A propos de quelques cas…

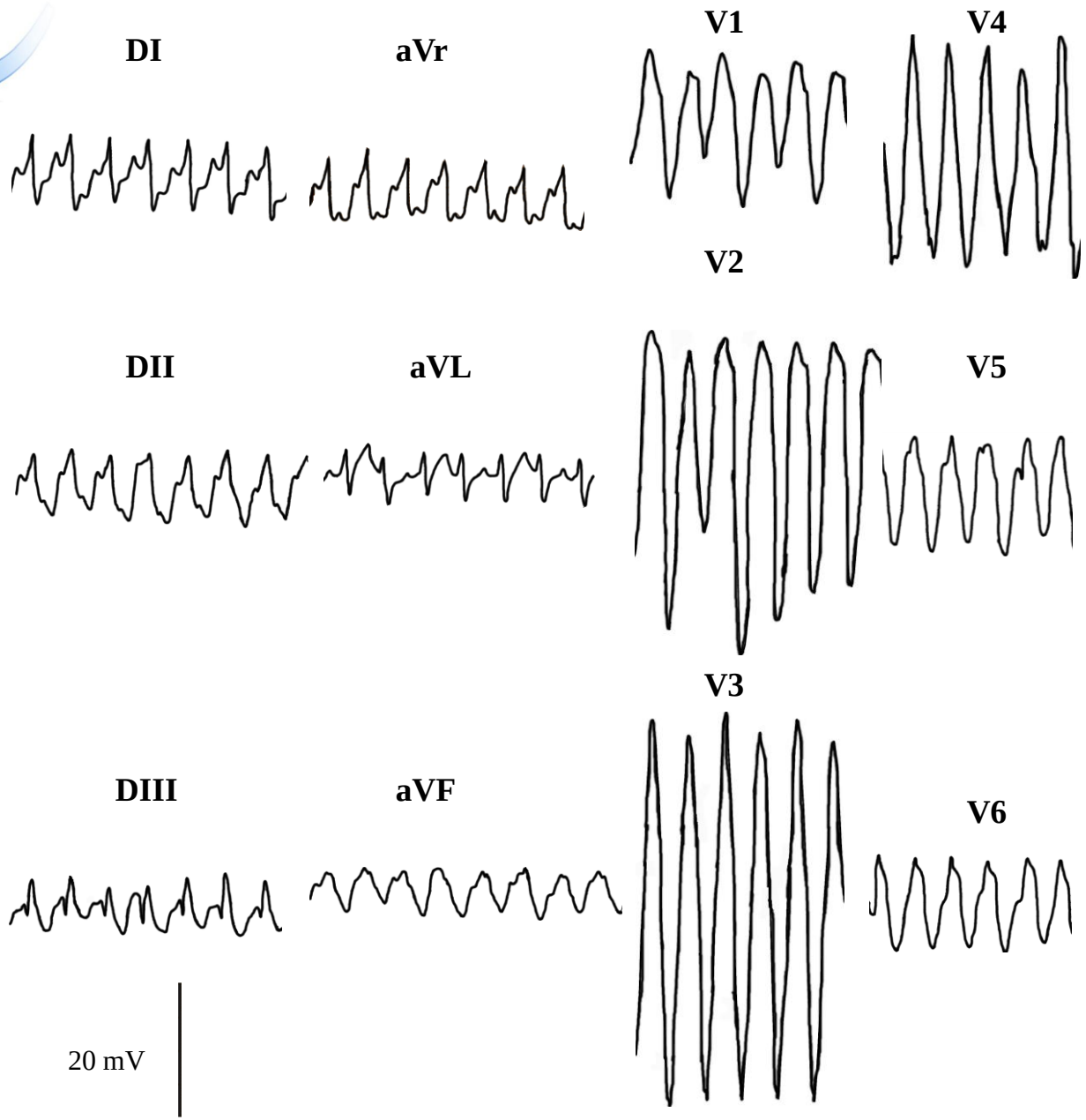
Vincent Probst,

Service de cardiologie et U915

L'institut du thorax, Nantes

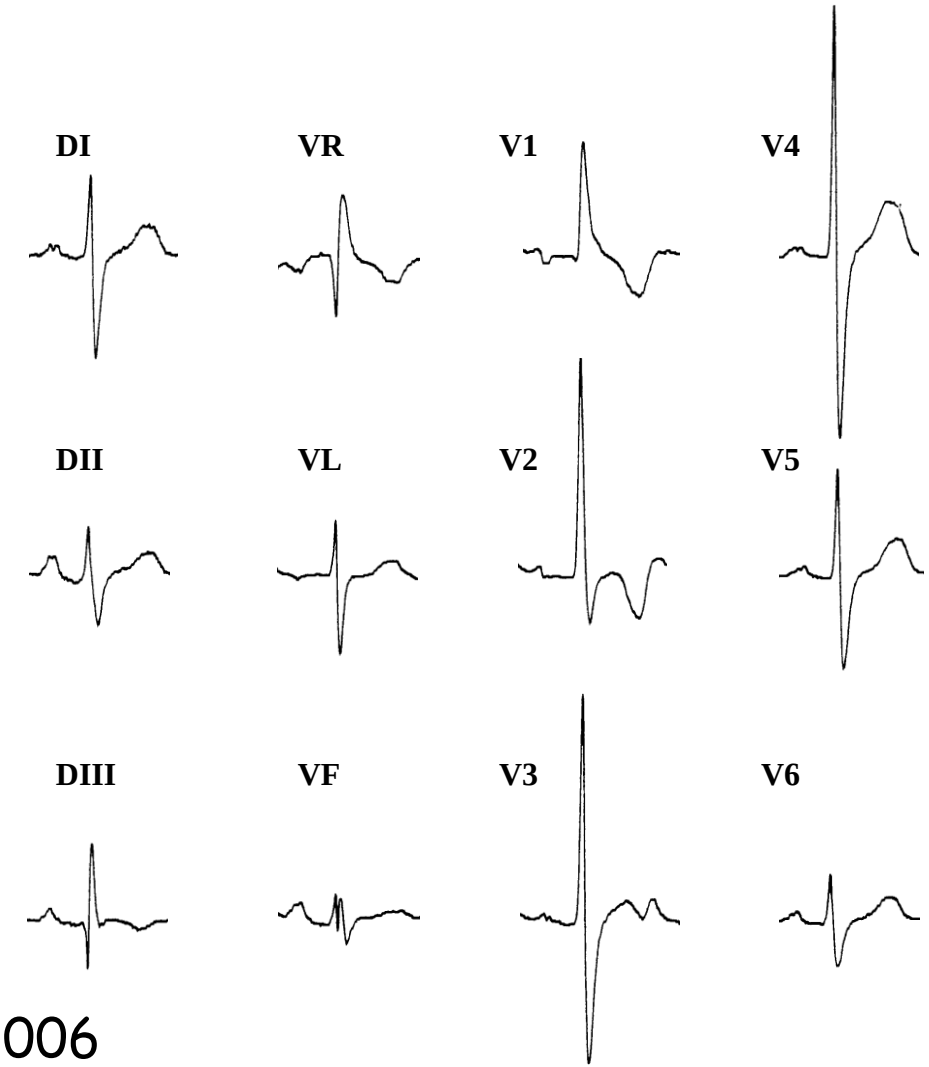
Cas clinique

- Romane enfant de 3 ans, 12kg, sans antécédent personnel ni familial
- Hospitalisée pour fièvre et vomissement
- TA 83/55, FC 240 bpm, tachypnée à 46/min



Probst, JCE 2006

ECG après réduction

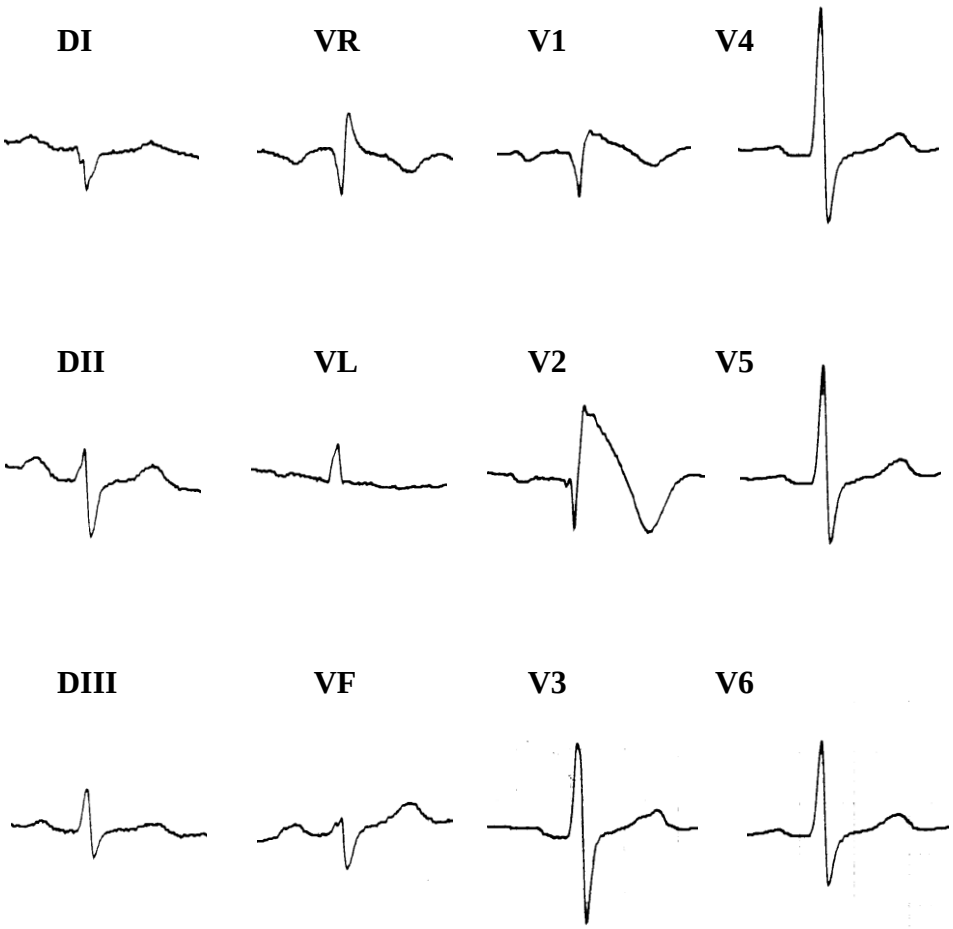


Probst, JCE 2006

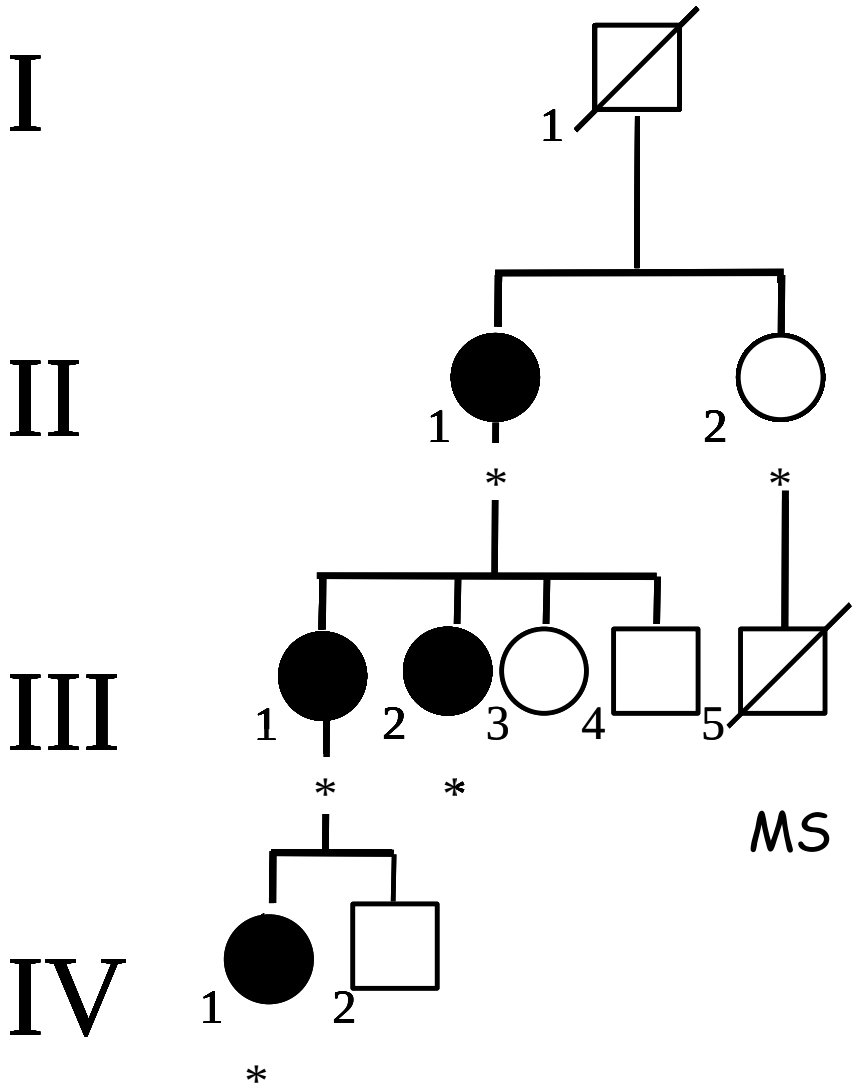
Que proposez-vous?

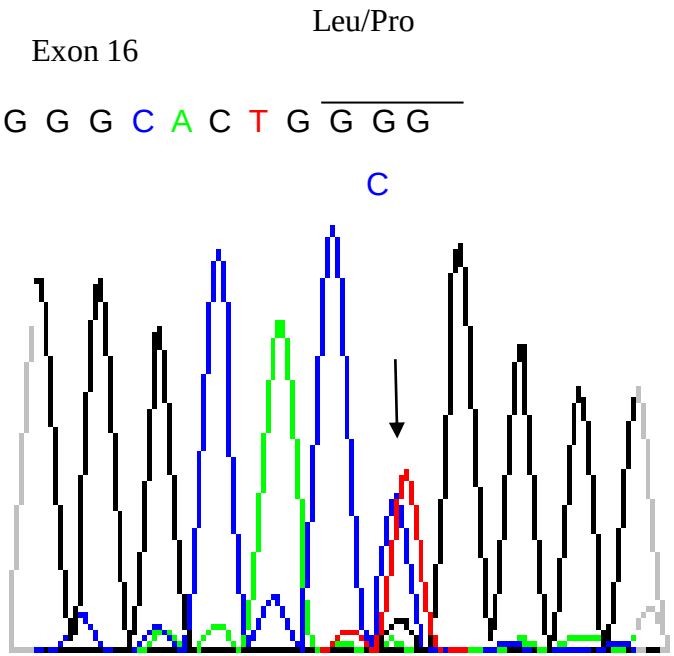
- IRM cardiaque?
- Épreuve d'effort?
- Echographie cardiaque?
- Test à l'ajmaline?
- Autre?

ECG de la maman



Enquête familiale





Quel traitement proposez-vous chez Romane?

- Abstention thérapeutique?
- Traitement médical?
- DAI?
- Ablation?

Suivi

- Enfant est traitée par hydroquinidine depuis 3 ans (150 mg deux fois par jour)
- Hospitalisée à de nombreuses reprises pour fièvre
- Pas de récidive de malaise

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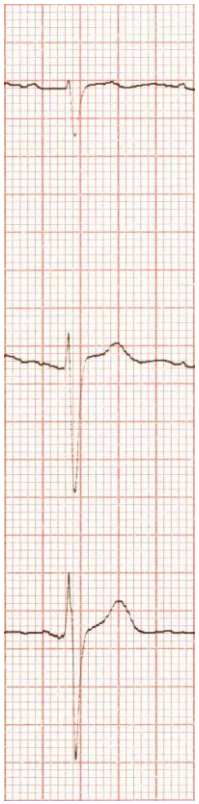
ECG de la tante

Basal

V1

V2

V3

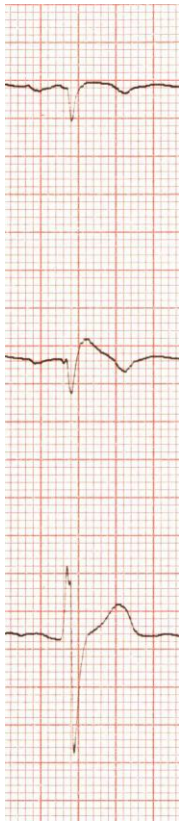


Ajmaline

V1

V2

V3



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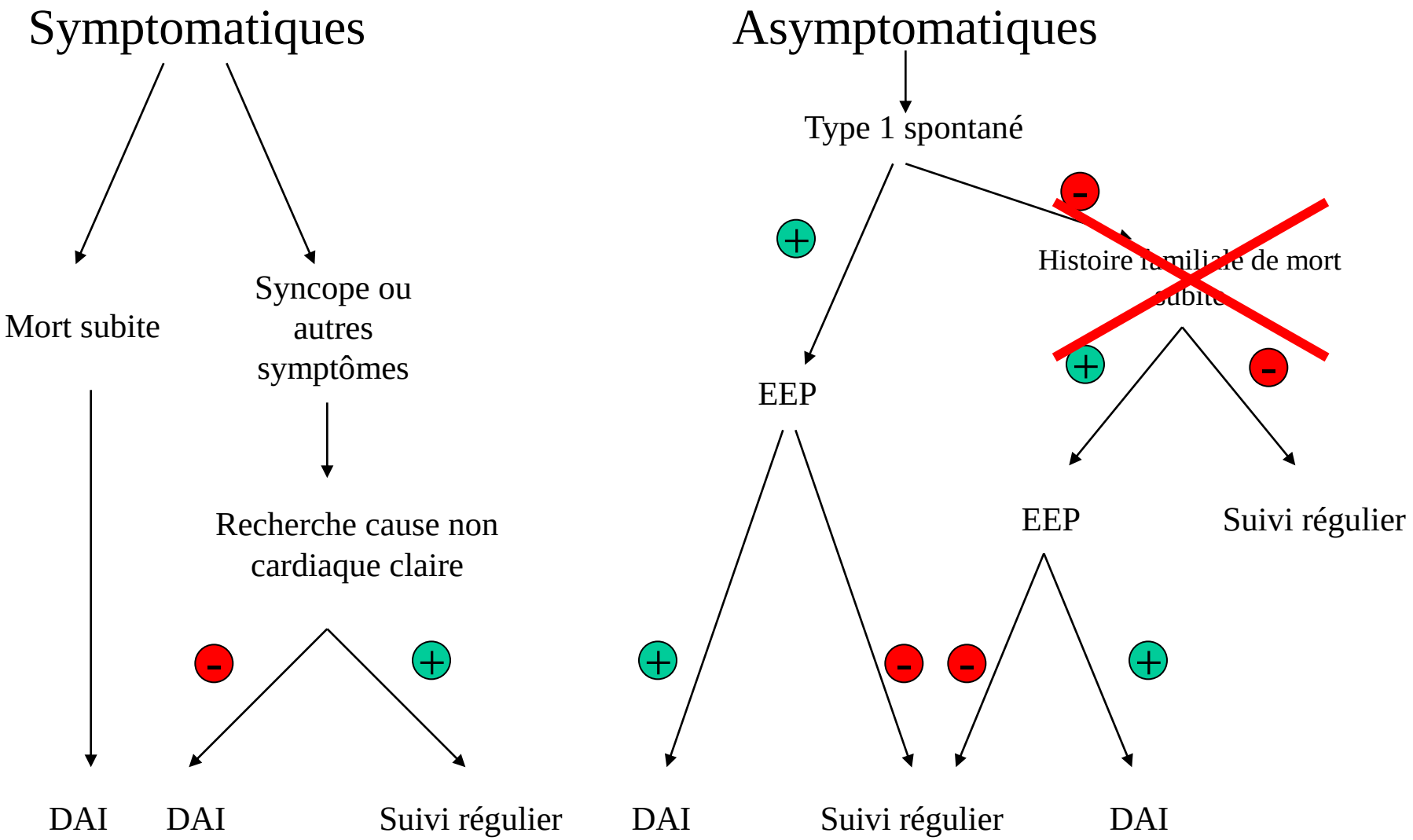
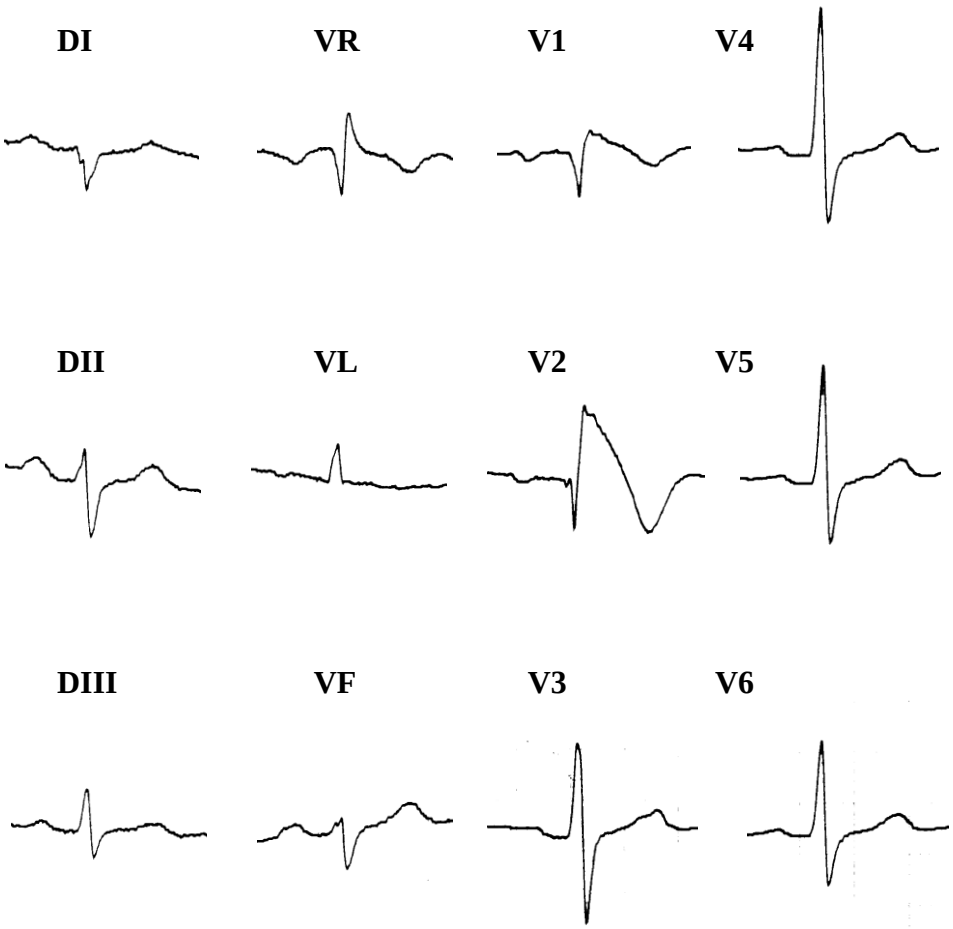
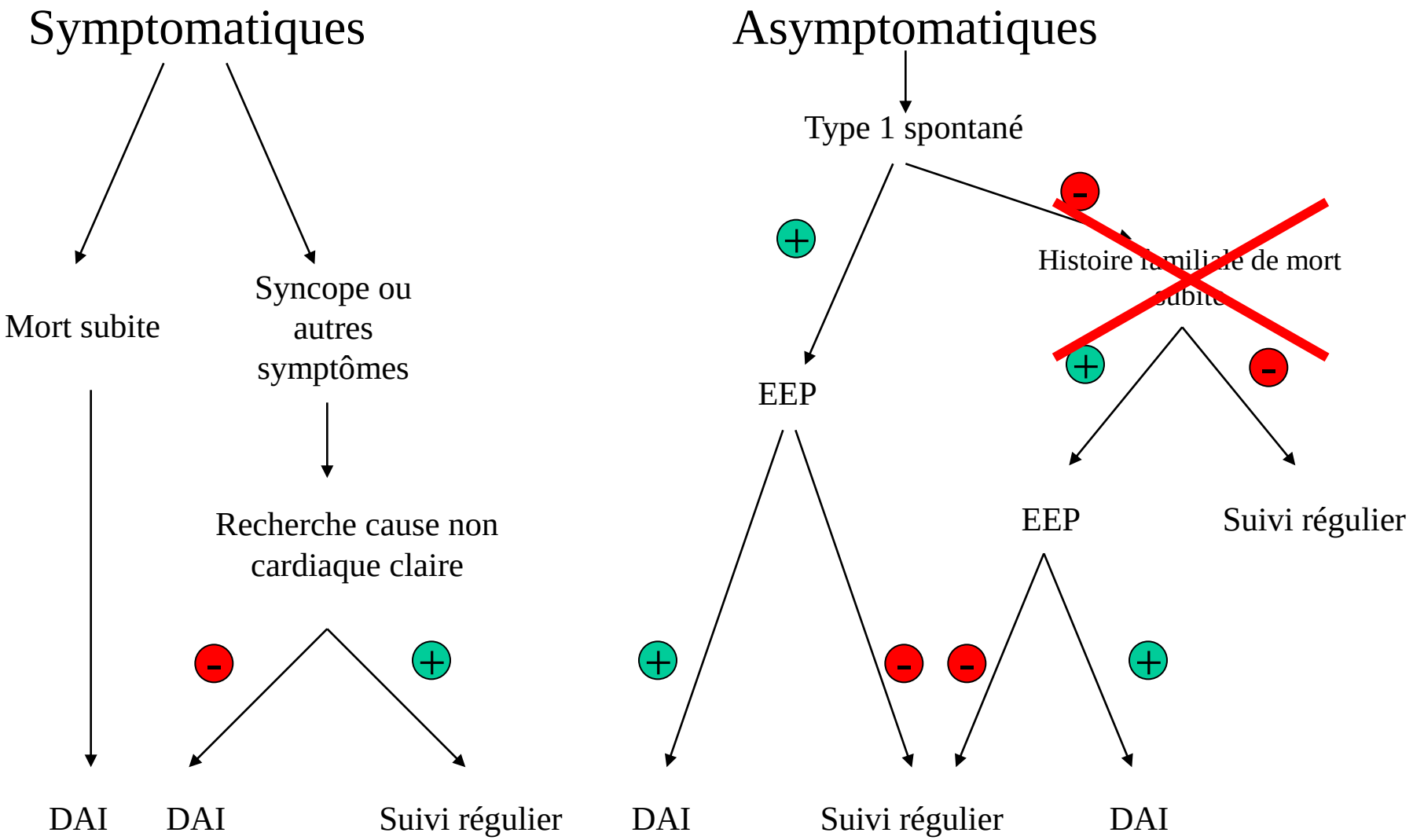


Circulation 2005

ECG de la maman





Circulation 2005

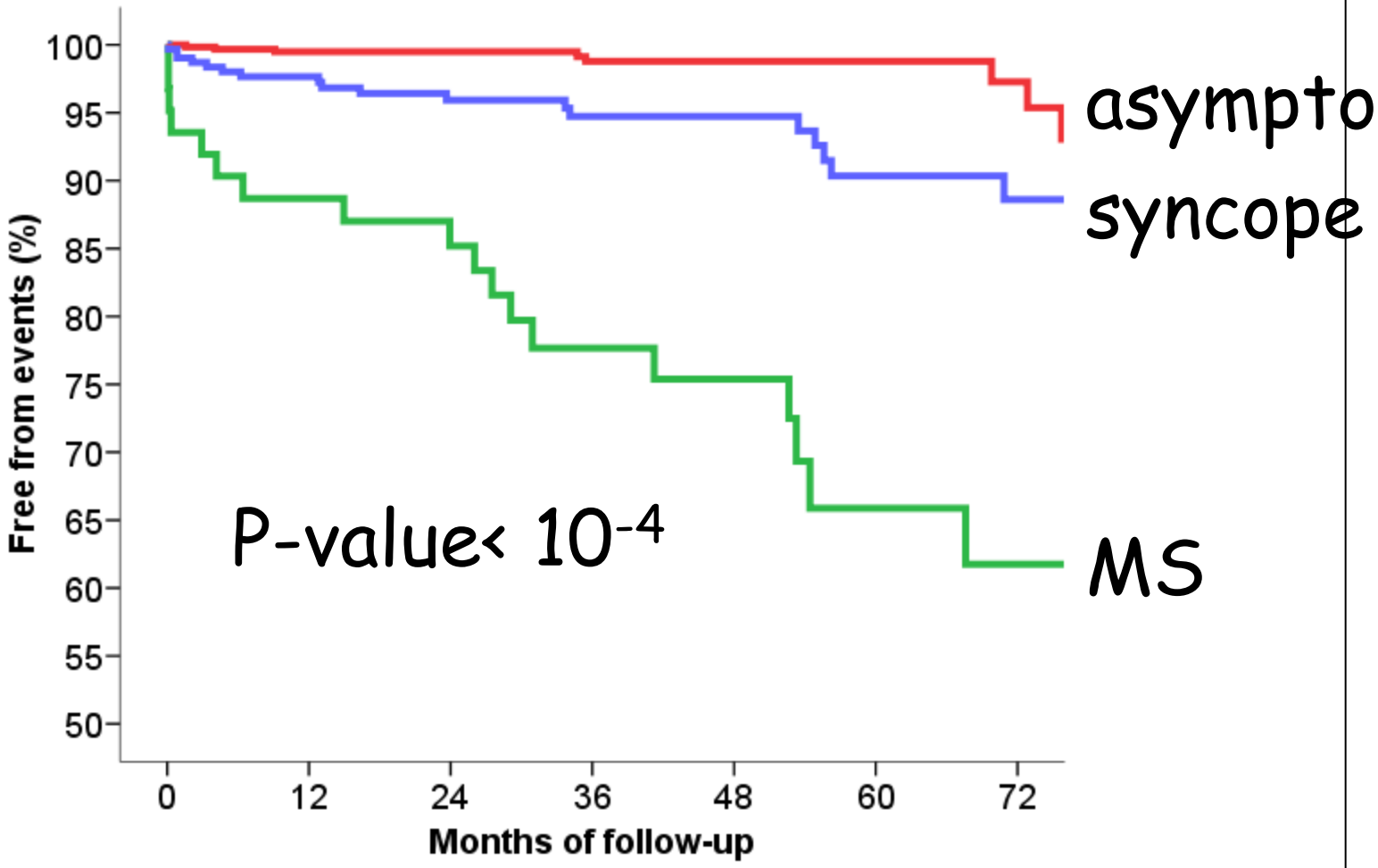
FINGER Registry
1029 patients

Gender	
male	745 (72%)
Female	284 (28%)
Type of symptoms	
scd	62 (6%)
syncope	313 (30%)
asymptomatic	654 (64%)
Spontaneous type 1	
no	561 (55%)
yes	468 (45%)
EPS	
no	391 (38%)
yes	638 (62%)

Probst V, Circulation 2009

Follow-up

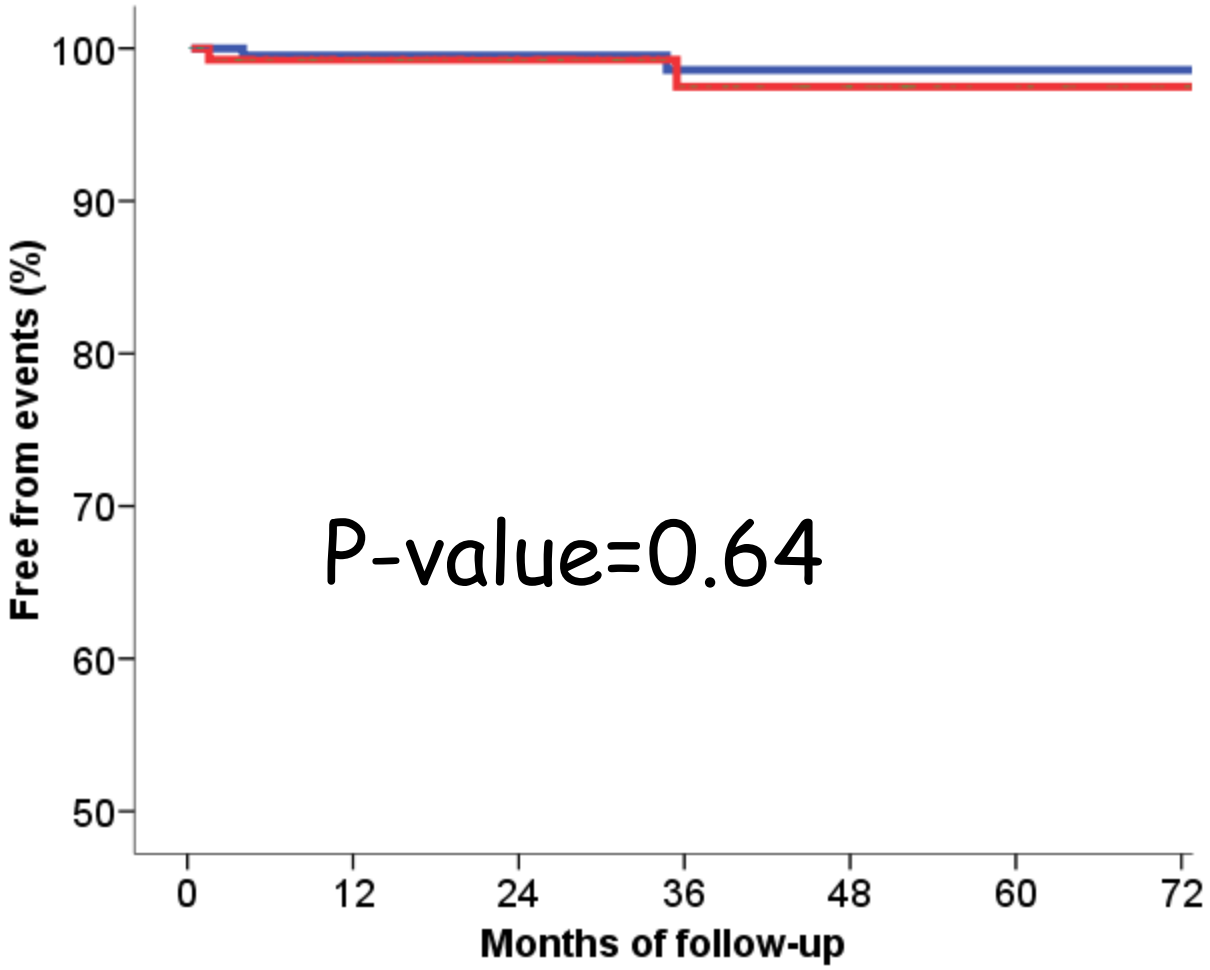
Follow-up=37+/-31 months



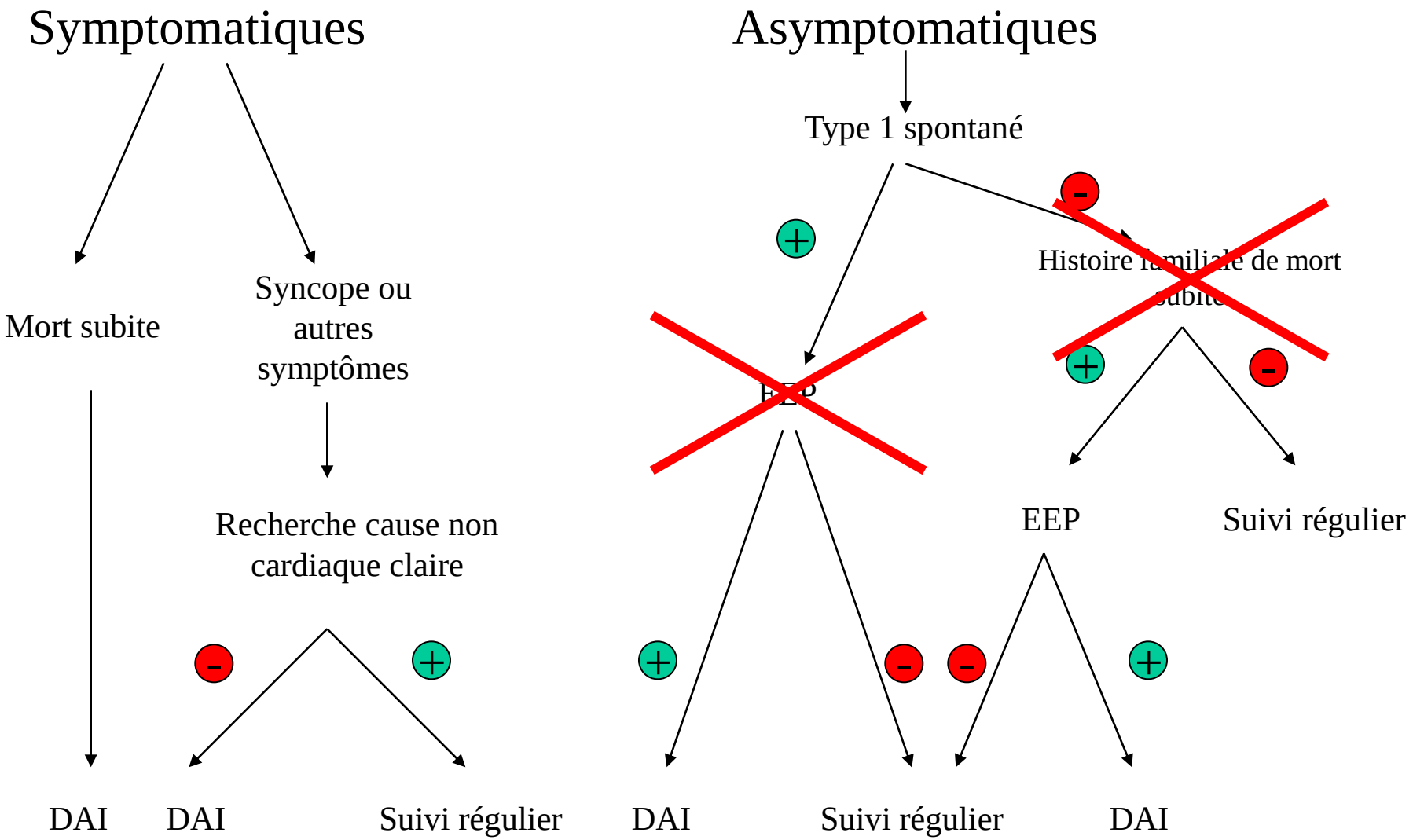
Probst V, Circulation 2009

EPS in asymptomatic patients

n=369

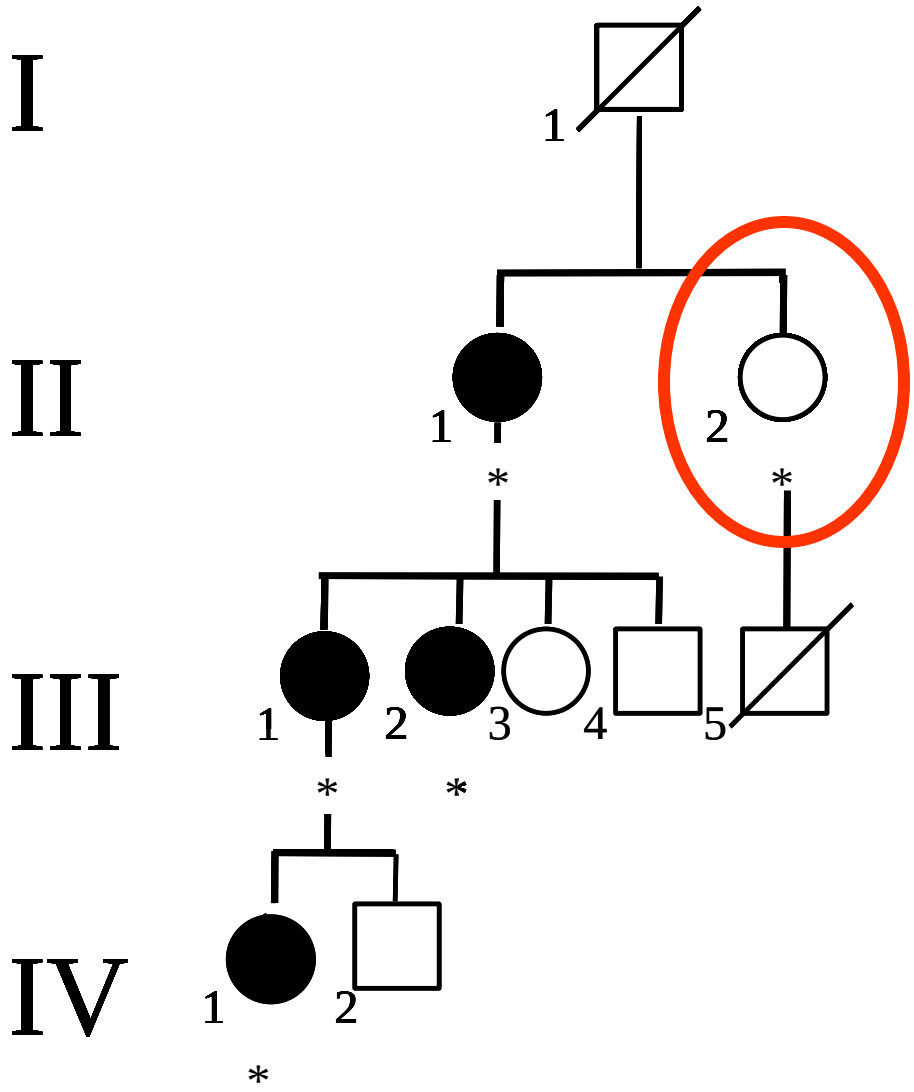


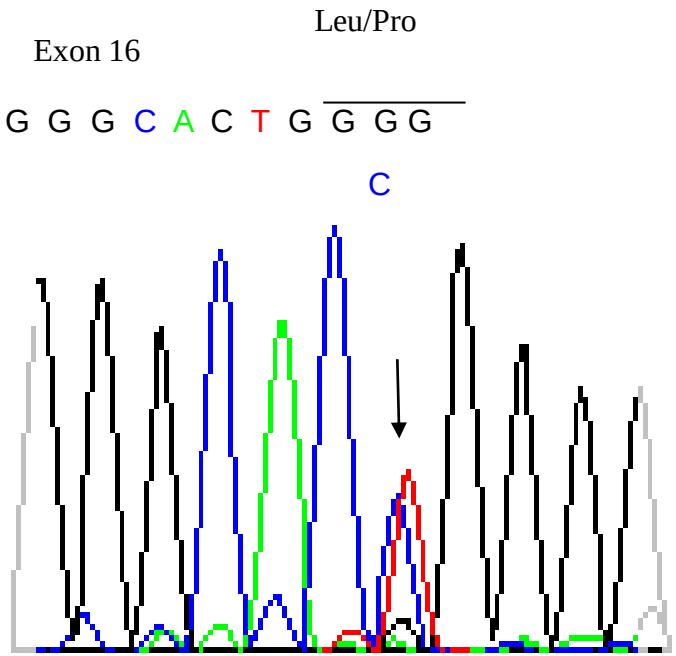
Probst V, Circulation 2009

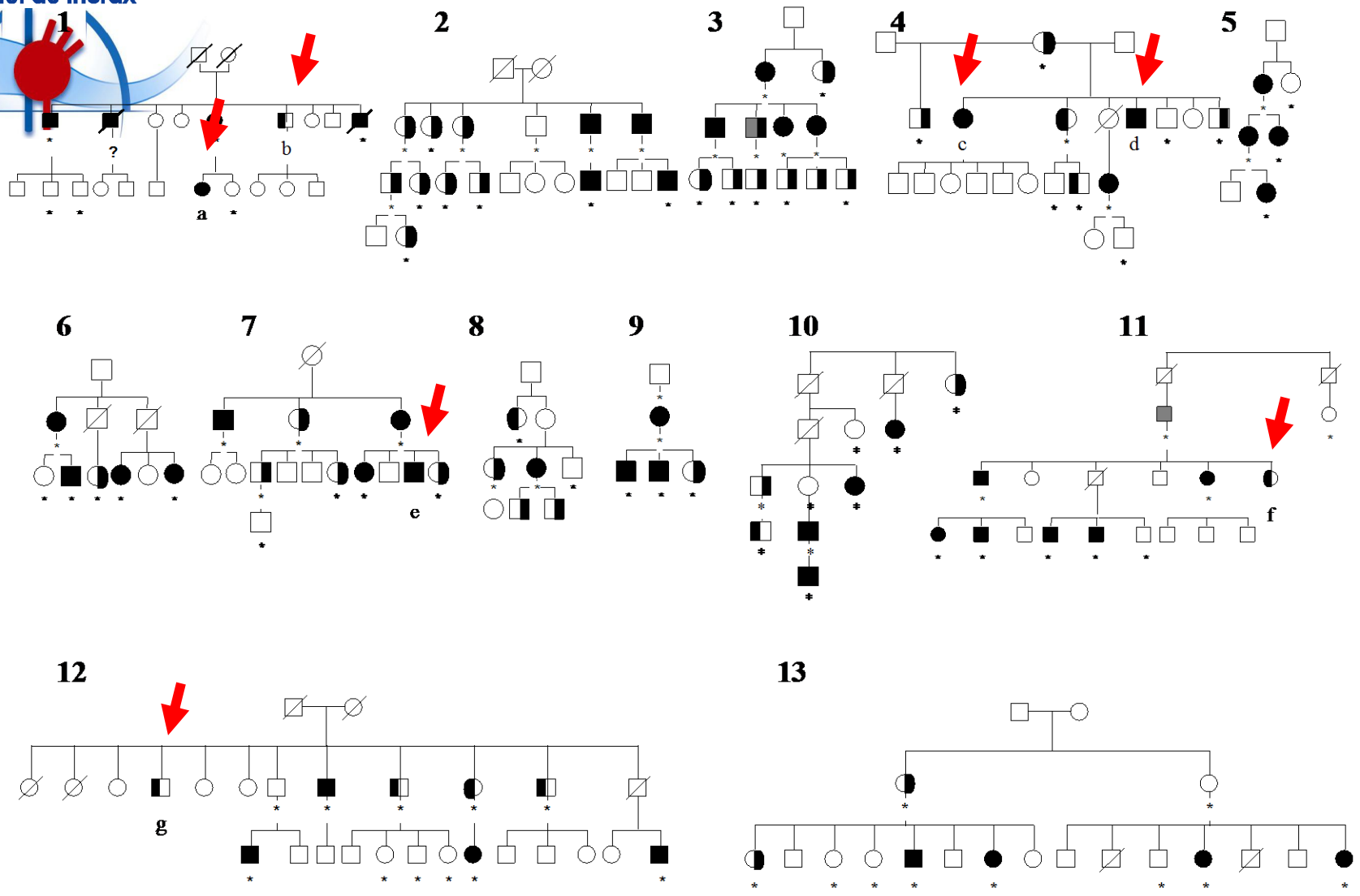


Circulation 2005

Enquête familiale







Probst V,
Circulation Genet 2009

Pénétrance troubles conduction:88%
Pénétrance BrS avant ajmaline: 18%
Pénétrance BrS après ajmaline: 48%

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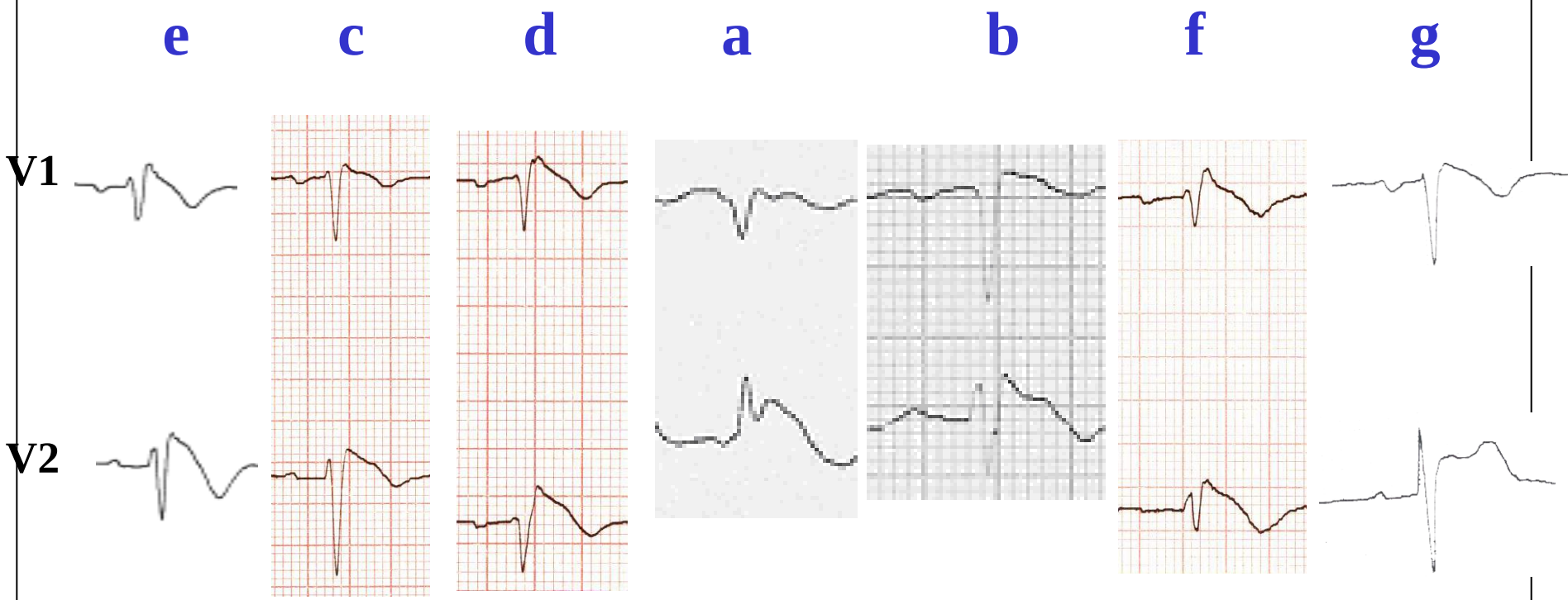
ECG des patients non mutés



Probst V,
Circulation Genet 2009

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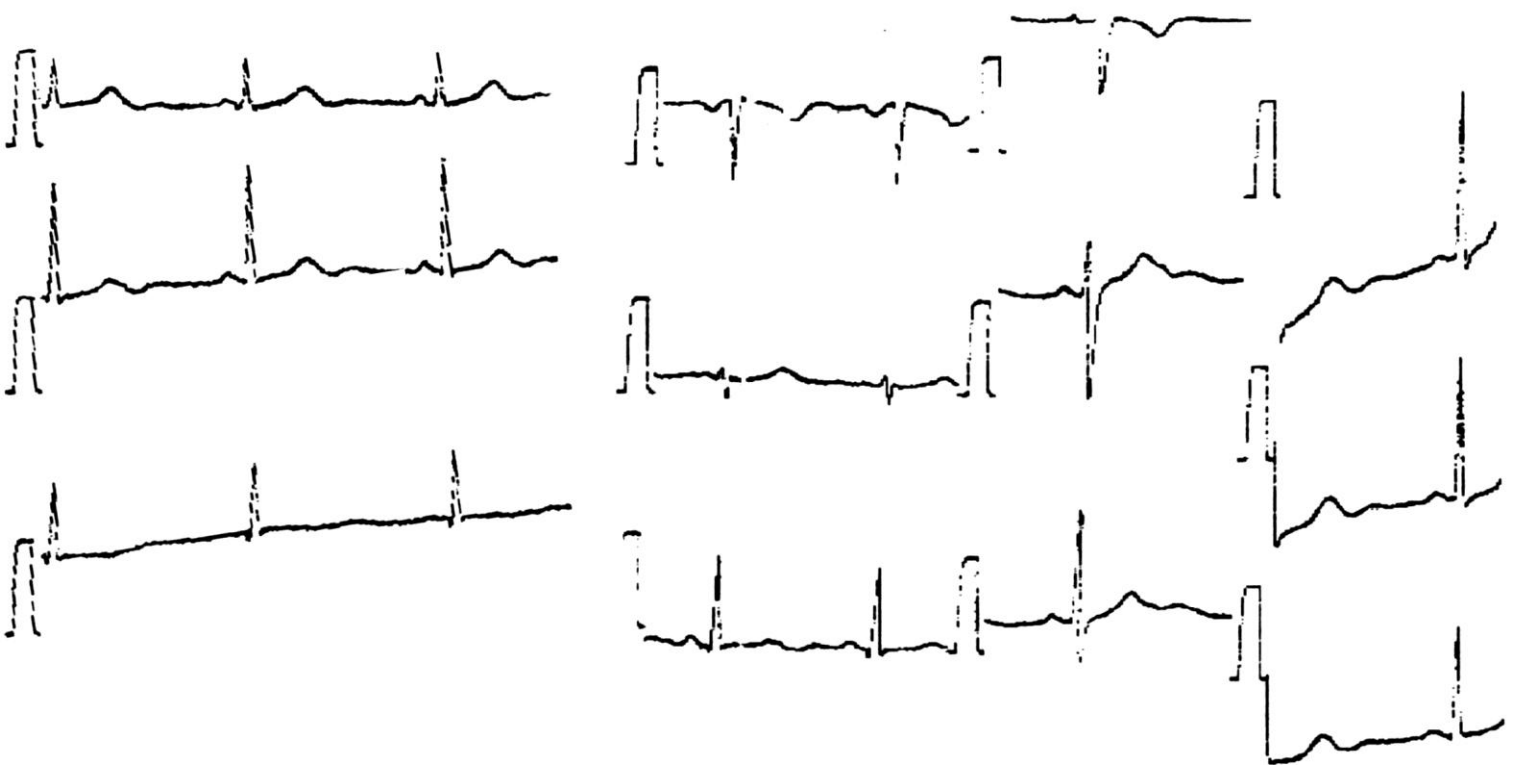
Cas numéro 2

- Une jeune fille de 15 ans qui se plaignait de malaises d'allures vagaux survenant préférentiellement pendant des épisodes de stress
- Pas d'autres ATCD
- Échographie cardiaque normale
- ECG

ECG



- Quelques semaines plus tard, elle est hospitalisée pour arrêt cardiaque sur fibrillation ventriculaire.
- Elle décède quelques heures plus tard

Enquête familiale

- La sœur du propositus âgée de 11 ans
  - Convulsions au stress
  - Echographie normale

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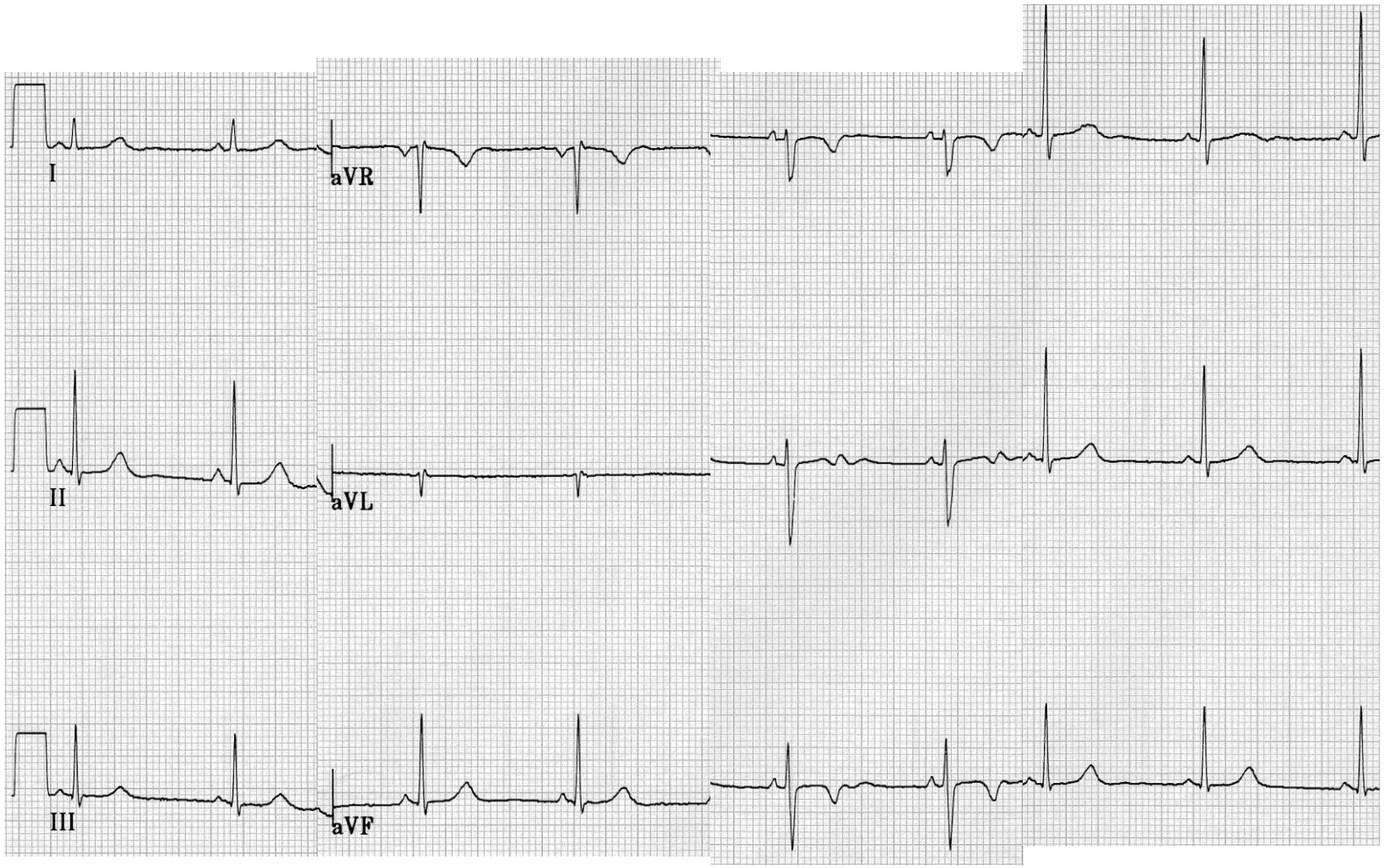
ECG de la sœur



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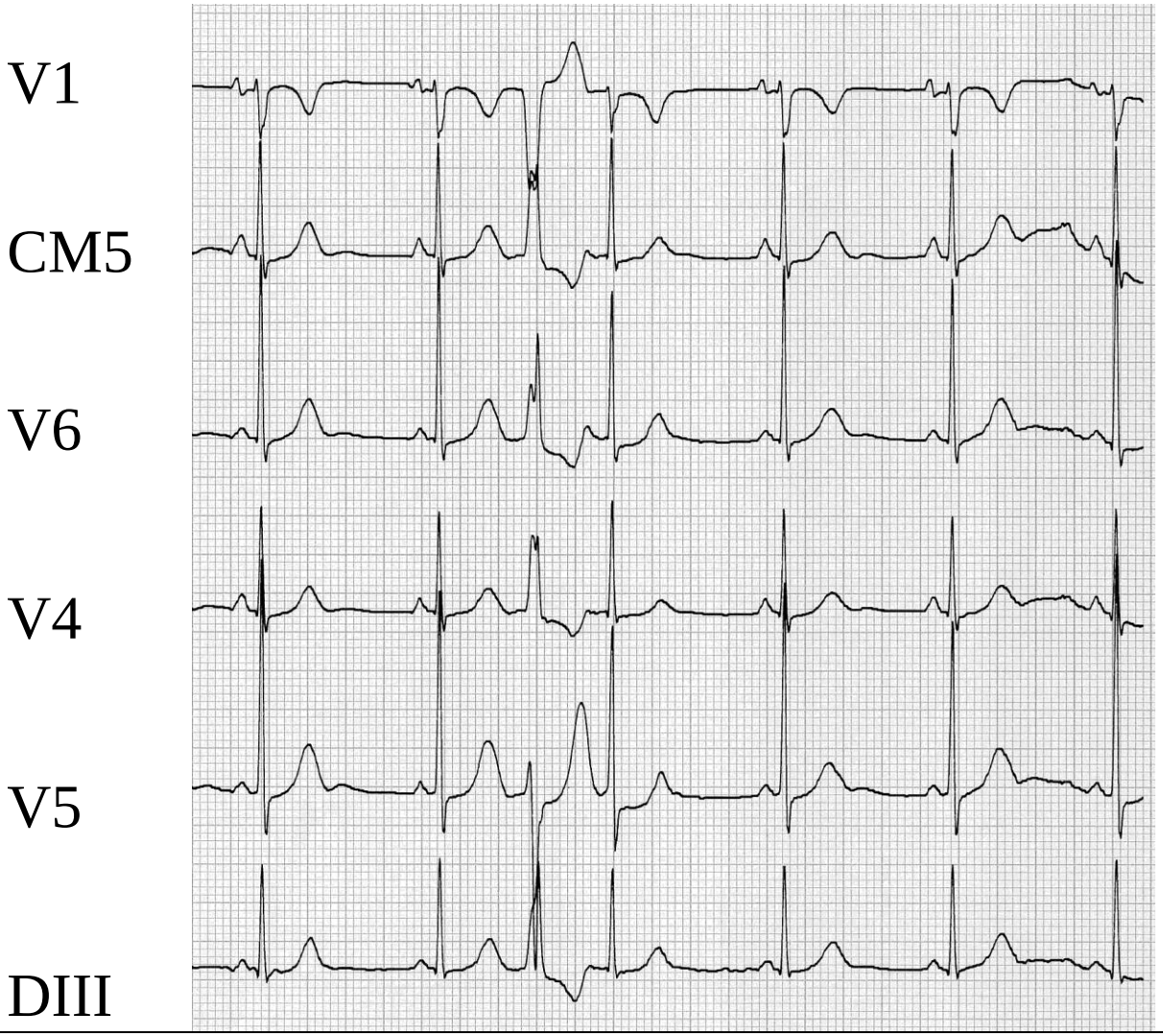
Epreuve d'effort de la sœur



Mère du propositus

- Femme âgée de 39 ans
- Malaises au repos étiquetés crises comitiales depuis l'âge de 27 ans
- ECG normal
- EE normal
- Holter

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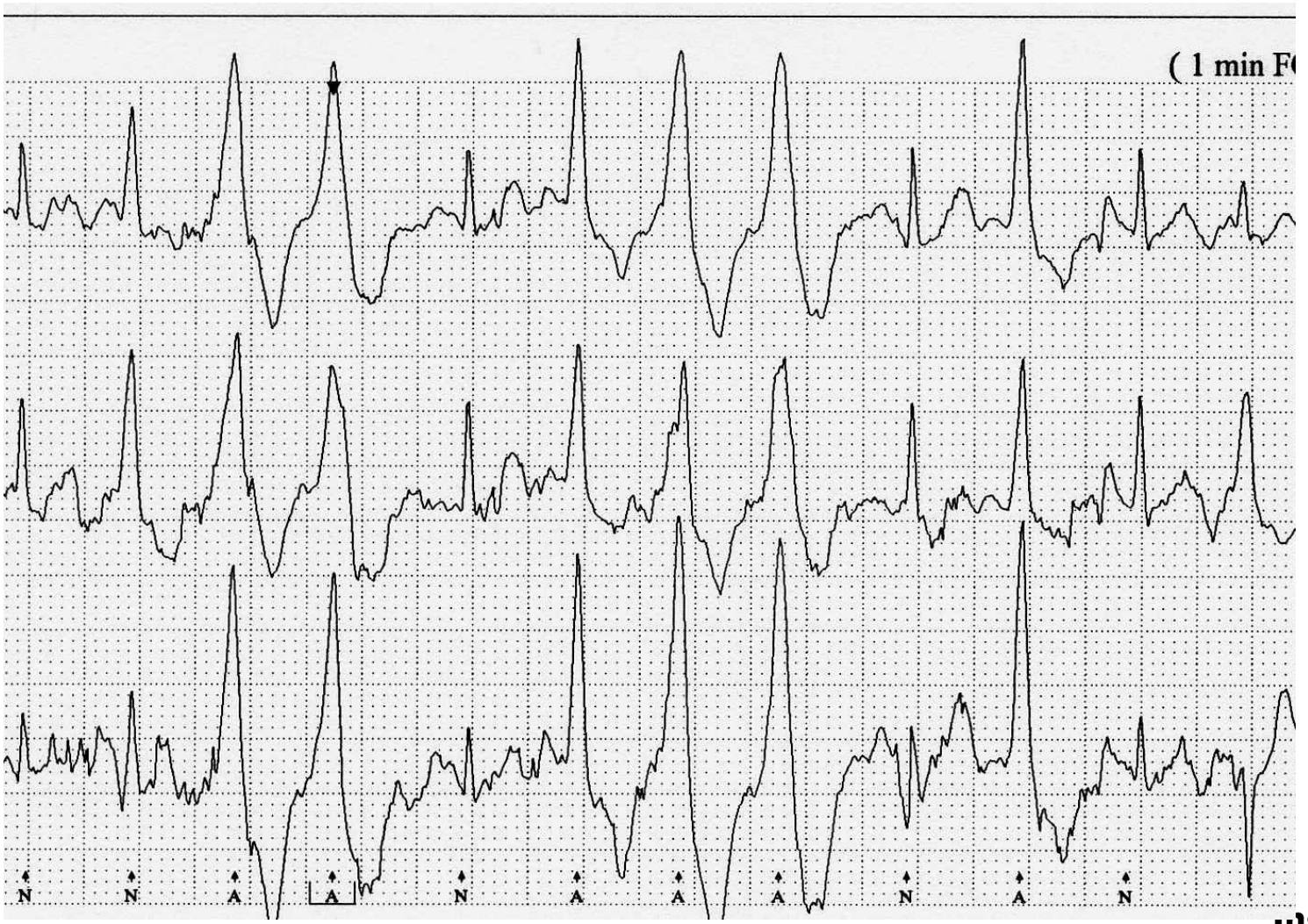
Holter de la mère



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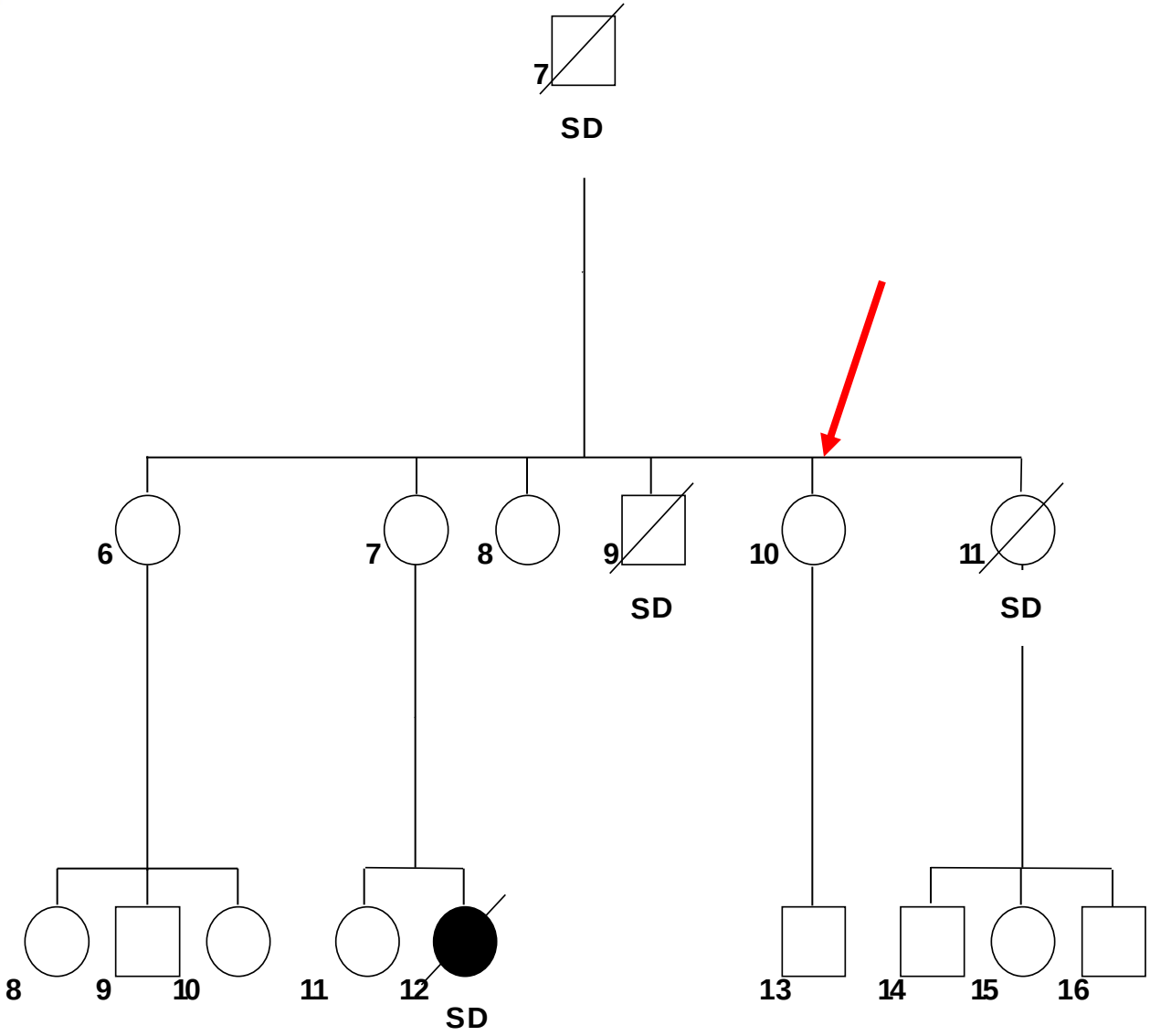
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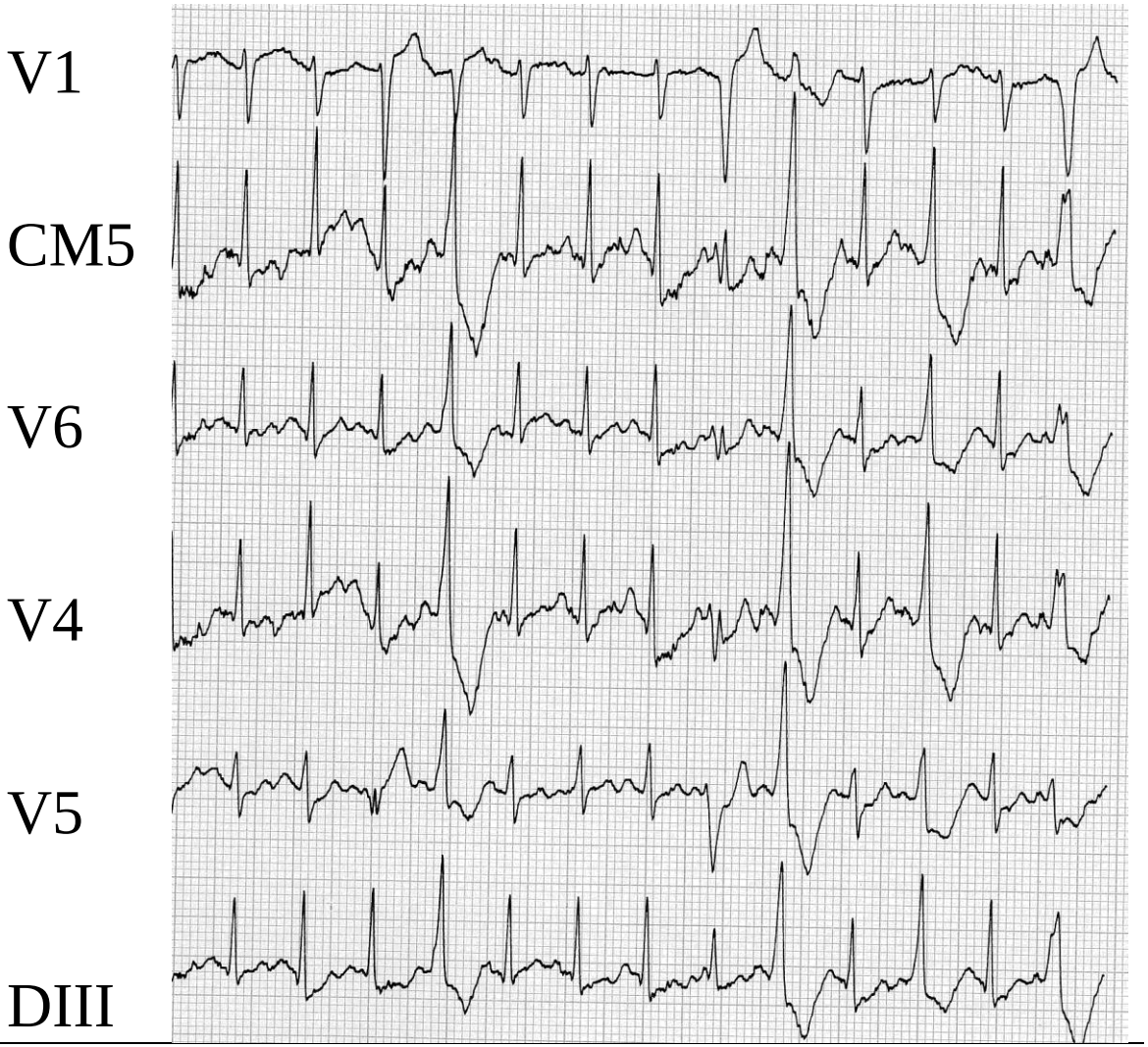
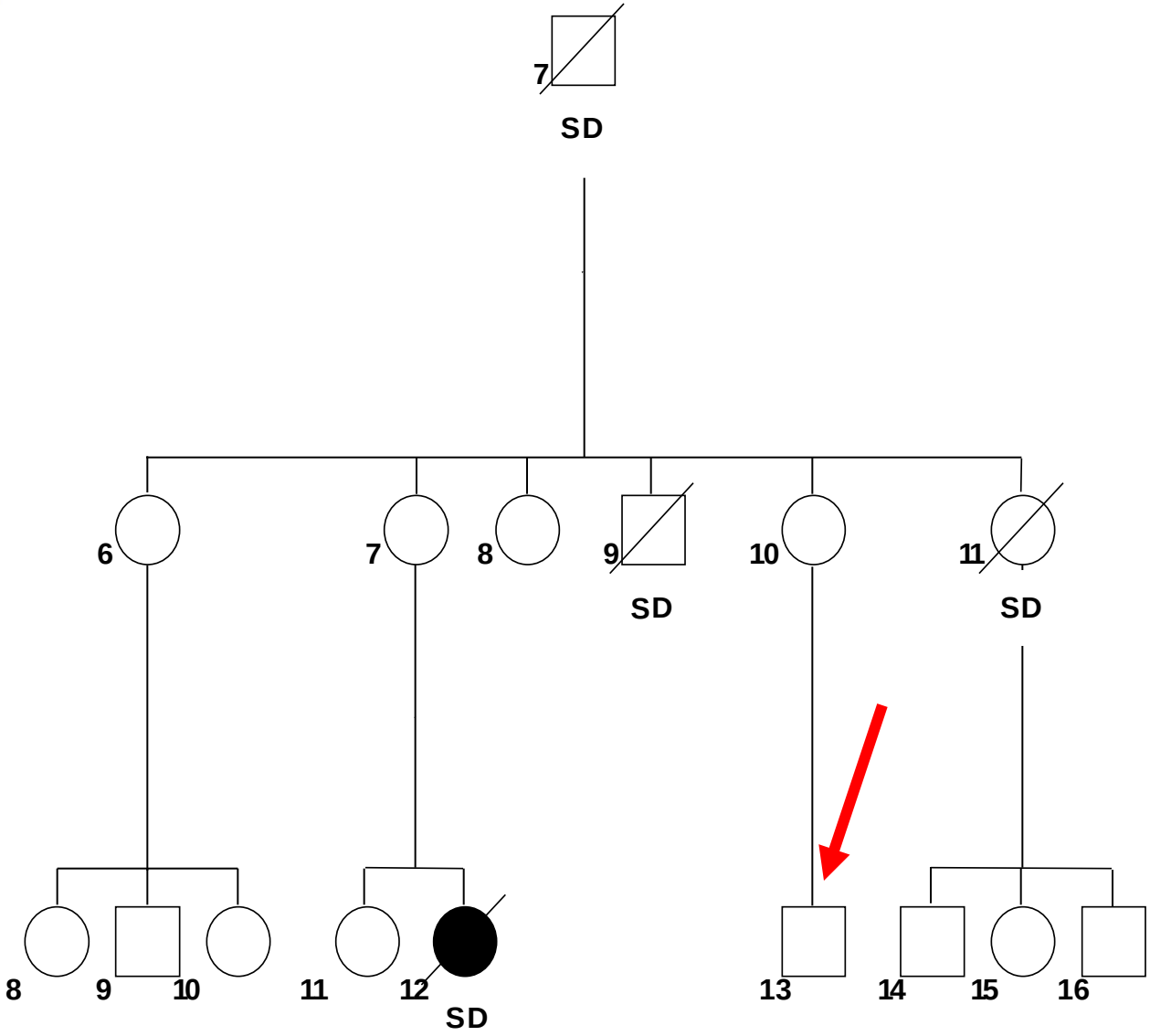
Tante du propositus

- Femme âgée de 32 ans
- Syncope pendant l'effort depuis l'âge de 20 ans
- ECG normal

Épreuve d'effort

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Le fils de cette tante

- Âgé de 12 ans
- Aucun ATCD, pas de syncope
- Joueur de foot régulier
- Échographie normale

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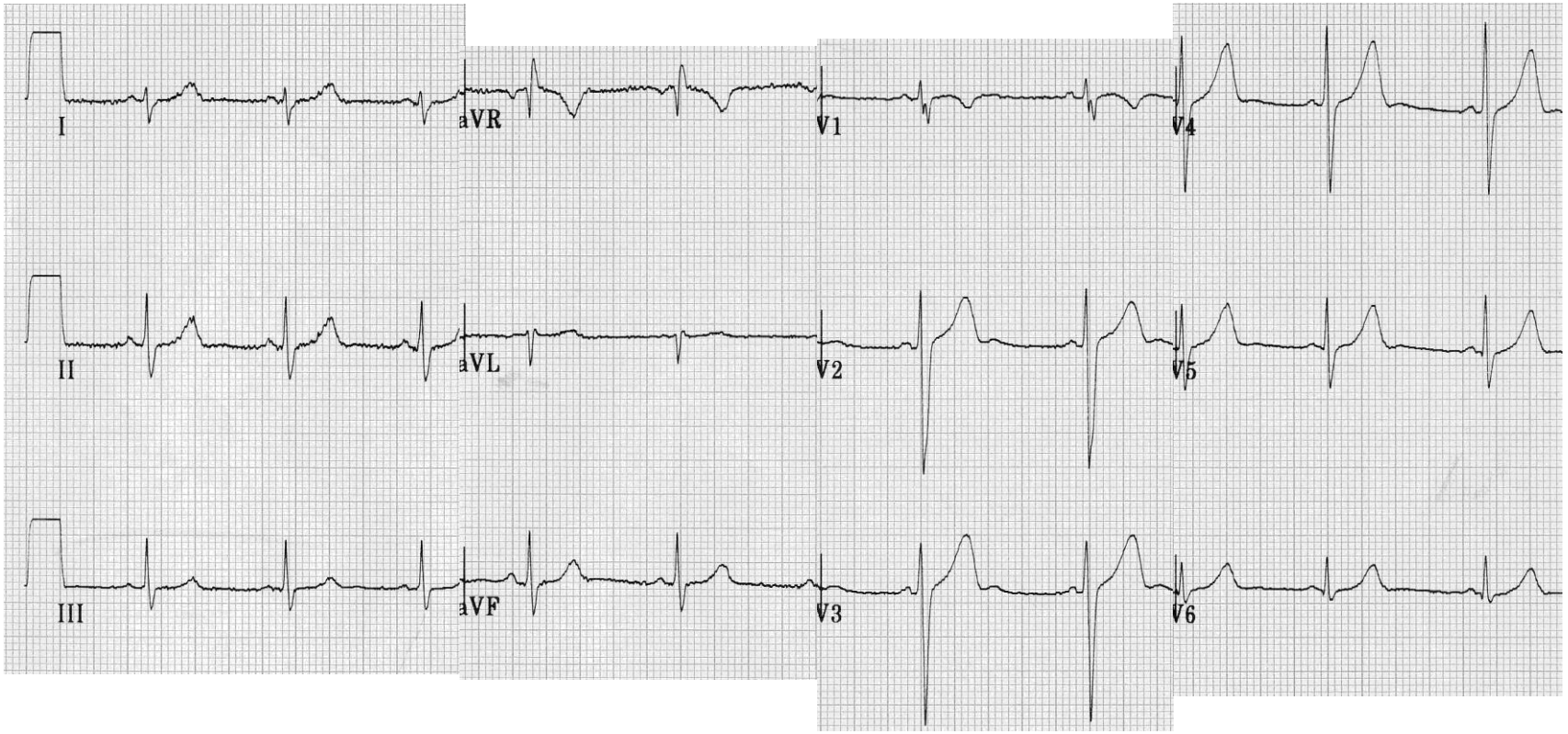
ECG du fils de la tante



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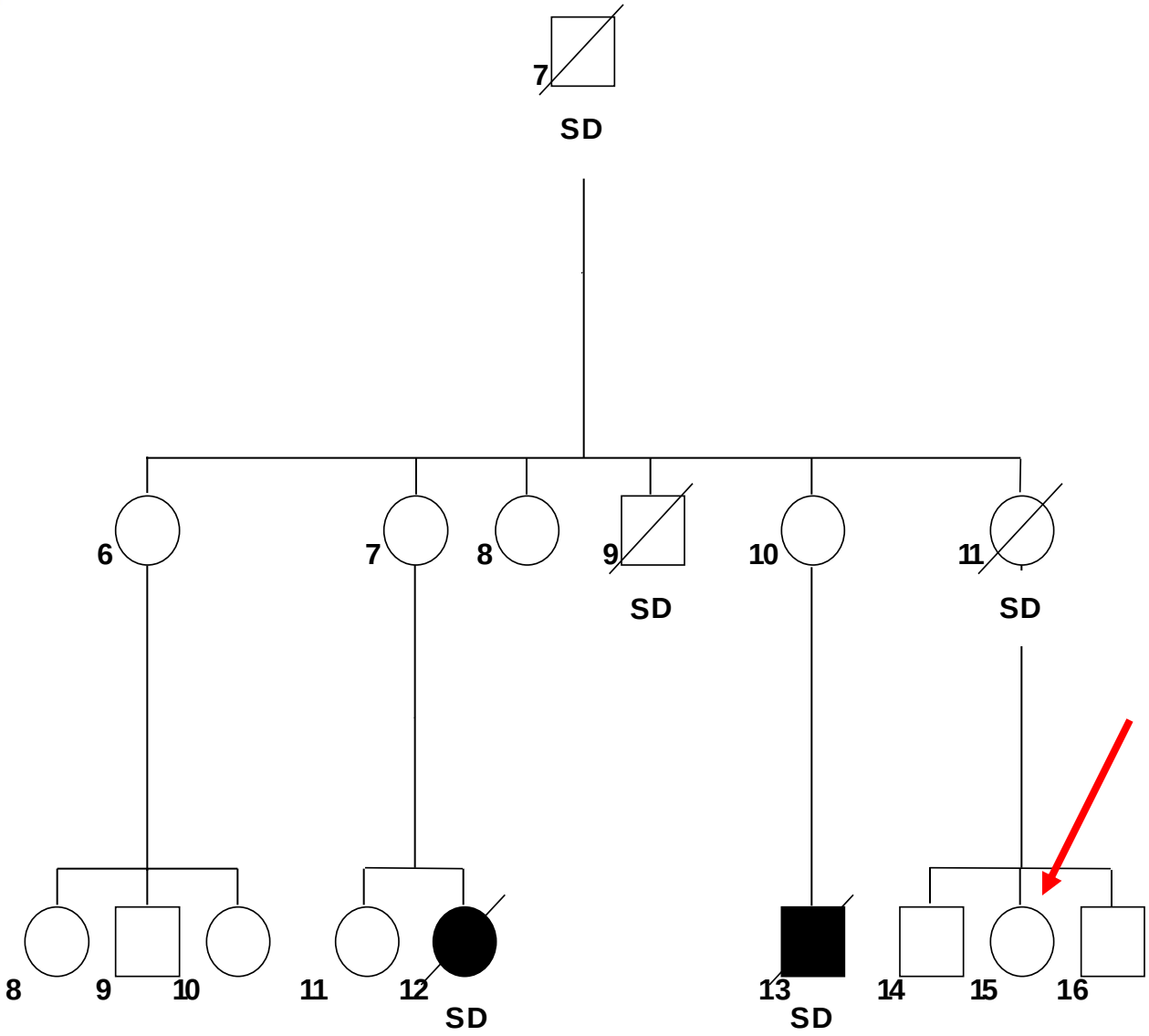
Évolution

- Décès brutal quelques mois plus tard pendant la nuit
- Pas d'anomalie retrouvée lors de l'autopsie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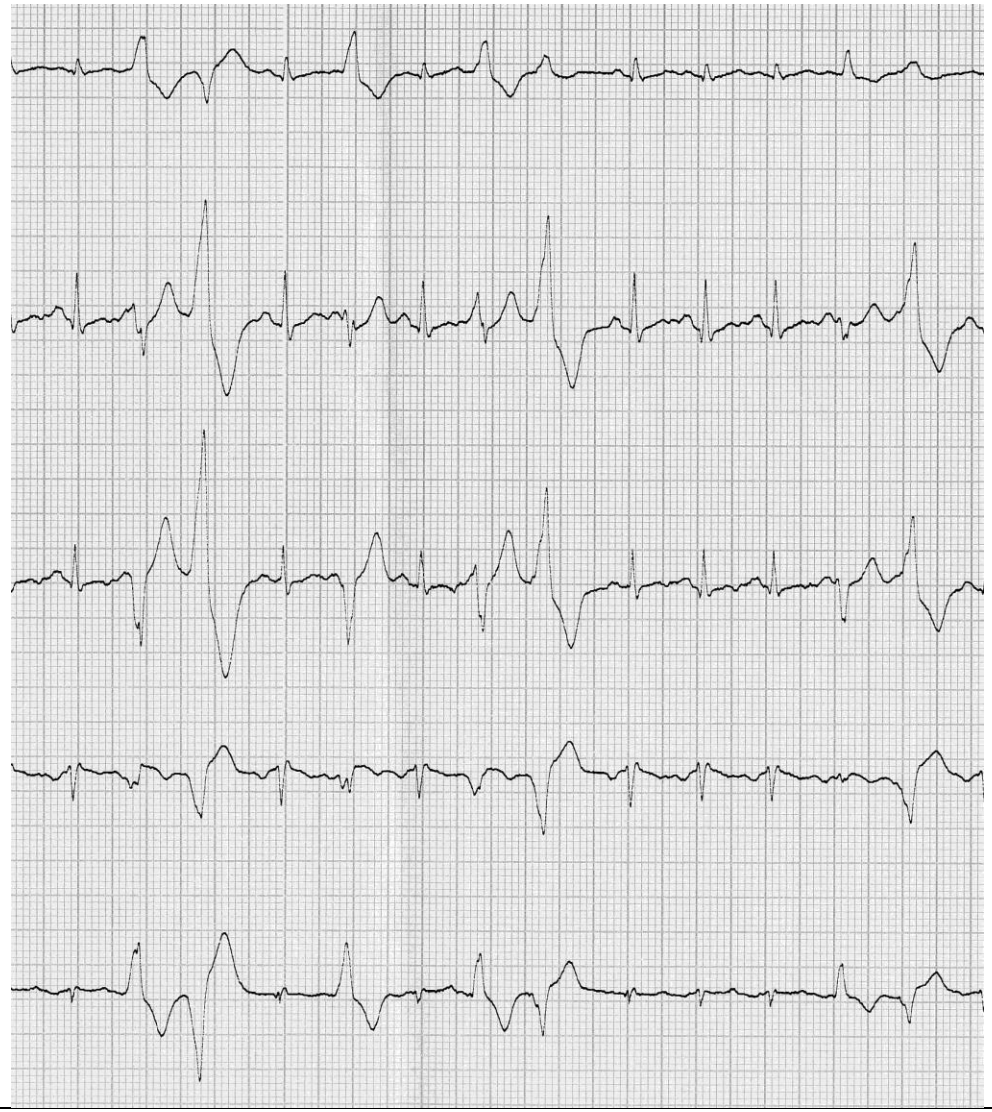
- Jeune fille âgée de 13 ans
- Notion de crise d'épilepsie depuis l'âge de 12 ans
- Syncope pendant l'effort

Épreuve d'effort



Quelques mois plus tard…

- Jeune enfant de 10 ans ayant présenté à l'âge de 7 ans une noyade en piscine
- Diagnostic de malaise vagal et réflexe oculo-cardiaque positif
- Persistance de malaise à l'effort

Épreuve d'effort à 7 ans

CM5

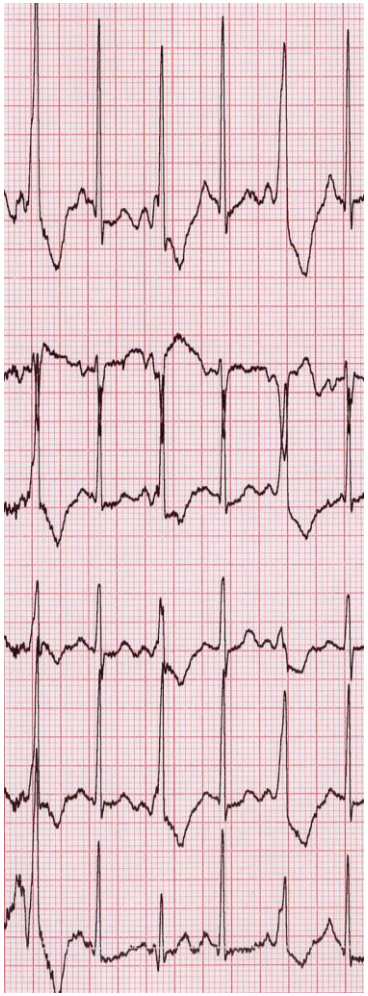
V1

V6

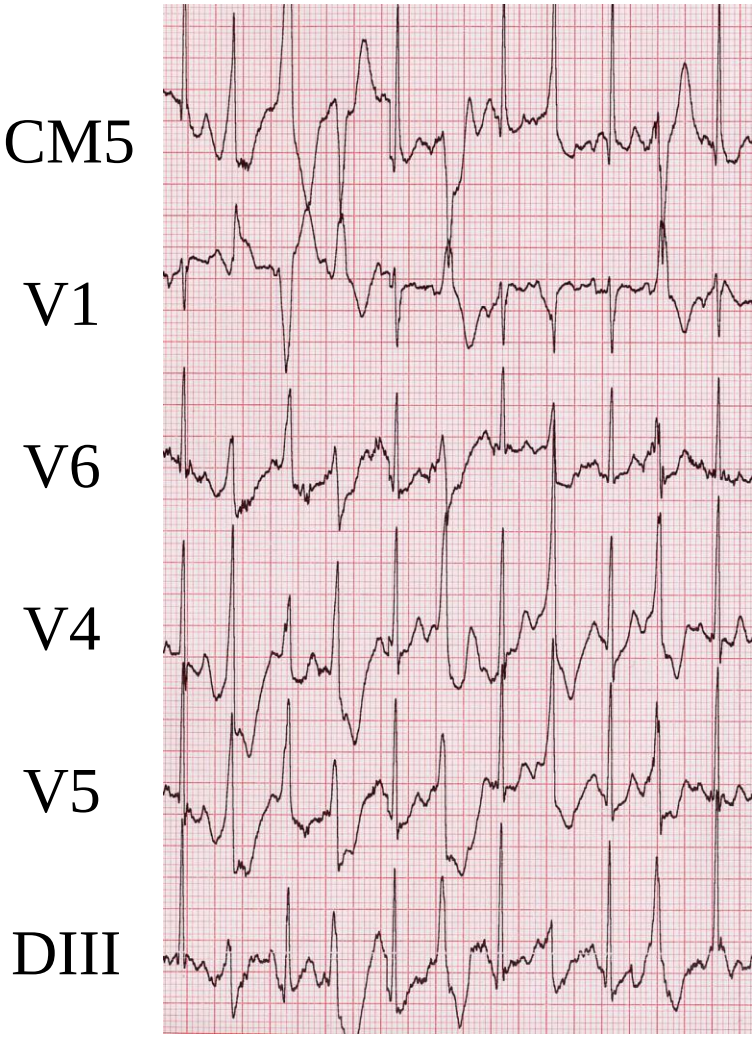
V4

V5

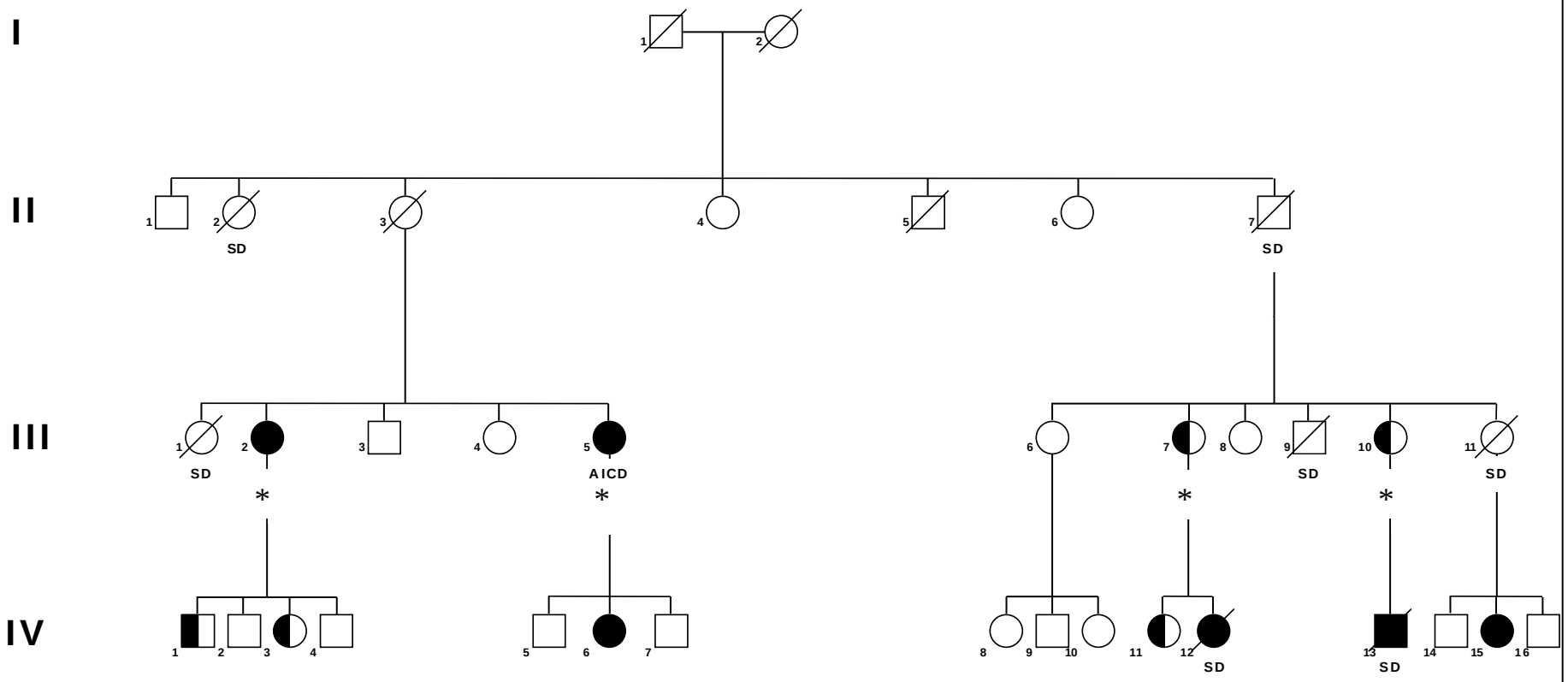
DIII



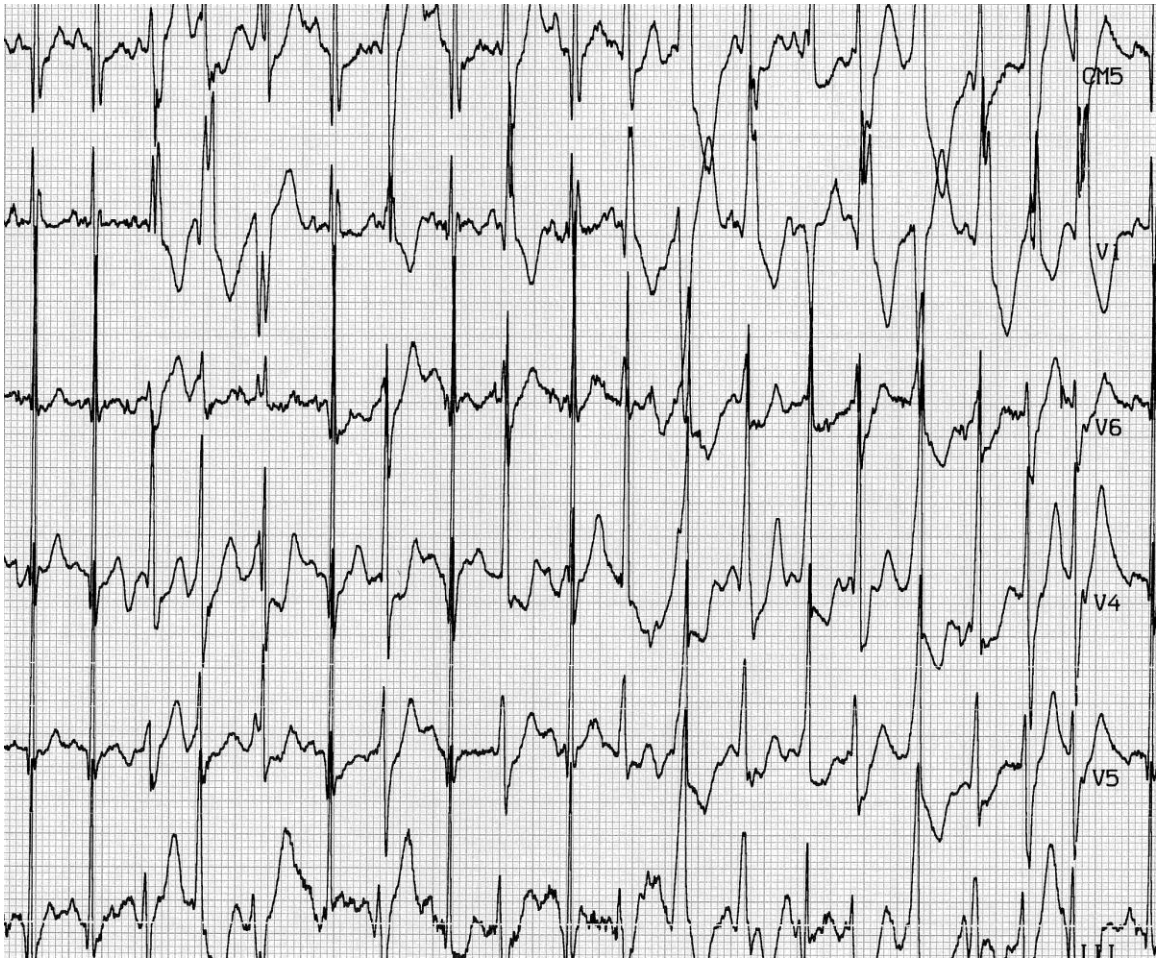
Épreuve d'effort à 10 ans



Un lien familial avec l'autre famille est identifié



Plusieurs membres de cette famille ont des ECG typiques de CPVT



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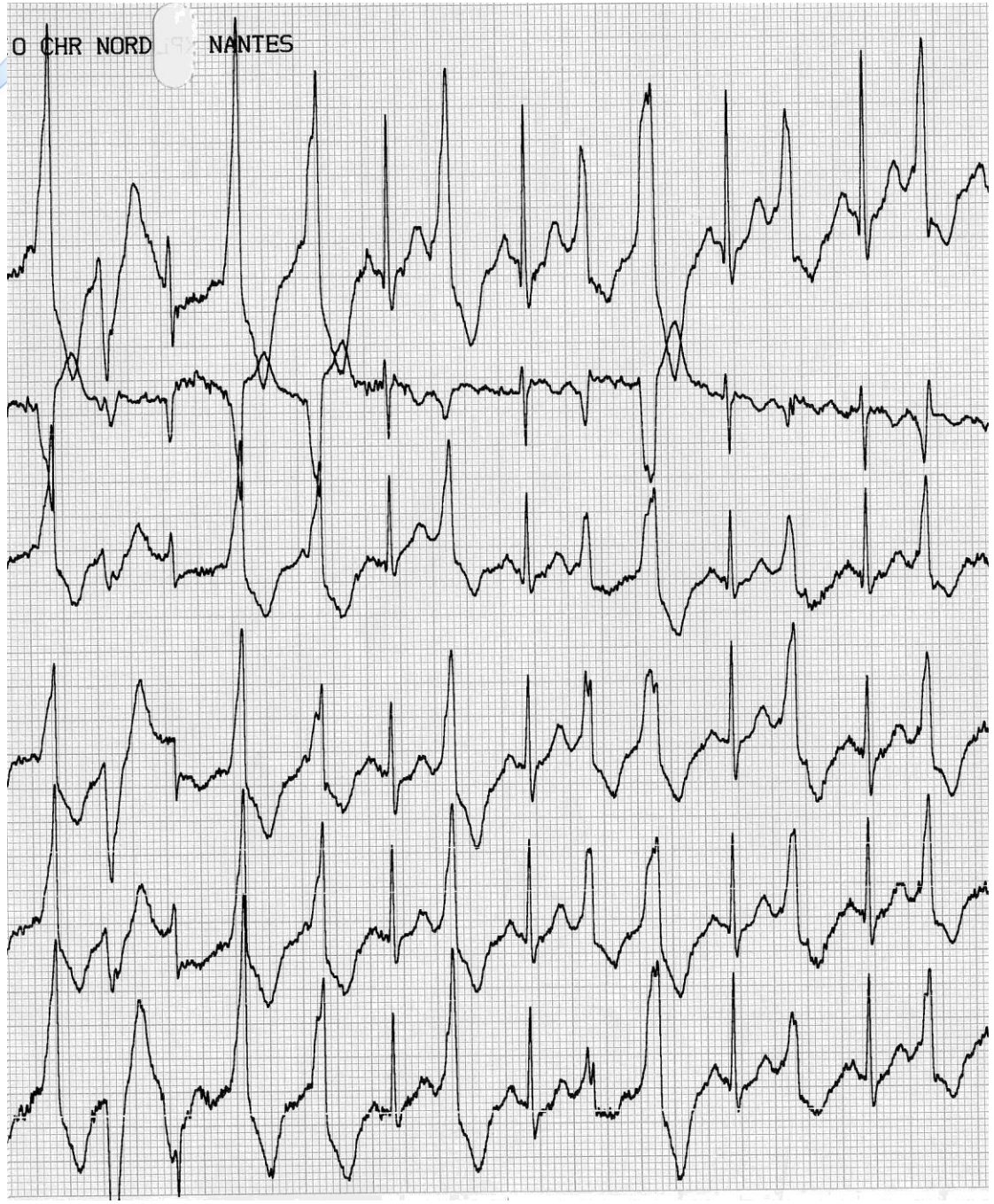

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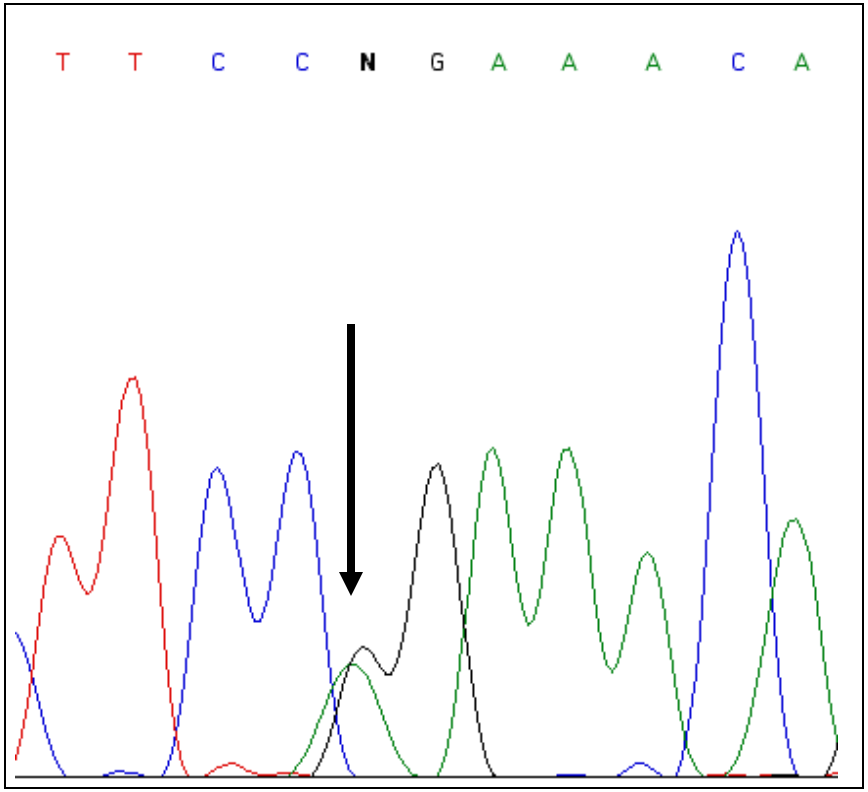
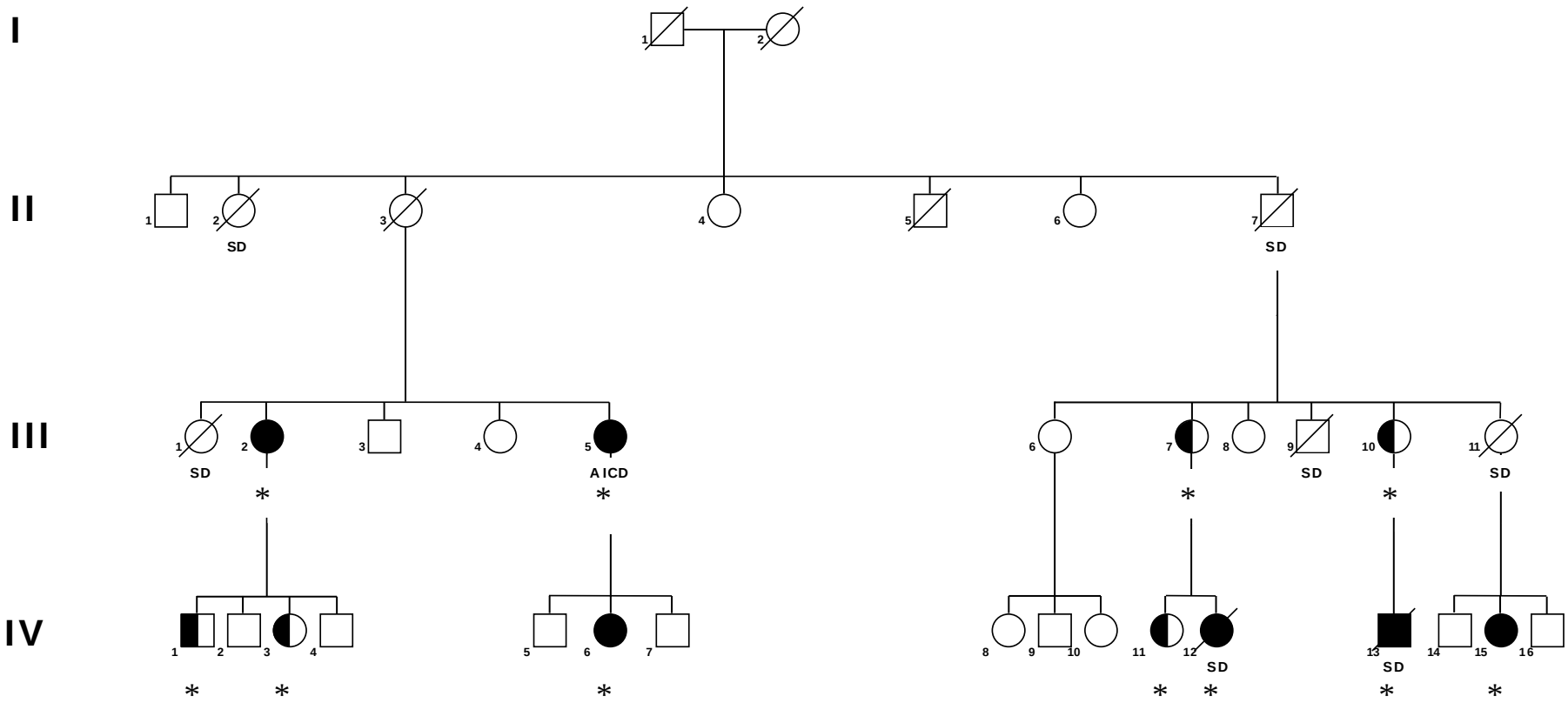
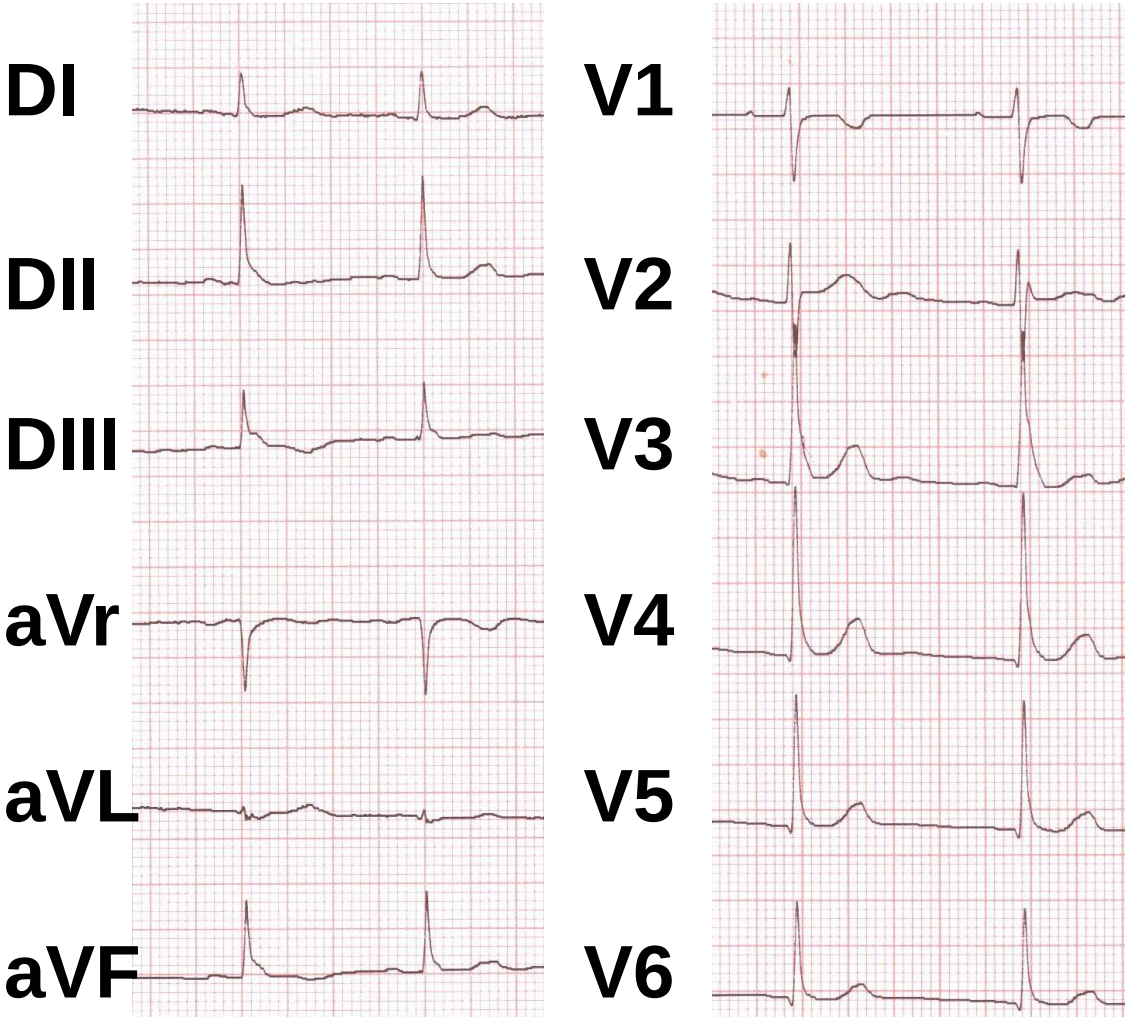
Une mutation dans le gène du récepteur à la ryanodine est identifiée



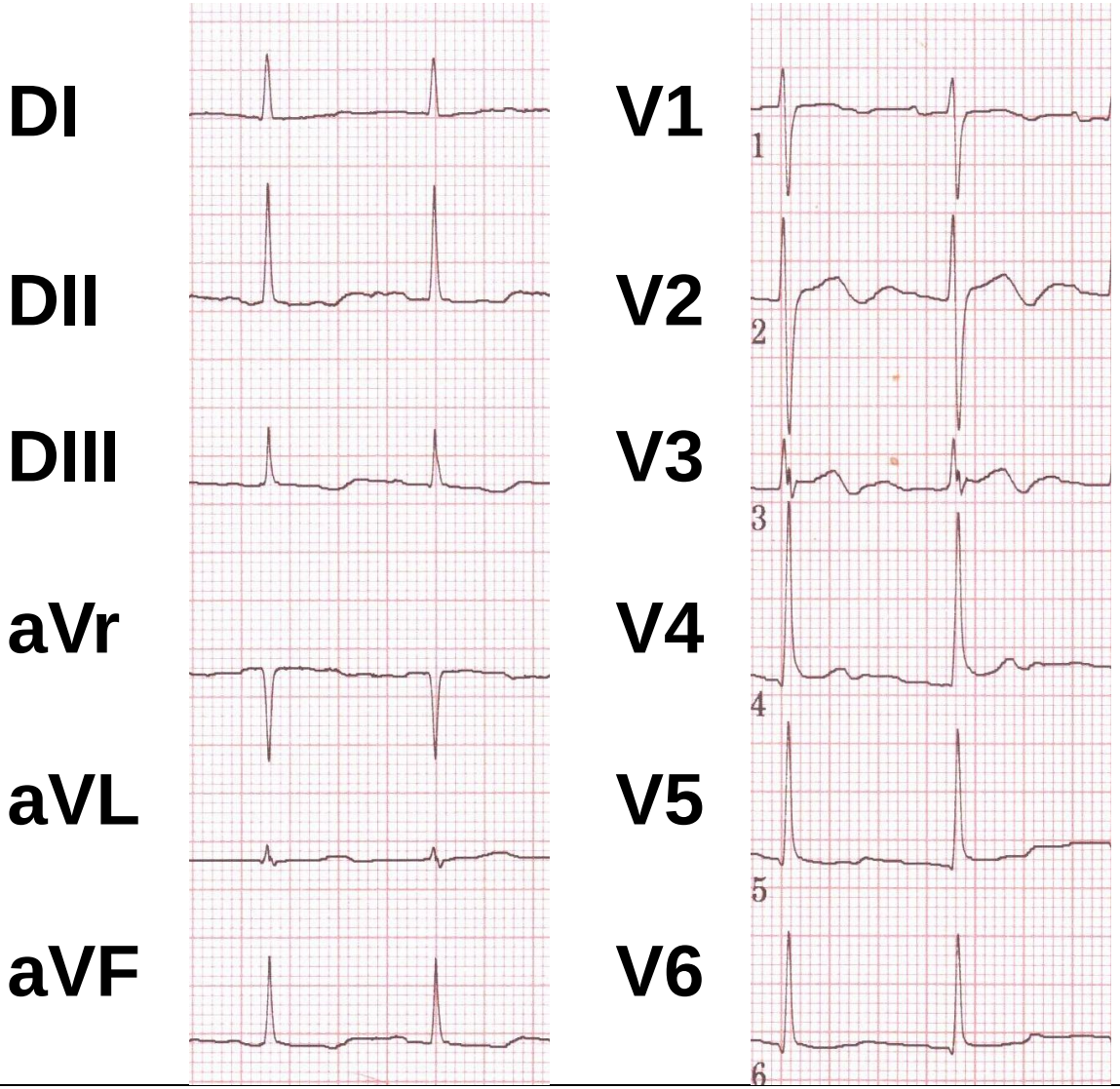
Tous les patients porteurs de la mutation sont traités par bêta-bloquant



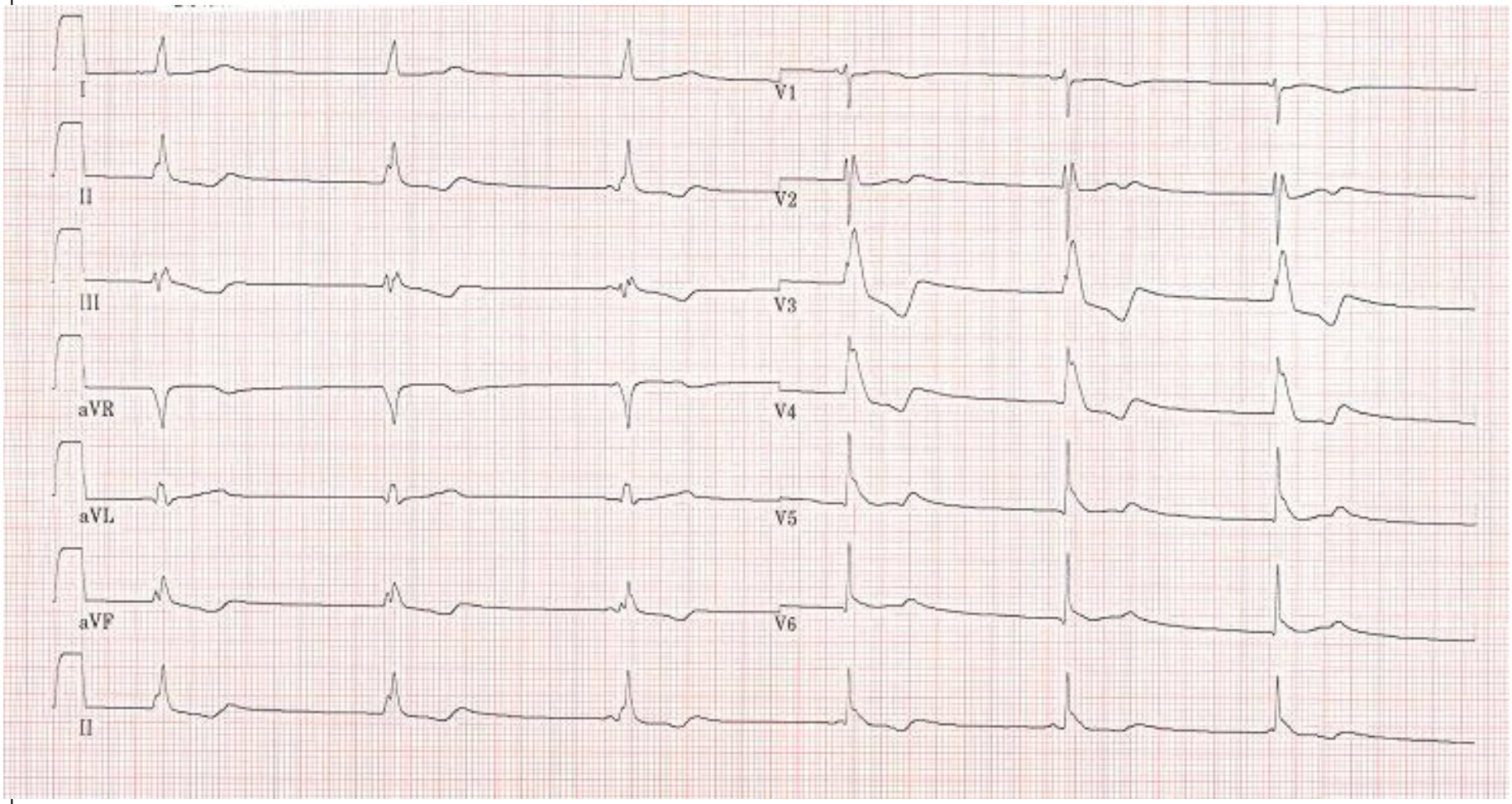
Enfant de 10 ans asymptomatique



Sous hydroquinidine



Après 3 ans de quinidine



Genetic Councelling in cardiology

Vincent Probst, MD, PhD

Reference center for hereditary arrhythmic diseases

l'Institut du thorax

Nantes

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

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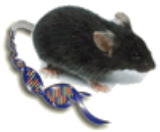
Petits rappels

23 paires de chromosomes 3.2 milliards pb



21 paires de chromosomes 2.5 milliards pb

39 paires de chromosomes 2.4 milliards pb

24 paires de chromosomes

3 milliards pb

1995 : Puces à ADN

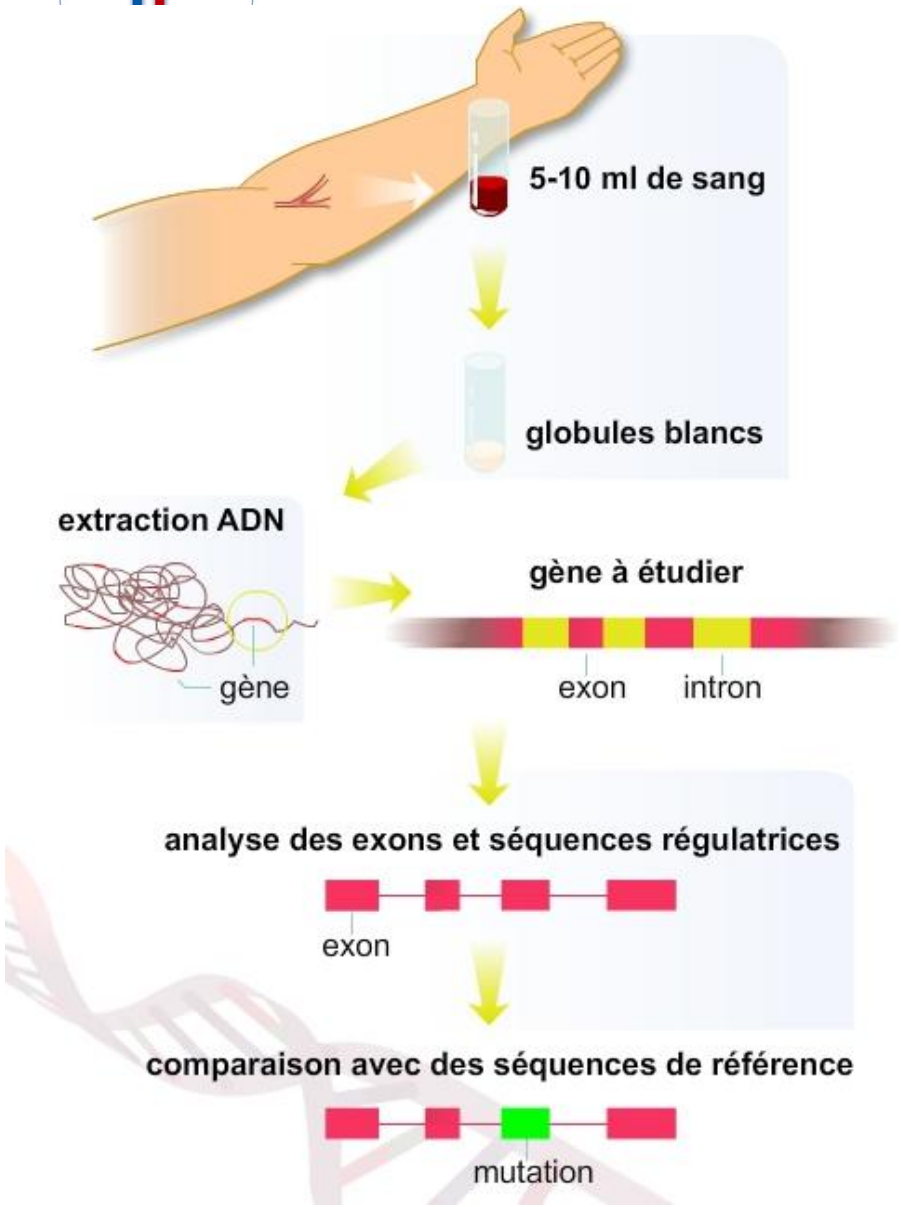
1990 : BLAST

1989 : Microsatellites

1985 : PCR

1977 : Séquençage

L'approche gène candidat



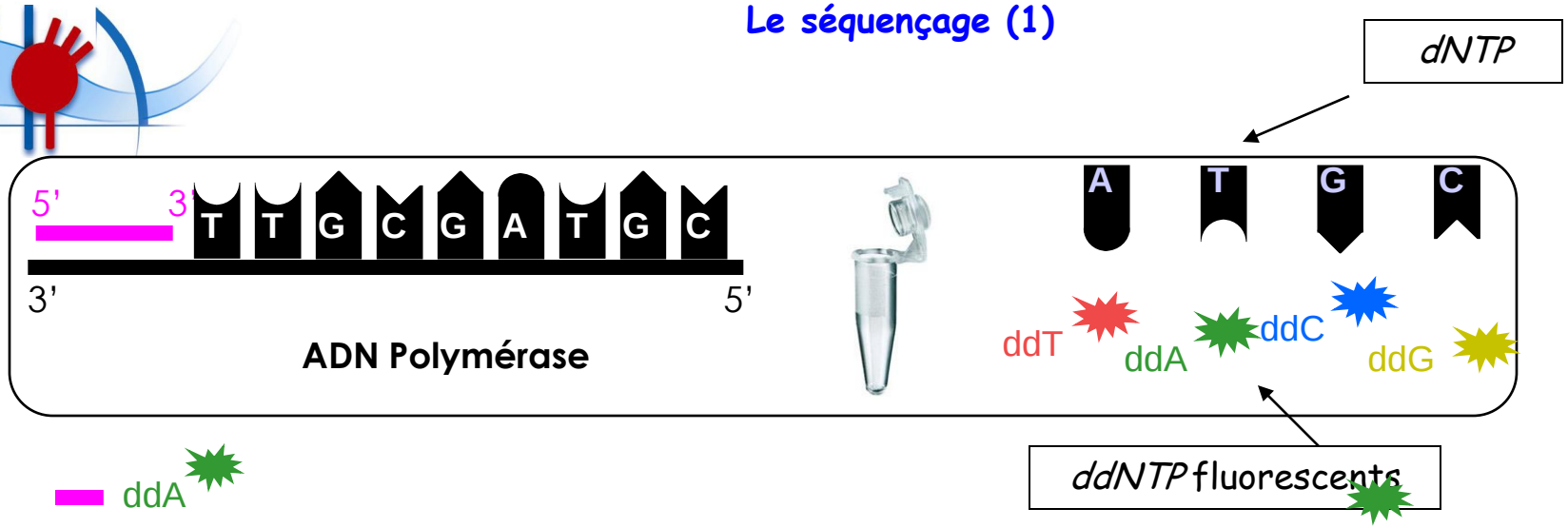
➢**Mutations par substitution (une base):**

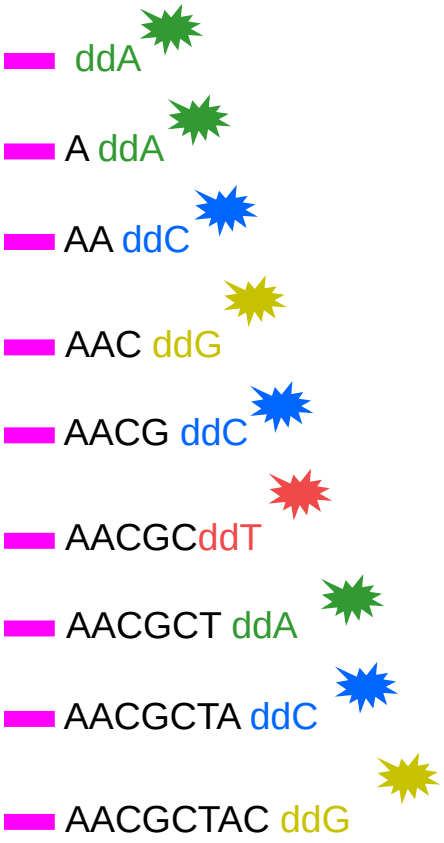
-mutation faux-sens :
changement d'acide aminé.
- mutation non-sens :
apparition d'un codon stop.
- mutation silencieuse:
pas de changement d'acide aminé.

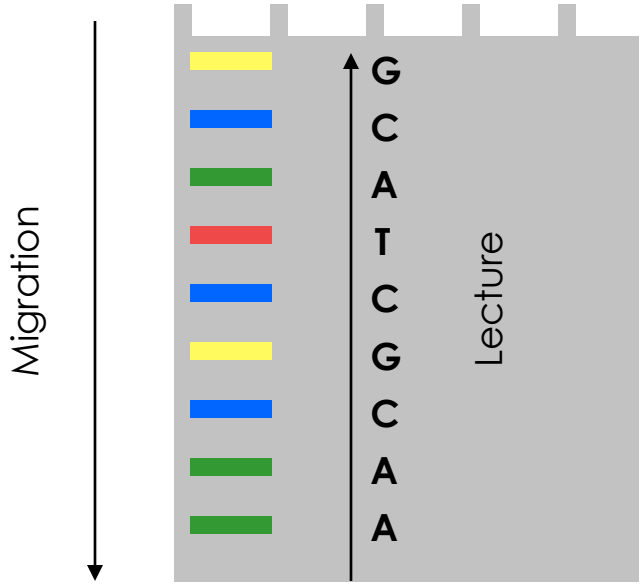
➢**Insertions et délétions :**

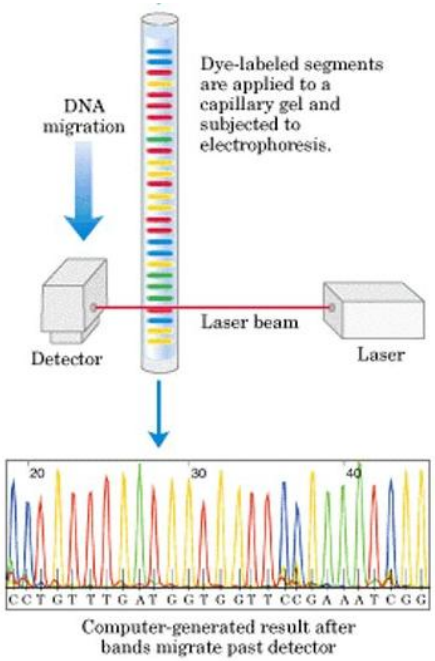
-mutations décalantes:
addition ou une suppression de nucléotides provoquant un changement de cadre de lecture
→ Apparition d'un codon-stop prématuré
→ Protéine tronquée

Le séquençage (1)

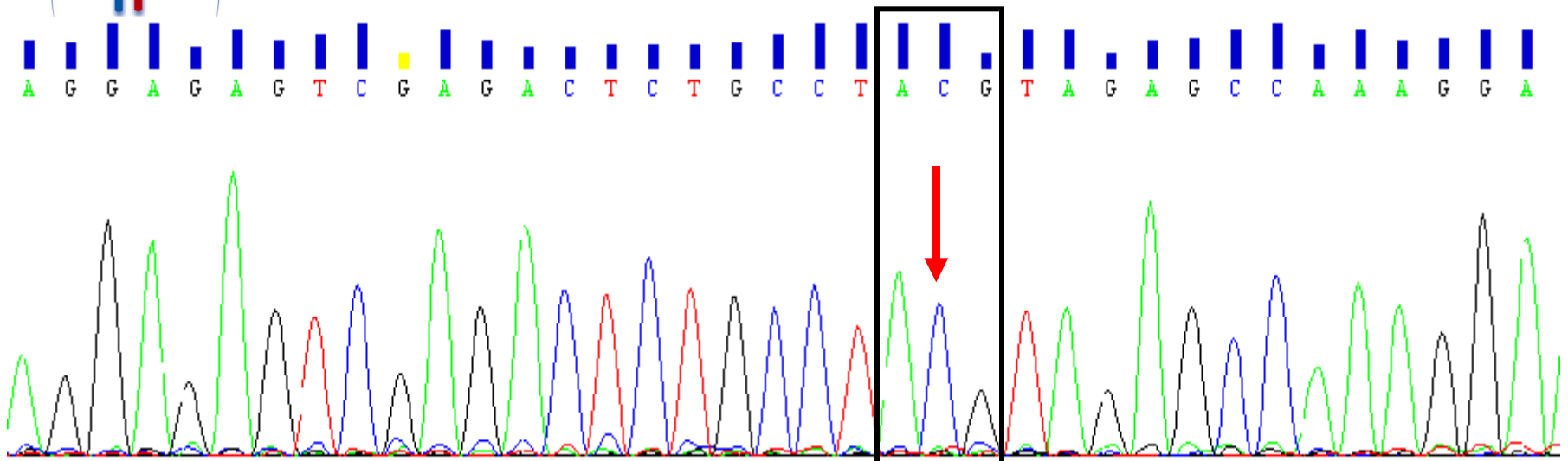




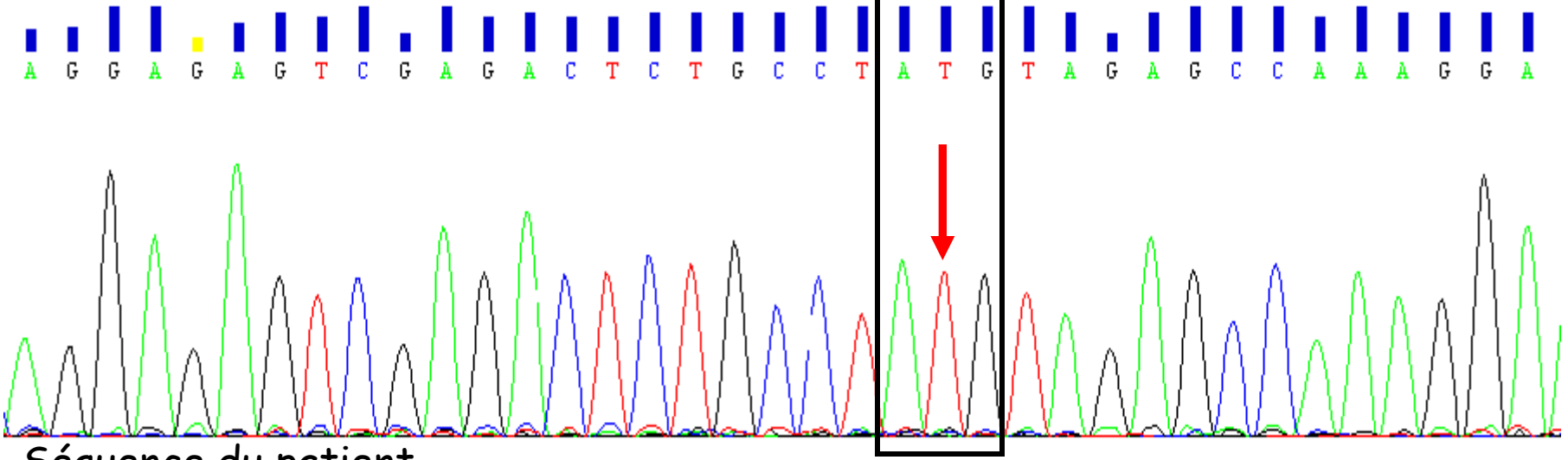




Le séquençage (2)



Séquence de référence



Séquence du patient

Cardiac diseases: genetic basis

- Essentially autosomal dominant transmission mode
- Incomplete penetrance
- Variable expressivity
- Genetic heterogeneity
- Molecular basis incompletely known

Genetic testing: Why?

- To confirm the diagnosis in the index patient
- To give a specific treatment to the index patient
- To facilitate the detection of the family members carrier of the familial mutation and possibly affected by the disease
- To prevent sudden death in the family members

Genetic counselling

The genetic test

A simple blood test but…

The genetic test:
The index patient

- First step of the familial screening
- Always in a clearly affected patient
- Level of detected mutation < 50%
- Time and money consuming
- Difficult interpretation of real rule of certain mutations

The genetic test: the familial screening

- Family members don't have to be directly contact by the practitioner
- Before the genetic test, the patient need to have understood the nature of the test and the potential consequences
- This information have to be give by a practitioner with competency in medical genetic
- A writing consent must be obtain before the test and a writing information concerning the disease and the test must be give to the patient
- The notification of the results must be done during a individual consultation with a clear explanation of the consequences of the results

Genetic counselling
Diagnosis in presymptomatic family members

- Certainly the main interest of the genetic test
- But can't predict
  - Age of the first symptoms
  - Type, severity and evolution of the symptoms
- Psychological impact before and after the results of the test
- Social impact of the test
  - Work
  - Insurance

Genetic counselling and sudden death
The under age

- No guideline for the age of the genetic test
  - Age of the first symptoms
  - Expressivity and penetrance of the disease
  - Possibility of a preventive therapy
- At birth?
  - Long QT syndrome, Short QT syndrome, CPVT
- When the child can understand the result of the test for the other diseases
  - Brugada syndrome
  - ARVD

Genetic counselling
Antenatal genetic test

- Very rare indication because:
  - No voluntary interruption of pregnancy
  - Quick genetic test after birth

Genetic counselling and sudden death
Interest and difficulties

Some examples…

Genetic counselling and sudden death
Long QT Syndrome

- 12 genes, 5 usually tested
- Mutations identified in 70% cases
- 31% of the patients have a borderline QT duration (400-460 msec)
- Sudden death is the first symptom in 10-15% of the cases
- Prognosis interest of the compound mutations
- Efficient preventive treatment
  - Avoidance of the drugs which lengthen the QT duration
  - 10% without treatment <1% under betablocker therapy
  - ICD for LQT3 patients

Genetic counselling and sudden death
Brugada Syndrome

- *SCN5A* mutation in <20% of the index patients
- Low penetrance < 50%
- Expressivity of the *SCN5A* mutations is highly variable
- Presence of a *SCN5A* does not change the prognosis

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). [ACC/AHA collaboration/endorsement to be requested after initial peer review]

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En général

Recommendations

1. Genetic counseling principally **is recommended** for all patients and relatives with the familial heart diseases detailed in this document and should include discussion of the risks, benefits, and options available for clinical testing and/or genetic testing.
2. Treatment decisions **should not** rely solely on his/her genetic test result but **should be** based on an individuals' composite profile.
3. It **can be useful** for pre-genetic test counseling, genetic testing, and the interpretation of genetic test results to be performed in centers experienced in the genetic evaluation and family-based management of the heritable arrhythmia syndromes and cardiomyopathies described in this document.

Table 1 – Summary of Common Cardiac Channelopathy/Cardiomyopathy-Associated Genes (>5% of Disease)

Gene	Locus	Protein	% of Disease
Section I - Long QT Syndrome (LQTS)			
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (Kv7.1)	30-35%
KCNH2 (LQT2)	7q35-q36	I_{Kr} potassium channel alpha subunit (Kv11.1 or hERG)	25-40%
SCN5A (LQT3)	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5-10%
Section II - Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)			
RYR2 (CPVT1)	1q42.1-q43	Ryanodine Receptor 2	60%
Section III - Brugada Syndrome (BrS)			
SCN5A	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	20-30%
Section IV - Cardiac Conduction Disease (CCD)			
SCN5A	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5%
Section V - Short QT Syndrome (SQTS)			
None of the 3 known disease associated genes have been shown to account for ≥ 5% of this disease			
Section VI - Atrial Fibrillation (AF)			
None of the known disease associated genes have been shown to account for ≥ 5% of this disease			
Section VII - Hypertrophic Cardiomyopathy (HCM)			
MYBPC3	11p11.2	Cardiac myosin-binding protein C	20 – 45%
MYH7	14q11.2-q12	β-Myosin heavy chain	15 – 20%
TNNT2	1q32	Cardiac troponin T type 2	1-7%
TNNI3	19q13.4	Cardiac troponin I type 3	1-7%

Table 1 – Summary of Common Cardiac Channelopathy/Cardiomyopathy-Associated Genes (>5% of Disease)

Gene	Locus	Protein	% of Disease
Section VIII - Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)			
PKP2	12p11	Plakophilin 2	25-40%
DSG2	18q12.1	Desmoglein 2	5-10%
DSP	6p24	Desmoplakin	2-12%
DSC2	18q12.1	Desmocollin 2	2-7%
Section IX - Dilated Cardiomyopathy (DCM)			
None of the >25 known disease associated genes have been shown to account for ≥ 5% of this disease			
Section IX - Dilated Cardiomyopathy with Cardiac Conduction Defect (DCM + CCD)			
SCN5A	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	5-10%
LMNA	1q22	Lamin A/C	5-10%
Section X - Left Ventricular Non-Compaction (LVNC)			
LBD3	10q22.2-q23.3	LIM binding domain 3	~5%
Section XI – Restrictive Cardiomyopathy (RCM)			
MYH7	14q11.2-q12	β-Myosin heavy chain	~5%
TNNI3	19q13.4	Cardiac troponin I type 3	~5%
Section XIII - Sudden Unexplained Death Syndrome (SUDS)			
RYR2	1q42.1-q43	Ryanodine Receptor 2	10-15%
KCNQ1	11p15.5	I_{Ks} potassium channel alpha subunit (Kv7.1)	5-10%
KCNH2	7q35-q36	I_{Kr} potassium channel alpha subunit (Kv11.1 or hERG)	~5%
Section XIII - Sudden Infant Death Syndrome (SIDS)			
SCN5A	3p21	Cardiac sodium channel alpha subunit (NaV1.5)	3-5%

Table 2 – Yield and Signal-to-Noise Associated with Disease-Specific Genetic Testing

Section – Disease	Yield of Genetic Test*	% of Controls with a Rare VUS#	Signal-to-Noise (S:N) Ratio+
Section I – LQTS	75% (80%)	4%	19:1
Section II – CPVT	60% (70%)	3%	20:1
Section III – BrS	20% (30%)	2% (just *SCN5A*)	10:1
Section IV – CCD	Unknown	Unknown	Unknown
Section V – SQTS	Unknown	3%	Unknown
Section VI – AF	Unknown	Unknown	Unknown
Section VII – HCM	60% (70%)	~5% (unpublished data)	12:1
Section VIII – ACM/ARVC	60%	16% (JACC paper, in press)	4:1
Section IX – DCM	30%	Unknown	Unknown
Section IX – DCM + CCD	Unknown	4% (for SCN5A and LMNA)	Unknown
Section X – LVNC	17-41%	Unknown	Unknown
Section XI – RCM	Unknown	Unknown	Unknown

Figure 1 - Impact of Index Case Genetic Testing for the Index Case

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	+	+	+