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

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

Bioinformatics analyses with a custom pipeline developed by SOPHiA GENETICS

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

RESULTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>CARDIOMYOPATHIES</th>
<th>ARRYTHMIAS</th>
<th>SUDDEN CARDIAC DEATH</th>
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</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Pathogenic or likely pathogenic variant: 33%</td>
<td>Most frequent variants were in: MYBPC3 (55% [75% truncating]), MYH7 (21% [mainly missense])</td>
<td>Recurrent variants: MYBPC3-c.1928-2A&gt;G (n = 30), MYH7-p. Thr1377Met (n = 15)</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>Pathogenic or likely pathogenic variant: 28% &gt;80% of variants were in: TTN, FLNC, LMNA, DSP, MYH7, TNNT2, BAG3, MYBPC3</td>
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<tr>
<td>Sudden cardiac death</td>
<td>Pathogenic or likely pathogenic variant: 21% 33% in arrhythmia genes, 68% in cardiomyopathy genes</td>
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</tbody>
</table>

Other variant types

<table>
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<th>Copy number variations (CNVs)</th>
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<tr>
<td>~3.1% of those with a (likely) pathogenic variation</td>
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Likely pathogenic variations identified in 28% of all probands

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

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

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

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