SOPHiA™

CARDIO SOLUTIONS

Getting to the heart of inherited cardiac diseases

HIGHLIGHTS

- Customizable gene content covering arrhythmias and cardiomyopathies
- Advanced analytical performance
- Robust solutions designed to detect complex variants, including CNVs
- High productivity workflow with short turnaround time

The SOPHiA Cardio Solutions includes two genomic applications, Cardio (CAS) and Extended Cardio (ExtCAS), that bundle a smart capture-based target enrichment kit with the analytical power of SOPHiA™ AI and full access to the SOPHiA DDM™ platform. Expertly designed, these solutions target up to 128 genes associated with the most prevalent inherited arrhythmias and cardiomyopathies.

SMART KIT DESIGN

- High affinity probe design ensuring extremely uniform coverage of the target region
- Comprehensive applications targeting:
  - 31 genes for CAS
  - 128 genes for ExtCAS, including all the CAS genes

ANALYTICAL POWER

- Advanced analytical performance (i.e. 100% sensitivity and reproducibility)
- High-confidence calling of SNVs, Indels and CNVs in all the genes of the two applications

UNIVERSAL PLATFORM

- Intuitive and user-friendly interface
- Secure storage of anonymized data
- Dedicated features for simplified data visualization and interpretation
- Fully customizable report

Democratizing Data-Driven Medicine

SOPHiA GENETICS helps clinical researchers better analyze and interpret genomic data. Experts who use our solutions benefit from:

SOPHiA AI
Over 200 genomic applications supported

Set Up Program
Rapid adoption of genomic applications

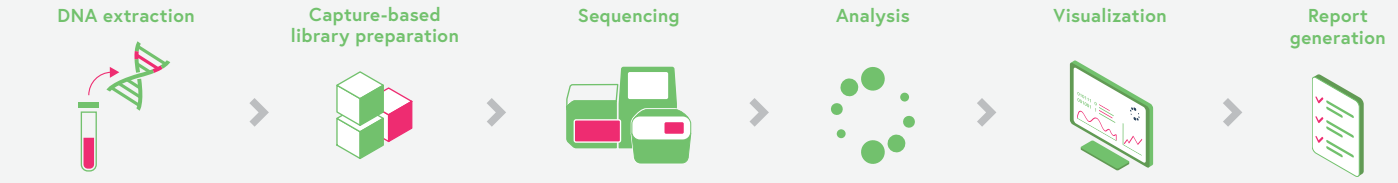
Data security policy
Compliance with national privacy laws, GDPR, HIPAA guidelines and applicable legislation

SOPHiA's community
Anonymized and safe knowledge sharing among experts worldwide

Cardio Solutions

Streamlined workflow from DNA extraction to variant report generation

CAS and ExtCAS provide a straightforward library preparation workflow. Ready-to-sequence target-enriched libraries are generated in just 1.5 working days, starting from 200ng of DNA. For high-throughput needs, DNA extraction and library preparation can be fully automated, using pre-optimized protocols for a variety of liquid handling robots. Library preparation of both applications is compatible with Illumina and Thermo Fisher Scientific platforms. Sequencing output files are then analyzed by SOPHiA, that adapts to the specifics of each sequencer, always ensuring advanced performance. Results are displayed on the SOPHiA DDM platform where clinical researchers can easily interpret them and generate a complete variant report.



Relevant gene content

The CAS and ExtCAS applications cover complete coding sequence (± 25bp and ± 5bp of exon-flaking regions respectively) of the 31 and 128 most relevant genes related to arrhythmias and cardiomyopathies. ExtCAS has been developed under the same guiding principles as the smaller solution with further optimization to include 97 additional genes. In both cases, probe design is optimized to provide high coverage uniformity throughout the entire target region, resulting in valuable data quality. For specific needs, the gene content can be fully customized.

ARRHYTHMIA		CARDIOMYOPATHY
AKAP9, ANK2, ***CACNA1C****,* ***CACNA2D1****,* ***CACNB2****, CALM1, CALM2,* ***CASQ2****, CAV3,* ***CTNNA3****, DPP6,* ***DSC2****, EMD, FGF12, FHL1, GJC1, GPD1L, JUP, KCNA5, KCNAB2, KCND3,* ***KCNE1****,* ***KCNE2****, KCNE3, KCNE5,* ***KCNH2****,* ***KCNJ2****, KCNJ5, KCNJ8,* ***KCNQ1****,* ***LMNA****, MOG1,* ***NKX2-5****, NOS1AP, NUP155,* ***PKP2****,* ***RYR2****,* ***SCN10A****, SCN1B, SCN2B, SCN3B, SCN4B, SLC8A1, SLMAP, SNTA1, TBX5, TGFB3,* ***TMEM43****,* ***TRDN****, TRPM4, TRPM7*	*ATP2A2, CACNA1D, CALM3, CALR3, DES,* ***DSG2****,* ***DSP****, GJA5,* ***HCN4****, HEY2, NPPA, PDLIM3,* ***PLN****,* ***SCN5A****, STRN, TTN*	*ABCC9, ACTA1, ACTC1, ACTN2, ALPK3, ANKRD1, APOA1, BAG3, CHRM2, CRAYB, CSRP3, CTF1, DMD, DOLK, DTNA, EYA4, FHL2, FKTN, FLNC, GAA, GATA4, GATA6, GATAD1, GJA1, GLA, HFE, JPH2, LAMA4, LAMP2, LDB3,* ***MYBPC3****,* ***MYH6****,* ***MYH7****,* ***MYL2****, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, PRDM16,* ***PRKAG2****, PSEN1, PSEN2, PTPN11, RAF1, RBM20, SCO2, SGCD, SURF1, TAZ, TBX20, TCAP, TMPO, TNNC1,* ***TNNI3****,* ***TNNT2****, TPM1,* ***TTR****, VCL*

SOPHiA CAS: **31 relevant genes**
SOPHiA ExtCAS: 128 relevant genes (including CAS genes)

Smart kit specifications

Parameter	Details
Sample source	Blood
DNA input requirement	200 ng
Target region	131 kb (CAS)
	470 kb (ExtCAS)
Library preparation time	1.5 days

Sequencing and multiplexing recommendations

Sequencers	Flow Cell / Ion Chip Kit	Recommended samples per run (for 250x median coverage depth)	
		CAS	ExtCAS
MiniSeq™	High Output Kit (2x150bp)	24	8
MiSeq®	v3 (2x300bp)	32	12
NextSeq® 500/550	Mid Output Kit v2 (2x125bp)	96*	48
	High Output Kit v3 (2x150bp)	96*	96*
Ion S5™	Ion 530	12	4
	Ion 540	48	16

* maximum number of indices available
Sequencing recommendations and specifications for other sequencing kits and instruments available upon request. Delivery time may vary according to the selected sequencing platform.

Extremely uniform coverage

CAS and ExtCAS achieve very high on-target read percentage, which assures reliably high coverage uniformity within 0.2x and 5x the median coverage value across all the target regions, even in those with high GC-content (Fig. 1). Equal read coverage in all genes guarantees maximum sample multiplexing capability, resulting in an optimum cost per sample.

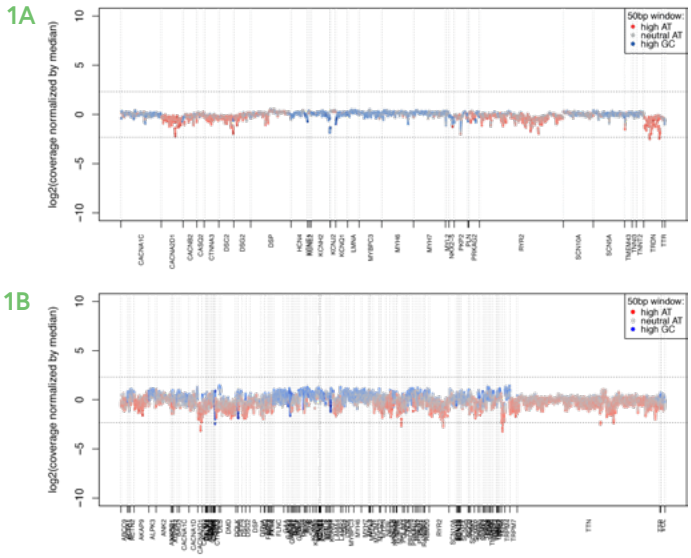


Figure 1: Coverage uniformity profile of a typical sample analyzed with CAS (1A) and ExtCAS (1B).
The X-axis represents the genes included in CAS (1A) and ExtCAS (1B), whereas the Y-axis the $\log_2$ coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are covering each target. Dashed lines represent 20% (lower line) and 500% (upper line) of the median coverage.

Advanced analytical performance

SOPHiA analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels and CNVs in all the genes covered by CAS and ExtCAS in a single experiment. SOPHiA reaches advanced analytical performance:

	CAS		ExtCAS
	Observed	Lower 95% CI	Observed
Sensitivity	100%	97.36%	100%
Specificity	100%	99.99%	99.99%
Accuracy	100%	99.99%	99.99%
Precision	100%	96.94%	98.68%
Repeatability	100%	99.98%	99.99%
Reproducibility	100%	99.97%	99.98%
Average on-target rate	100%		89.60%
Coverage uniformity	99.51%		99.84%
Average % of target region > 200x	99.78%		99.96%

Analysis time from FASTQ files: 4 hours
Analysis time may vary depending on the number of samples multiplexed and server load

High-confidence calling of Copy Number Variations

Several studies have identified Copy Number Variations (CNVs) as responsible for cardiac diseases associated with sudden cardiac death (SCD)[1,2].
SOPHiA detects CNVs in all genes of both applications* at a resolution of 1 exon (Fig. 2). This analysis is performed by evaluating the coverage levels of the target regions across all samples within the same sequencing run. For each sample, SOPHiA automatically selects a set of reference samples from the same run, based on the similarity of coverage patterns. Subsequently, the coverage is normalized by sample and target region using the reference samples, enabling CNV calling.
Thanks to its accuracy, the use of SOPHiA Cardio Solutions reduces the need for additional assays by allowing the detection of SNVs, Indels and CNVs. Moreover, the number of samples multiplexed in a run can be increased by avoiding supplementary reference samples. The result is a fast, nimble and more cost-effective workflow.

* 2 regions are excluded from the CNV detection in ExtCAS due to the presence of homologous regions: *TTN* exons 172-197 and *FLNC*_ex47.

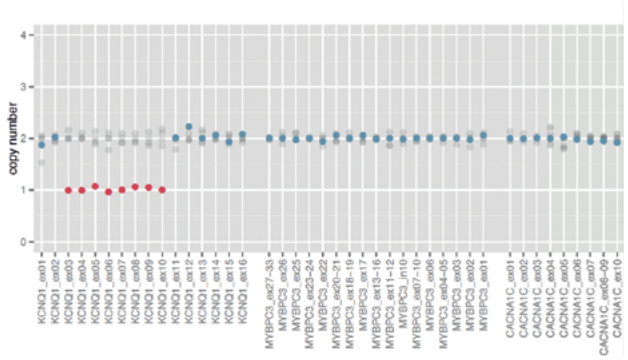
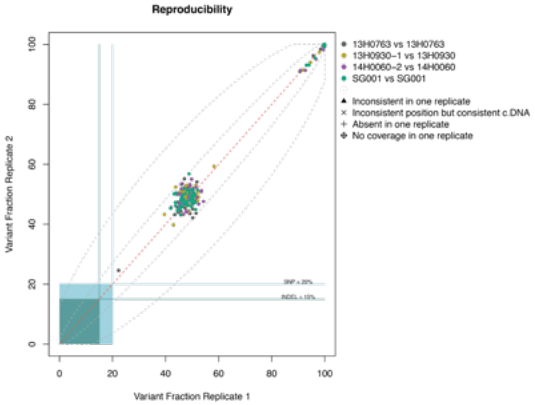


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and red dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence CNV predictions.

Very high repeatability and reproducibility

Required elements for establishing precision of any NGS-based application, repeatability and reproducibility must be determined by sequencing the same sample several times under same conditions (i.e. intra-run replicates) or under different conditions (i.e. inter-run replicates) respectively. CAS and ExtCAS have been tested extensively, ensuring almost 100% repeatability and reproducibility (Fig.3), giving genomic experts confidence in NGS sequencing.

3A



3B

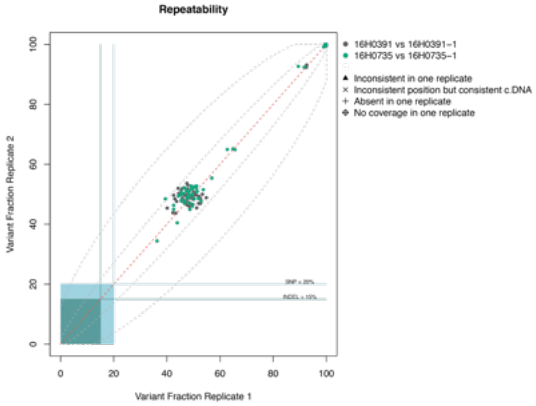


Fig.3: ExtCAS reaches 99.98% reproducibility (3A) and 99.99% repeatability (3B). The variant fractions, depicted by the colored dots, are typically 0.5 (heterozygous) or 1.0 (homozygous), as expected for germline variants. The grey, dotted lines represent the 5% and 10% deviation from identity (diagonal = red dashed line). 3A) Samples were processed 2 times in different runs to assess reproducibility. The replicated samples show an almost perfect match in variant fractions between 2 runs. 3B) Samples were processed 2 times in the same run to assess repeatability. The replicated samples show almost perfect match in variant fraction between the 2 replicates.

Cardio Solutions

Enhanced variant visualization and interpretation

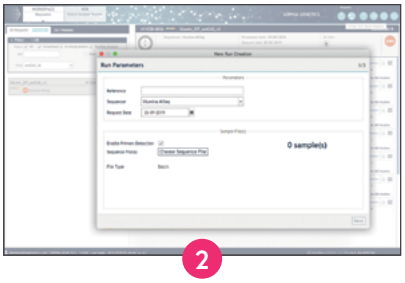
The SOPHiA DDM platform features intuitive variant filters, dual variant pre-classification and reporting functionalities to simplify data visualization and interpretation.

The platform enables clinician researchers to explore and interpret genomic variants and also to report significant findings.

1

Secure login

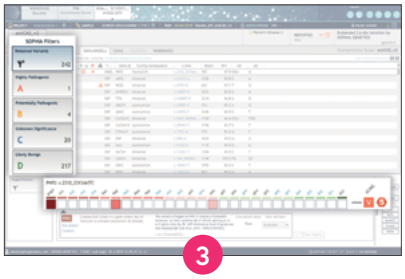
Access to SOPHiA DDM is restricted to registered users only. Login features a 2-step verification procedure.



2

Quick and simple data upload

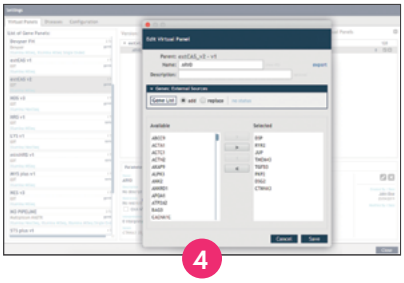
Once sequencing output files are uploaded, all relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



3

Dual variant pre-classification (ACMG score and SOPHiA's prediction)

Detected variants are displayed by variant type (SNVs, Indels and CNVs). Users can easily visualize an overview of the major SNVs and Indels pre-classified by level of pathogenicity according to both ACMG guidelines and SOPHiA's predictions.



4

Customized filtering

Virtual Panels can be created to limit the interpretation to a subset of genes available in the panel for quicker screening of relevant variants.

5

Variant flagging

Users can flag the pathogenicity of variants. Flagging decisions are greatly supported by the shared knowledge of the SOPHiA's global community and a wide range of databases, combining relevant information on variants (e.g., population frequency, pathogenicity scores and others).

6

Variant report generation

After interpretation, a variant report is generated. The report is fully customizable and includes information on variants that have been selected by the user.

Access to SOPHiA's community

In SOPHiA DDM, experts from hundreds of healthcare institutions interpret the results and flag the pathogenicity level of variants according to their knowledge and experience. This highly valuable information feeds the variant knowledge base and is anonymously and safely shared among the members of the community.

Respect data privacy

SOPHiA DDM encrypts all data to the highest industry standards before storing it redundantly in secured and private data centers. The platform ensures data protection and respects national privacy laws, GDPR, HIPAA guidelines and applicable legislation regarding data privacy.

Summary

The SOPHiA Cardio Solutions are comprehensive genomic applications that detect and characterize germline variants associated with the most prevalent inherited arrhythmias and cardiomyopathies. They enable the assessment of up to 128 genes in a single assay by leveraging the advanced analytical power of SOPHiA. As a result, these solutions globally offer a streamlined and standardized workflow, that can be easily implemented by any healthcare institution.

References:
1Mademont-Soler I, Mates J, Yotti R, et al. Additional value of screening for minor genes and copy number variants in hypertrophic cardiomyopathy. PLos ONE. 2017;12:e0181465.
2Mademont-Soler I, Pinsach-Abuin ML, Riuró H, et al. Large genomic imbalances in Brugada syndrome. PLoS ONE. 2016;11: e0163514.