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%**

Sudden cardiac death
n = 190

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

33% in arrhythmia genes
68% in cardiomyopathy genes

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

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

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

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