The Genetics and Prevention of Sudden Cardiac Death
Sudden cardiac death (SCD), a serious public health problem

→ Every day, between 1,600 and 2,000 people die worldwide from genetically caused SCD.¹

→ SCD is a complex disease. Its pathogenesis involves different genetic variants.²

→ Some heart diseases, particularly cardiomyopathies and channelopathies, play a fundamental role in SCD.³

SCD can be prevented

The identification of at-risk patients helps to prevent a fatal outcome.⁴
Genetics, key for a comprehensive diagnosis

Comprehensive diagnosis

Clinical diagnosis

Based on signs and symptoms.

Molecular diagnosis

It can be determined before the disease is expressed.

- Medical record
- Electrocardiogram
- Echocardiography
- Magnetic resonance imaging
- Pharmacological tests
- Electrophysiological studies

Genetics

Clinical diagnosis + Molecular diagnosis

Genes involved in channelopathies.
Adapted from text ref. 5.

Genes involved in cardiomyopathies.
Adapted from text ref. 3.
Selection of the genes that make up our panels is based on the following criteria:

- Recommended in guidelines and consensuses
- Less common genes, but with demonstrated causality
- Highly suspect in disease causation
- Causality of phenotype subtypes

When a diagnosis is unclear, Ferrer inCode recommends the analysis of a broad gene panel that contains all phenotypes.

When there is a specific clinical suspicion, we recommend testing to specific panel related to the phenotype and its associated genes.6-9

We add genes to our panels as and when they meet the inclusion and validation criteria.
Clinical utility of SudD inCode

Benefits

- Confirmation of diagnosis*
- Establishment of preventive measures
- Reproductive counselling

* when the causal mutation is found

- Presymptomatic diagnosis
- Establishment of preventive measures
- Reproductive counselling
- Adjustment of frequency of clinical monitoring
- Provides the basis for the pathogenicity study**

**Familial segregation studies are essential to analyse pathogenicity. 10, 11

Graphs adapted from text ref. 10.
Current guidelines\textsuperscript{12, 13} recommend genetic analysis of the genes associated with the clinical suspicion.

There are more than 50 different genes associated with channelopathies and cardiomyopathies\textsuperscript{14}, so next-generation sequencing (NGS) is the solution of choice for identifying them.\textsuperscript{15}

Sequencing the complete gene is extremely important.\textsuperscript{16}
Our panels and their phenotype coverage

**Undetermined diagnosis**
- Sudden infant death syndrome (SIDS)
- Idiopathic ventricular fibrillation
- Unexplained syncope
- Unexplained sudden death
- Suspected hereditary sudden death

**Structural disease**
- Arrhythmogenic Right Ventricle Cardiopathy (ARVC)
- Hypertrophic Cardiomyopathy (HCM)
- Unexplained Cardiac Hypertrophy (UCH)
- Dilated Cardiomyopathy (DCM)
- Left Ventricular Noncompaction Cardiomyopathy [adult and neonatal] (LVNC)
- Restrictive cardiomyopathy

**Arrhythmogenic disease**
- Long QT syndrome (LQTS)
- Brugada syndrome (BrS)
- Short QT syndrome (SQTS)
- Unexplained bradycardia
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Progressive cardiac conduction defect
- Atrial Fibrillation
- Sudden Death associated to epilepsy
- Early repolarisation syndrome
- Sick sinus syndrome

**Aortic vascular disease**

*Non-syndromic:*
- Familial thoracic aortic aneurysm and dissection (TAAD)

*Syndromic:*
- Marfan Syndrome (MS)
- Type IV Ehlers–Danlos syndrome
- Loeys–Dietz syndrome
- Aneurysm/osteoarthritis syndrome (AOS)

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*This panel includes new phenotypes and new genes with lower prevalence than the phenotypes included in the less extensive version (familial cardiopathy panel).
NGS, the present and the future of genetic analysis for clinical diagnosis

- Multiple studies have been published that have led to genetic diagnosis programmes based on the use of NGS.\textsuperscript{17, 18}

- NGS sequencing is around 20 times cheaper than Sanger sequencing as well as being much faster, without losing precision.\textsuperscript{13}

- NGS, technological evolution.\textsuperscript{15*}
  - More genes analysed
  - Lower cost
  - Less time
  - With the same precision

*Compared to the Sanger technique, used to date.
Our NGS service

- NGS panels are performed using the oligonucleotide-based target-capture technique (enrichment array designed and validated for exclusive use by Ferrer inCode).

- Ultracequencing on Illumina\textsuperscript{inc} platform (HiSeq2000 or MiSeq).

- Obtaining genetic variants combines SAMTOOLS and our own program (GendiCall) to identify possible variations.

- Data are expressed based on the hg19 version of the genome.

- NGS is supplemented with Sanger technology (ABI 3710) to obtain > 99.9% coverage of encoding areas and exon-intron boundaries.

- More than 99.9% of substitution variants (SNPs) are detected, as well as small insertions and deletions of 1 to 6 nucleotides.

- All variants with possible pathogenic classification are confirmed by Sanger sequencing.
## Technical specifications of the SudD inCode service

<table>
<thead>
<tr>
<th>NGS panels</th>
<th>Genes analysed</th>
<th>Exons analysed</th>
<th>Bases analysed</th>
<th>Call rate NGS at 30x</th>
<th>SudD service call rate (NGS + Sanger)</th>
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</thead>
<tbody>
<tr>
<td>Extended familial cardiopathy</td>
<td>108</td>
<td>1,908</td>
<td>387,450</td>
<td>99.83%</td>
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<td>Familial cardiopathy</td>
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<td>1,493</td>
<td>306,966</td>
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<td>Arrhythmogenic I</td>
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<td>598</td>
<td>105,144</td>
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<td>Arrhythmogenic II</td>
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<td>482</td>
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<td>&gt; 99.99%</td>
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<td>235,908</td>
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<td>HCM</td>
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<td>TAAD and Marfan syndrome</td>
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<td>47,283</td>
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<td>Sanger</td>
<td>Variable according to selected genes</td>
<td>N/A</td>
<td>100%</td>
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</tbody>
</table>
References:
Ability to analyse related genetic variants in a single process.

NGS, a cost-effective technological evolution in the genetic analysis of SCD.

Analytical quality, analysis of more than 99.99% in gene sequencing.

Genetic and clinical counselling from specialists with extensive international experience.