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cardiogen
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What genetic abnormalities should we search for after a sudden death?

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Disclosure

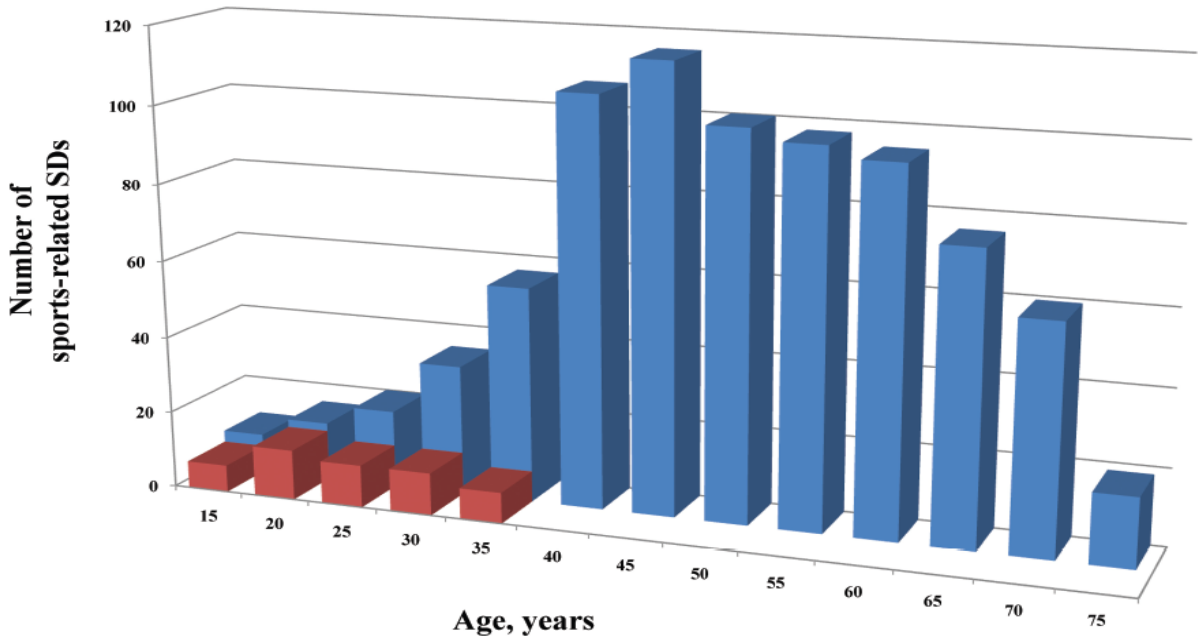
I have the following potential conflicts of interest to report:

Consulting: Sorin, Medtronic, Boston

Sports-Related Sudden Death in the General Population

Eloi Marijon, Muriel Tafflet, David S. Celermajer, Florence Dumas, Marie-Cécile Perier, Hazrije Mustafic, Jean-François Toussaint, Michel Desnos, Michel Rieu, Nordine Benameur, Jean-Yves Le Heuzey, Jean-Philippe Empana and Xavier Jouven

Circulation. 2011;124:672-681; originally published online July 25, 2011;



Distribution by age of sports-related sudden deaths (SDs) in the overall population (blue) and among young competitive athletes (red).

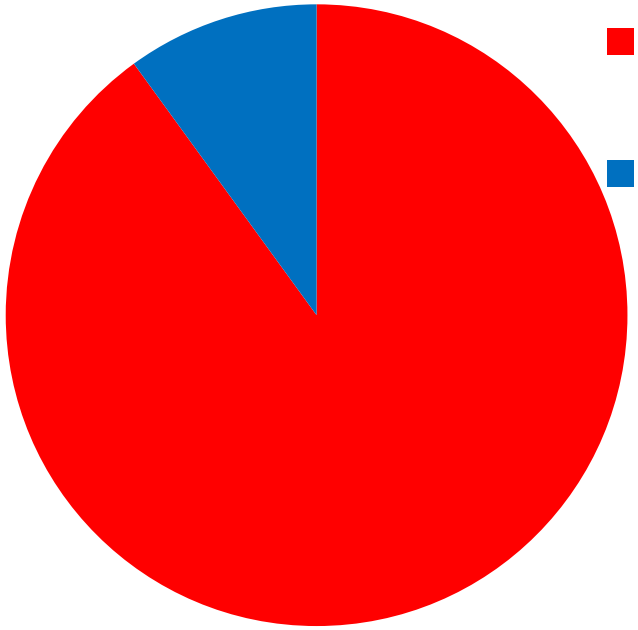
Marijon E, et al. Circulation 2011

Necropsy study: SCD causes according to age

< 40 Y

- CHD
- myocarditis
- HCM
- ARVC/D
- other
- unknown (USCD)

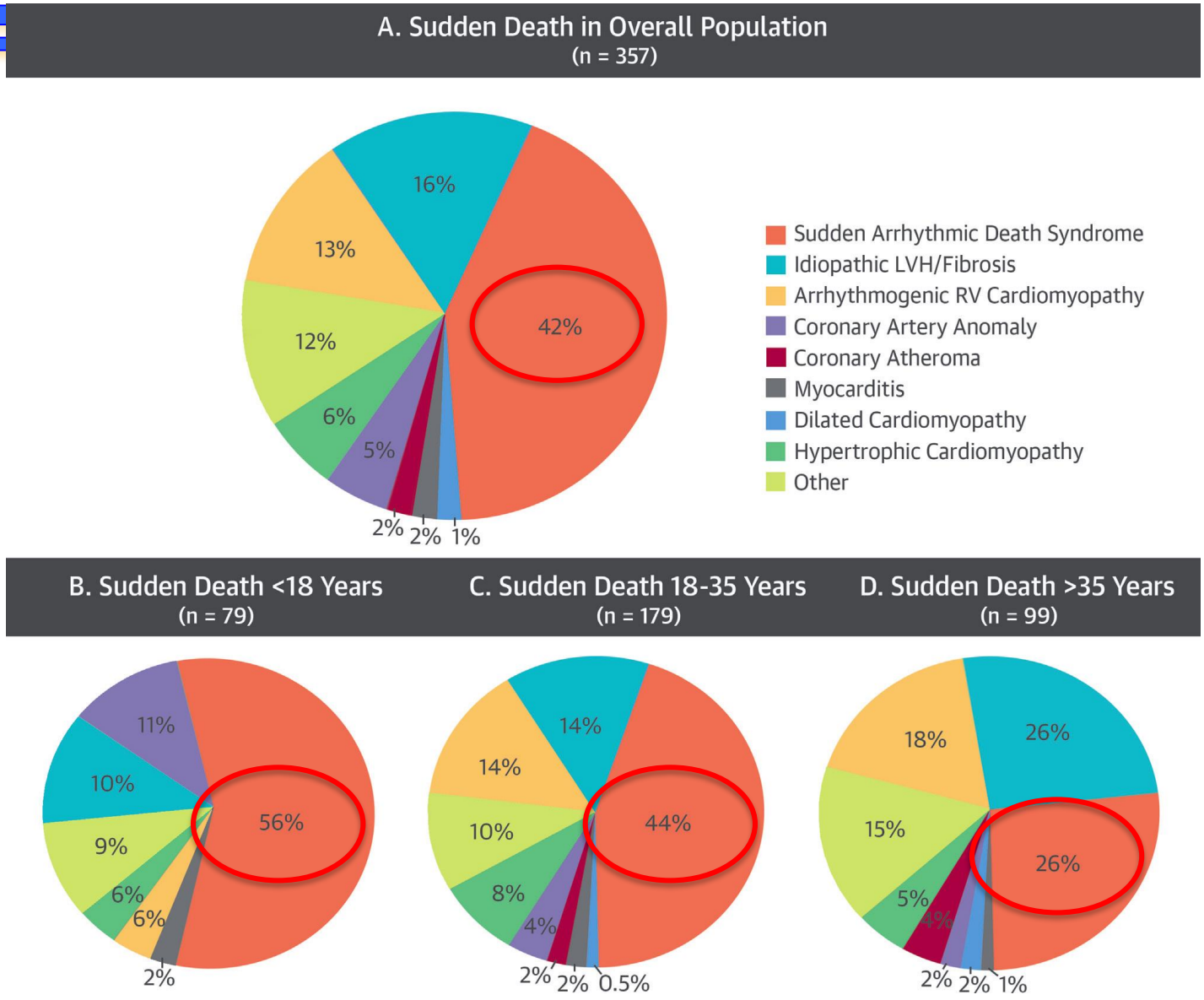
> 40 Y



- CHD
- others

Semsarian et al. EHJ, 2015 review

SCD in athletes (> 3 hours per week) : UK series

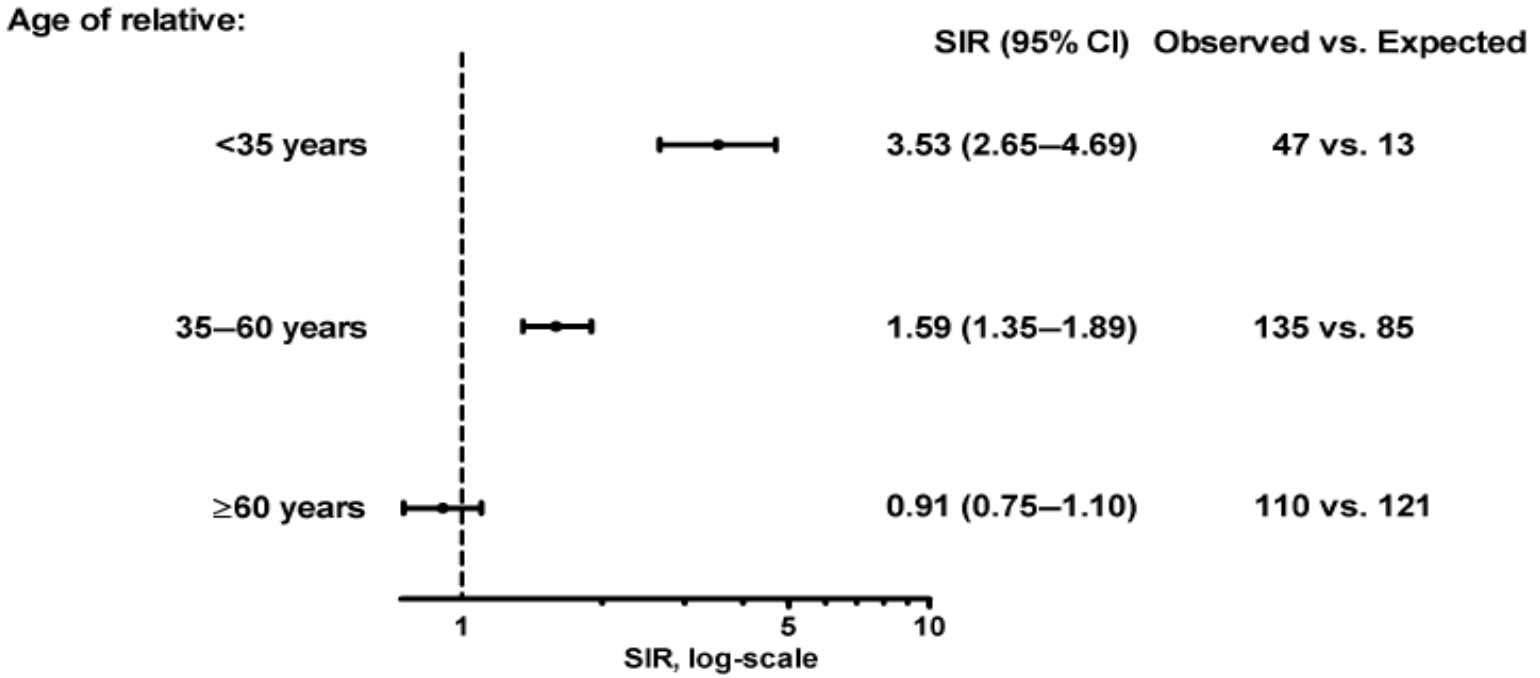


Finocchiaro *et al*. JACC 2016

Risk of cardiovascular disease in family members of young sudden cardiac death victims

Denmark 2000-2006
n=470 SD
Screening and follow-up of 3073 relatives

Risk of any cardiovascular disease in relatives of young first degree relatives



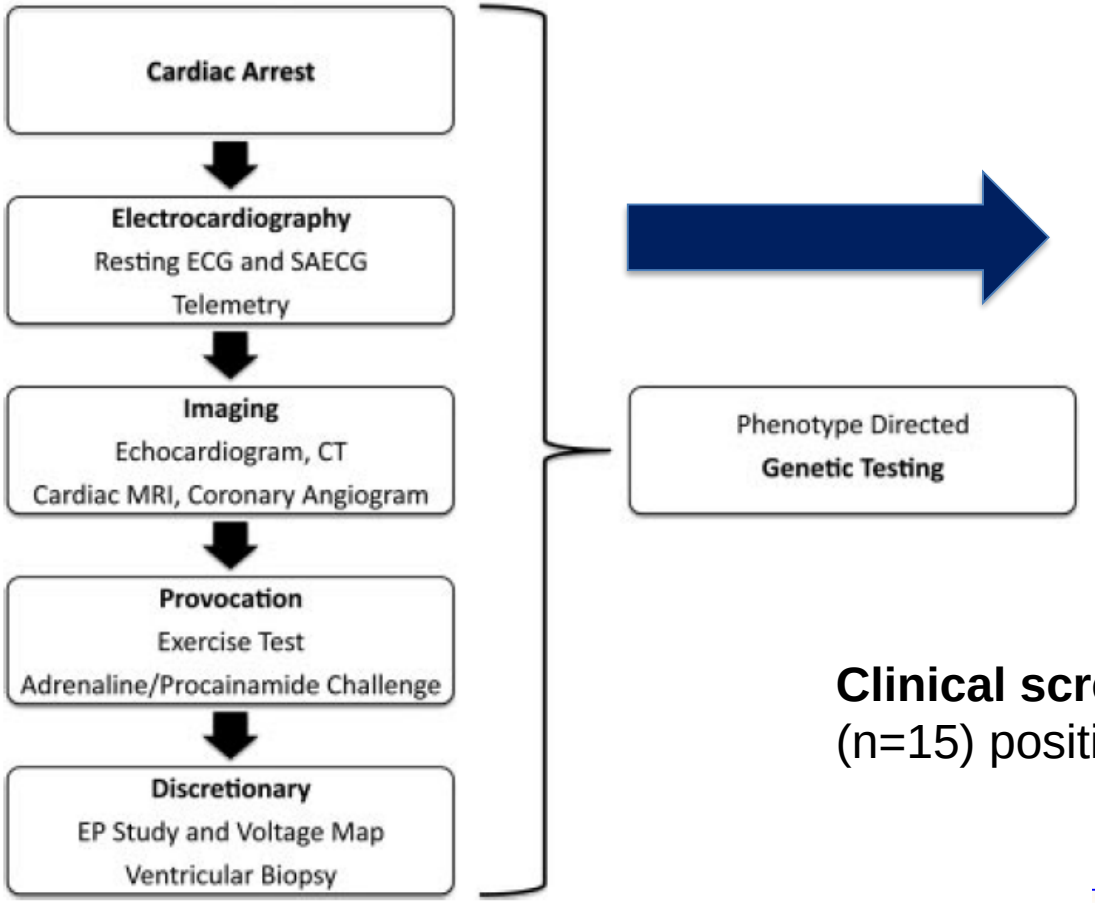
Risk increases were even more dramatic for first-degree relatives and persons <35 years of age

Ranthe et al. EHJ

Importance of a complete clinical screening in patients with USCD (Casper study)

Unexplained SCD:
normal cardiac function on echocardiogram, no evidence of coronary artery disease, and a normal ECG

63 USCD (mean age=43 Y)



Diagnosis in 56% of patients

LQTs: 8 patients
CPVT: 8 patients
ARVC: 6 patients
Early repolarisation: 5 patients
Coronary Spasm: 4 patients
Brugada: 3 patients
Myocarditis: 1 patient

Clinical screening of 64 relatives → 24% (n=15) positives

Krahn et al., Circulation 2009

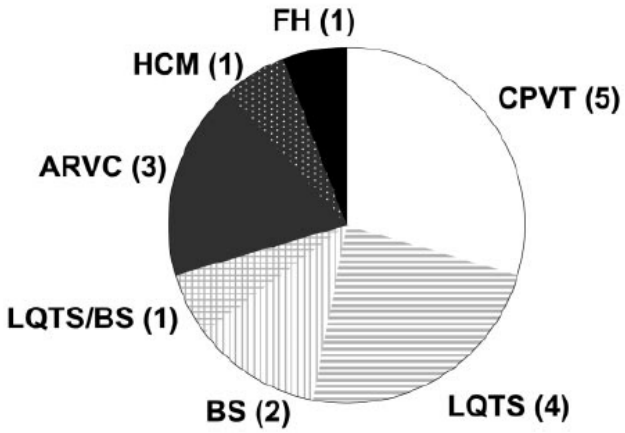
Diagnostic yield of clinical and genetic screening of relatives

Relatives of USCD victim (negative of no post mortem analysis) < 40 Y = 43 families

- ECG
- Exercice test
- TEE
- Lipid analysis
- Ajmaline challenge if suspect ECG
- MRI if suspect ARVC

+

Targeted genetic testing if positive phenotype



Identification of cause in 17/43 familles (40%)

Exercice test ++

333 1st and 2nd-degree relatives screened

Tan et al. Wilde et al, Circulation 2005

Diagnostic yield of clinical and genetic screening of relatives (CASPER)

398 Relatives of 212 USCD victim (negative of no post mortem analysis)

- ECG
- Exercice test
- TEE
- SA ECG
- Ajmaline challenge if suspect BrS ECG/ER or nocturnal SCD
- epinephrine challenge if non diagnosis exercice test and exercise induced SCD
- MRI if suspect cardiomyopathy

Identification of possible cause in 120 relatives (30%) Including 17% with probable/definite diagnosis

Mutation in only 5% relatives (targeted testing)

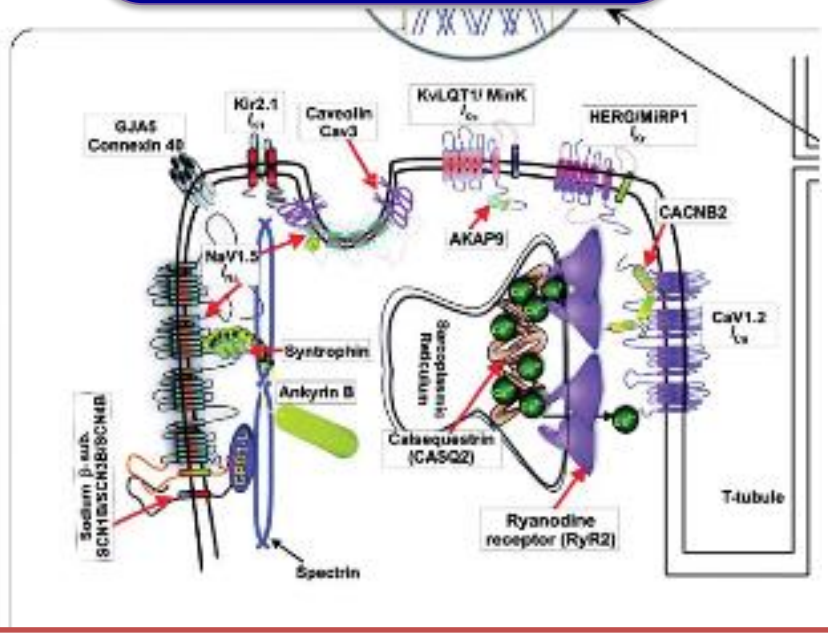
+

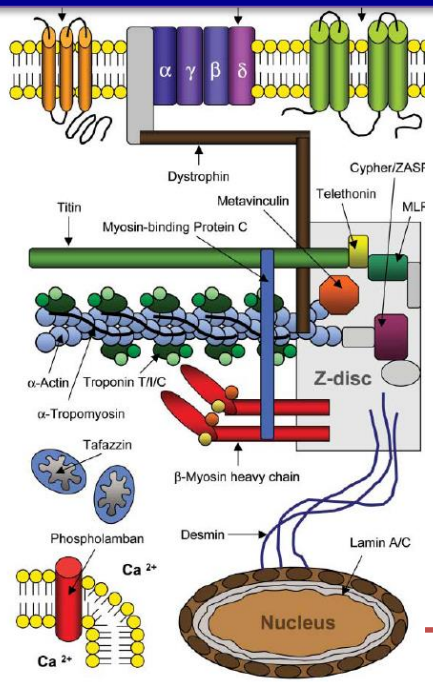
Targeted genetic testing if positive phenotype
Bs: *SCN5A*, ARVC: *PKP2-DSP*, CPVT: *RYR2*, LQT: 5 genes

Steinberg et al. Circ EP 2016

CHANNELOPATHY

CARDIOMYOPATHY
Sarcomere,
cytoskeleton, nuclei





- Brugada: > 10 genes , modifier effect ++ (PGS 25%)
- LQT : >10 genes, PGS 60-70%
- SQT : >6 genes
- AVB, SSS :>5 genes
- CPVT : 4 genes
- …

- HCM >15 genes
- DCM > 30 gènes
- ARVC 10 genes
- LMNA
- LVNC >7 genes
- RCM… >10 genes

Large genetic heterogenity++
Not all causative genes are known

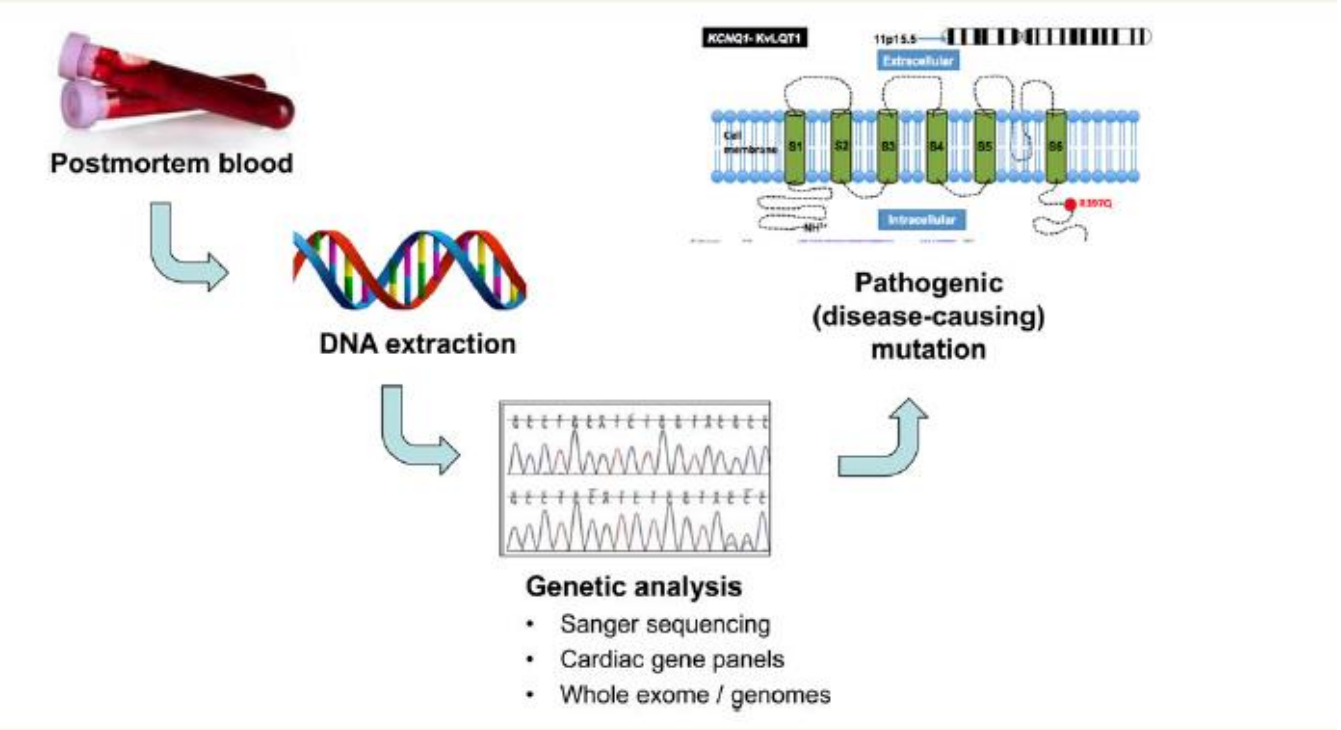
Molecular autopsy

=Post mortem genetic screening

Analysis impossible from hair
Difficult from parrafin blocks

Blood samples before death

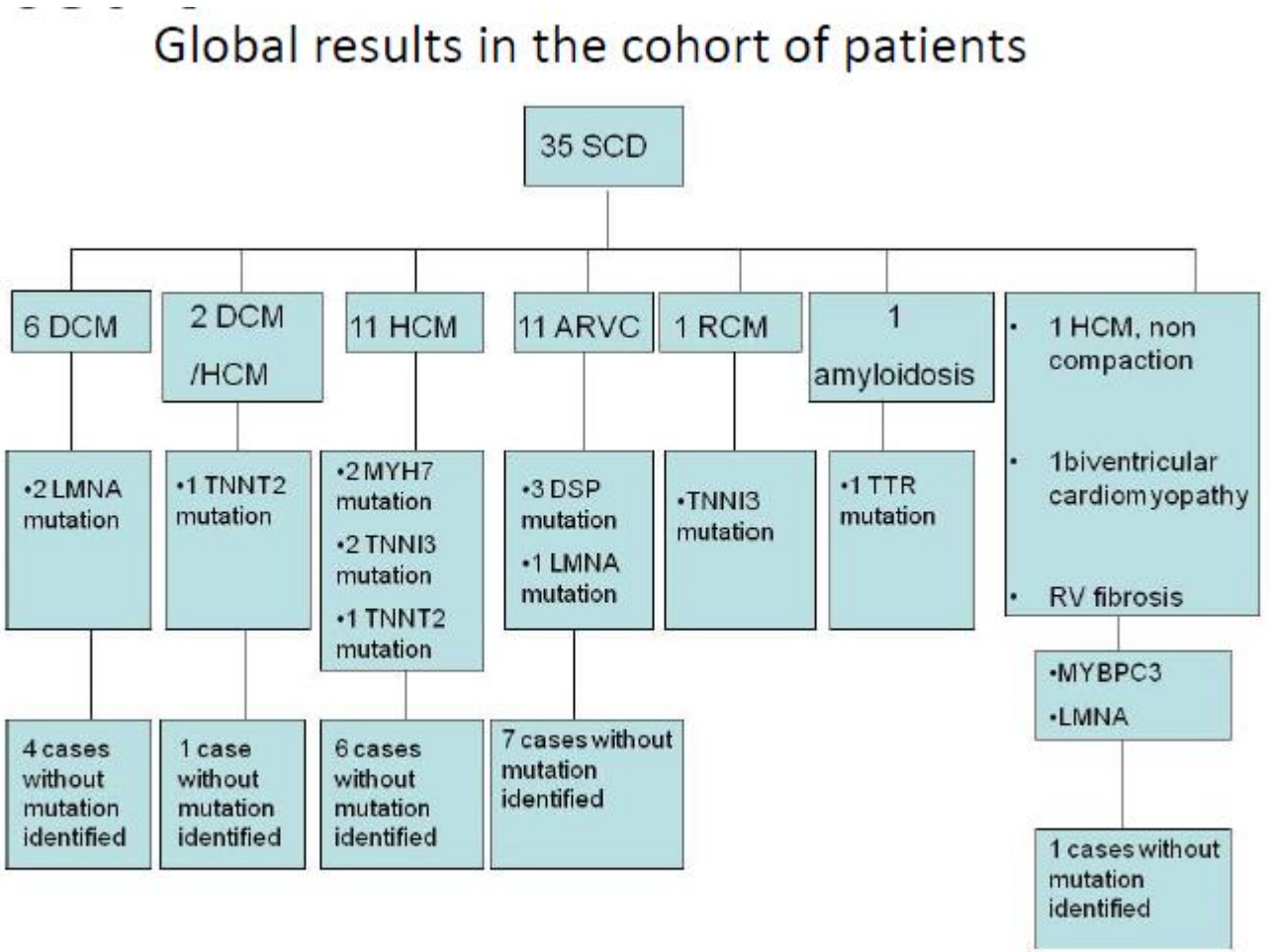
Necropsy tissue (liver++)



Legal issues

- **Rightholder consent ++**
- **Result to right holder**

Targeted post mortem genetic screening in cardiomyopathy: Case series from GHPS



→ **15 mutations** in 15 patients were identified out of 35 patients **(43%)**

Marey, Charron et al. GHPS data

Post mortem genetic screening in USCD

Post mortem screening of *KCNQ1, KNCH2, SCN5A, RYR2 in unexplained SCD* → *mutation yield:* 15% of cases

Table 3 Current 4-gene molecular autopsy

Gene Name	Encoded protein	Disease	% of disease	% of SADS[a]
KCNQ1	I_{Ks} K^+ channel α-subunit	LQTS1	35–40	10–15
KCNH2	I_{Kr} K^+ channel α-subunit	LQTS2	30–35	1–5
SCN5A	I_{Na} Na^+ channel α-subunit	LQTS3 BrS	5–10 15–25	<1 <1
RYR2	Ryanodine receptor	CPVT1	60–65	10–15

32 patients with exercice related USCD

KCNQ1, KNCH2, SCN5A, RYR2

Mutation in 11

Negative in 21

100 gènes (exome)

Mutation in 3 cases:
CALM2 (TVC)
PKP2 (DVDA)
GVUS in 7 cases

Semsarian et al. EHJ, 2015 review

Andersen et al. Circ genetics, 2016

Post mortem genetic screening in USCD

Genetic screening identifies a high proportion of mutations in patients with idiopathic ventricular fibrillation and sudden cardiac death

Vincent Probst (1), Solena Le Scouarnec (2), Florence Kyndt (3), Jean-Jacques Schott (2), Jean-Baptiste Gourraud (1), Frederic Sacher (4), Philippe Mabo (5), Matilde Karakachoff (2), Stéphanie Bonnaud (2), Jade Violleau (2), Eloi Marijon (6), Florence Dumas (6), Alain Cariou (6), Estelle Baron (2), Pierre Lindenbaum (2), Xavier Jouven (6), Richard Redon (2)

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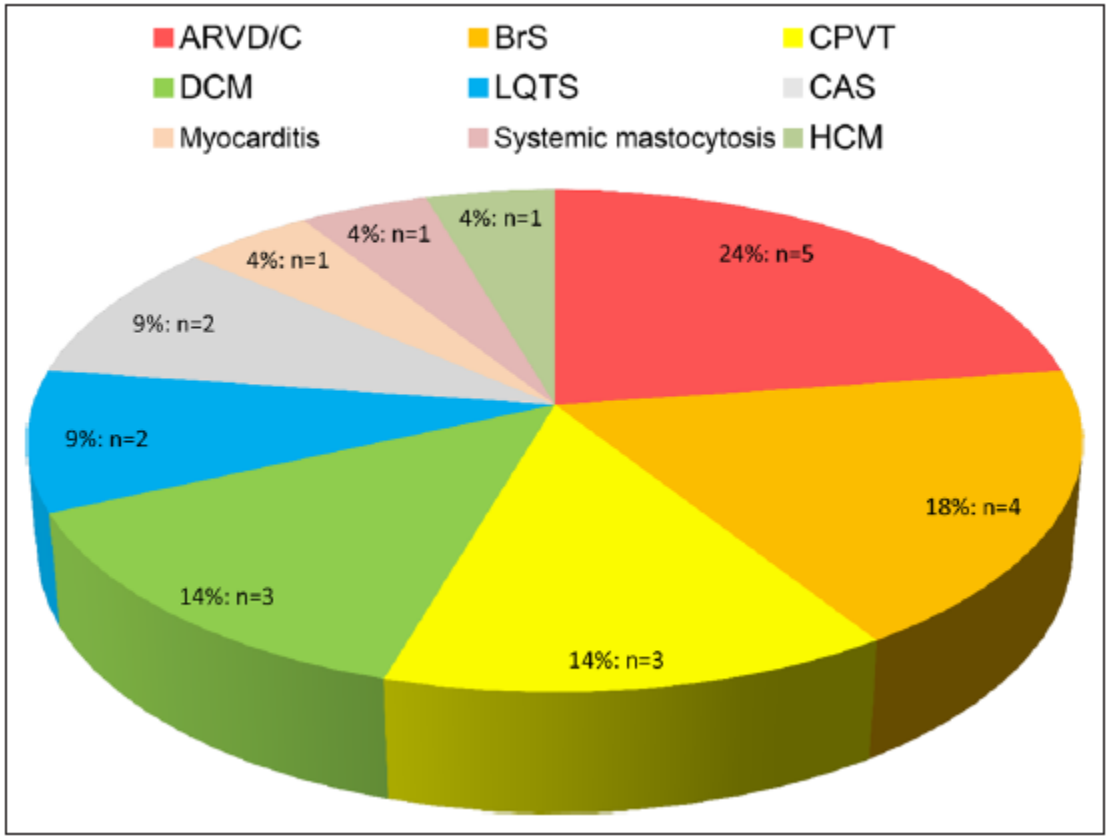
Abstract 0185-Table

	Cohort 1 (n=75)	Cohort 2 (n=99)
SCN5A	7 (9%)	0
HCM and DCM genes	22 (29%)	17 (17%)
ARVD/C genes	4 (5%)	3 (3%)
LQTS genes (excluding SCN5A)	4 (5%)	4 (4%)
CPVT genes (excluding SCN5A)	7 (9%)	3 (3%)
BRS genes	3 (4%)	1 (1%)
Other	3 (4%)	2 (2%)

Limit of large genetic screening: interpretation of rare missense variants?
→ EXAC database, prediction sofware, Study of familial segregation +++

Long term follow-up after USCD

79 patients with USCD→ median FU =10 Y
Identification of cause in 20% of cases



AKAP9	*CASQ2*	*DSP*	*KCNE2*
KCNJ8	*RYR2*	*SNTA1*	*ANK2*
CAV3	*GPD1L*	*KCNE3*	*KCNQ1*
SCN1B	*TGFB3*	*CACNA1C*	*DES*
HCN4	*KCNH2*	*LMNA*	*SCN3B*
TMEM43	*DSC2*	*JUP*	*KCNJ2*
DSG2	*KCNE1*	*KCNJ5*	*PLN*
CACNA2D1	*PKP2*	*SCN4B*	*CACNB2*
SCN5A	*DPP6* (VF risk haplotype only)		

Pathogenic mutation in 15% (n=12)
GVUS in13 patients

Familial screening and long term follow-up ++

Visser et al, Circ EP, 2016

Index case with SCD

In all cases, long term follow-up of probands and relatives ++

Resuscitated SCD

SCD

Psychological support

Complete clinical investigation
Coronarography/CT scan
TEE, MRI
Pharmacological challenges (ajmaline, adrenaline, isoproterenol..)
Exercice test
EP study

Propose **necropsy +++**
Blood sample for genetics++

Patient screening

USCD

Cause

Large genetic screening in <40 Y

Targeted genetic screening

Genetic screening

Large relative screening: ECG, TEE, exercise test, Holter, SA ECG+/- MRI and pharmacological challenges

Targeted relative screening

Relative screening

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