Amicale ACPR le 23 janvier 2024

Génétique en Cardiologie
Dépistage étiologique des CMH

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Disclosures

I currently have, or have had over the last four years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company :

- Consulting Fees/Honoraria:

  Alnylam; *Amicus; Bristol-Myers Squibb; Owkin; Pfizer; Sanofi*

- No other disclosures

- Introduction
- Pourquoi faire un test génétique ?
- Comment faire un test génétique?
- Intégration de la génétique dans le diagnostic étiologique de la CMH

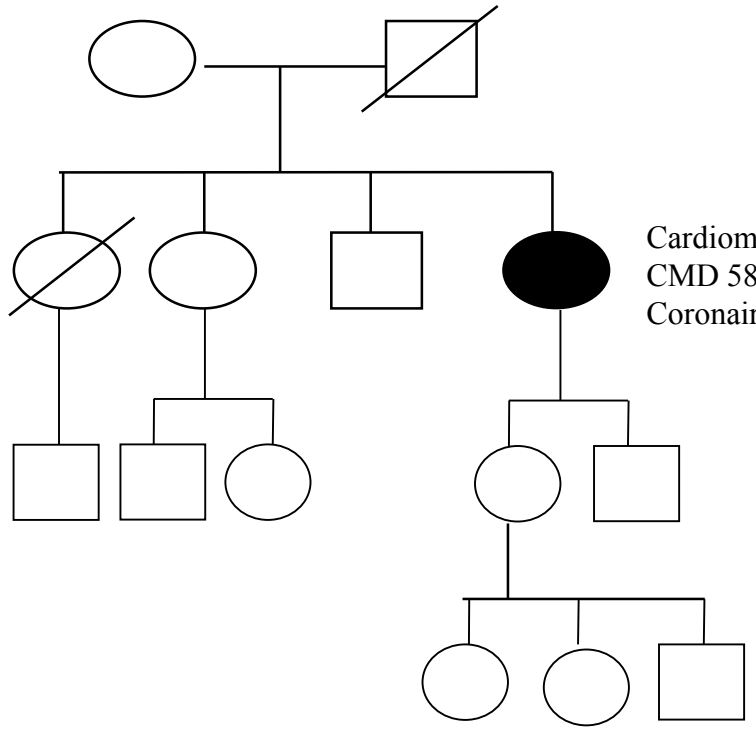
Un cas clinique

I.

II.

III.

IV.



Cardiomyopathie Dilatée
CMD 58 ans (FE VG 37%,
Coronaires saines)

Q1. Quelle probabilité d'origine génétique?

A. Très forte
B. Significative
C. Très faible

Q2. Quel impact du test génétique? / PEC particulière selon le gène sous jacent?

A. TTT spécifique ?
B. Indication particulière du DAI?
C. Surveillance ≠ des apparentés?
D. Discussion ≠ grossesse chez apparentée?

Un cas clinique

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II.

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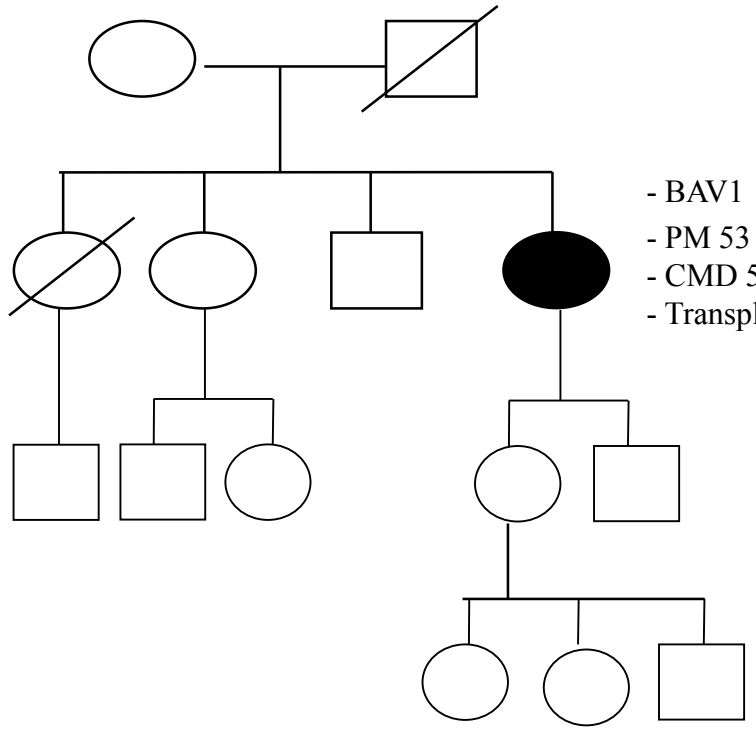
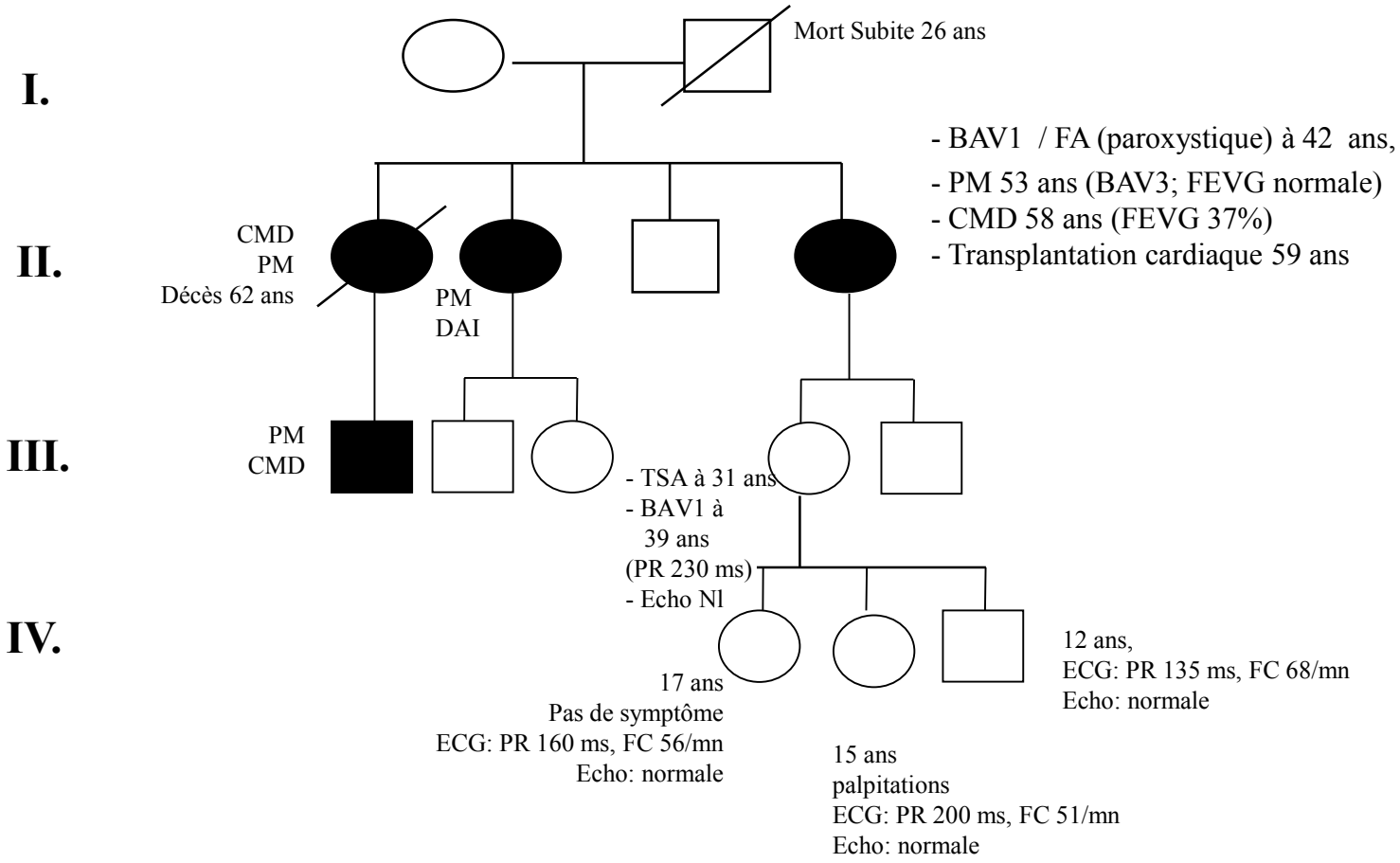
IV.

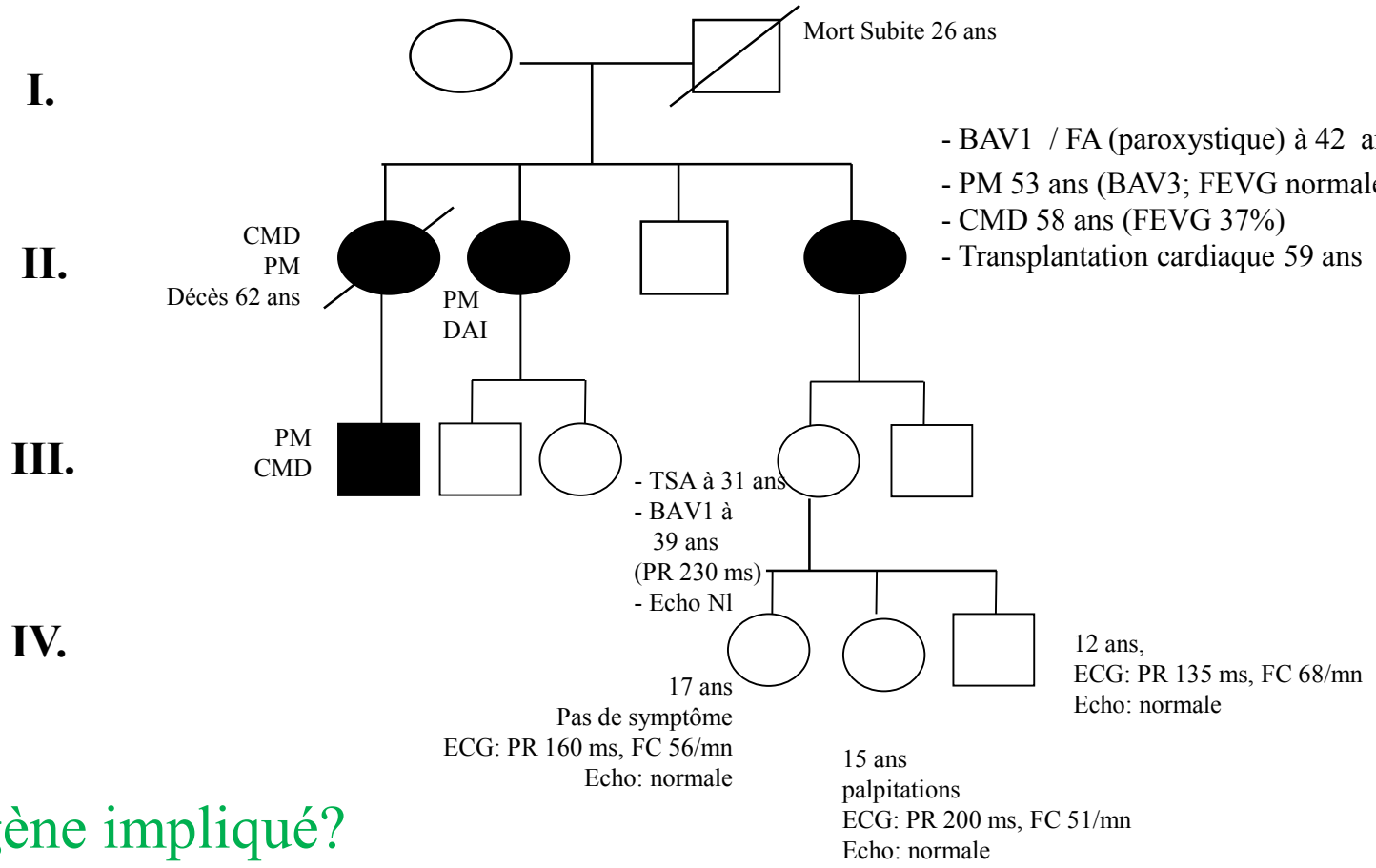


- BAV1 / FA (paroxystique) à 42 ans,
- PM 53 ans (BAV3; FEVG normale)
- CMD 58 ans (FEVG 37%)
- Transplantation cardiaque 59 ans

Un cas clinique



Un cas clinique



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Quel gène impliqué?

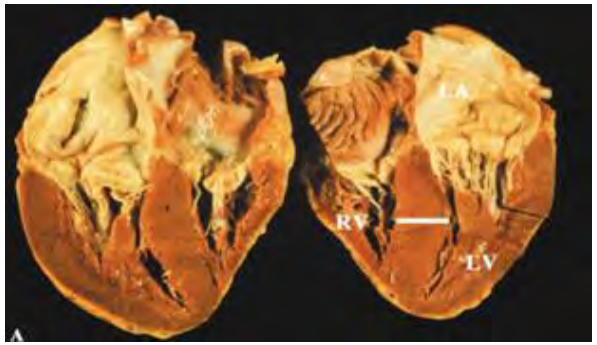
→ ***Variant pathogène (classe 5) hétérozygote du gène LMNA (lamines A/C)***

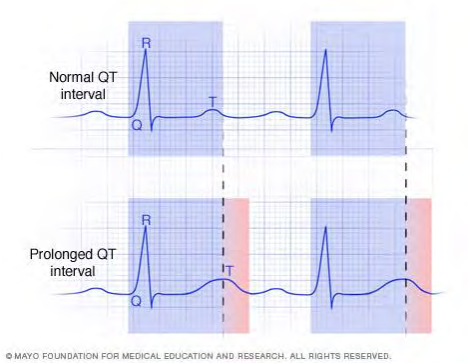
Les maladies cardiaques héréditaires

Cardiomyopathies

- **Cardiomyopathie Hypertrophique** (prévalence 1/500)
- **Cardiomyopathie Dilatée** (prévalence 1/ 2500)
- **Cardiomyopathie Restrictive**
  - amylose TTR, hémochromatose, desminopathie, etc
- **Dysplasie ventriculaire droite arythmogène** (prévalence 1/5.000)

- Associées à Myopathies (Steinert, Becker, Duchenne…)
- Syndromiques (Noonan, Pompe, Friedreich, Fabry…)
- Non classifiées (Non compaction VG…)





> 1/200 personnes en pop. générale
(330,000 personnes en France)

Troubles du rythme et conduction

- **Syndrome du QT long** (prévalence 1/5.000)
- **Syndrome de Brugada** (prévalence 1/2.000-5.000)
- **TV catécholergique** (prévalence 1/10.000?)
- **Syndrome du QT court, formes familiales de FA, de BAV, etc**

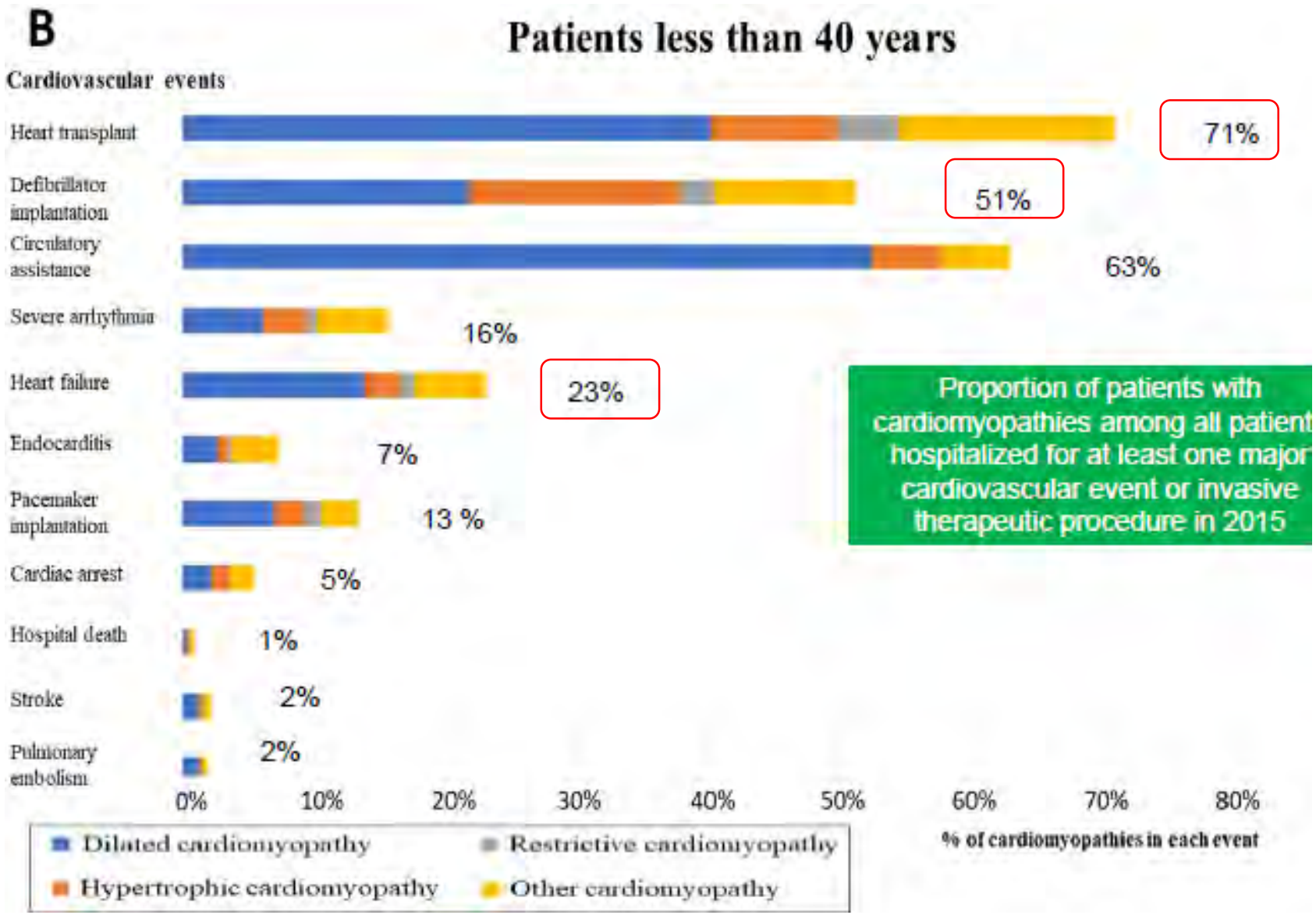
Maladies Artérielles

- **Hyperchol.fam.** (prévalence 1/500)
- **Syndrome de Marfan** (1/5.000)
- **Syd Ehlers Danlos, Rendu-Osler, etc**

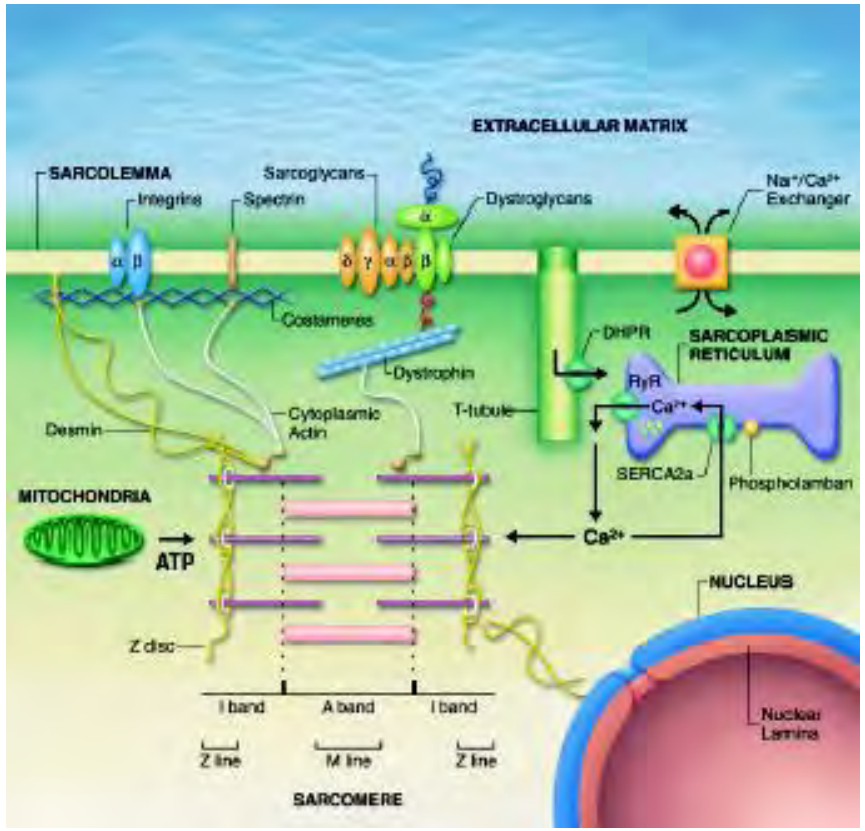
Epidémiologie & Place des **Cardiomyopathies**

Registre hospitalier national PMSI

Lannou, …Charron.
J Clin Med 2020



Identification des genes & Compréhension de la physiopathologie



- Cardiomyopathies
  - Hypertrophiques (proteines du sarcomère)
  - Dilatées (proteines titine, lamines A/C, etc)
  - DVDA (desmosomes: jonctions inter C)
- Troubles du rythme
  - Syndrome du QT long (canaux K et Na)
  - Brugada (canal Na)
- Maladie de la paroi artérielle
  - Maladie de Marfan (Fibrilline: matrice EC)

- Transmission: le plus svt **autosomique dominante**
- Gènes nombreux (hétérogénéité génétique)
- Mutations : nombreuses (aucune ne prédomine)

Intégration du test génétique dans la pratique

→Reco class I
for genetic testing
in patients with HCM

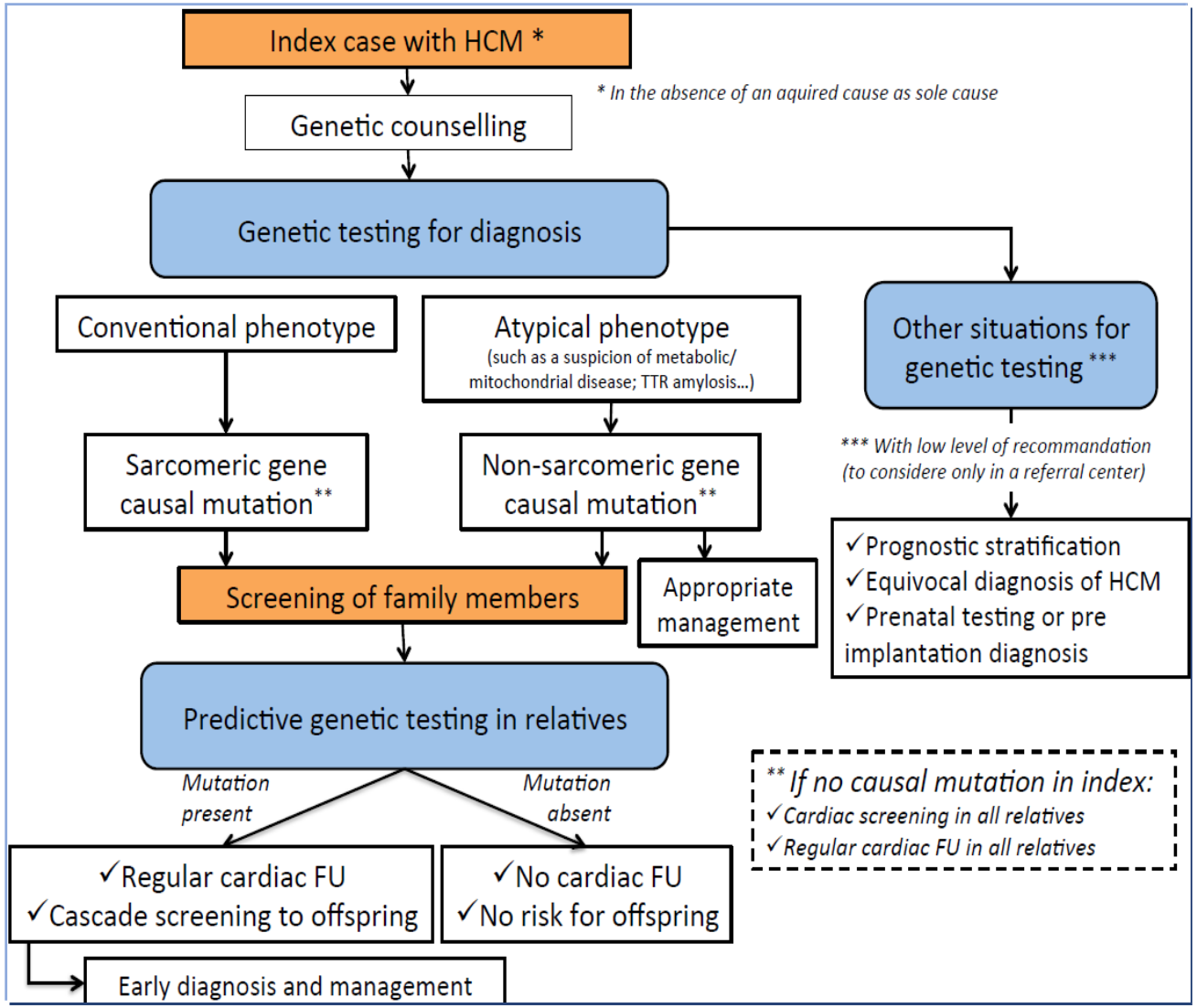
ESC WG 2010
ESC GL 2014
PNDS nov 2021

→Reco

International Consensus Statement 2022
Genetic testing in cardiac diseases
Wilde et al. Europace

ESC GL 2022
patients with VA & prevention of SCD
Zeppenfeld et al. EHJ

ESC GL 2023
Management of Cardiomyopathies
Arbelo et al. EHJ

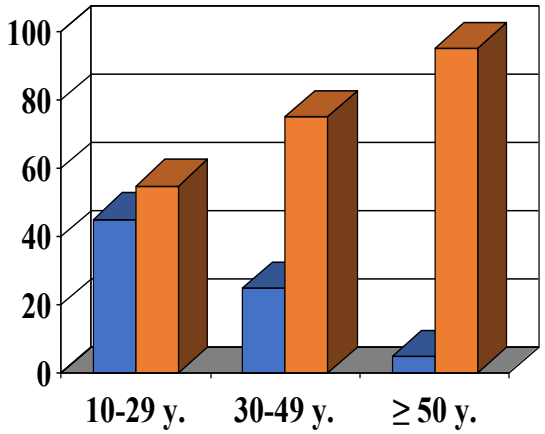


ESC Textbook, chapter on HCM & Genetics. Charron P & al, 2018

- Introduction
- **Pourquoi faire un test génétique ?**
- Comment faire un test génétique?
- Intégration de la génétique dans le diagnostic étiologique de la CMH

(1) Test génétique pour le dépistage familial

- Delayed cardiac expression (penetrance)



Clinical diagnosis of HCM during life in mutation carriers

Charron P et al. Circulation 1997

- Confirmed by FU of mutation carriers

Following a first negative screening, approximately 50% of mutation carriers develop HCM over 15 years of FU.

Lorenzini et al, JACC 2020

- Paediatric population (524 children < 18 y.)

In children < 10 y. of age: 9.9% had HCM on echo;
Freedom from a MaCE at 10 y. was 98.4% and freedom from death/aborted SCD was 99.6% at 10 y.

Lafreniere-Roula et al, EHJ 2019

Family screening is a major issue for early detection and early management

Cascade-screening according to genetic testing is the optimal strategy

(stop FU in genotype-negative relatives and continue FU in genotype-positive relatives)

Very rare major CV complications before 10 years *(but some)*

Organiser le bilan ♥ familial - *cardiomyopathies*

(en l'absence de données génétiques disponibles)

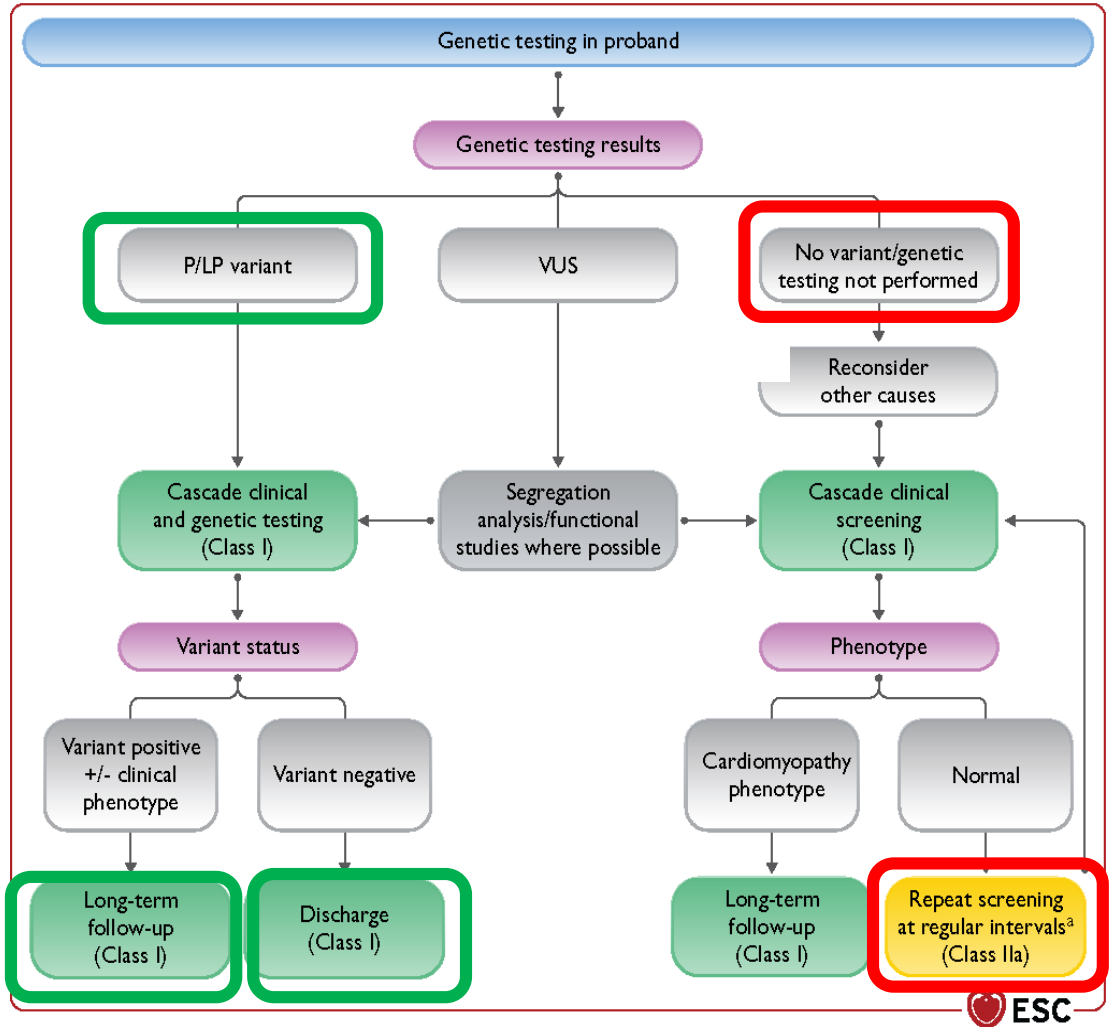
Qui ? Quels examens ? Quand débuter ? Quel rythme de surveillance ?

	CMH	CMD	CVDA	CMR	NCVG
Evaluation cardiaque	ECG, Echocardiographie	ECG, Echocardiographie	ECG, Echocardiographie, Holter-ECG, ECG-HA	ECG, Echocardiographie	ECG, Echocardiographie
Age début évaluation	10 ans	Enfance (sauf laminopathies: 10 ans)	10 ans	10 ans	Néonatal
Périodicité des examens	- tous les 1-2 ans entre 10 et 20 ans - tous les 2-5 ans après 20 ans	- Tous les 1-3 ans avant 10 ans - tous les 1-2 ans entre 10 et 20 ans - tous les 2-5 ans après 20 ans	- tous les 1-2 ans entre 10 et 20 ans - tous les 2-5 ans après 20 ans	- tous les 1-2 ans entre 10 et 20 ans - tous les 2-5 ans après 20 ans	- Tous les 1-3 ans avant 20 ans - Tous les 2-5 ans après 20 ans
Age arrêt évaluation	50-60 ans	50-60 ans	50-60 ans	50-60 ans	50-60 ans

→ ***Donner support écrit / lettre à transmettre dans famille***

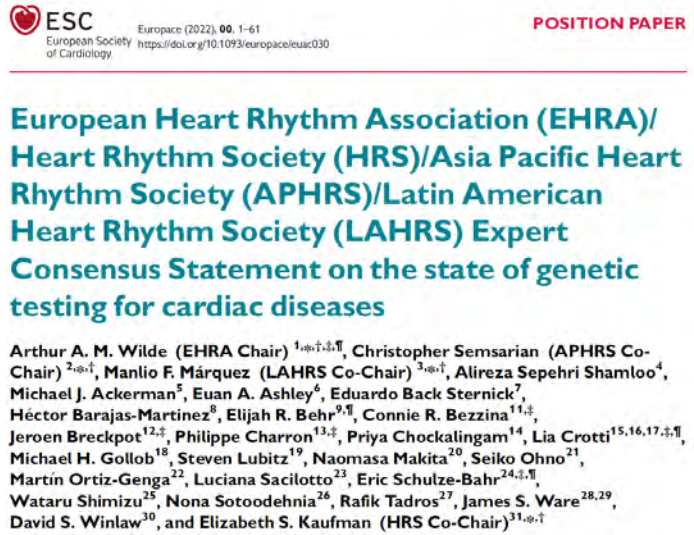
d'après ESC WG Position Statement paper, EHJ 2010

Test génétique et screening familial (test prédictif)



Arbelo E et al. ESC CMPs Guidelines 2023

Recommendation	Class
Predictive genetic testing in related children is recommended in those aged >10-12 years.	
Predictive genetic testing in related children aged below 10-12 years may be considered, especially where there is a family history of early-onset disease.	


ESC European Society of Cardiology Europace (2022), 00, 1–61 https://doi.org/10.1093/europace/euac030

POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Arthur A. M. Wilde (EHRA Chair) [1,*,†,‡,¶], Christopher Semsarian (APHRS Co-Chair) [2,*,†], Manlio F. Márquez (LAHRS Co-Chair) [3,*,†], Alireza Sepehri Shamloo[4], Michael J. Ackerman[5], Euan A. Ashley[6], Eduardo Back Sternick[7], Héctor Barajas-Martinez[8], Elijah R. Behr[9,¶], Connie R. Bezzina[11,‡], Jeroen Breckpot[12,‡], Philippe Charron[13,‡], Priya Chockalingam[14], Lia Crotti[15,16,17,‡,¶], Michael H. Gollob[18], Steven Lubitz[19], Naomasa Makita[20], Seiko Ohno[21], Martín Ortiz-Genga[22], Luciana Sacilotto[23], Eric Schulze-Bahr[24,‡,¶], Wataru Shimizu[25], Nona Sotoodehnia[26], Rafik Tadros[27], James S. Ware[28,29], David S. Winlaw[30], and Elizabeth S. Kaufman (HRS Co-Chair)[31,*,†]

Wilde et al. Europace 2022

Impact du test génétique prédictif chez les apparentés

Mutation identifiée dans la famille (chez le cas index)

Test génétique chez l'apparenté « sain »

Pas de mutation

- **Pas de suivi médical** ++
- Pas de risque de transmission à la desendance ++

Présence d'une mutation

Suivi médical ++
(écho, ECG…)

Dépistage précoce de l'expression cardiaque

Mise en place traitement
(ex IEC si CMD aΣ)

Prévention
Décès cardiaque ++

Discuter restriction sportive
(CVDA/DVDA surtout)

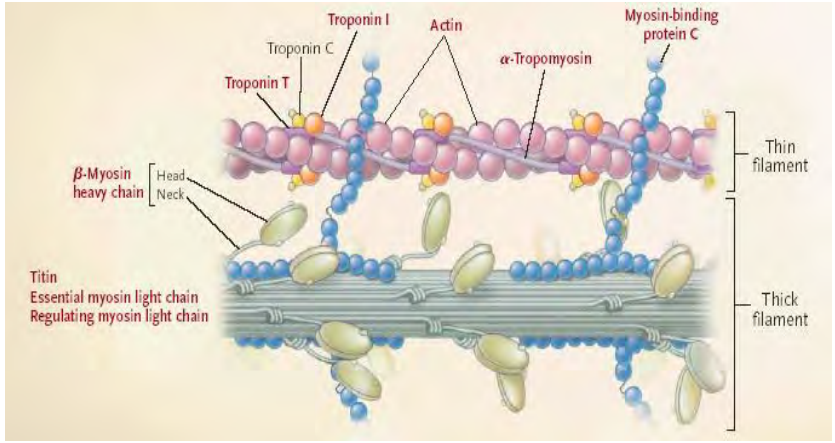
Discuter ttt médical
(BêtaBloq /QTL)

Liste Md contre indiqués
(QTL, Brugada)

(2) Test génétique pour le bilan étiologique et la prise en charge thérapeutique

Causes génétique hétérogènes pour une même maladie, ex CMH

HCM and sarcomeric causes
(30-60%)
autosomal dominant inheritance



Main prevalent sarcomeric genes	Gene	Locus	Frequency
Thick filament :			
β-myosin heavy chain	*MYH7*	14q11.2	20-30%
Regulatory myosin light chain	*MYL2*	12q23-q24	2-4%
Essential myosin light chain	*MYL3*	3p21.3	1-2%
Intermediate filament :			
Cardiac myosin-binding protein C	*MYBPC3*	11p11.2	30-40%
Thin filament :			
Cardiac troponin T	*TNNT2*	1q32.1	5-10%
Cardiac troponin I	*TNNI3*	19q13.4	4-8%
α-tropomyosin	*TPM1*	15q22.1	<1%
α-cardiac actin	*ACTC1*	15q11q14	<1%

HCM & genetic but *non* sarcomeric causes
(5-25%)

Main *non*-sarcomeric genes	Gene	Associated phenotype	Inheritance /Frequency
Galactosidase, alpha	*GLA*	Fabry disease	X Linked / 1-2% of males
Transthyretin	*TTR*	Amyloidosis	Dominant / 1-5%
Lysosomal-associated membrane protein 2	*LAMP2*	Danon disease	X Linked / rare
Protein kinase, AMP-activated, gamma 2 subunit	*PRKAG2*	Wolff Parkinson White synd.	Dominant / rare
Four and a half LIM domains 1	*FHL1*	FHL1 related diseases	X Linked / rare
Glucosidase, alpha	*GAA*	Pompe disease	Recessive / rare
Protein tyrosine phosphatase, non-receptor type 11	*PTPN11*	Noonan disease	Dominant / rare
Frataxin	*FXN*	Friedreich disease	Recessive / rare
Mitochondrial genes	*Mitochondrial DNA*	MERFF & MELAS	Mitochondrial / rare

Unknown
25-50%

Non genetic causes
AL or senile TTR amyloidosis
Newborn of diabetic mother
Drug-induced (tacrolimus, hydroxychloroquine, steroid)

Veselka, Anavekar & Charron. Lancet 2017 389(10075):1253

(1a) Impact thérapeutique direct du diagnostic étiologique (ex CMH)

Important to make appropriate diagnosis of **genetic**
but *non* sarcomeric causes
causes (5-25%)

>40 genes

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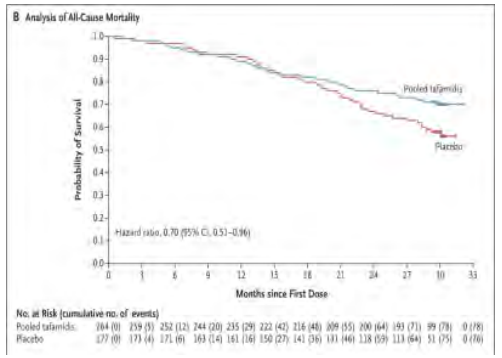
Veselka, Anavekar & Charron. Lancet 2017

Delay in diagnosis
= delay in therapy
= loss of chance

Important to make
appropriate etiology diagnosis

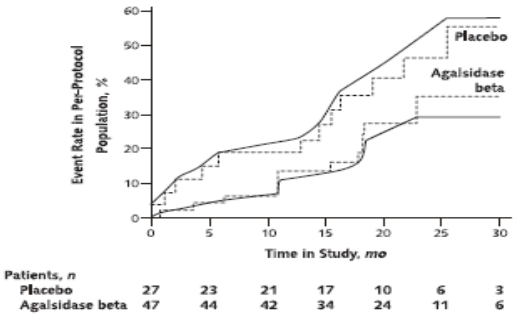
.since inheritance may be ≠,
.complications may be ≠,
.therapy may be very different,

especially for non-sarcomeric causes



Tafamidis
In TTR cardiac amyloidosis

Maurer et al. New Engl J Medicine 2018



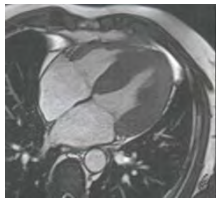
Enzyme replacement ERT or
chaperone drug in Fabry disease

Banikazemi *et al. Ann Intern Med* 2007

Pourquoi est il important de faire le diagnostic de maladie de Fabry ?

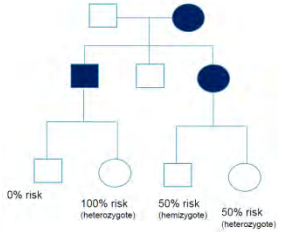
1. Une maladie pas si rare

1,5% des CMH

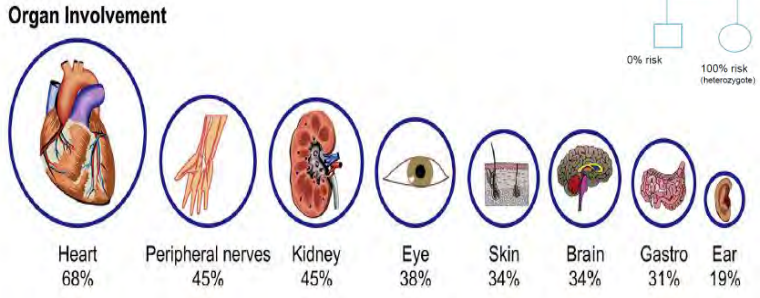


2. Une atteinte ♥ sévère

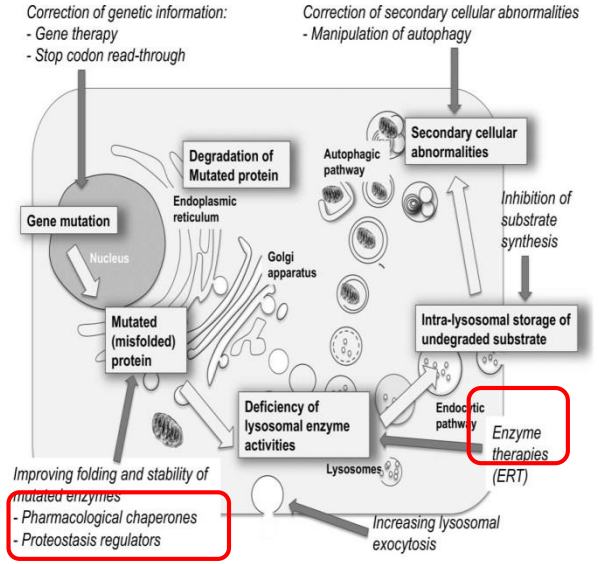
Décès 55 ans chez H



3. Une maladie liée à l'X



4. Des traitements spécifiques



Parenti et al. IJMM 2012

5. Un lien entre retard au diagnostic & efficacité du TT

Germain DP. *Orphanet J Rare Dis*. 2010;5:30;
Parenti G et al. Int J Mol Med 2012;nov12:11
Protocole National de Diagnostic et de Soins. Maladie de Fabry. Novembre 2021.

(1b) Impact thérapeutique direct du diagnostic étiologique (ex CMH)

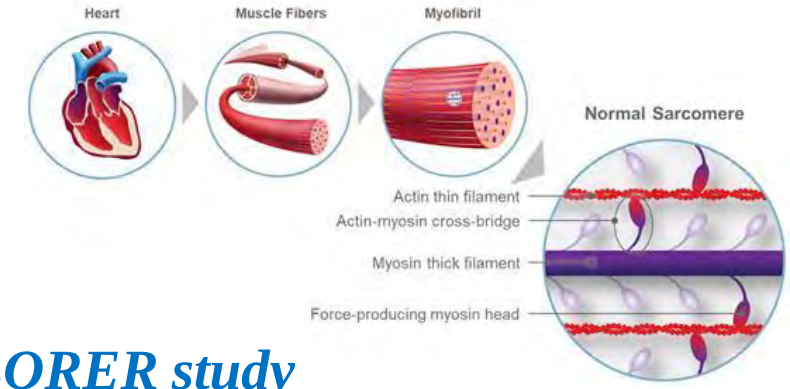
More and more important **to affirm a sarcomeric genetic origin**:

- Appropriate therapeutic management, including risk stratification (SCD) & ICD decision
- Appropriate genetic counselling & family screening
- Appropriate new therapy?

New pharmacological targets (small molecules)

mavacamten, aficamten in sarcomeric HCM

(targeted myosin inhibitor)



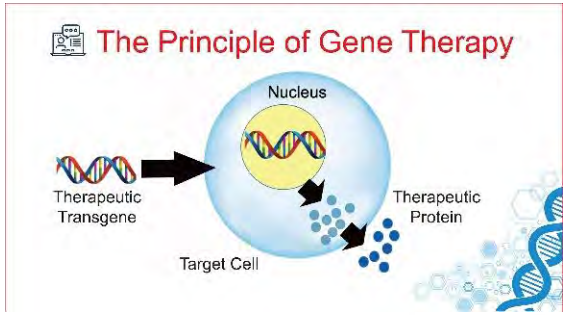
EXPLORER study

Olivotto I. et al. Lancet 2020;396:759

→ Mavacamten: Early access in France November 2023 ++

New therapeutic strategies

ARNi, microRNA, ASO antisense oligonucleotide, gene therapy



TENAYA™ THERAPEUTICS

Tenaya Therapeutics Doses First Patient in the MyPeak-1™ Phase 1b Clinical Trial of TN-201 for the Treatment of MYBPC3-Associated Hypertrophic Cardiomyopathy

October 5, 2023

→ 1st case of gene therapy in sarcomeric HCM (phase 1b, Cleveland) in human, October 2023 ++

→ Towards precision medicine related to etiology-directed therapy

(1b) Impact thérapeutique direct du diagnostic étiologique (ex QT long)

Syndrome du QT long

- KCNQ1
- HERG
- SCN5A
- KCNE1
- KCNE2
- Ankyrine B…

Bbloquant

Gène SCN5A (canal sodique)

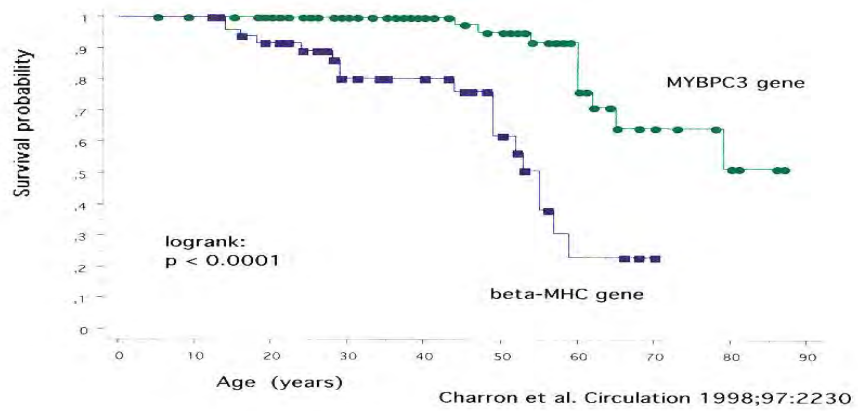
- Impliqué dans 5-8% environ
- Gain de fonction du canal
- Contexte torsades/FV: repos surtout
- **Moins bonne efficacité des Beta-bloquants +**
- **Indication inhibiteur canaux sodiques (mexiletine)**
- Indication plus facile à un défibrillateur

Mexiletine is indicated in LQT3 patients with a prolonged QT interval.[94B]	I

ESC guideline 2022 on SCD

(3) Test génétique pour le bilan étiologique et la stratification du pronostic *(et la décision d'implantation de défibrillateur en prévention primaire)*

(3a) diagnostic étiologique & stratification pronostique (ex CMH)



- **SCD more important in TNNT2 vs MYBPC3 families**

Circ Cardiovasc Genet 2012;5(2):156 & 2012;5(1):10

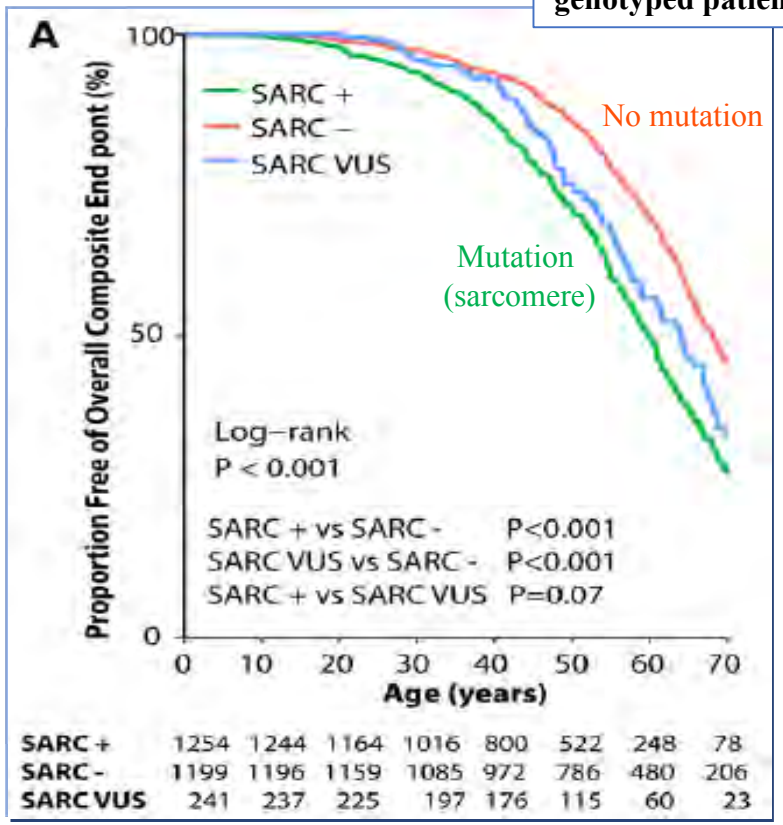
- **Poor prognosis in patients with multiple mutations**

Richard P, Circulation 2003 *Biagini E, Am J Cardiol 2014;114:769*

- **Poor prognosis in HCM pts with sarcomeric mutation vs non-sarcomeric mutation (unknown cause)**

Van Velzen, AJC 2016;118:881 *Ho CY Circulation 2018;138:1387*

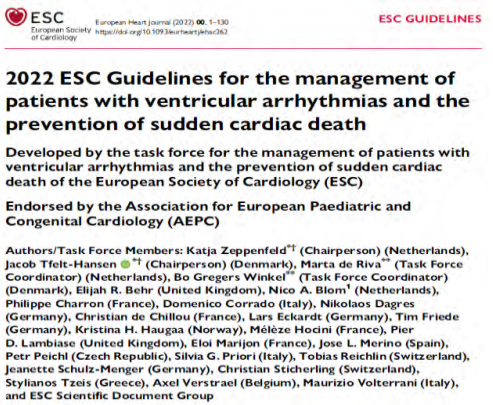
2763 HCM genotyped patients



Ho CY Circulation 2018;138:1387

Intérêt d'analyses prospectives et multivariées → PHRC national OPTIM-HCM (en cours, PI P Charron)

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death


ESC European Heart Journal (2022) 00, 1–130 https://doi.org/10.1093/eurheartj/ehac262 ESC GUIDELINES

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Katja Zeppenfeld*† (Chairperson) (Netherlands), Jacob Tfelt-Hansen*† (Chairperson) (Denmark), Marta de Riva** (Task Force Coordinator) (Netherlands), Bo Gregers Winkel** (Task Force Coordinator) (Denmark), Elijah R. Behr (United Kingdom), Nico A. Blom† (Netherlands), Philippe Charron (France), Domenico Corrado (Italy), Nikolaos Dagres (Germany), Christian de Chillou (France), Lars Eckardt (Germany), Tim Friede (Germany), Kristina H. Haugaa (Norway), Mélèze Hocini (France), Pier D. Lambiase (United Kingdom), Eloi Marijon (France), Jose L. Merino (Spain), Petr Peichl (Czech Republic), Silvia G. Priori (Italy), Tobias Reichlin (Switzerland), Jeanette Schulz-Menger (Germany), Christian Sticherling (Switzerland), Stylianos Tzeis (Greece), Axel Verstrael (Belgium), Maurizio Volterrani (Italy), and ESC Scientific Document Group

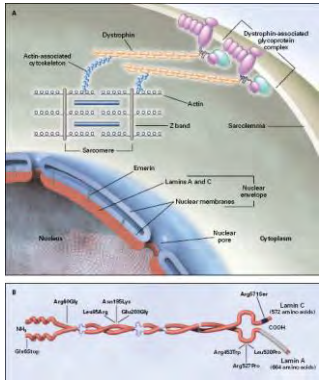
Zeppenfeld et al. Eur Heart J 2022

Recommandations in HCM	Class	LOE
ICD implantation should be considered in patients aged 16 years or more with an estimated 5-year risk of SD ≥6%.*	IIa	B
ICD implantation should be considered in HCM patients aged 16 years or more with an intermediate 5-year risk of SCD (≥4 to <6%)* and with (a) significant LGE at CMR (usually ≥15% of LV mass); or (b) LVEF <50%; or (c) abnormal blood pressure during exercise test &; or (d) LV apical aneurysm; or (e) presence of sarcomeric pathogenic mutation.	IIa	B
ICD implantation may be considered in individual HCM patients aged 16 years or more with a low estimated 5-year risk of SCD (<4%)* and with (a) significant LGE at CMR (usually ≥15% of LV mass); or (b) LVEF < 50%; or (c) LV apical aneurysm.	IIb	B

But genetics ***not*** recommended in ESC GL 2023 on Cardiomyopathies…

(3b) diagnostic étiologique & stratification pronostique (ex CMD)

*DCM related to **Lamin A/C mutations** **(LMNA gene)***



- Particular phenotype :
  - early AVB / sinus dysfunction
    +/- SV or V arrhythmia
  - DCM
  - +/- skeletal myopathy
- Inheritance:
  - autosomal dominant

Fatkin et al., NEJM 1999;341:1715
Bonne et al, Nat Genet 1999;21:285

Meta-analysis of 8000 DCM patient
Kayvanpour Clin Res Cardiol 2017;106(2):127

LMNA gene associated with:

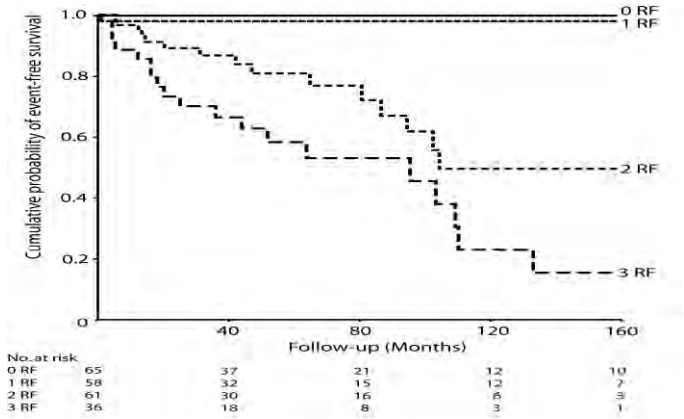
- Highest rate of conduction defect (73%)
- Highest rate of malignant ventricular arrhythmia (50%)
- Highest rate of Heart Transplant (27%)

High risk of MACE → pro-active therapy *(including early ICD)*

Indication for defibrillator in lamin A/C gene ?

van Rijsingen et al. J Am Coll Cardiol 2012

269 mutation carriers, FU 46 months



- European Registry to identify predictors of malignant ventricular arrhythmia:

→ 4 independent predictors :

- NSVT,
- LVEF < 45%,
- Male gender
- Truncating mutation (Ins-del/nonsense/splice site)

ICD reasonable if 2 criteria

Nota bene: C index 0.76 in Thuillot et al. EJHF 2019

Whabi K et al. Circulation 2019

444 French pts (derivation) + 145 pts (replication), FU 3.6 & 5.1 years

Table 2. Associations between predictors and survival in the derivation sample

	Model			
	Full multiple variable	***p***	**Final**	***p***
Age at baseline, years	0.99 (0.97-1.01)	0.200		
Men	1.80 (1.1-2.95)	0.029	1.67 (1.1-2.55)	0.017
Non-missense *LMNA* mutation	1.78 (1.12-2.85)	0.043	1.76 (1.16-2.65)	0.007
AV block				
1st degree*	2.74 (1.34-5.61)	0.002	2.35 (1.34-4.12)	0.003
>1st degree†	3.51 (1.5-8.19)	0.001	2.86 (1.54-5.31)	<0.001
Atrial arrhythmia	1.19 (0.71-1.99)	0.524		
Non-sustained VT	2.25 (1.34-3.79)	0.002	2.15 (1.36-3.41)	0.001
Left ventricular ejection fraction, %	0.98 (0.96-1.00)	<0.001	0.98 (0.97-1)	0.017

- **Modelisation** of risk of life-threatening ventricular tachyarrhythmia (LTVTA) / **risk calculator**:
- Derivation sample, C-index of the model was 0.776 and calibration slope 0.827. External validation sample, C-index 0.800 and calibration slope 1.082.
- A 5-year estimated risk threshold ≥7% predicted 96.2% of LTVTA; and net reclassified 28.8% of patients with LTVTA compared with the guidelines-based approach.

ICD implantation should be considered in DCM/HNDCM patients with a pathogenic mutation in *LMNA* gene, if the estimated 5-year risk of life-threatening VA is ≥10%* **AND** in the presence of NSVT or LVEF <50% or AVB. (Class IIa) **Based on the risk calculator*

2022 ESC Guidelines for the prevention of sudden cardiac death

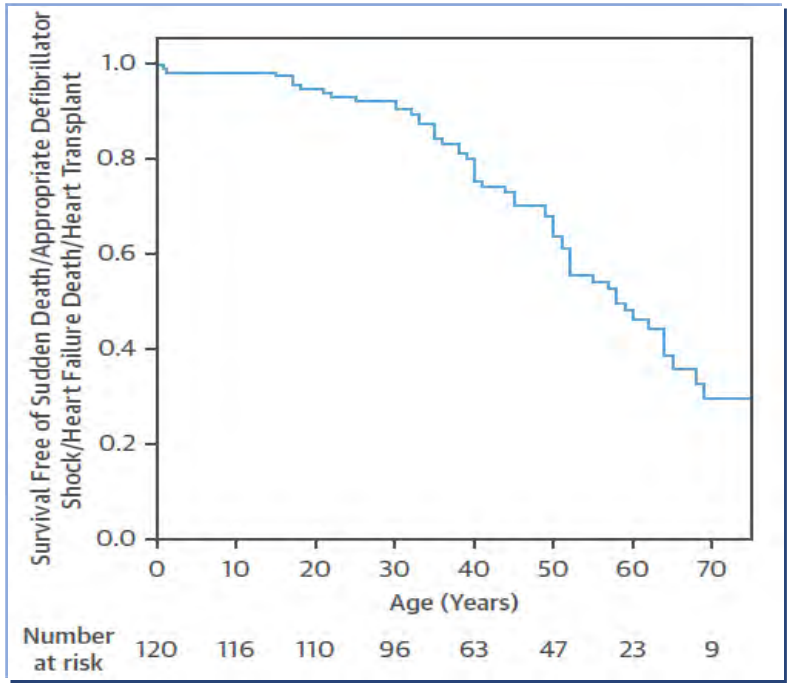
*DCM related to **Filamin C mutations** (FLNC gene)*

FLNC pathogenic variants in patients with cardiomyopathies: Prevalence and genotype-phenotype correlations

Flavie Ader[1,2,3] | Pascal De Groote[4] | Patricia Réant[5] | Caroline Rooryck-Thambo[6] | Delphine Dupin-Deguine[7] | Caroline Rambaud[8] | Diala Khraiche[9] | Claire Perret[2] | Jean François Pruny[10] | Michèle Mathieu-Dramard[11] | Marion Gérard[12] | Yann Troadec[12] | Laurent Gouya[13] | Xavier Jeunemaitre[14] | Lionel Van Maldergem[15] | Albert Hagège[16] | Eric Villard[2] | Philippe Charron[2,10] | Pascale Richard[1,2,10]

- An FLNC pathogenic variant was identified in 1% to 8% of 1150 index cases with a CMP, depending on the cardiomyopathy subtype.
- **Truncating variants** were always identified in patients with dilated cardiomyopathy, while missense or in-frame indel variants were found in other phenotypes.
- A personal or family history of **sudden cardiac death** (SCD) was significantly **higher in patients with truncating variants** than in patients carrying missense variants (P =0.01).

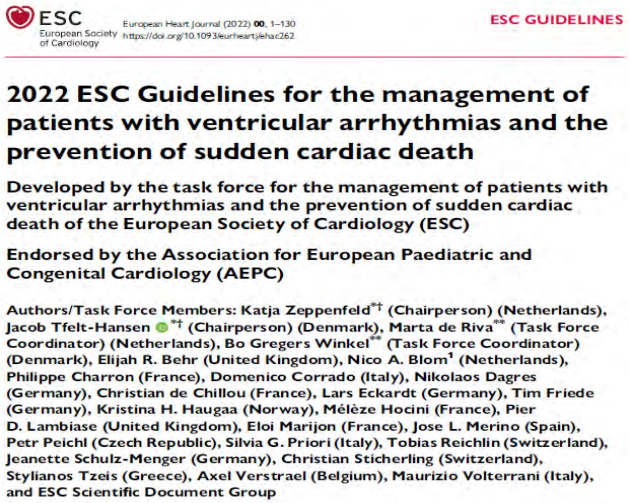
Ader F, Clin Genet 2019;96(4):317-329



High risk of SCD / VA associated with **Filamin C** (FLNCtv) mutations

Ortiz-Genga, JACC 2016;68(22):2440-2451

→ Génétique et stratification du risque de MS dans la CMD


ESC European Society of Cardiology European Heart Journal (2022) 00, 1–130 https://doi.org/10.1093/eurheartj/ehac262 ESC GUIDELINES

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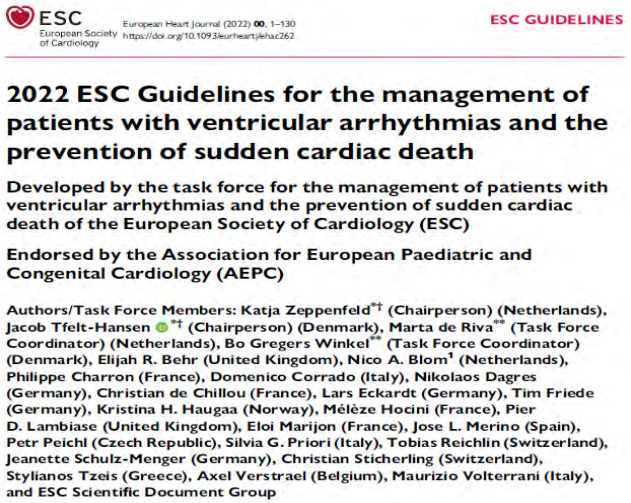
2022 ESC Guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death

Recommandations in DCM	Class	LOE
ICD implantation should be considered in patients with DCM/HNDCM, symptomatic heart failure (NYHA class II-III), and LVEF ≤35% after ≥3 months of optimal medical therapy.	IIa	A

Zeppenfeld et al. Eur Heart J 2022

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death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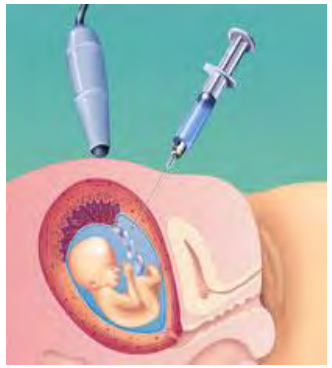
Recommandations in DCM	Class	LOE
ICD implantation should be considered in patients with DCM/HNDCM, symptomatic heart failure (NYHA class II-III), and LVEF ≤35% after ≥3 months of optimal medical therapy.	IIa	A
ICD implantation should be considered in DCM/HNDCM patients with an LVEF<50%) and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at EPS, pathogenic mutations in *PLN*, *FLNC*, and *RBM20* genes).	IIa	C
ICD implantation should be considered in DCM/HNDCM patients with a pathogenic mutation in *LMNA* gene, if the estimated 5-year risk of life-threatening VA is ≥10%* **AND** in the presence of NSVT or LVEF <50% or AVB. **Based on the risk calculator*	IIa	B

Zeppenfeld et al. Eur Heart J 2022

(4) Test génétique et Procréation



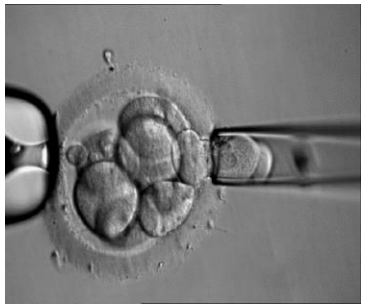
- **Prenatal diagnosis**
  - Through amniocentesis or chorionic villus sampling
  - Then, discuss pregnancy termination if mutation present
  - Only case by case discussion in HCM

PRENATAL DIAGNOSIS
Prenat Diagn 2004; **24**: 701–703.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/pd.969

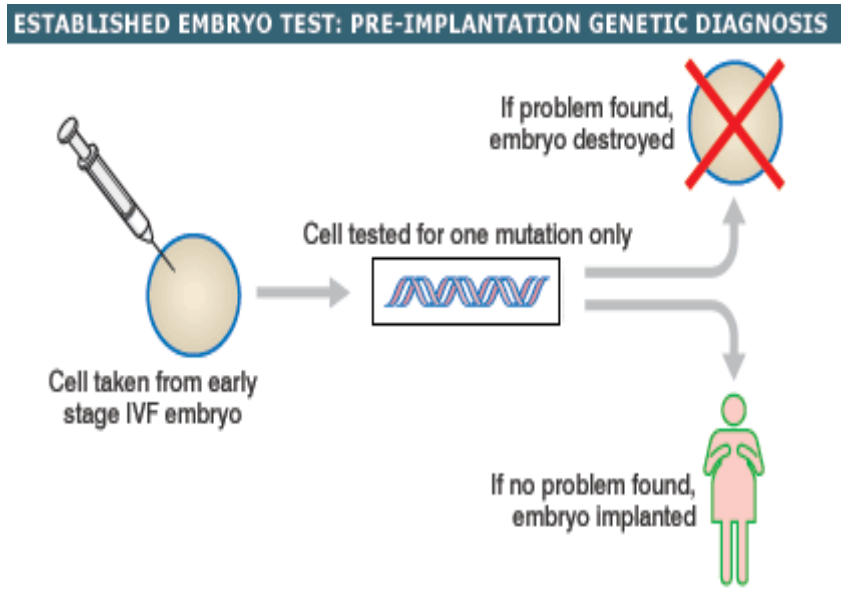
SHORT COMMUNICATION

Prenatal molecular diagnosis in hypertrophic cardiomyopathy: report of the first case

Philippe Charron[1,2]*, Delphine Héron[1], Marcela Gargiulo[1], Josué Feingold[1], Jean-François Oury[3], Pascale Richard[4] and Michel Komajda[2]



- **Pre-implantation diagnosis**

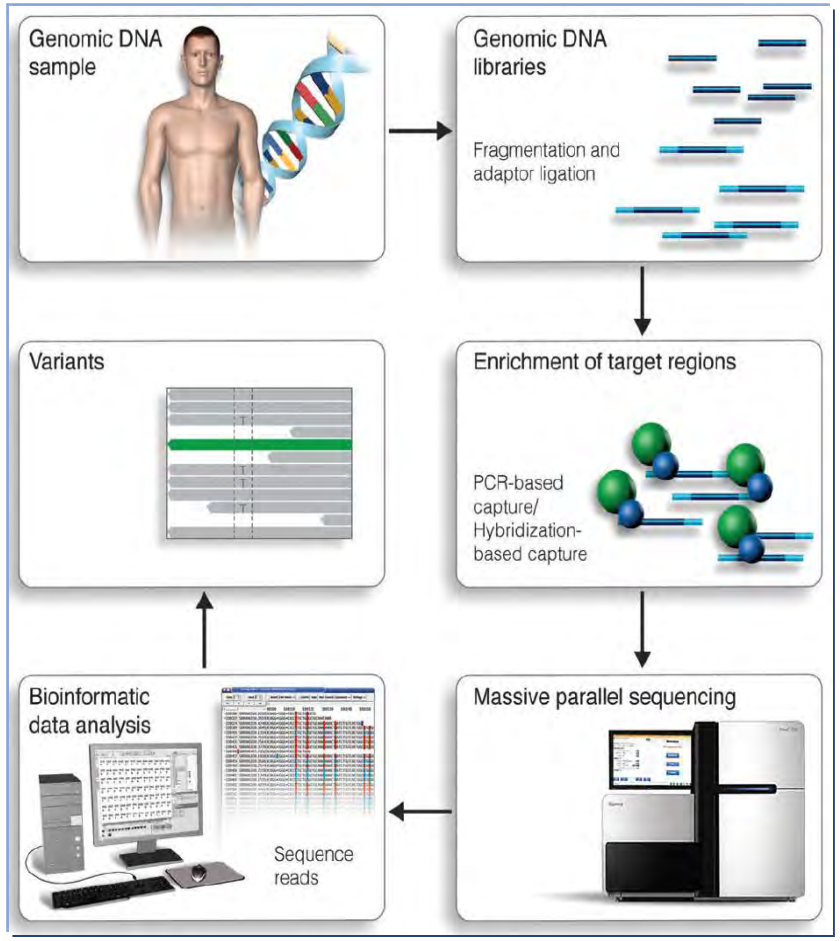


Kuliev A, et al. Reprod Biomed Online. 2012 Apr;24(4):443-53

- Introduction
- Pourquoi faire un test génétique ?
- **Comment faire un test génétique?**
- Intégration de la génétique dans le diagnostic étiologique de la CMH

Modalités du test génétique?

Next generation sequencing / High throughput sequencing



Ho, Charron, et al. Cardiovasc Res 2015;105(4)397

Panels for routine diagnosis

Pascale Richard & Ph. Charron, Hôpital Pitié-Salpêtrière, Paris

Cardiomyopathies

- Level 1: Panel **16 genes (CMH)**

(MYBPC3, MYH7, TNNT2, TPM1, TNNC1, TNNI3, MYL2, MYL3, ACTC1, ACTN2, FHL1, FLNC, GLA, LAMP2, PRKAG2, TTR)

- Level 2: Panel **>70 genes (autre CMP)**

(all phenotypes, phenocopies, & neonatal forms)

cardiogen
filière nationale de santé maladies cardiaques héréditaires ou rares

New 2020: décision Filière Cardiogen passer de 5 à 16 gènes au niveau nationa

Whole Genome Sequencing

- Plan France Médecine Génomique

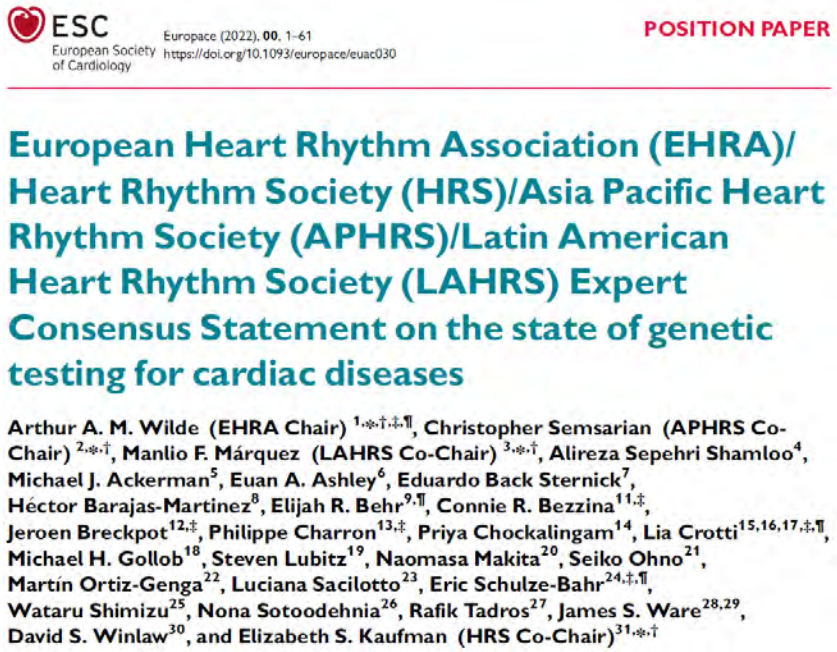
(pré-indication « cardiomyopathies », Ph Charron & P Richard, étude pilote en cours en soin courant)

HCM in EHRA/HRS/AHRS/LHRS genetic testing consensus statement *(2022)*

-which genes to test?

Recommendation	Class
For genetic testing in a proband with HCM (including those cases diagnosed post-mortem), the initial tier of genes tested should include genes with definitive or strong evidence of pathogenicity (currently *MYH7, MYBPC3, TNNI3, TPM1, MYL2, MYL3, ACTC1,* and *TNNT2*).	
For genetic testing in a proband with HCM, the initial tier of genes tested may include genes with moderate evidence of pathogenicity (*CSRP3, TNNC1, JPH2*).	

Wilde et al. Europace 2022



ESC European Society of Cardiology

Europace (2022), 00, 1–61
https://doi.org/10.1093/europace/euac030

POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Arthur A. M. Wilde (EHRA Chair)[1,*,†,‡,¶], Christopher Semsarian (APHRS Co-Chair)[2,*,†], Manlio F. Márquez (LAHRS Co-Chair)[3,*,†], Alireza Sepehri Shamloo[4], Michael J. Ackerman[5], Euan A. Ashley[6], Eduardo Back Sternick[7], Héctor Barajas-Martinez[8], Elijah R. Behr[9,¶], Connie R. Bezzina[11,‡], Jeroen Breckpot[12,‡], Philippe Charron[13,‡], Priya Chockalingam[14], Lia Crotti[15,16,17,‡,¶], Michael H. Gollob[18], Steven Lubitz[19], Naomasa Makita[20], Seiko Ohno[21], Martín Ortiz-Genga[22], Luciana Sacilotto[23], Eric Schulze-Bahr[24,‡,¶], Wataru Shimizu[25], Nona Sotoodehnia[26], Rafik Tadros[27], James S. Ware[28,29], David S. Winlaw[30], and Elizabeth S. Kaufman (HRS Co-Chair)[31,*,†]

Evaluating the Clinical Validity of Hypertrophic Cardiomyopathy Genes

ClinGen Clinical Genome Resource

Genetic panels include most high-evidence genes; but also genes lacking robust evidence. We recommend caution with the interpretation of variants & genes!

Ingles J al. Circ Genom Precis Med. 2019;12:e002460

Aspects médico-légaux du test génétique prédictif

Décret n° 2000-570 du 23 juin 2000

Conditions de prescription et communication des résultats

« Le consentement…doit être libre et éclairé par une information préalable... et donné par écrit »

« Chez une personne asymptomatique…la prescription …ne peut avoir lieu que dans le cadre d ’une consultation médicale individuelle…effectuée par un médecin oeuvrant au sein d ’une équipe pluridisciplinaire rassemblant des compétences cliniques et génétiques. Cette équipe doit…être déclarée au ministre chargé de la santé »

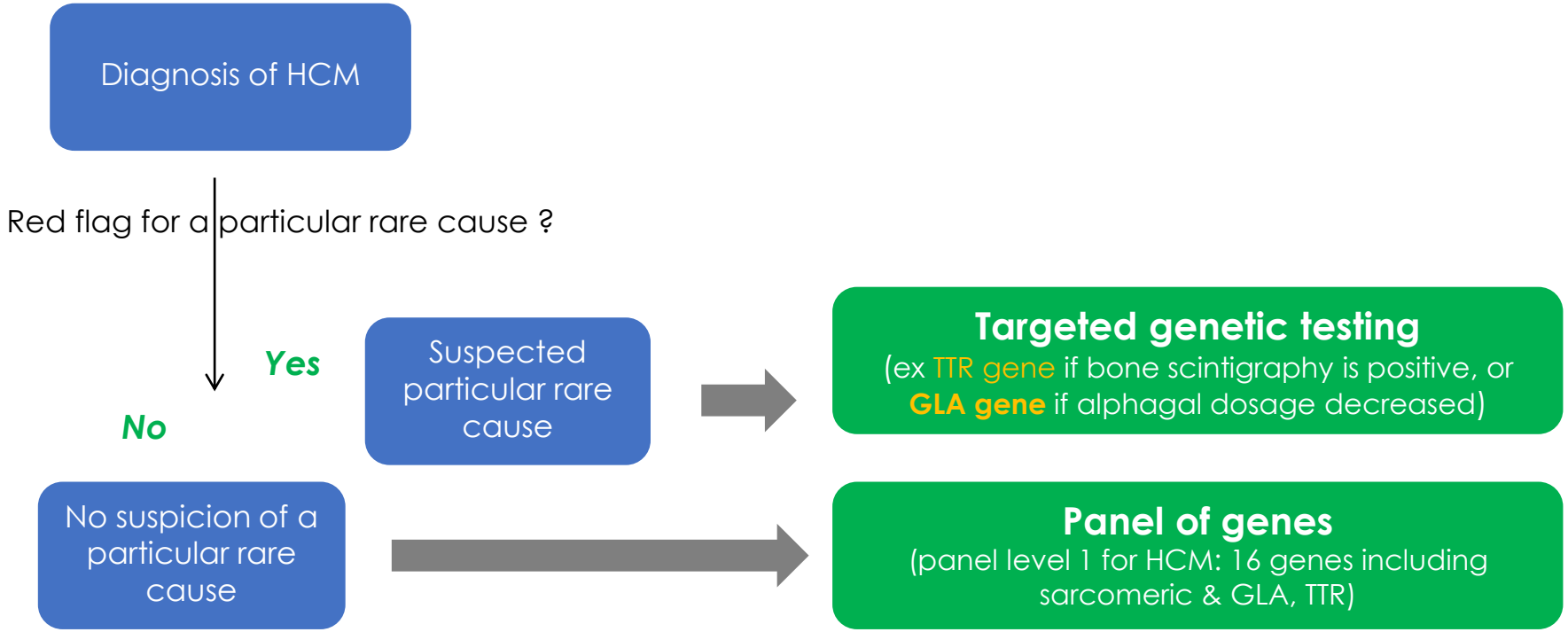
« Le médecin consulté délivre une attestation… (qui) est remise au praticien agrée réalisant l ’examen »

« le compte rendu d ’analyse…signé par un praticien responsable agréé…doit être adressé exclusivement au praticien prescripteur des examens génétiques »

« Le médecin prescripteur ne doit communiquer les résultats de l ’examen… qu’à la personne concernée…(et) dans le cadre d ’une consultation médicale individuelle »

Stratégies pour le test génétique?

2 stratégies en fait pour le test génétique dans une cardiomyopathie (ex CMH)



Role of expert multidisciplinary teams for genetic testing/counselling

- **Expertise in interpretation of variants (pathogenic versus uncertain significance, genes of interest or not, etc)**
- **Legal issues (informed consent, prescription attestation, report to transmit or not , etc)**
- **Multidisciplinary consultation (cardiologist, geneticist, psychologist) and regular multidisciplinary meetings**

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares

cardiogen
filière nationale de santé
maladies cardiaques héréditaires ou rares

www.filiere-cardiogen.fr

Centres ressources
Des équipes médicales/paramédicales pluridisciplinaires labellisées par le Ministère de la Santé

3 thématiques:
CMP: cardiomyopathies
TDR: troubles du rythme
CCC: cardiopathies congénitales complexes

- **4** Centres de **référence**

  Hôpital Pitié Salpêtrière Paris – Pr. Philippe CHARRON *(CMP & TDR)*
  10 Sites constitutifs : APHP Ambroise Paré, Bichat, HEGP, Henri Mondor, Necker ,
  Bordeaux, Marseille, Toulouse, Rennes, Nantes

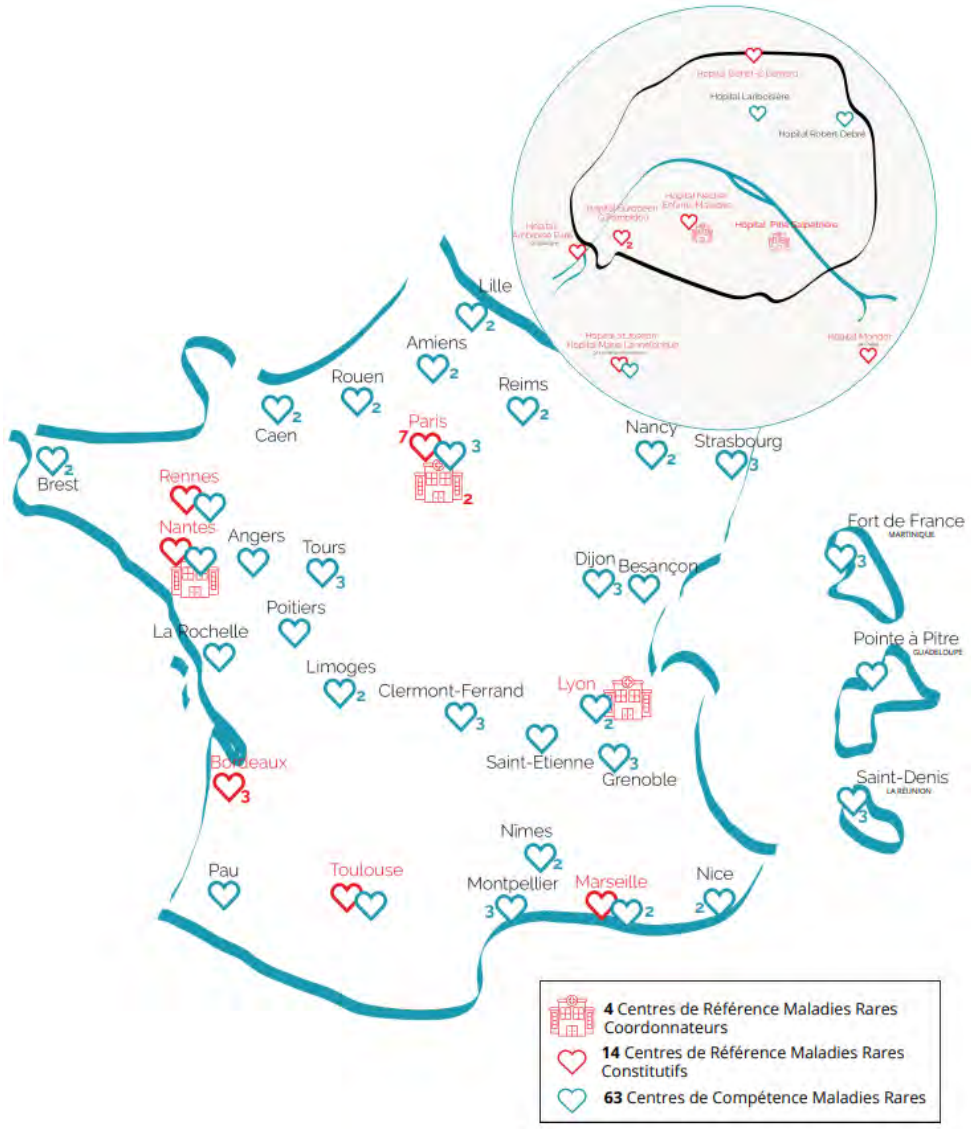
  Hôpital Nantes – Pr. Vincent PROBST *(TDR)*
  1 Site constitutif : CHU Bordeaux

  Hôpital Lyon - Pr. Philippe CHEVALIER *(TDR)*

  Hôpital Necker Paris – Pr. Damien BONNET *(CCC)*
  3 Sites constitutifs : CHU de Bordeaux, HEGP,
  Centre Chirurgical Marie-Lannelongue,

- **64** Centres de **compétence** (métropole et Outre-mer)
- **11 Associations de patients**
- **5 Laboratoires** médicaux de diagnostic **génétique**
  4 Laboratoires de recherche (Inserm/CNRS)

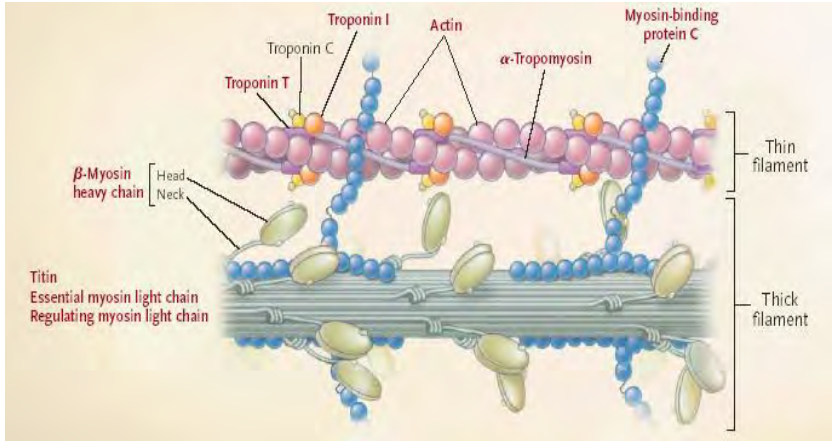
- Collège des cardiologues libéraux ; des MG; UNFCV,
- Société Française de cardiologie;
- Société Française de génétique humaine



- Introduction
- Pourquoi faire un test génétique ?
- Comment faire un test génétique?
- **Intégration de la génétique dans le diagnostic étiologique de la CMH**

La CMH est basiquement une maladie génétique

HCM and sarcomeric causes
(30-60%)
autosomal dominant inheritance



Main prevalent sarcomeric genes	Gene	Locus	Frequency
Thick filament :			
β-myosin heavy chain	*MYH7*	14q11.2	20-30%
Regulatory myosin light chain	*MYL2*	12q23-q24	2-4%
Essential myosin light chain	*MYL3*	3p21.3	1-2%
Intermediate filament :			
Cardiac myosin-binding protein C	*MYBPC3*	11p11.2	30-40%
Thin filament :			
Cardiac troponin T	*TNNT2*	1q32.1	5-10%
Cardiac troponin I	*TNNI3*	19q13.4	4-8%
α-tropomyosin	*TPM1*	15q22.1	<1%
α-cardiac actin	*ACTC1*	15q11q14	<1%

HCM & genetic but *non* sarcomeric causes
(5-25%)

Main *non*-sarcomeric genes	Gene	Associated phenotype	Inheritance /Frequency
Galactosidase, alpha	*GLA*	Fabry disease	X Linked / 1-2% of males
Transthyretin	*TTR*	Amyloidosis	Dominant / 1-5%
Lysosomal-associated membrane protein 2	*LAMP2*	Danon disease	X Linked / rare
Protein kinase, AMP-activated, gamma 2 subunit	*PRKAG2*	Wolff Parkinson White synd.	Dominant / rare
Four and a half LIM domains 1	*FHL1*	FHL1 related diseases	X Linked / rare
Glucosidase, alpha	*GAA*	Pompe disease	Recessive / rare
Protein tyrosine phosphatase, non-receptor type 11	*PTPN11*	Noonan disease	Dominant / rare
Frataxin	*FXN*	Friedreich disease	Recessive / rare
Mitochondrial genes	*Mitochondrial DNA*	MERFF & MELAS	Mitochondrial / rare

Unknown
25-50%

Non genetic causes
AL or senile TTR amyloidosis
Newborn of diabetic mother
Drug-induced (tacrolimus, hydroxychloroquine, steroid)

Veselka, Anavekar & Charron. Lancet 2017 389(10075):1253

Comment identifier la cause d'une CMH?

→ Step by step strategy for diagnostic work-up

- **Pedigree analysis / cardiac screening**
- **Medical history and symptoms**
- **Physical examination**
- **ECG**
- **Laboratory**
- **Echocardiography**
- **MRI**
- **Genetic testing**
- Bone scintigraphy…
- Endomyocardial biopsy
- Skeletal muscle biopsy

European Heart Journal (2013) 34, 1448–1458
doi:10.1093/eurheartj/ehs397

SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*

1st level investigations

↓

Hypotheses

↓

2d level investigations

↓

Diagnosis of cause / sub-type disease

Rapezzi et al. ESC WG Position Paper, EHJ 2013;34:1448
Elliott et al. ESC Guidelines, EHJ 2014;35(39):2733-79.

Age and pedigree

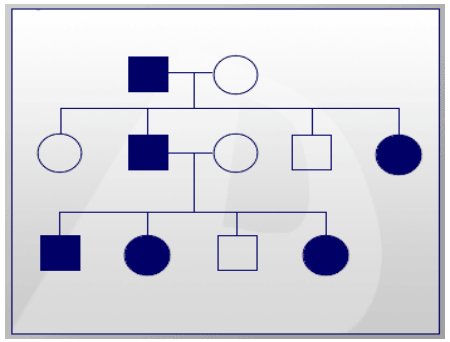
Sarcomeric HCM:

- Age at diagnosis: typically teen-agers and young adults, but possible at any age

→if neonates or >75 years of age

- Pedigree: typically familial form and autosomal dominant inheritance, but apparently sporadic form are frequent ++

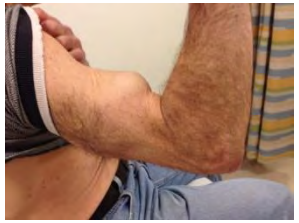
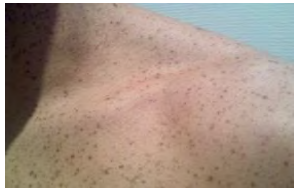
→ male-to-male inheritance (= autosomal dominant only)

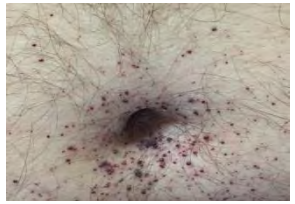


Medical history, symptoms, physical examination

Sarcomeric HCM: no extra cardiac signs

Symptom/sign	Diagnosis
Gait disturbance	• Friedreich's ataxia
Paraesthesia/sensory abnormalities/neuropathic pain	• Amyloidosis • Anderson-Fabry disease
Carpal tunnel syndrome	• TTR-related amyloidosis (especially when bilateral and in male patients)
Muscle weakness	• Mitochondrial diseases • Glycogen storage disorders • FHL1 mutations • Friedreich's ataxia
Palpebral ptosis	• Mitochondrial diseases • Noonan/LEOPARD syndrome • Myotonic dystrophy
Lentigines/café au lait spots	• LEOPARD/Noonan syndrome
Angiokeratomata, hypohidrosis	• Anderson-Fabry disease

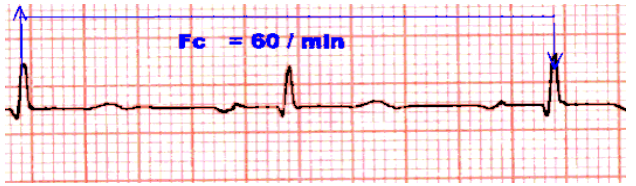


And similar for family history *(renal insufficiency, myopathy, early CVA, etc)*

Elliott et al. ESC Guidelines, EHJ 2014;35(39):2733
Rapezzi et al. ESC WG Position Paper, EHJ 2013;34:1448

Look at ECG

Sarcomeric HCM: no particular sign
(except LVH, Q wave, abnormal repolarization)

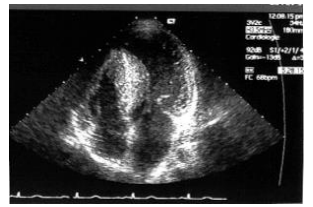


Finding	Comment
Short PR interval/pre-excitation	Pre-excitation is a common feature of storage diseases (Pompe, PRKAG2, and Danon) and mitochondrial disorders (MELAS, MERFF). A short PR interval without pre-excitation is seen in Anderson-Fabry disease.
AV block	Progressive atrioventricular conduction delay is common in mitochondrial disorders, some storage diseases (including Anderson-Fabry disease), amyloidosis, desminopathies and in patients with PRKAG2 mutations.
Extreme LVH (Sokolow score ≥50)	Extremely large QRS voltage is typical of storage diseases such as Pompe and Danon disease, but can be caused by pre-excitation alone.
Low QRS voltage (or normal voltages despite increased LV wall thickness)	Low QRS voltage in the absence of pericardial effusion, obesity and lung disease is rare in HCM (limited to cases with end-stage evolution) but is found in up to 50% of patients with AL amyloidosis and 20% with TTR amyloidosis. Differential diagnosis between HCM and cardiac amyloidosis is aided by measuring the ratio between QRS voltages and LV wall thickness.

Elliott et al. ESC Guidelines, EHJ 2014;35(39):2733
Rapezzi et al. ESC WG Position Paper, EHJ 2013;34:1448

Look at Echocardiography

Sarcomeric HCM: typical when asymetrical LVH, small LV, SAM/LVOT (gradient), abnormal mitral valve,
but not specific nor mandatory ++

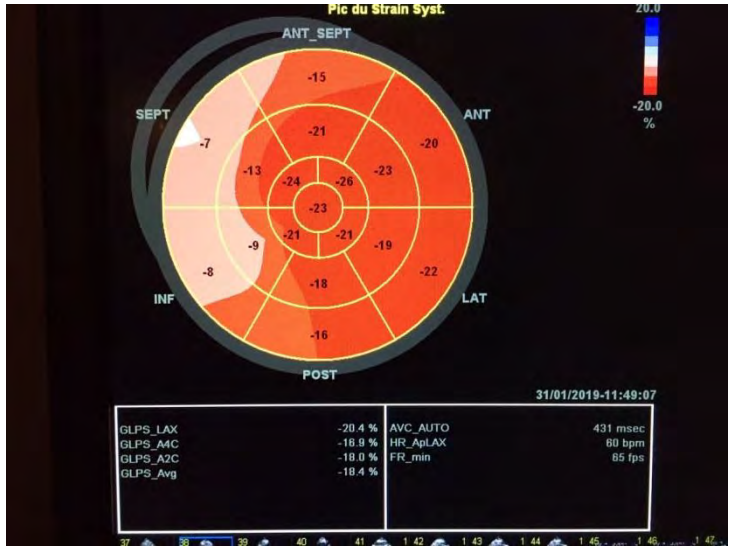


Echocardiographic features that suggest specific aetiologies[a]	
Finding	**Specific diseases to be considered**
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson-Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson-Fabry disease, Noonan syndrome and related disorders
Mild to moderate pericardial effusion	Amyloidosis, myocarditis
Ground-glass appearance of ventricular myocardium on 2-D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson-Fabry disease, PRKAG2 mutations
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, PRKAG2 mutations, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson-Fabry disease
Right ventricular outflow tract obstruction	Noonan syndrome and associated disorders

Elliott et al. ESC Guidelines, EHJ 2014;35(39):2733
Rapezzi et al. ESC WG Position Paper, EHJ 2013;34:1448

Look at Echocardiography (2)

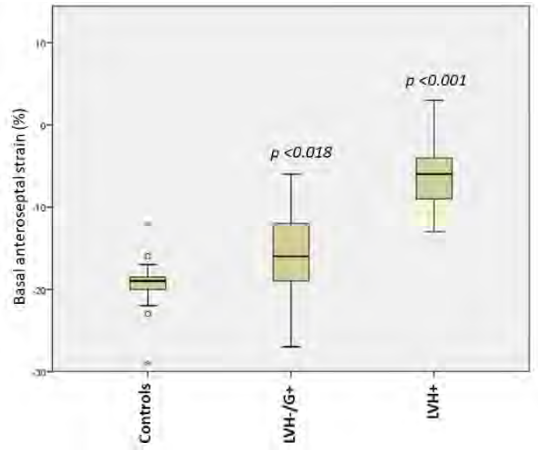
Sarcomeric HCM: typical <u>regional strain</u>: early and marked abnormality in <u>basal antero septal segment</u>



And early before LVH

Global and regional echocardiographic strain to assess the early phase of hypertrophic cardiomyopathy due to sarcomeric mutations

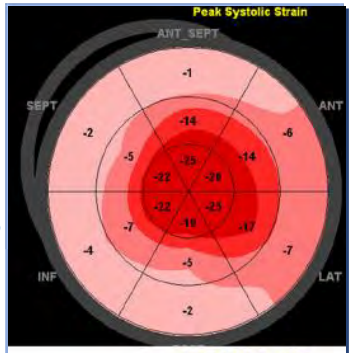
Guillaume Baudry[1,2], Nicolas Mansencal[3,4], Amelie Reynaud[5], Pascale Richard[6], Olivier Dubourg[3,4], Michel Komajda[1,7], Richard Isnard[1,8], Patricia Réant[5], and Philippe Charron [1,8]*

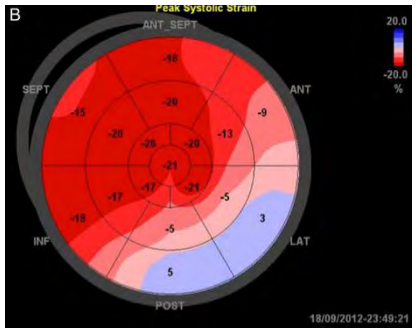


Eur Heart J Cardiovasc Imaging. 2020;21(3):291

Non sarcomeric cause of LVH:

Amylose

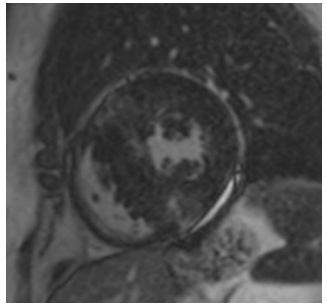




Fabry

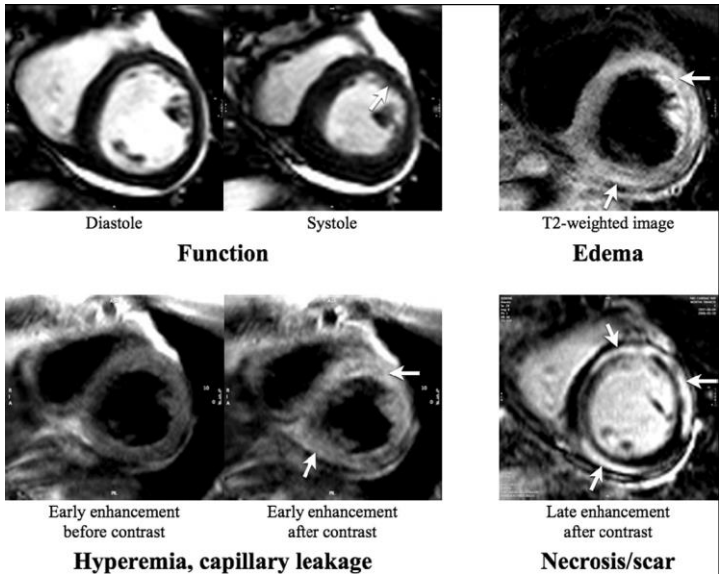
Look at MRI

Sarcomeric HCM:
-typical LVH (see Echo: asymetrical etc)
-typical Late Enhancement (post Gado): patchy or in septal segment and hypertrophic segment or RV/LV junction

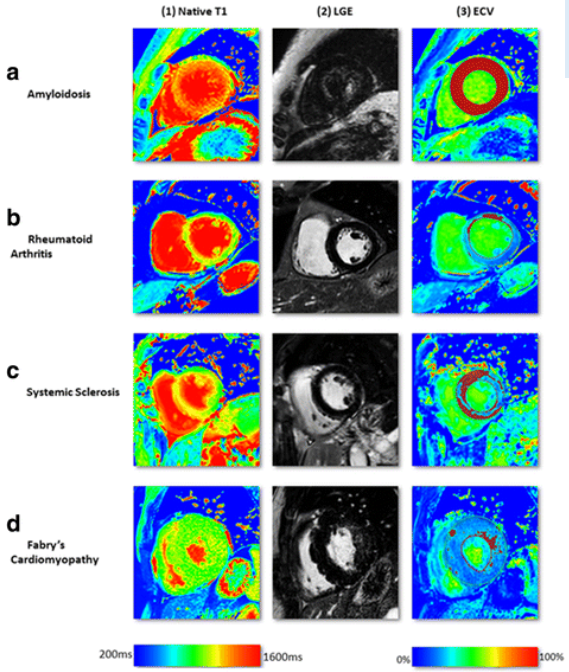


Red flag if abnormal regional LE
If very abnormal natif T1, or T2, or ECV

Fabry:
-RT en inférolatéral
-T1 mapping abaissé



Skouri, JACC 2006;48:2085



Haaf P et al. J of CVMR 2017;18:89

Look at Basic Biology

Sarcomeric HCM: no abnormality (except BNP, troponine that might be increased)

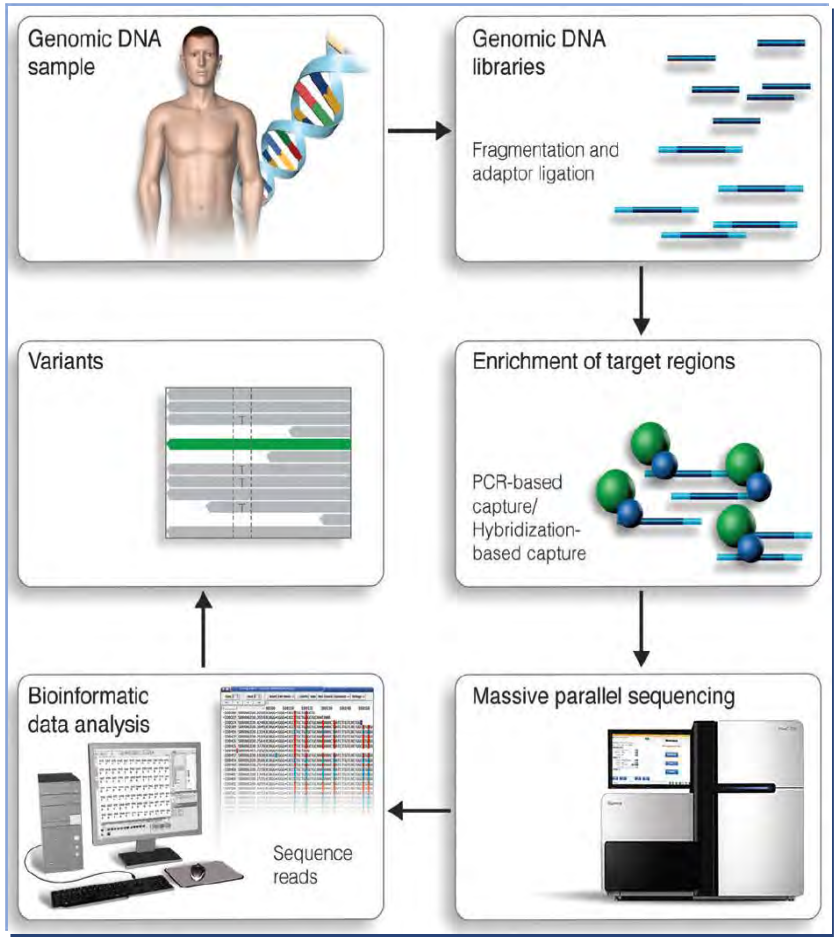
Recommended laboratory tests in adult patients with hypertrophic cardiomyopathy	
Test	**Comment**
Haemoglobin	Anaemia exacerbates chest pain and dyspnoea and should be excluded whenever there is a change in symptoms.
Renal function	Renal function may be impaired in patients with severe left ventricular impairment. Impaired GFR and proteinuria may be seen in amyloidosis, Anderson-Fabry disease and mitochondrial DNA disorders
Liver transaminases	Liver tests may be abnormal in mitochondrial disorders, Danon disease and ß-oxidation defects.
Creatine phosphokinase	Serum creatine phosphokinase is raised in metabolic disorders such as Danon and mitochondrial disease.

+ additional biology according to situations
(alpha-galactosidase A recommended in males > 30 y etc)

Elliott et al. ESC Guidelines, EHJ 2014;35(39):2733
Rapezzi et al. ESC WG Position Paper, EHJ 2013;34:1448

Role of Genetic testing

Next generation sequencing / High throughput sequencing



Ho, Charron, et al. Cardiovasc Res 2015;105(4)397

Panels for routine diagnosis

Pascale Richard & Ph. Charron, Hôpital Pitié-Salpêtrière, Paris

HCM

New 2020: décision Filière Cardiogen passer de 5 à 16 gènes au niveau national

- Level 1: Panel **16 genes**

  (MYBPC3, MYH7, TNNT2, TPM1, TNNC1, TNNI3, MYL2, MYL3, ACTC1, ACTN2, FHL1, FLNC, GLA, LAMP2, PRKAG2, TTR)

- Level 2: Panel **>75 genes**

  (all phenotypes, phenocopies, & neonatal forms)

Ou Test ciblé
Si 1 gène suspecté

Whole Genome Sequencing

- Plan France Médecine Génomique

  (« pré-indication « cardiomyopathies », PI Ph Charron & P Richard) = pilot study for diagnosis

Centre de Référence des Maladies Cardiaques Héréditaires ou Rares

Conclusions

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- *HCM is basically a genetic disease, with various sarcomeric and non sarcomeric causes*
- *Genetic testing in index patients is currently based on next generation sequencing, with comprehensive analysis through panels of genes*
- *Genetic testing is part of clinical management and recommended:*
  - *particularly useful for aetiology evaluation and appropriate diagnosis of precise sub-type disease & management*
  - *particularly useful in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives (predictive testing)*
  - *Genetic testing may be considered in other selected situations (prognostic stratification, procreation, personalized therapy etc) on a case-by case basis*
- *Multi-disciplinary teams with expertise in that field can help you for organization of investigations and for appropriate interpretation of investigations and decisions*

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Le défibrillateur
un ange gardien au quotidien

Document réalisé avec le soutien financier de l'Agence nationale de sécurité du médicament et des produites de santé (ANSM) dans le cadre d'un appel à projet compétitif (2015)

Carte d'urgence patient (2023)

e-RDV mensuels avec les Familles depuis 2021

DIU sur les maladies cardiaques héréditaires: Depuis 2017-2018

RCP nationales « recours » depuis 2021 (Amylose, CMPs, TduR, Grossesse…) via le WEB

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Journées annuelles de la filière CARDIOGEN: 04-05 avril 2024, Paris