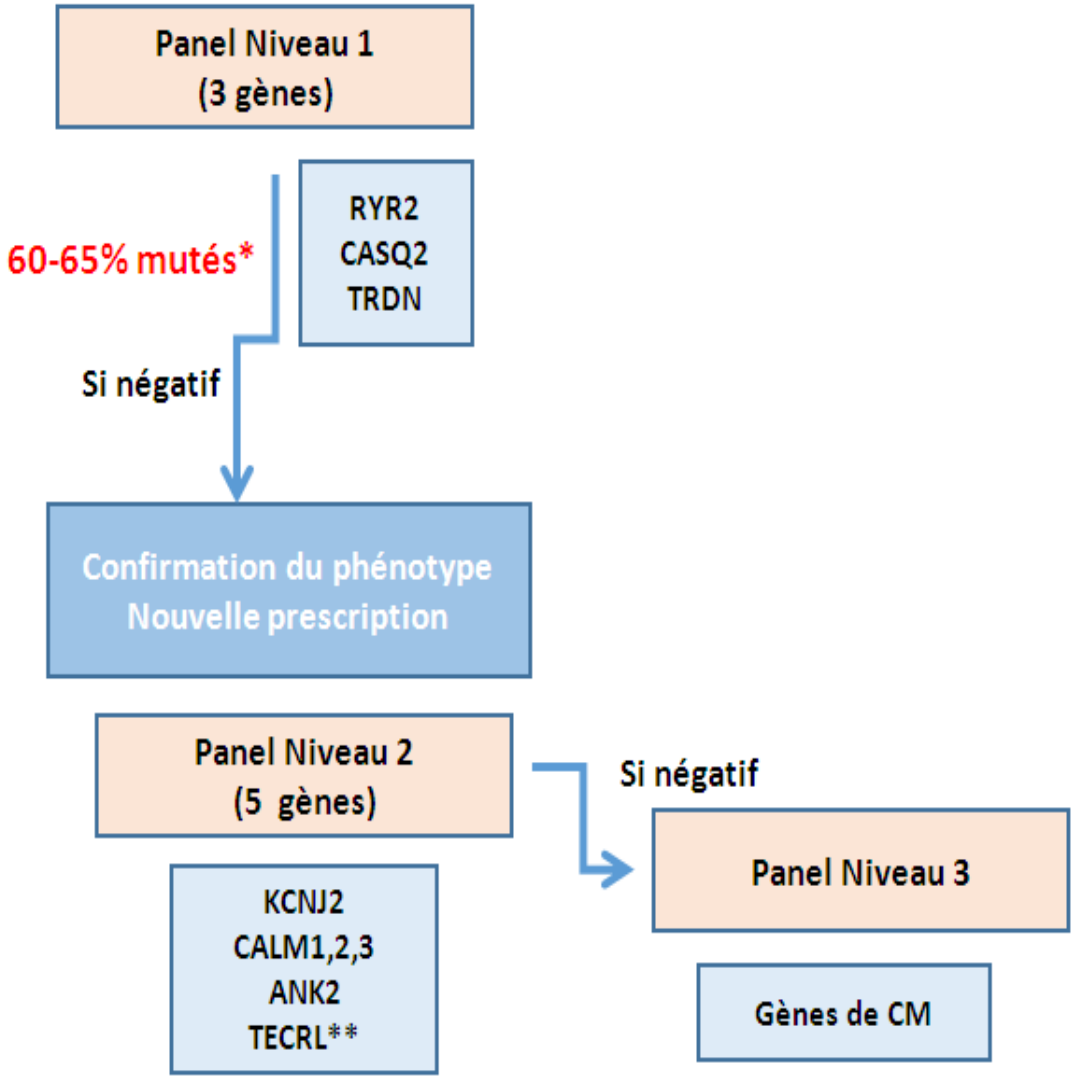


Laurent *et al. J Am Coll Cardiol* 2012;60:144–56.

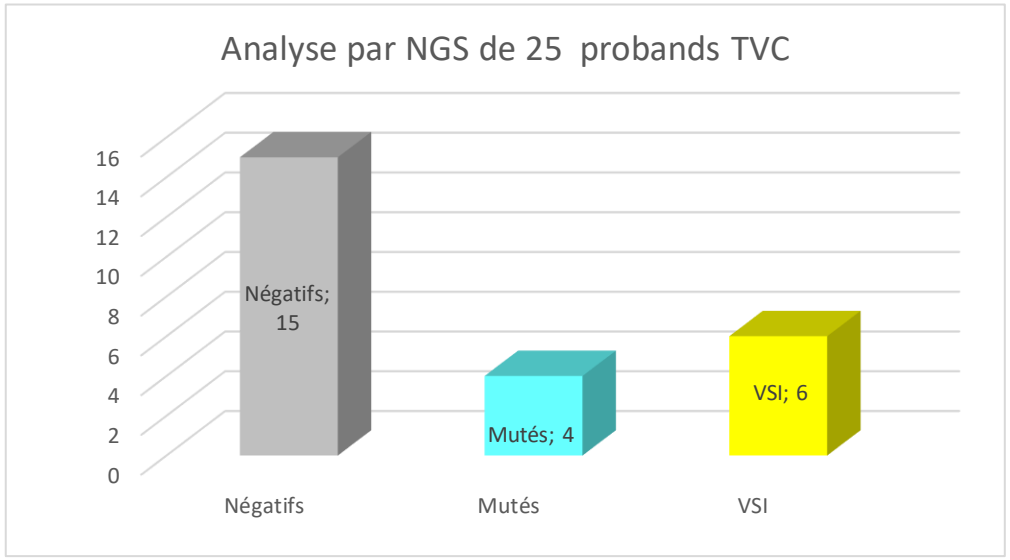
Cathecholergic polymorphic ventricular tachycardia



CPVT is diagnosed in the presence of a structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.	I	C
CPVT is diagnosed in patients who are carriers of a pathogenic mutation(s) in the genes *RyR2* or *CASQ2*.	I	C

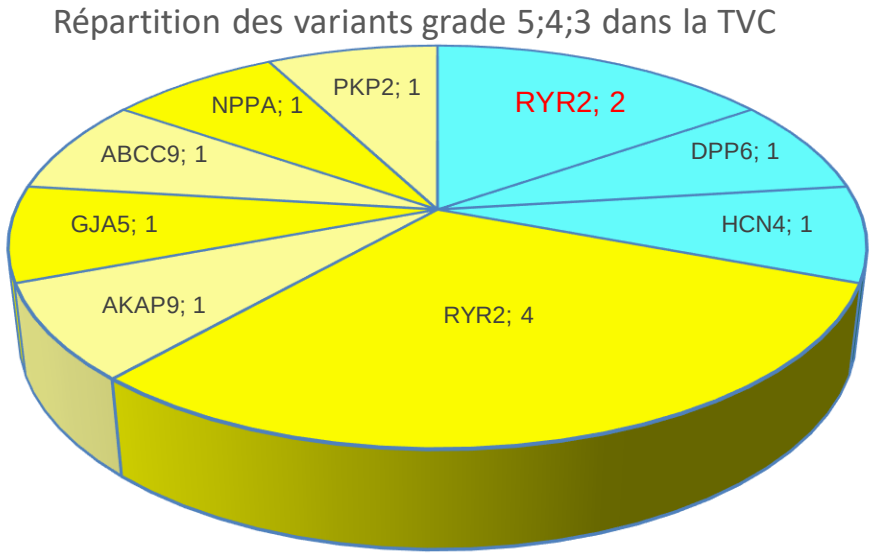


Kawamura M et al. Circ J. 2013;77(7):1705-13.



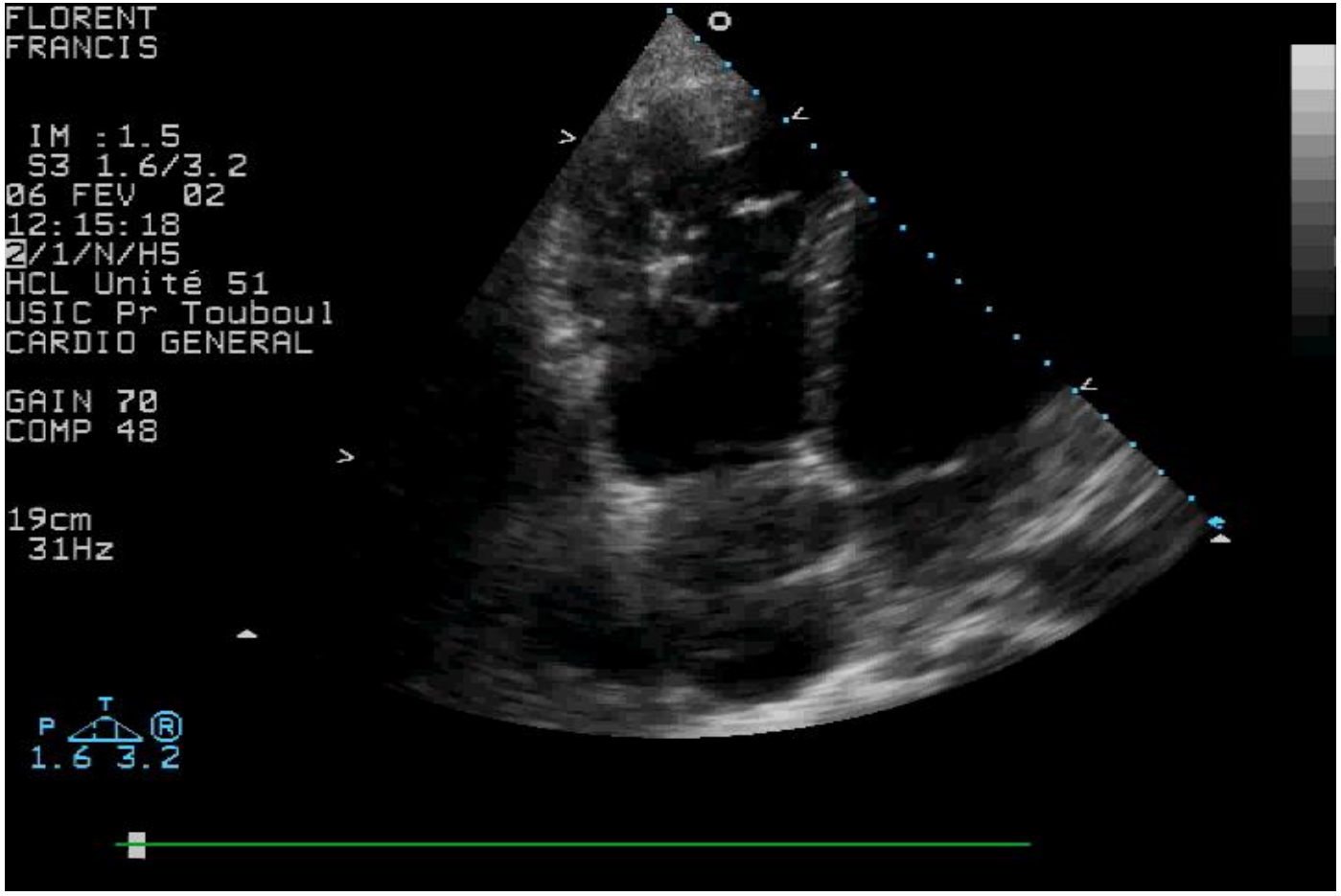
Niveau1
RYR2
CASQ2 récessif
TRDN (triadin) récessif

Niveau2
ANK2/ANKB
CALM1
CALM2
KCNJ2



Arrhythmogenic cardiomyopathy

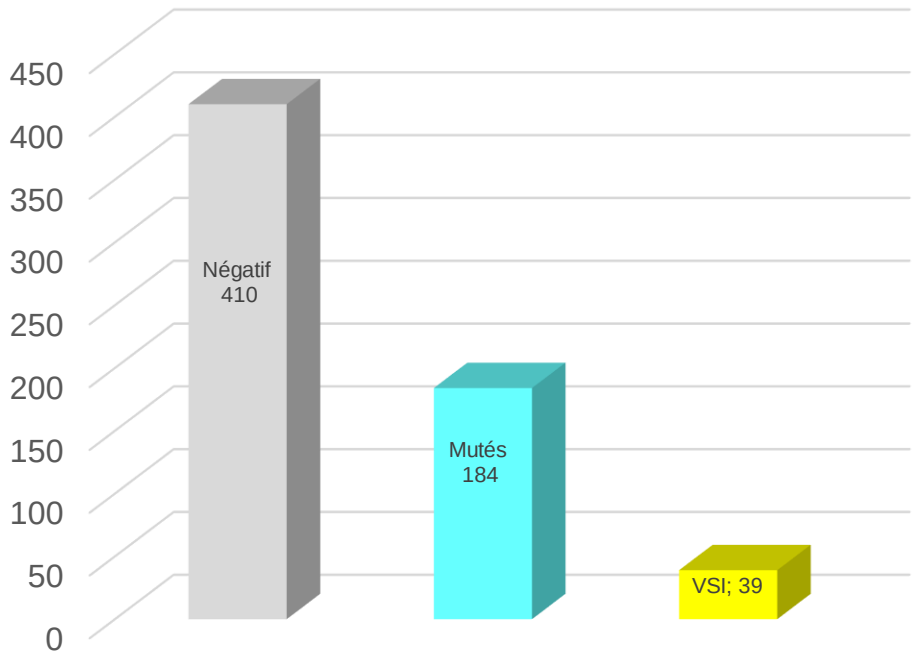
DSG2
DSC2
PKP2
PKG
DSP

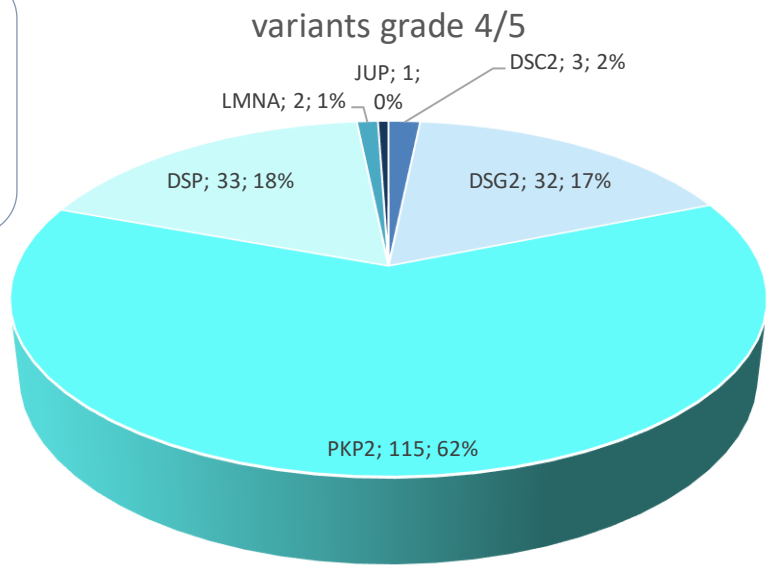


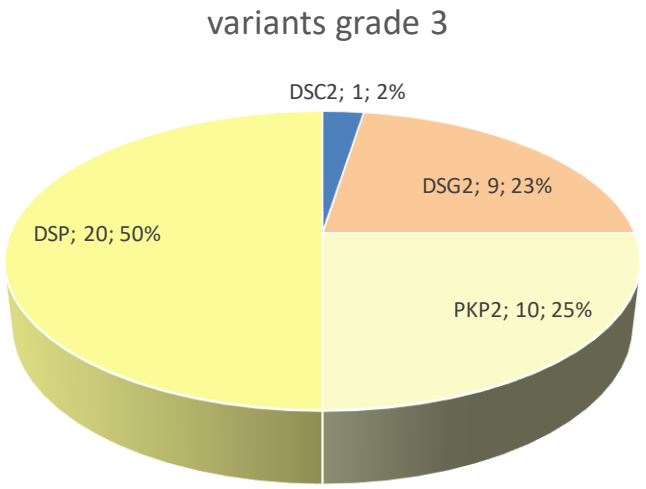
Arrhythmogenic cardiomyopathy

NGS Niveau1
PKP2/DSG//DSC2/DSP

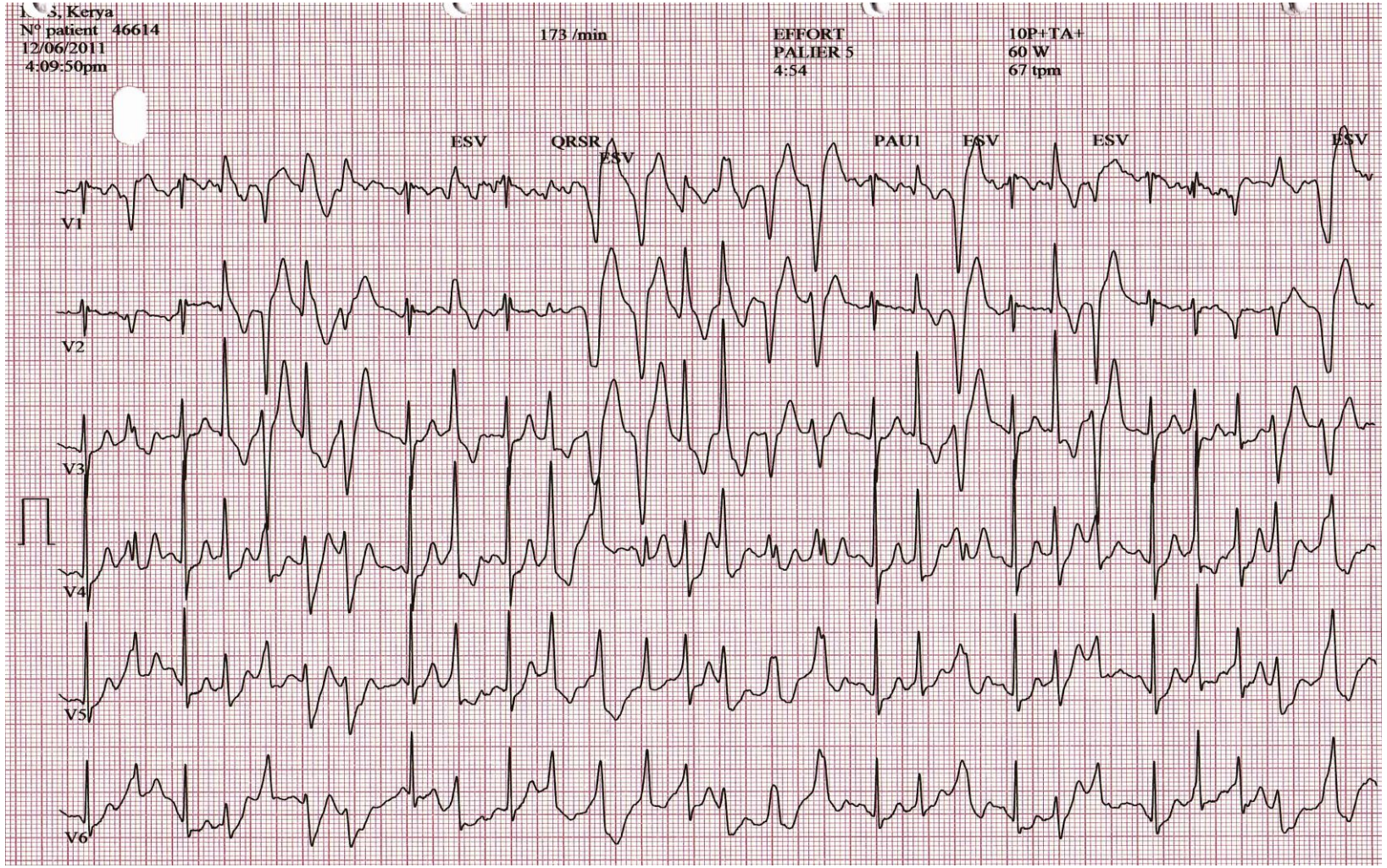
NGS Niveau2
RYR2
JUP
TMEM43 PLN
DES
TGFB3





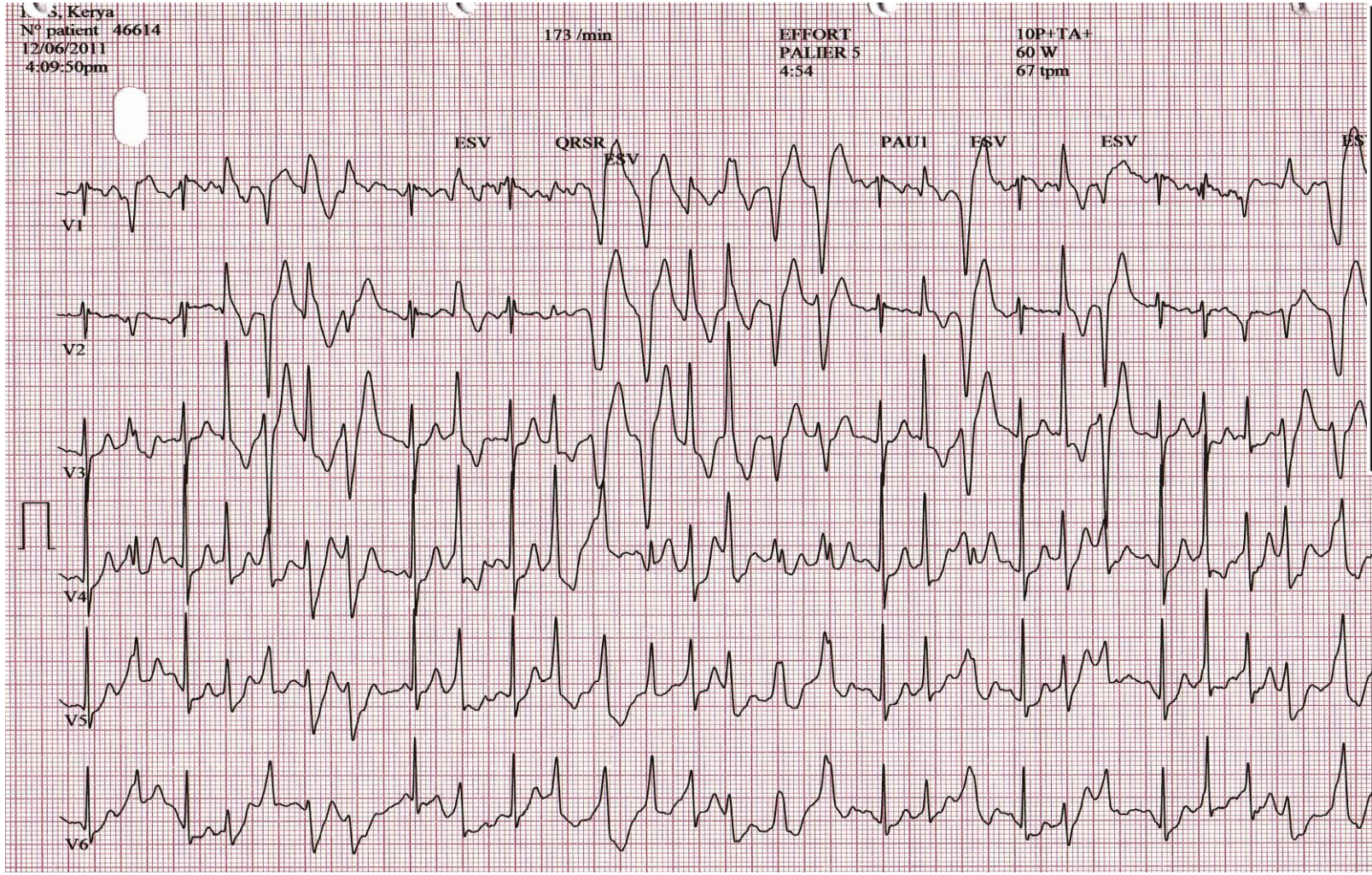


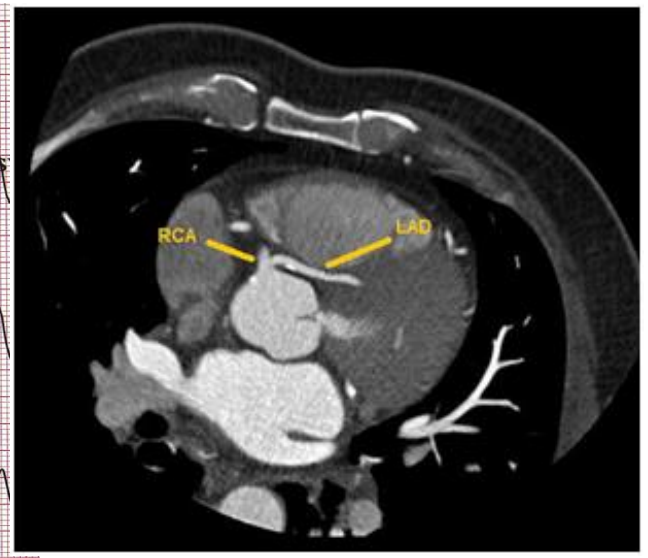
15 year old/ syncope



Anomalous origin of coronary arteries

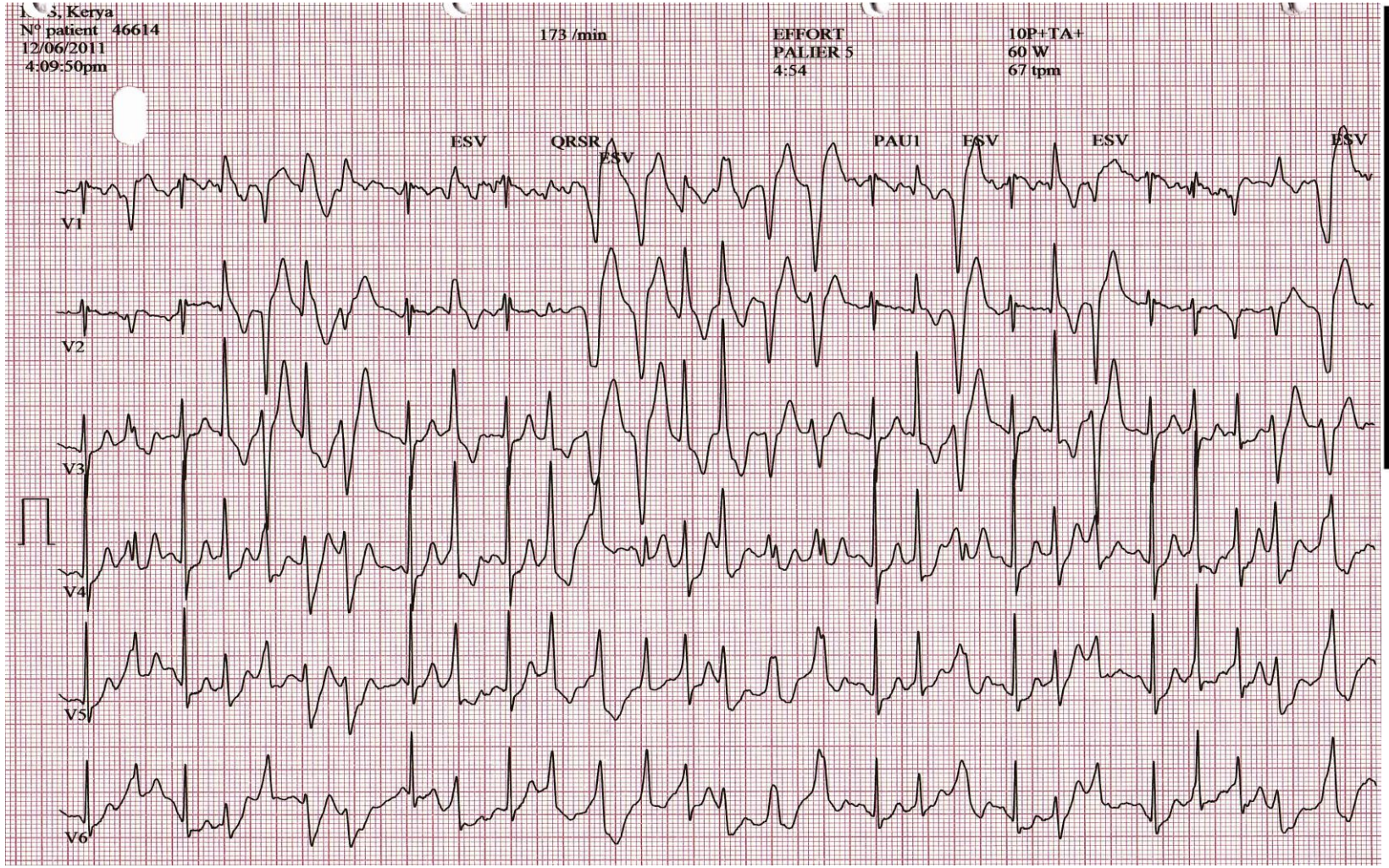
15 year old/ syncope

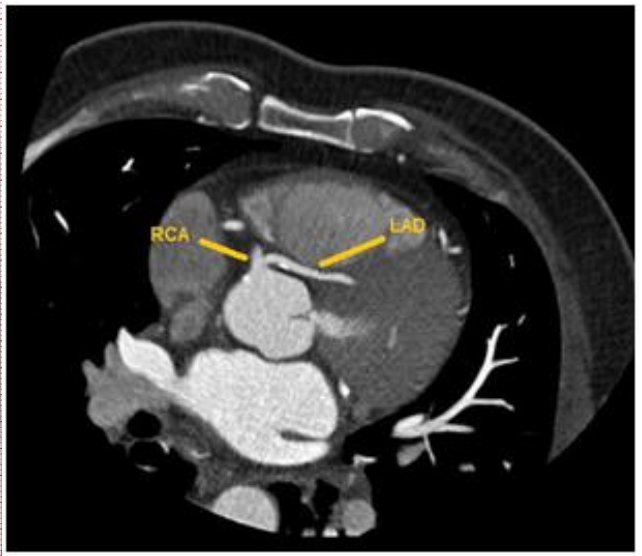


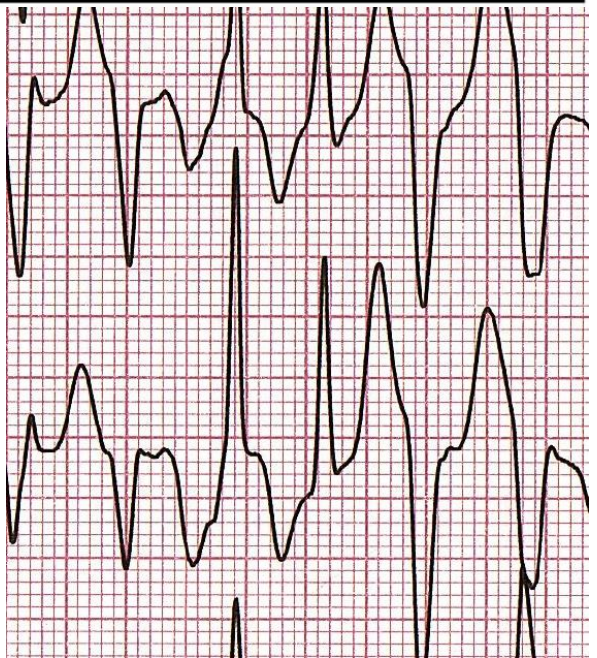


Anomalous origin of coronary arteries

15 year old/ syncope

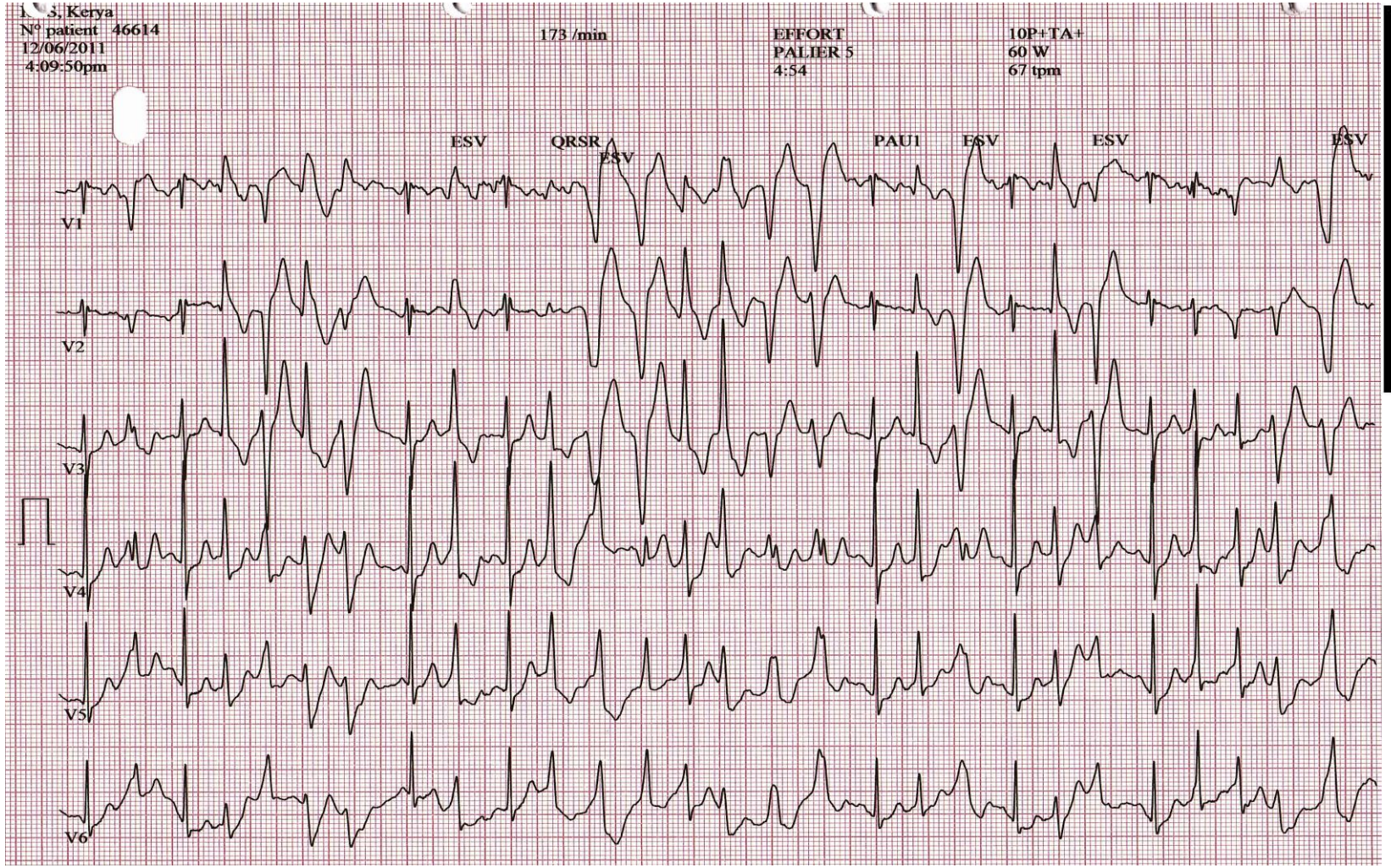


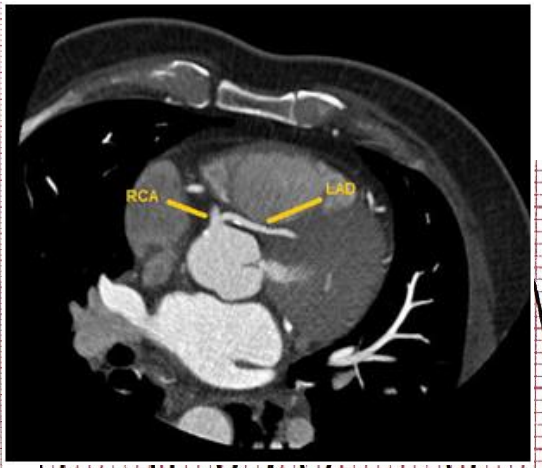


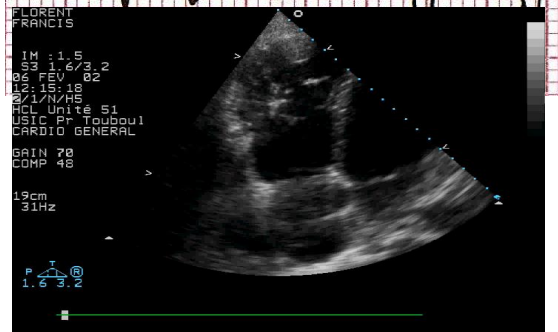


Anomalous origin of coronary arteries
RYR2 variant

15 year old/ syncope







Anomalous origin of coronary arteries
RYR2 variant
ARVD

Genetic testing :
So what ?

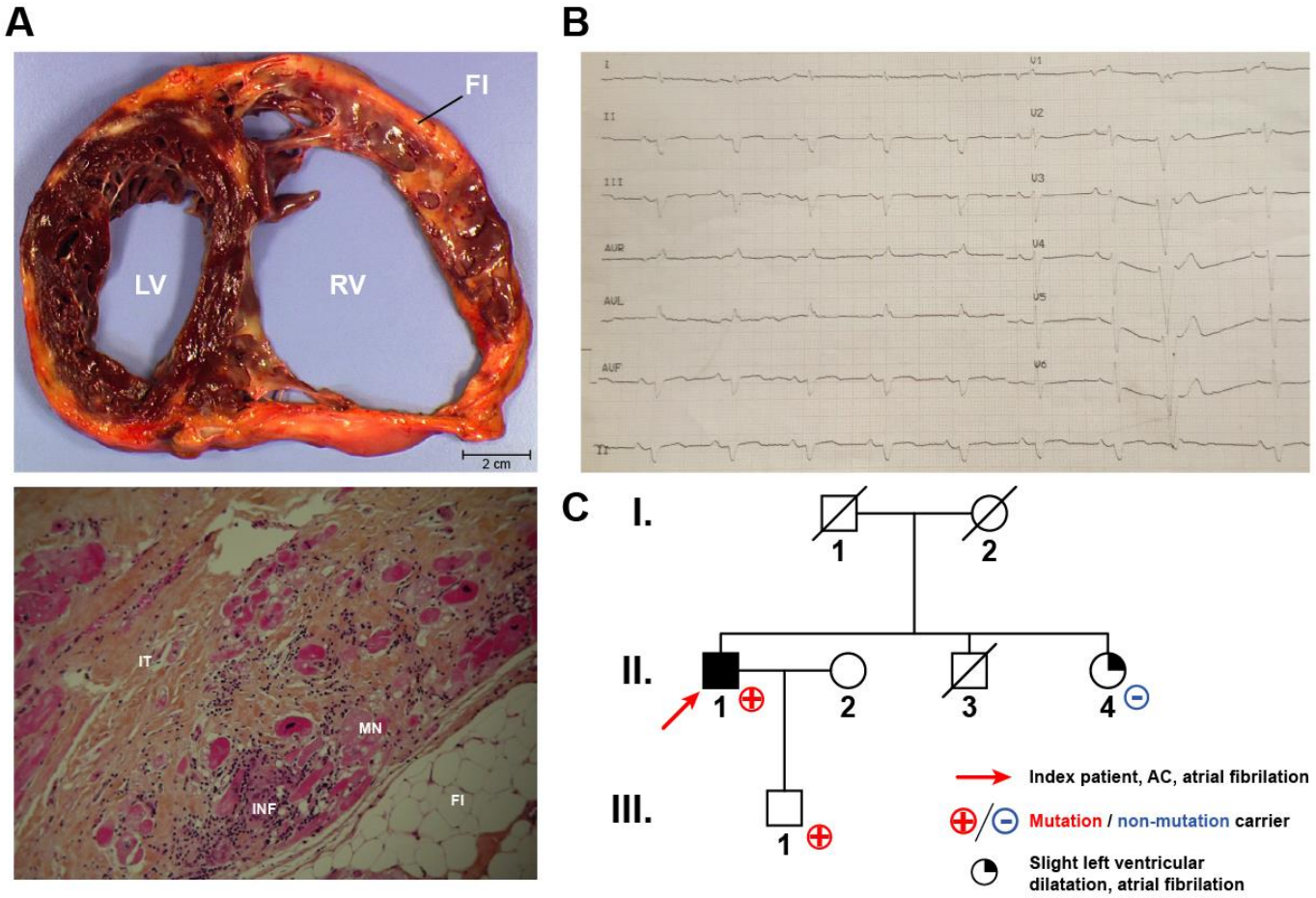
- Classification of the variant
- Patient information : Probabilistic diagnosis
- Cascade screening/testing/co-segregation/functionnal studies
- Gene guided follow-up/therapy

Variants classification
Class 1 to 5

- ✓**Benign**: does not cause disease
- ✓**Likely benign**: not expected to have a major effect on disease. Additional evidence is expected
- ✓**Uncertain significance**: no enough information to support a definitive classification.
- ✓**Likely pathogenic**: There is a high likelihood that it is disease-causing. *Additional evidence is expected.*
- ✓**Pathogenic**: Directly contributes to the disease. *Some variants may not be fully penetrant.*

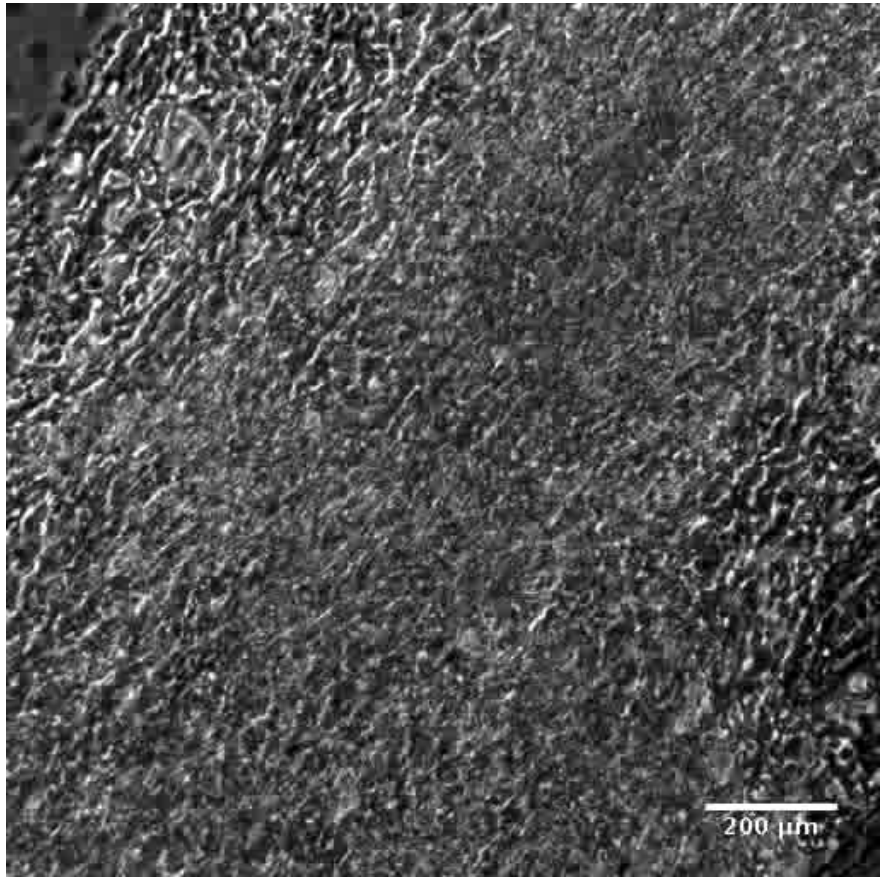
Arrhythmogenic cardiomyopathy

DSC2 classe 3?

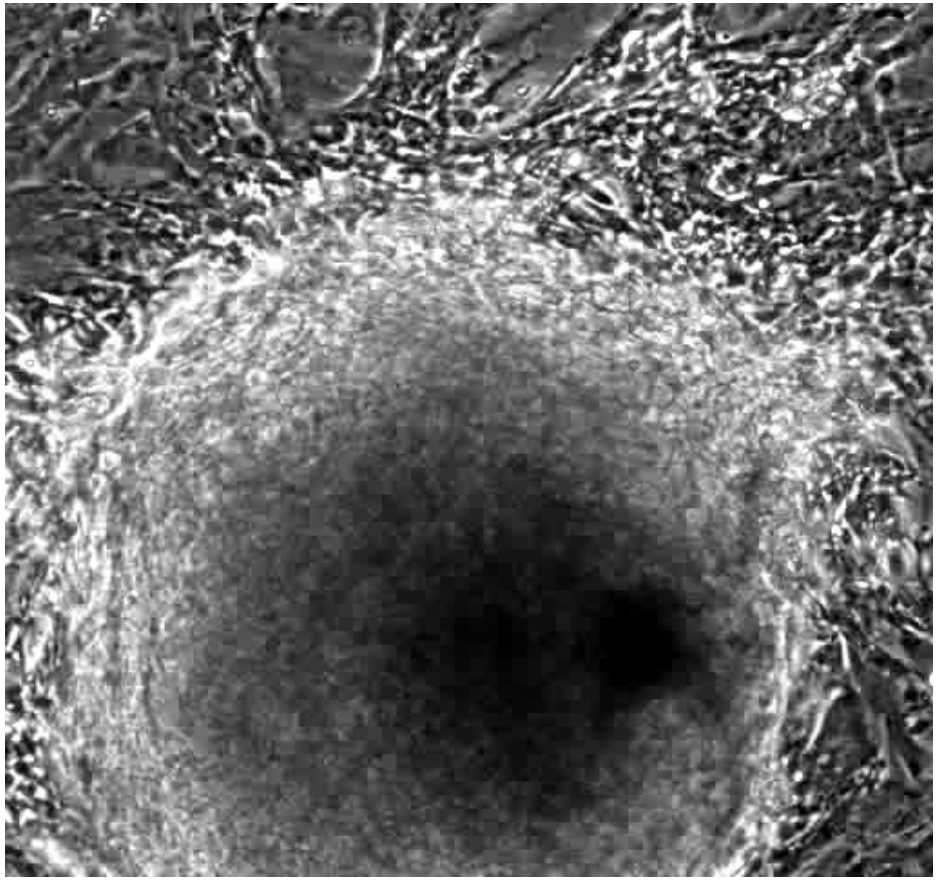


DSC2 Variant reclassified by in vitro investigation

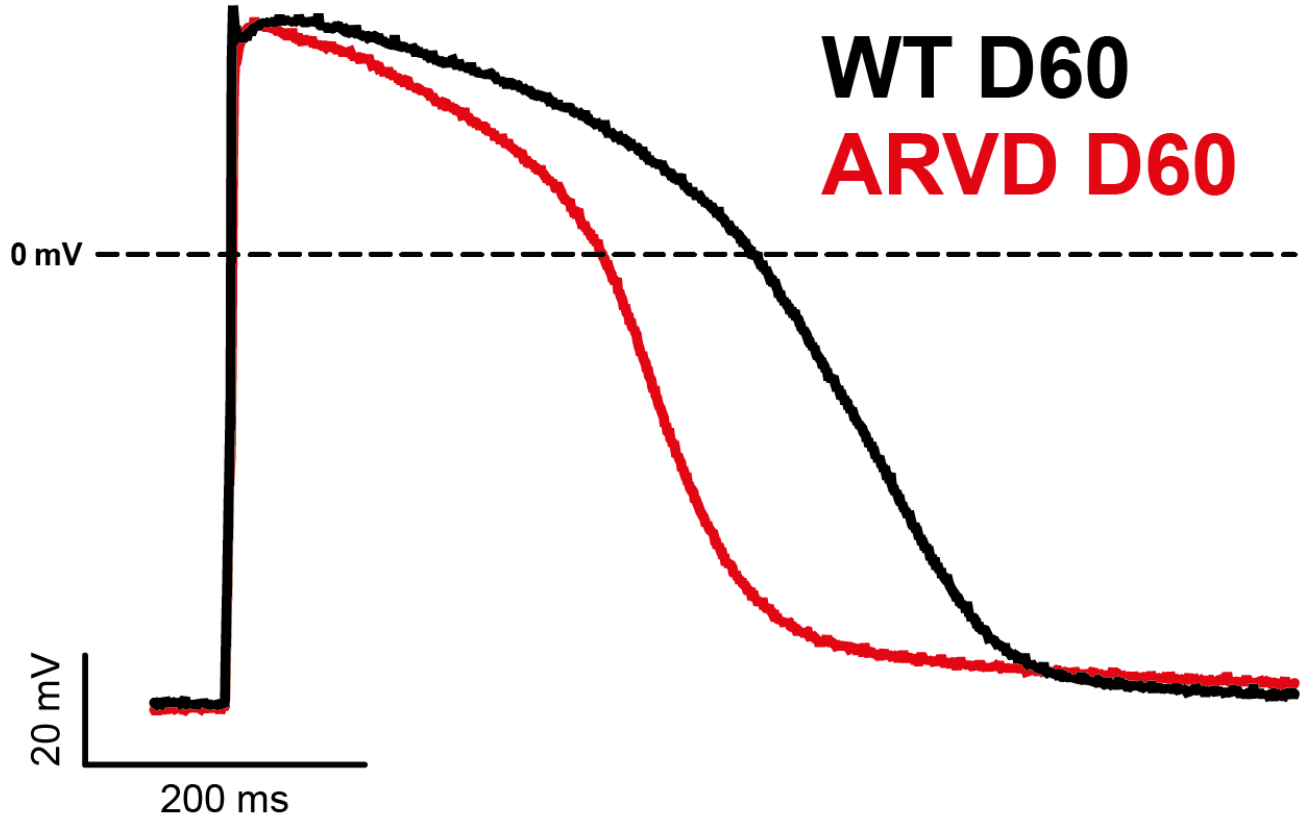
WT

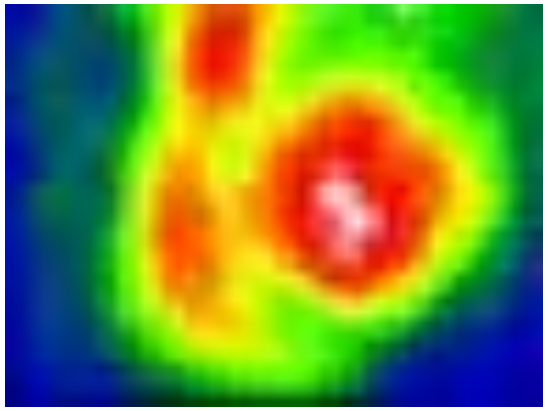


Mutated

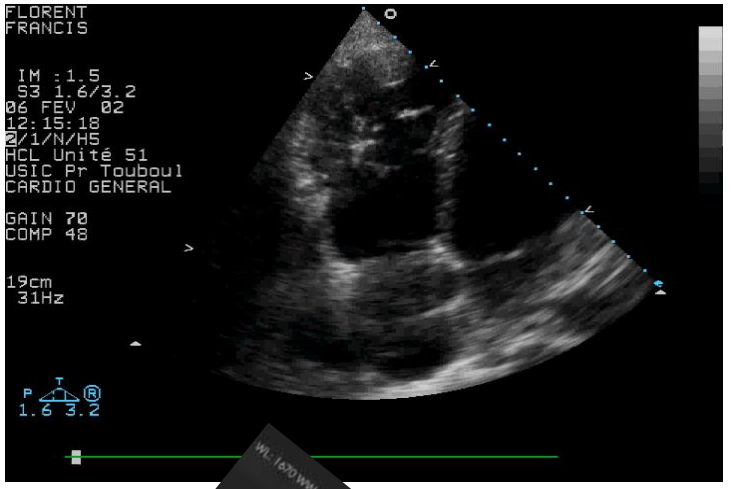


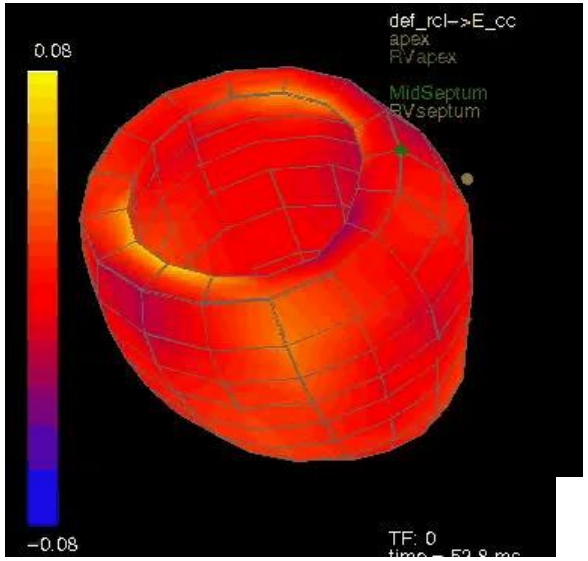
DSC2 : Electrical activity

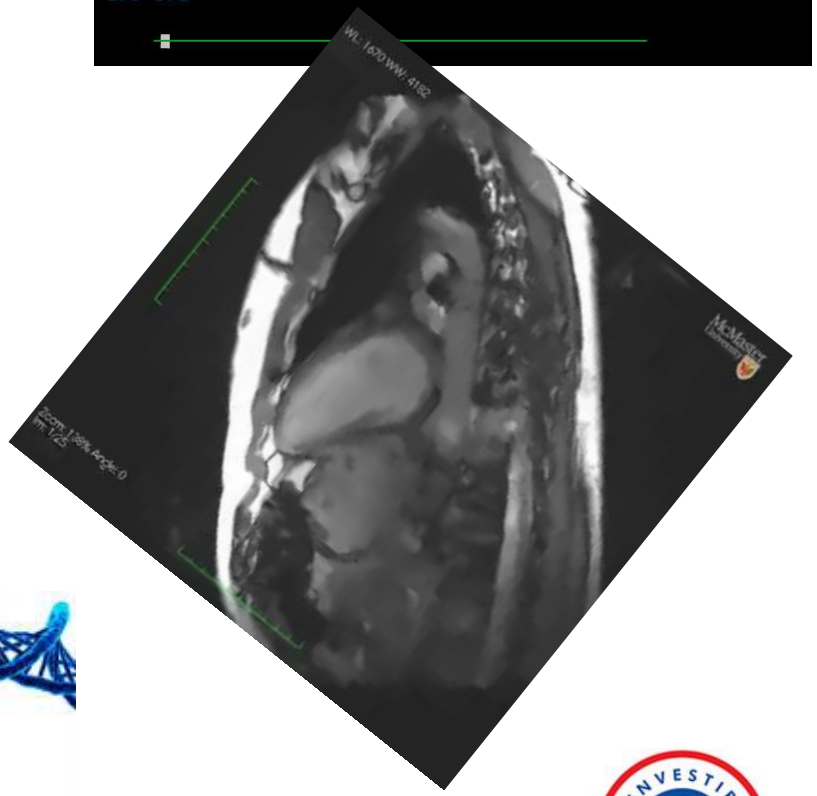




The future ?



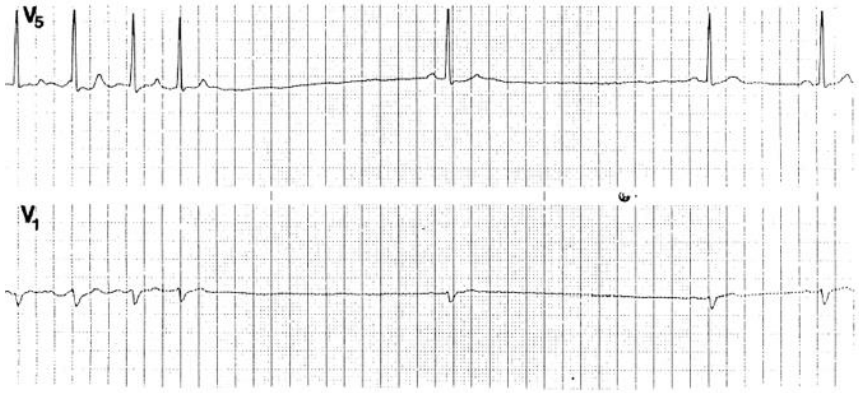


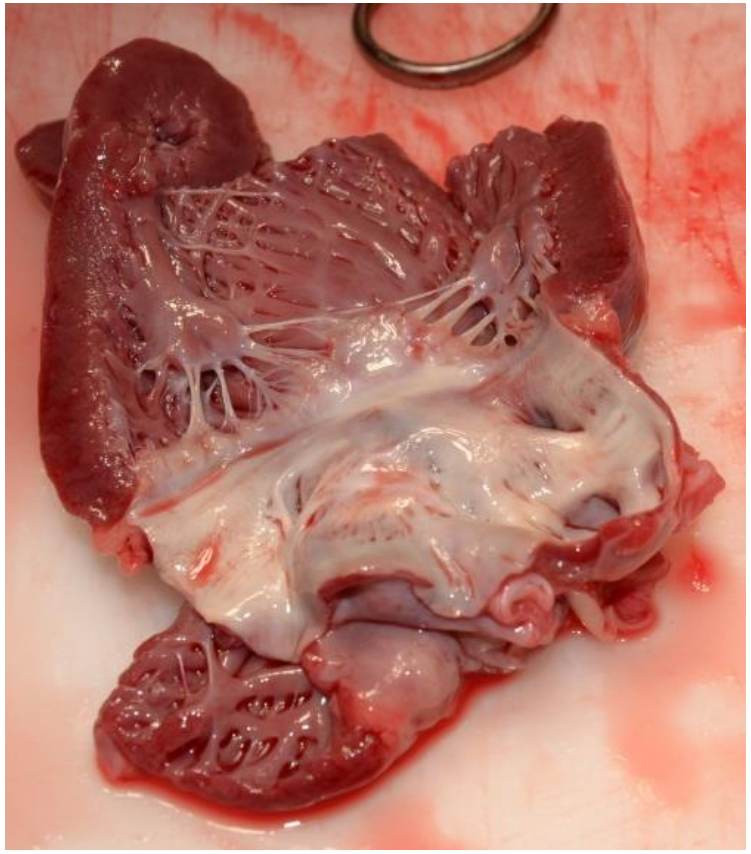


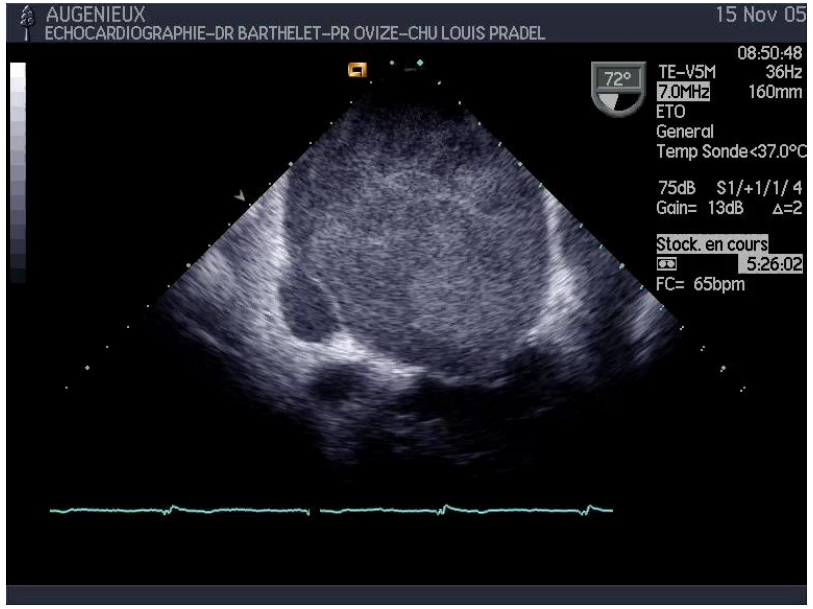
AGENCE NATIONALE DE LA RECHERCHE
ANR

INVESTIR L'AVENIR

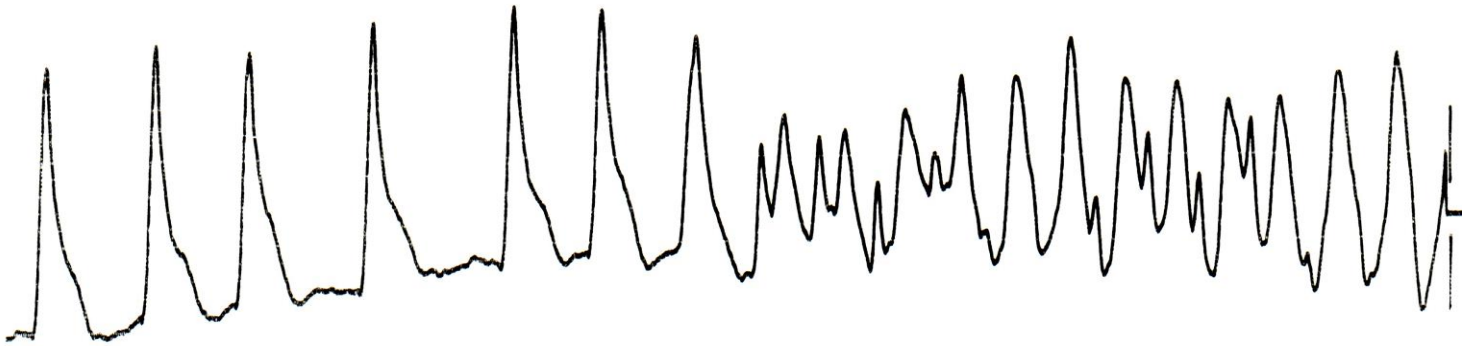
Atrial Myopathy

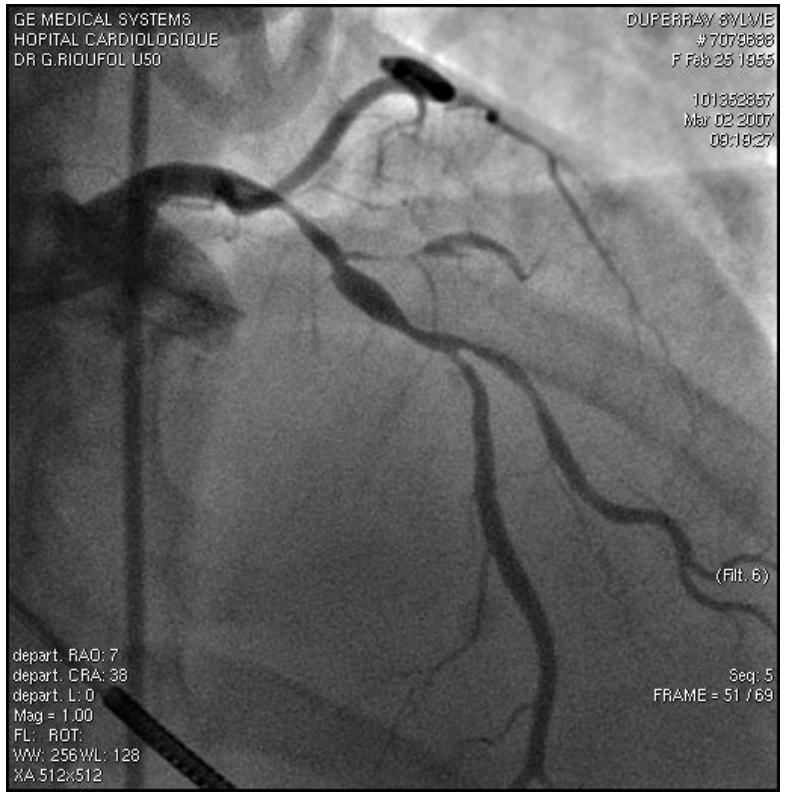






Etude MAP-IDM





Enquête génotypique

Genetic testing in arrhythmology :
What to do with the results?

- Classification of the variants *make sure that there is concordance with both the genotypic and phenotypic data*

- Cascade screening/testing

- Gene-or follow-up guided therapy

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