

# Molecular diagnosis of inherited cardiac diseases in the era of next-generation sequencing.

A single center's experience over 5 years.

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## KEY POINTS

**4,185**  
cases  
2015 -2020



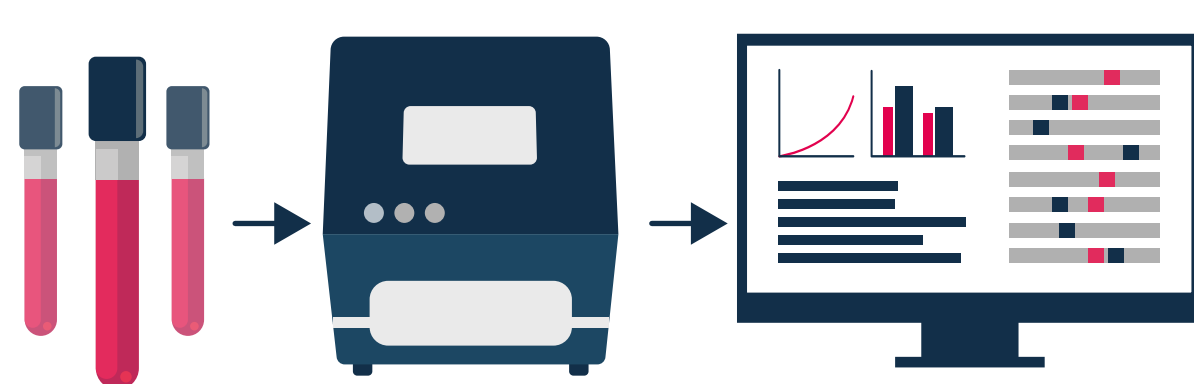
**Unexpected variants and incidental findings** were identified in **28** probands, demonstrating the clinical **relevance of genetic analysis** for inherited cardiac diseases.

**CNVs** detected in **~3.1%** of probands with a pathogenic or likely pathogenic variant.

Whole genome sequencing could be considered, but would likely yield limited results as **pathogenic variations** were mainly clustered in genes with **strong evidence of disease causation**.

## METHODS

Next-generation sequencing workflow based on a panel of **105 genes**



Conducted in accordance with the principles of the Declaration of Helsinki. Informed consent obtained for all cases.

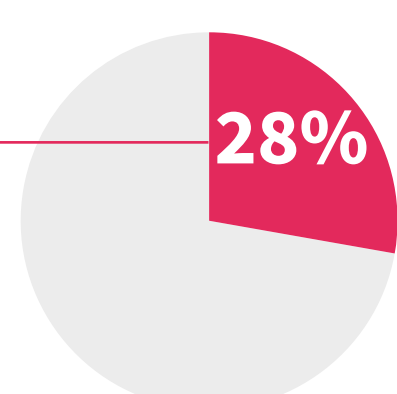
Bioinformatics analyses with a custom pipeline developed by SOPHiA GENETICS

## RESULTS

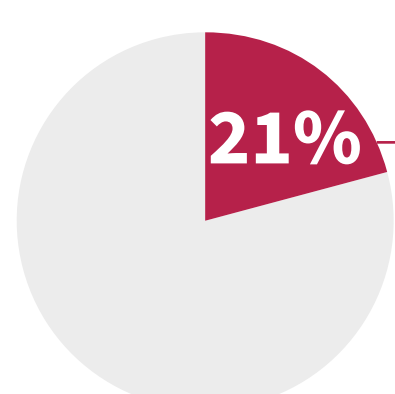


- Cardiomyopathies **n = 3,235 (77%)**
- Arrhythmias **n = 760 (18%)**
- Unexplained sudden cardiac arrest **n = 190 (5%)**

**Likely pathogenic** variations identified in **28%** of all probands



**Likely pathogenic** variations identified in **21%** of those with **sudden cardiac death**



### Hypertrophic cardiomyopathy n = 1,622

- Pathogenic or likely pathogenic variant: **33%**
- VUS: **31%**

Most frequent variants were in:  
**MYBPC3**: 55% (75% truncating)  
**MYH7**: 21% (mainly missense)

Recurrent variants:  
**MYBPC3-c.1928-2A>G** (n = 30)  
**MYH7-p.Thr1377Met** (n = 15)

### Dilated cardiomyopathy n = 1,361

- Pathogenic or likely pathogenic variant: **28%**

>80% of variants were in:  
**TTN, FLNC, LMNA, DSP, MYH7, TNNT2, BAG3, MYBPC3**

### Brugada syndrome n = 273

- Pathogenic or likely pathogenic variant in **SCN5A**: **14%**

### Long QT syndrome n = 335

- Pathogenic or likely pathogenic variant: **29%**

Most frequent variants were in:  
**KCNQ1**: **46%**  
**KCNH2**: **40%**  
**SCN5A**: **7%**

### Other variant types

#### Copy number variations (CNVs)

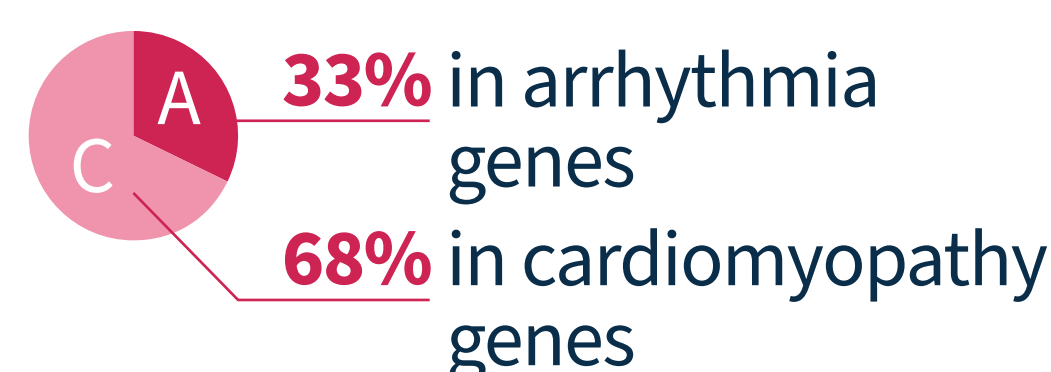
- In **~3.1%** of those with a (likely) pathogenic variation

Cardiomyopathies: **0.7%**  
Arrhythmias: **1.6%**  
Sudden cardiac death: **1.1%**

**Homozygous variations**: 14 cases

### Sudden cardiac death n = 190

- Pathogenic or likely pathogenic variant: **21%**



Most frequent variants were in:  
**MYBPC3** (n = 6), **RYR2** (n = 5),  
**PKP2** (n=4), **FLNC** (n = 3),  
**KCNH2** (n = 3), **LMNA** (n = 3),  
**SCN5A** (n = 3), **TTN** (n = 3)

**~2-week turnaround**  
**Costs ~130€ per patient**

## INTERESTING FINDINGS

- Variations in arrhythmia-associated genes were identified in probands with cardiomyopathies, and vice versa
- Variations in hypertrophic cardiomyopathy-mimicking genes were found in probands identified as having hypertrophic cardiomyopathy