PEDIRHYTHM VII:

Pediatric and Congenital Rhythm Congress

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GENETICS OF SUDDEN CARDIAC DEATH

WHEN to perform genetic screening?

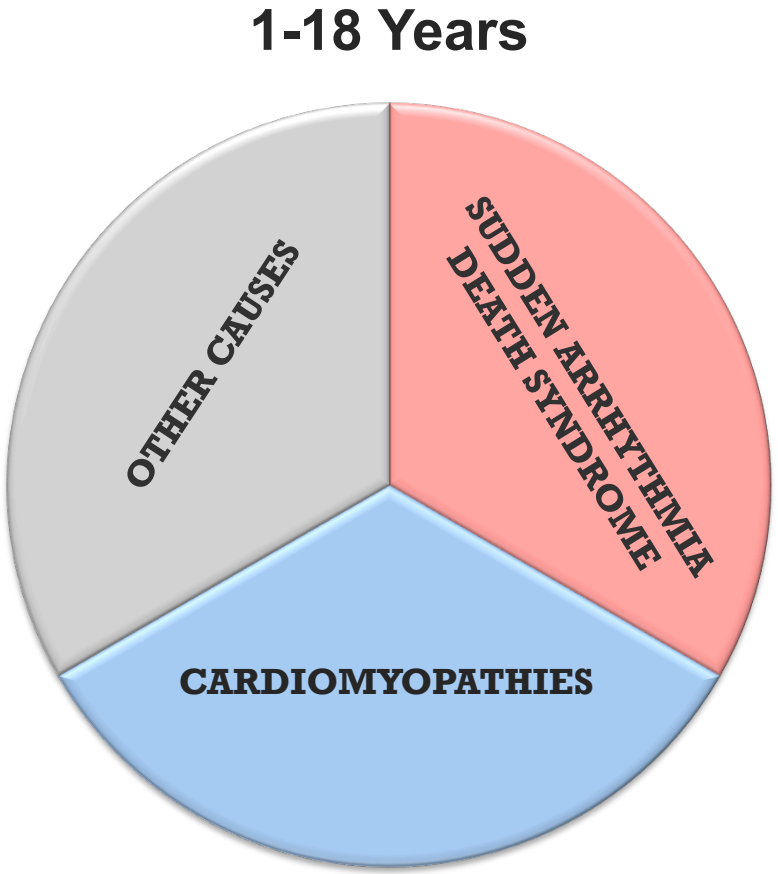
Sudden Cardiac Death (SCD)

- SCD in the young is uncommon.
- Incidence is less than 5 per 100.000 persons per year.[1]
- It is a great tragedy.
- Disastrous implications for the family and the society.

1. Ackerman, et al. *Circulation.* 2016.

Causes of SCD in the young

- Congenital heart diseases
- Myocarditis
- Cardiomyopathies
- Unexplained (SADS)



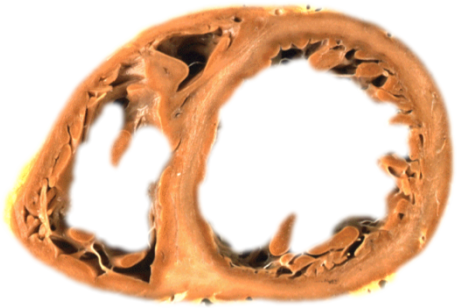
Meyer, et al. *Circulation.* 2012
Semsarian, et al. *Eur Heart J*. 2015.

WHY perform genetic screening in SCD cases?

- Because of the discovery that genetic mutations in isolated cases or in families with cardiac diseases are associated with increased risk of SCD.

- Because the same mutations or other mutations in the same genes may also be found in SCD cases.

Cardiomyopathies



DCM

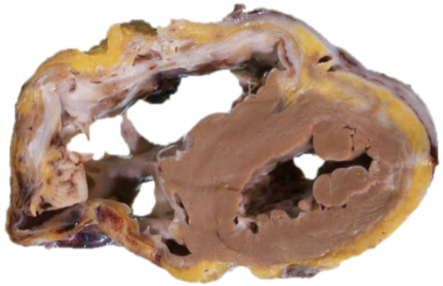
34 Genes

TTN
MYH7
LMNA
TNNT2

HCM

19 Genes

MYH7
MYBPC
TNNT2
TNNI3



ARVC

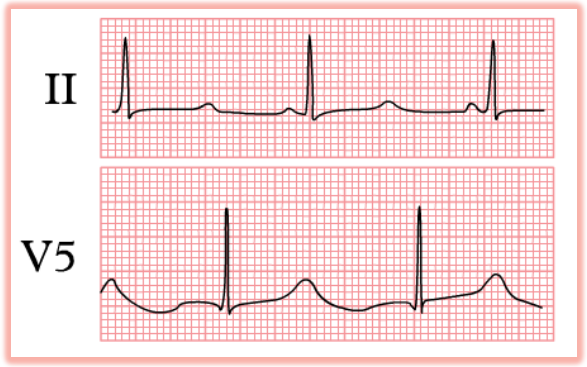
8 Genes

PKP2
DSP
DSC2
JUP

Post-mortem examination has a high probability of identifying these cause of SCD.

Genetic Home Reference (https://ghr.nlm.nih.gov).

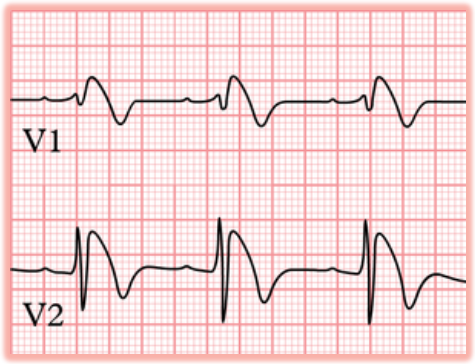
Primary arrhythmias (SADS)



Long QT Syndrome

16 Genes

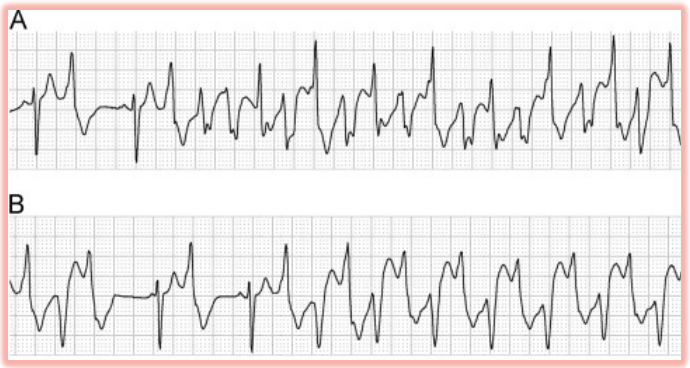
KCNQ1
KCNH2
SCN5A



Brugada Syndrome

20 Genes

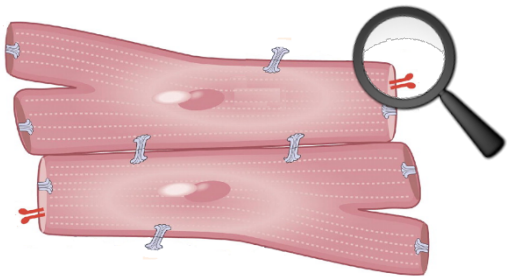
SCN5A

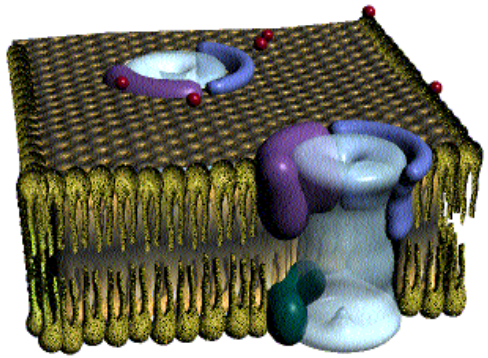


Catecholaminergic Polymorphic Ventricular Tachycardia

6 Genes

RyR2
CASQ2





Negative Autopsy

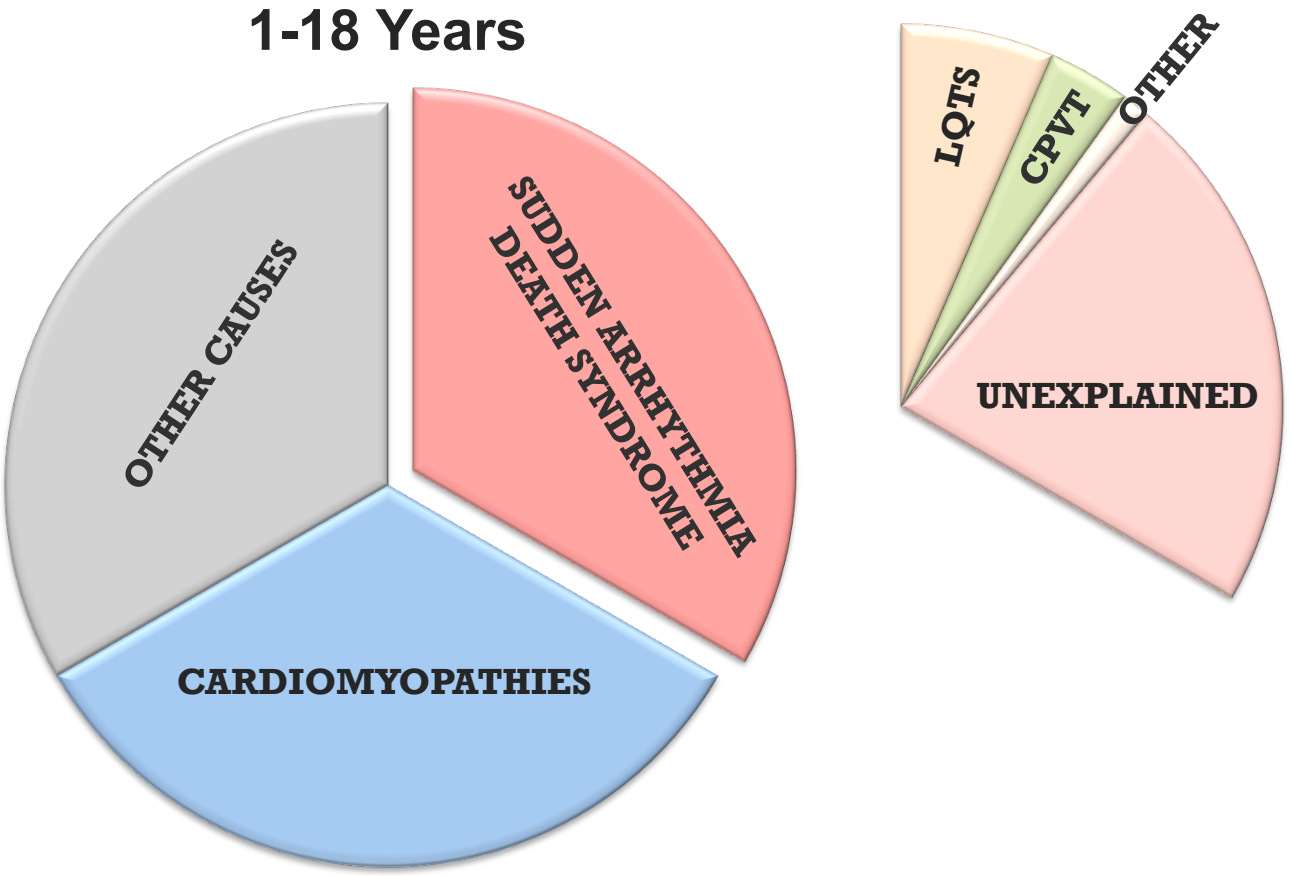
Genetic screening in SADS cases

- Post-mortem genetic studies in autopsy-negative SCD cases.
- Testing a small number of genes associated with inheritable

Gene	Protein	Disease	% of disease	% of SADS
KCNQ1	K^+ channel (I_{Ks})	LQTS1	35-40	10-15
KCNH2	K^+ channel (I_{Kr})	LQTS2	30-35	1-5
SCN5A	Na^+ channel (I_{Na})	LQTS3 BrS	5-10 15-25	<1 <1
RyR2	Ryanodine receptor	CPVT1	60-65	10-15

Semsarian, et al. Eur Heart J. 2015.
Lahrouchi, et al. Front Cardiovasc Med. 2016.

Genetic screening in SADS cases



Semsarian, et al. Eur Heart J. 2015.
Lahrouchi, et al. Front Cardiovasc Med. 2016.

WHEN to perform genetic testing?

Why not perform genetic testing in all unexplained SCD cases?

Because genetic testing is not harmless.

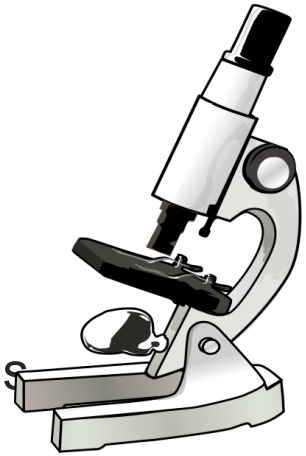
- There is a large background of genetic variation in the human genome.
- Not all these genetic changes are disease-causing mutations.
- Distinguishing mutations from benign genetic variants is extremely difficult.
- False assignment of causality has significant consequences for the families.

When to perform genetic testing?

- **When there is a phenotype!**
  - To reduce the number of genes needed to be tested.
  - To increase the probability of identifying a disease-causing mutation.
  - To decrease the risk of false-positive designation of a benign variant as a disease-causing mutation (and avoid “genetic purgatory”) .

- ***“If you are not sure of the phenotype, don’t go fishing for a genotype.”*** Dr. Michael Ackerman. Heart Rhythm. 2015;2:2325–

Obtaining a phenotype in SCD



- **Post-mortem examination**
  - Macroscopic and histologic examination of all organs
  - Evaluation of the heart by an expert cardiac pathologist.
  - Comprehensive toxicological testing.
  - Collection of blood or tissue samples for future DNA extraction (no paraffin-embedded tissues).

Obtaining a phenotype in SCD

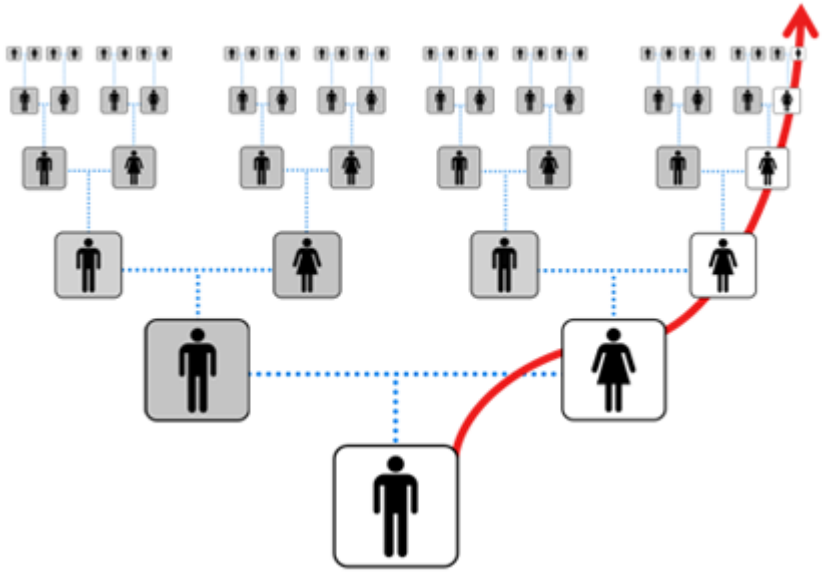
- **Clinical history**
  - Medical history (syncope, exertional symptoms, medications, ECGs).
  - Family history (cardiac disease, SCD, drowning, motor vehicle accidents, epilepsy, fainting).
  - Circumstances of death (activity at the time of death, preceding symptoms).
  - Information from family, general practitioner, ambulance and police.

Genetic testing

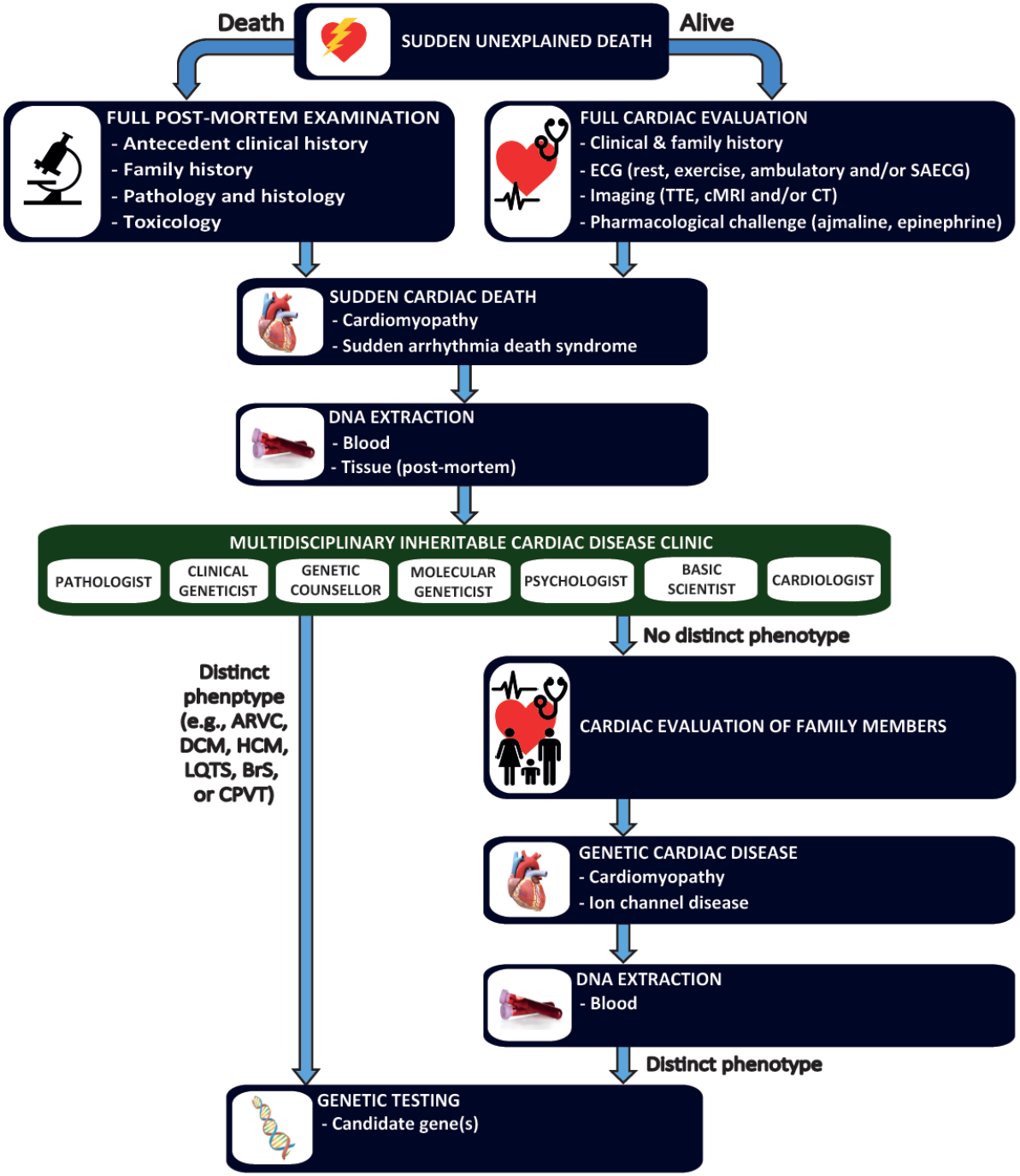
- A definite clinical diagnosis of an inheritable cardiomyopathy (e.g., HCM, ARVC, DCM).
- A definite clinical diagnosis of an inheritable arrhythmia syndrome (e.g., LQTS, CPVT, BrS).
- Candidate gene approach is possible (i.e., phenotype-driven sequencing of one gene or a panel of genes).

When to perform family screening first (before genetic testing)

- No cause of death is identified.
- A “possible” clinical diagnosis of inheritable cardiac disease (e.g., HCM, ARVC, DCM, LQTS, CPVT, or BrS).
- Family screening is an attempt to establish a more definite phenotype and enable phenotype-driven genetic testing.



An ideal diagnostic approach to SCD in the young



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