Introduction

Cardiomyopathies and arrhythmia syndromes are common genetic cardiac diseases leading to sudden cardiac death (SCD). Their incidence is estimated at 300,000 cases per year in Europe. Although the pathology is complex, coronary artery diseases account for 40 to 60% of SCD, when cardiomyopathies (dilated, hypertrophic, left ventricular noncompaction, and arrhythmogenic right ventricular cardiomyopathy) and arrhythmia syndromes (long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) account for the rest of SCD annual cases.

When looking at those cases, molecular genetic testing of validated SCD-causing genes is crucial since it allows to establish or confirm patients’ diagnostics. In some instances, it even permits to adopt the best treatment.

This white paper describes how SOPHiA GENETICS’ advanced analytical technology supported Dr. Gilles Millat’s “Cardiogenetic laboratory” at the Hospices Civils de Lyon to set up and use custom NGS test in clinical routine to provide the most accurate diagnosis for cardiomyopathies and arrhythmia syndromes.
**Detection of Genomic Variants Involved in Sudden Cardiac Death**

**Context**

SCD occurs in a broad spectrum of cardiac pathologies and is an important cause of mortality in the general population. Antiadrenergic therapeutic measures (e.g., use of beta-blockers, left cervicothoracic stellectomy), aiming to decrease the risk and lethality of cardiac events, are for instance the treatments of choice for patients suffering from long QT syndrome and presenting syncope symptoms. Even though beta-blockers are extremely protective in type 1 and 2 LQTS (LQT1 and LQT2), they may not provide sufficient protection in type 3 LQTS (LQT3).

In this case, clinicians might decide to offer a device therapy (e.g., use of pacemakers, implantable cardioverterdefibrillators) to patients.

The identification of genetic mutations that predispose to SCD would contribute to a better diagnosis and risk stratification.

**Hospices Civils de Lyon Cardiogenetic Laboratory**

Back in 2012, the Hospices Civils de Lyon were using High-Resolution Melting method (HRM) and conventional capillary Sanger sequencing to diagnose patients that were at risk of SCD. Dr. Gilles Millat's “Cardiogenetic laboratory” was analyzing 5 prevalent genes involved in cardiac arrhythmia (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2) in addition to 4 prevalent genes involved in cardiomyopathy (MYBPC3, MYH7, TNNT3, TNNI3). The turnaround time was over a year.

In 2013, the Hospices Civils de Lyon decided to implement NGS technology in routine clinical diagnostics. Thanks to SOPHiA GENETICS’ support, the laboratory rapidly adopted this high throughput method on the Ion Torrent Personal Genome Machine (PGM) based on multiplex PCR (AmpliSeq) for DNA enrichment.

Two intention panels were developed to do so. The first intention panel was covering 9 prevalent genes (as mentioned above) and the analysis was performed by SOPHiA, the collective Artificial Intelligence (AI), exclusively available on SOPHiA DDM® SaaS Analytical platform. This approach significantly shortened the turnaround time to 4-6 weeks versus one year.

The second intention panel was covering 40 genes for cardiac arrhythmia and 45 genes for cardiomyopathy. Here again, the turnaround time was drastically reduced to 6-8 weeks.

Two years later, in September 2015, Dr. Gilles Millat’s “Cardiogenetic Laboratory” decided to shift to the NextSeq500™ sequencing platform, based on capture enrichment method (Roche, NimbleGen), with the aim to develop a completely made-to-measure and redesigned large panel of 95 genes involved in SCD. With SOPHiA GENETICS’ Validation Program, the “Cardiogenetic Laboratory” from the Hospices Civils de Lyon rapidly implemented this change. Of note, the design of the larger gene panel was clustered in so called sub-panels, easily allowing the “Cardiogenetic Laboratory” to tackle different specific cardiac diseases. SOPHiA AI led to excellent analytical performance and the use of SOPHiA DDM and its automatized workflow led to a 20% increase in NGS activity and drastically lowered the turnaround time to just 2-3 weeks, thus enabling a faster and better diagnosis for patients. So far, 650 patients have been diagnosed using this custom panel.

In order to establish the cause of death for SCD cases and evaluate the NextSeq500™ technology’s sensibility, specificity, practicability and cost, a cohort of 90 previously genotyped cases were screened. 100% of targeted regions were efficiently covered and the systematic analysis of the raw data by PEPPER™ and MUSKAT™, SOPHiA GENETICS proprietary algorithms, powered by SOPHiA, showed a performance of 100% sensitivity and specificity for all common SNPs (Single Nucleotide Polymorphism), missense mutations, short INDELs (Insertion and Deletions) and all previously characterized CNVs (Copy Number Variations).
Conclusion

This case study shows that the NGS strategy adopted by Dr. Gilles Millat’s “Cardiogenetic Laboratory” represents a robust and low-cost genomic mutation detection method, ensuring the highest level of sensitivity and specificity at the same time. SOPHiA accurately detects, annotates and pre-classifies genomic variants involved in SCD. Therefore, the NGS technology can easily and immediately be adopted in laboratories for routine clinical diagnostics. Such rapid adoption will provide more accurate diagnostics and improve the quality of patients’ care.

About Us

Global leader in Data-Driven Medicine, SOPHiA GENETICS is a healthtech company which has developed SOPHiA AI, the most advanced technology for clinical genomics, helping healthcare professionals better diagnose and treat patients.

The global network of hundreds of institutions worldwide that use SOPHiA DDM® analytical platform powered by SOPHiA, form the world’s largest clinical genomics community.

By enabling the rapid adoption of genomic testing, turning data into actionable insights, and sharing knowledge through its community, SOPHiA GENETICS is democratizing Data-Driven Medicine to save lives.

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References


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