Autopsie moléculaire

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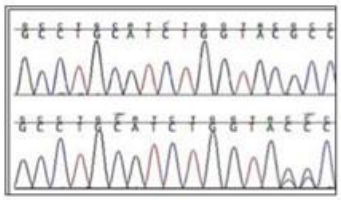
Autopsie moléculaire

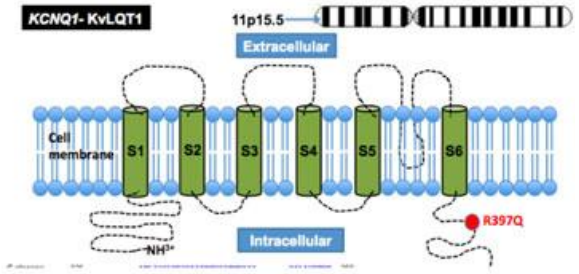
Postmortem blood

DNA extraction



Genetic analysis

- Sanger sequencing
- Cardiac gene panels
- Whole exome / genomes



Pathogenic (disease-causing) mutation

Résultats dans la littérature sur les 4 principaux gènes

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

Semsarian, Eur Heart J, 2015

Approche exome

- Approche séduisante car permet d'évaluer tous les gènes et donc toutes les causes potentiellement génétiques de mort subite

- Détection de variants potentiellement pathogénique dans 30-40% des cas

Evaluation chez 21 patients négatifs pour les principaux gènes de MS

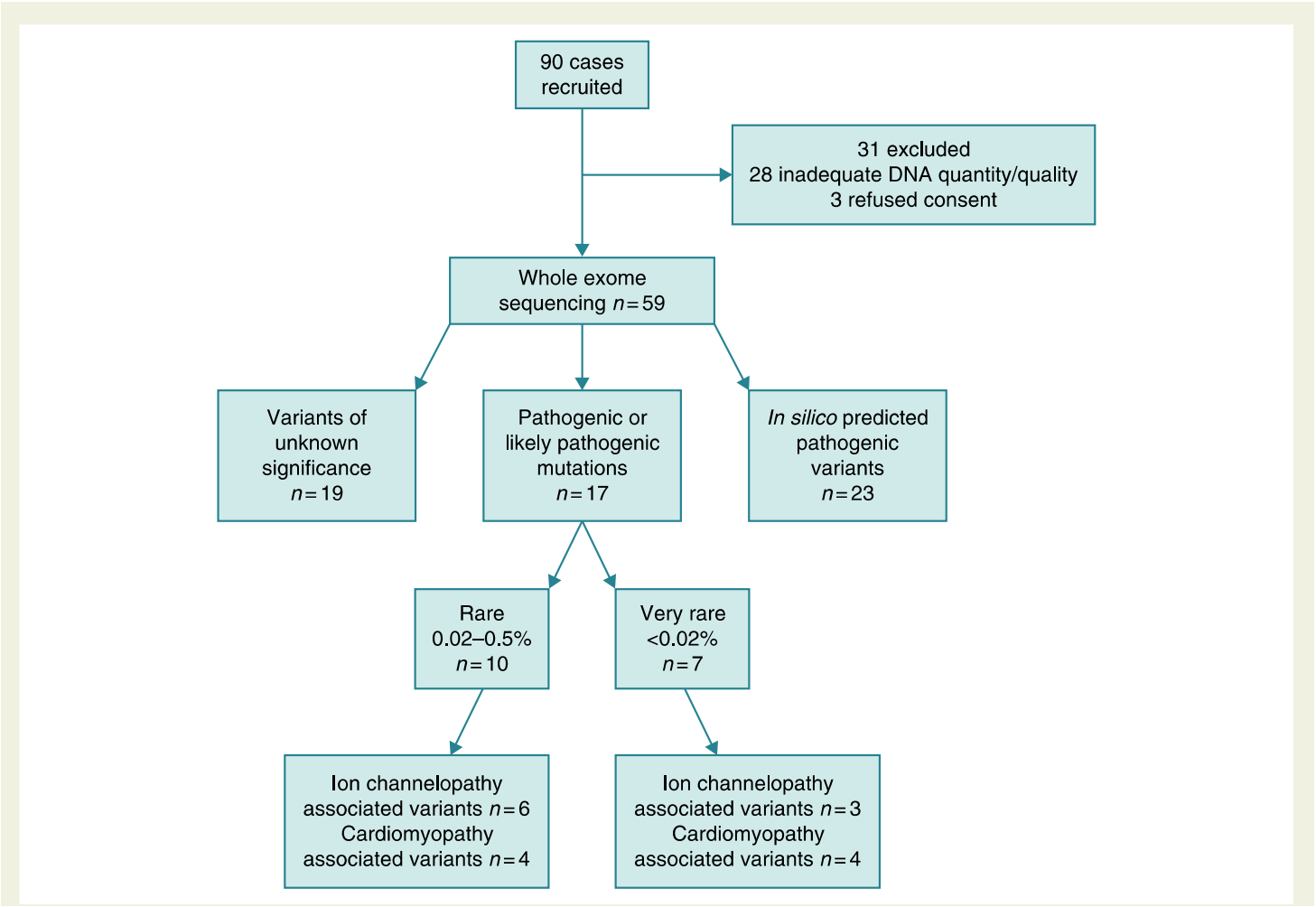
Table 2. Summary of Ultrarare Variants Identified via Whole-Exome Sequencing in the Exertion-Related SUDY Cohort

Age, y	Sex	Gene	Nucleotide Change	Amino Acid Change	ACMG Designation	ExAC Minor Allele Frequency	Personal History	Family History
16	M	*ACTN2*	c.2356G>A	p.G786S	VUS	…	Negative	Negative
6	F	*ANKRD1*	c.722G>A	p.C241Y	VUS	0.00001649	Negative	Negative
5	M	*CALM2*	c.268T>C	p.F90L	Pathogenic	…	Negative	Negative
2	M	*CALM2*	c.293A>G	p.N98S	Pathogenic	…	Negative	Negative
18	M	*CASQ2* *DMD*	c.289A>G c.4025G>A	p.K97E p.R1342H	VUS VUS	0.00000841 0.00002304	Negative Negative	Negative Negative
12	F	*GATAD1*	c.157G>T	p.G53W	VUS	…	Negative	SCD
19	M	*MYBPC3* *DSG2*	c.2374T>C c.3040G>A	p.W792R p.V1014I	VUS VUS	… 0.00004972	Negative Negative	Negative Negative
12	M	*MYBPC3*	c.2500C>T	p.R834W	VUS	0.00001658	Syncope	Syncope
17	F	*MYL2*	c.430C>A	p.P144T	VUS	0.00000825	Negative	SCD
16	M	*PKP2*	c.1901delA	p.N634fs	Pathogenic	…	Negative	Negative

Identification de variants chez 10 patients

Anderson, Circ card genet, 2016

Expérience anglaise



Nun, europace 2016

Inclusion criterias

- Families recruited between May 2009 and December 2014
- Screening was performed in the Nantes University hospital or in different tertiary hospitals in France, part of the Network of the Nantes reference center
- If no other possibility exist relatives are referred to general cardiologist

Quenin, Circ card genet, 2017

Inclusion criteria

For families

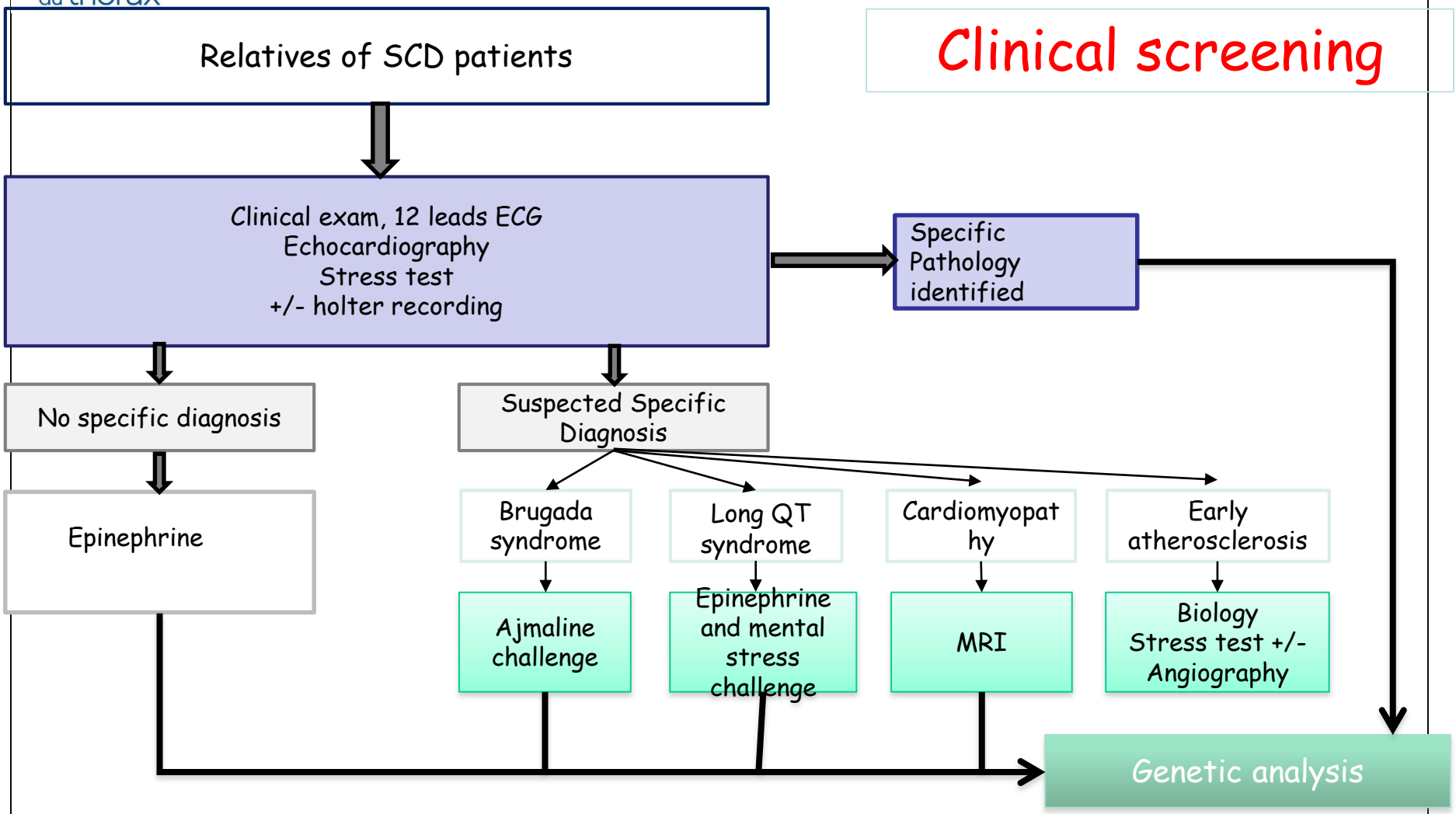
- **At least one case of SCD before age 45**
  - **No autopsy or negative autopsy**
  - **Negative toxicological analysis when available**
  - **No diagnosis at the time of SCD**

For family members

- First degree relative of SCD case
- If no first degree relative available in the family, second degree relatives should be included
- At least, physical exam of the family member and an ECG performed

Quenin, Circ card genet, 2017

Clinical screening



Quenin, Circ card genet, 2017

64 families were screened

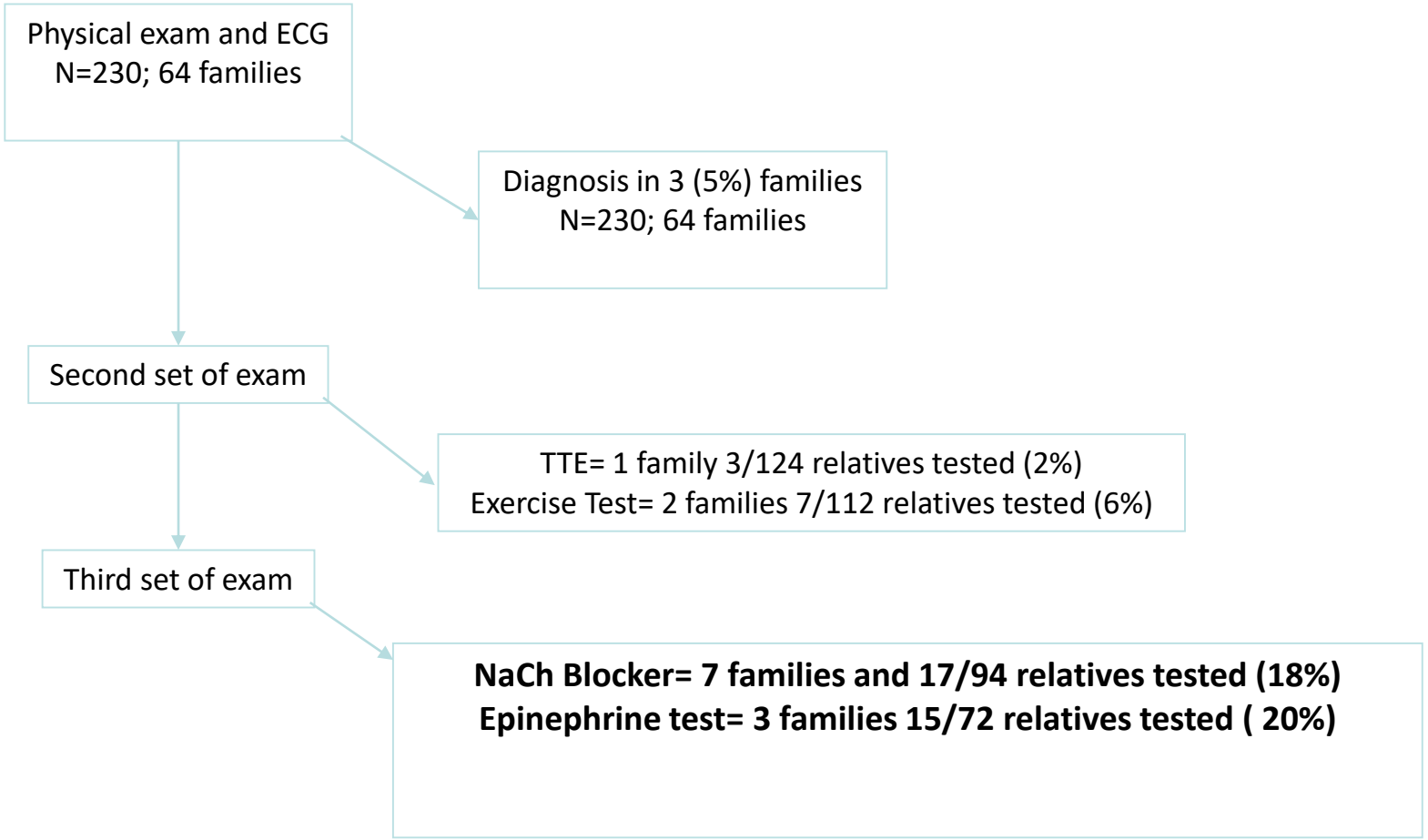
- 230 family members screened
- 80 cases of SCD
- 3.6 +/- 4.1 relatives screened per family
- 25 families with only one family member screened (39%)
- 9 families with 2 family members screened (14%)
- 30 families with at least 3 family members screened (47%)

- 65.6% are first degree relatives
- 11.8 % are second degree relatives

Circumstances of SCD

Characteristics of the probands (first SCD)		n= 64
Age (years), mean±SD		31 ± 14
Sex(male), n (%)		43(67)
Circumstances	Exercice, n(%)	9(14))
	Swimming, n(%)	2(3)
	Rest, n(%)	26 (41)
	No information , n(%)	27(42)

Quenin, Circ card genet, 2017



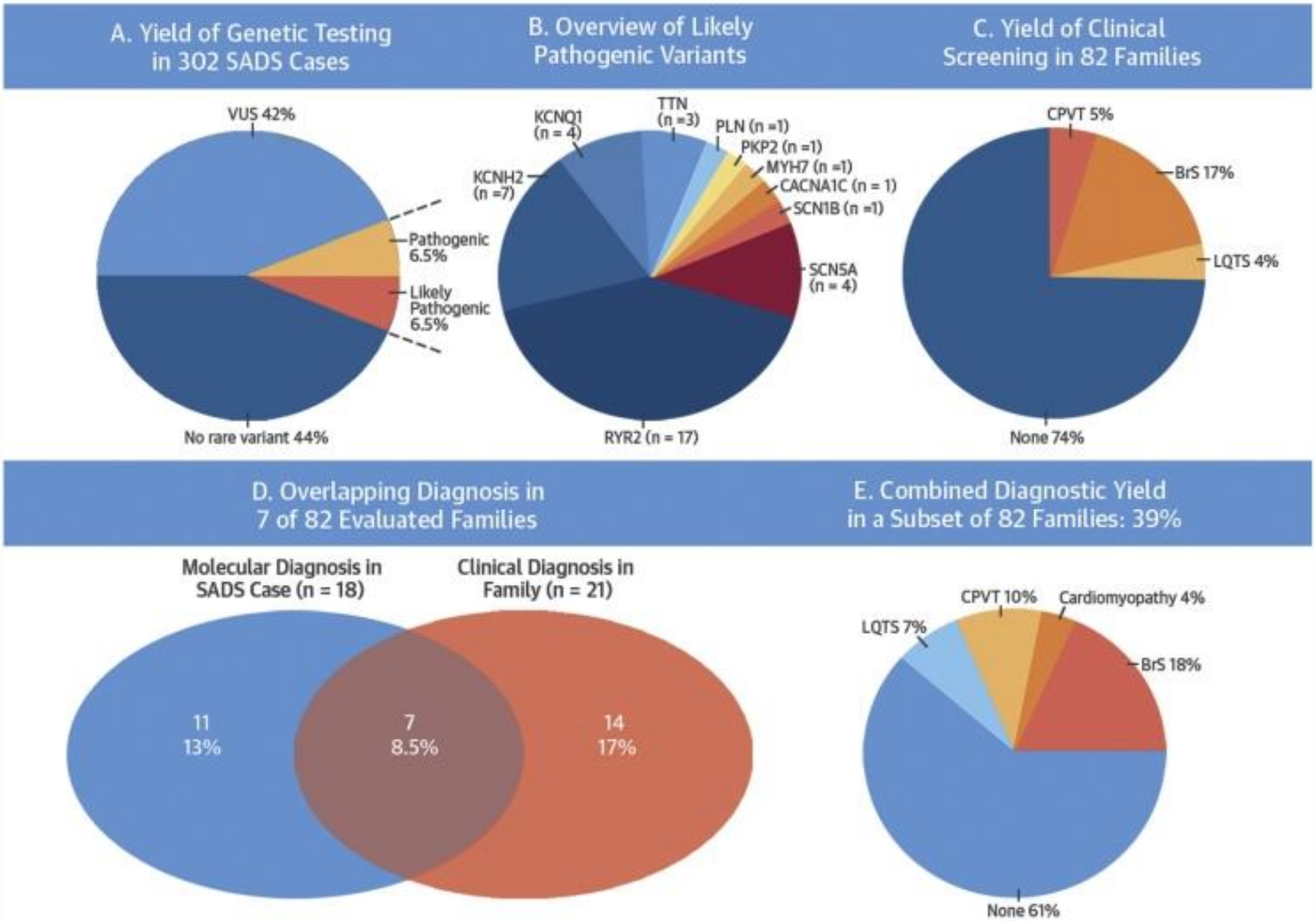
Quenin, Circ card genet, 2017

Genetic results

- DNA from the index patient : 19
- Mutation in the index patient : 6
- 1 KCNQ1 in Long QT syndrome family, 1 KCNH2 in a family without clinical diagnosis (no other family member carrier of the mutation)
- 1 SCN5A in a family without clinical diagnosis (no other family member carrier of the mutation)
- 2 MYH7 one in HCM family the second in one in a family without clinical diagnosis (no other family member carrier of the mutation)
- 1 DSC2 in a family without diagnosis (2 other family members carrier of the mutation)

Quenin, Circ card genet, 2017

CENTRAL ILLUSTRATION: Sudden Arrhythmic Death Syndrome: Genetic Testing and Clinical Screening



Lahrouchi, N. et al. J Am Coll Cardiol. 2017;69(17):2134-45.

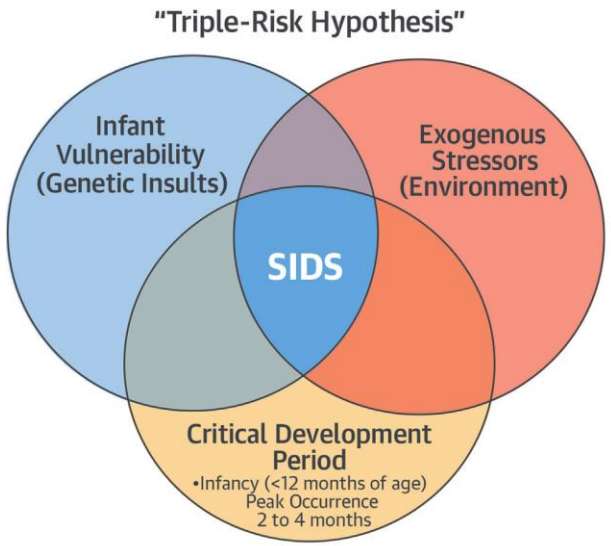
Analyses génétiques dans la FVI et la mort subite inexpliquée

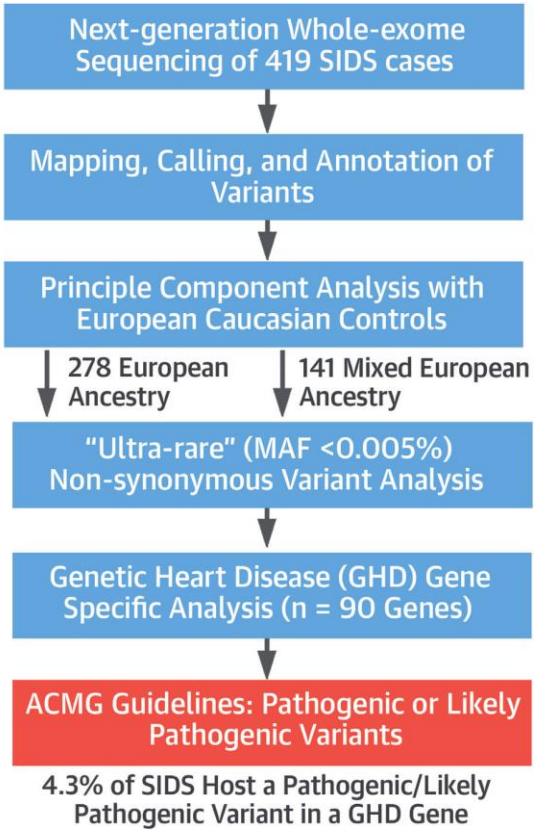
- 75 patients avec une FVI
- 99 patients avec une mort subite inexpliquée et non récupérée
- 167 patients controles
- Analyse génétiques utilisant le Kit Haloplex permettant d'analyser 160 gènes impliqués dans le risque de mort subite

Genes	FVI cases (n=75)	Internal controls (n=167)	p-value 1	UK10K controls (n=881)	p-value 1	SCD cases (n=99)	Internal controls (n=167)	p-value 1	UK10K controls (n=881)	p-value 1
NEXN	5,3% (4)	-	0,008*	0,6% (5)	0,003*	3,1% (3)	-	0,047*	0,6% (5)	0,035*
TRDN	9,3% (7)	1,8% (3)	0,011*	2,6% (23)	0,021*	1% (1)	1,8% (3)	1	2,6% (23)	0,501
TTN	60% (45)	43,7% (73)	0,025*	43,9% (387)	0,007*	50% (48)	43,7% (73)	0,368	43,9% (387)	0,28
SCN5A	9,3% (7)	2,4% (4)	0,038*	2,4% (21)	0,004*	1% (1)	2,4% (4)	0,655	2,4% (21)	0,715
DSP	12% (9)	4,2% (7)	0,045*	4,3% (38)	0,008*	2,1% (2)	4,2% (7)	0,493	4,3% (38)	0,418
AKAP9	12% (9)	4,2% (7)	0,045	7,9% (70)	0,381	4,2% (4)	4,2% (7)	1	7,9% (70)	0,225
CACNB2	5,3% (4)	1,2% (2)	0,076	0,9% (8)	0,181	1% (1)	1,2% (2)	1	0,9% (8)	0,607
MYH7	4% (3)	0,6% (1)	0,089	1,8% (16)	0,181	4,2% (4)	0,6% (1)	0,061	1,8% (16)	0,124
LMNA	4% (3)	0,6% (1)	0,089	6,2% (55)	0,614	1% (1)	0,6% (1)	1	6,2% (55)	0,035*
LAMP2	2,7% (2)	-	0,095	0,1% (1)	0,017	1% (1)	-	0,365	0,1% (1)	0,186
JPH2	2,7% (2)	-	0,095	0,5% (4)	0,074	3,1% (3)	-	0,047*	0,5% (4)	0,024*
CAV3	2,7% (2)	-	0,095	0,6% (5)	0,098	1% (1)	-	0,365	0,6% (5)	0,463266612
PSEN2	2,7% (2)	-	0,095	0,8% (7)	0,152	1% (1)	-	0,365	0,8% (7)	0,564
DES	2,7% (2)	0,6% (1)	0,227	0,2% (2)	0,032	1% (1)	0,6% (1)	1	0,2% (2)	0,2671
DTNA	2,7% (2)	0,6% (1)	0,227	1,2% (11)	0,271	1% (1)	0,6% (1)	1	1,2% (11)	1
RYR2	9,3% (7)	4,8% (8)	0,246	4,9% (43)	0,103	4,2% (4)	4,8% (8)	1	4,9% (43)	1
GPD1L	1,3% (1)	-	0,309	0,1% (1)	0,150	1% (1)	-	0,365	0,1% (1)	0,186
KCNE2	1,3% (1)	-	0,309	0,3% (3)	0,279	-	-	-	0,3% (3)	1

Et dans les MIN

CENTRAL ILLUSTRATION Whole Exome Sequencing and a Targeted Analysis of 90 GHD-Susceptibility Genes



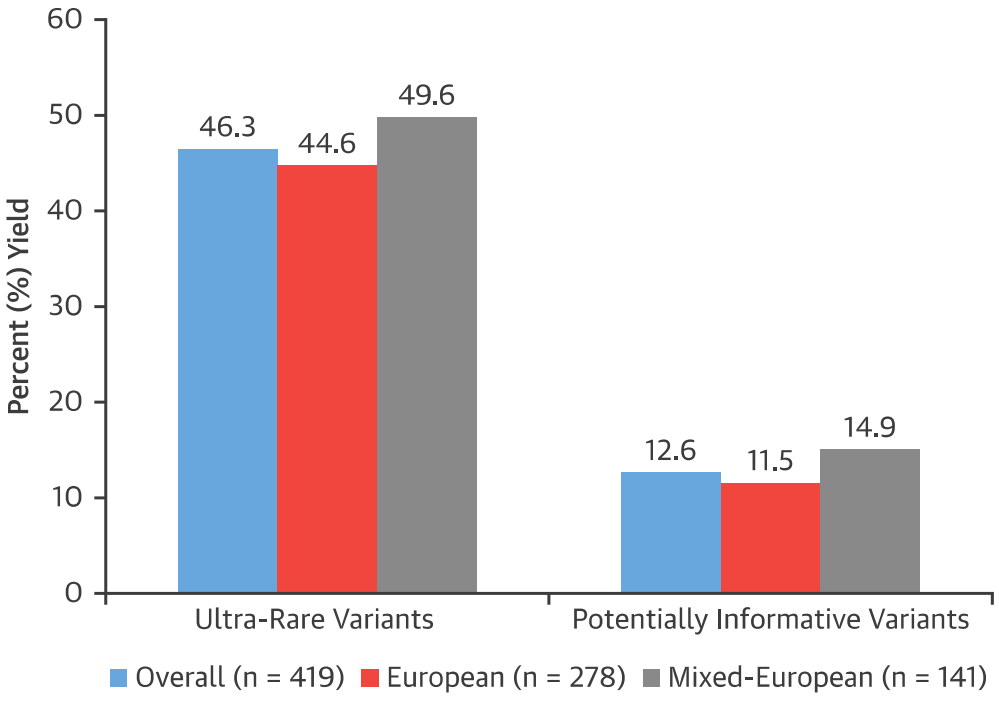


Tester, D.J. et al. J Am Coll Cardiol. 2018;71(11):1217–27.

The triple-risk hypothesis for SIDS highlighting genetic heart disease (GHD) as a potential explanation for infant vulnerability, and our whole exome sequencing strategy to detect American College of Medical Genetics and Genomics (ACMG) guideline-predicated "pathogenic" or "likely pathogenic" variants in SIDS cases. MAF = minor allele frequency; SIDS = sudden infant death syndrome.

Tester, JACC 2018

FIGURE 1 **Yield of Ultra-Rare and "Potentially Informative" GHD-Associated Gene Variants**



A bar graph depicting the percentage of yield of ultra-rare (minor allele frequency <0.00005), nonsynonymous variants and the "potentially informative" variants that were identified among the 90 genetic heart disease (GHD)–associated genes for the overall, European Caucasian, and mixed-European ancestry cohorts.

Tester, JACC 2018

Conclusion

- Un diagnostic étiologique en cas de mort subite chez un sujet jeune est possible dans 25% à 40% des cas
- Elle doit s'accompagner d'une autopsie moléculaire si l'ADN du sujet décédé est disponible
- Les résultats génétiques doivent être interprétés avec précaution et dans le contexte familial