SOPHiA GENETICS™

CARDIO SOLUTIONS

Getting to the heart of inherited cardiac disorders

The SOPHiA Cardio Solutions include two genomic applications, SOPHiA Cardio Solution (CAS) and SOPHiA Extended Cardio Solution (ExtCAS). Both applications bundle a smart capture-based target enrichment kit with the analytical performance and advanced features of 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

- Comprehensive applications targeting:
  - 31 genes with CAS
  - 128 genes with ExtCAS, including the CAS genes
- High affinity probe design, ensuring high on-target rate and coverage uniformity throughout the entire target regions
- Ready-to-sequence target-enriched libraries generated in just 1.5 days
- Optimal cost per sample ratio, due to the ability to multiplex more samples per run
- Automated workflow available on leading liquid handling robots for high-throughput library preparation needs

SOPHiA DDM™ PLATFORM

- Advanced analytical performance (i.e. 100% sensitivity and reproducibility)
- High-confidence calling of SNVs, Indels, and CNVs* in all genes covered by the applications
- Intuitive features for simplified data visualization and interpretation
- Customizable report
- Secure storage of anonymized data

*2 regions are excluded from CNV detection in ExtCAS due to the presence of homologous regions: *TTN* exons 172-197 and *FLNC* exon 47.

Discover the full power of your genomic data

The SOPHiA DDM™ platform helps to increase your productivity, enabling high-throughput assessment of genomic data. Designed to be secure, the platform offers a streamlined end-to-end workflow (from raw data to variant report) with machine learning-patented algorithms and intuitive features to detect, annotate and classify multiple types of variants in a single assay with a high level of accuracy.

Universal platform
Over 330 pipelines covering Oncology, Rare and Inherited Disorders, Cardiology, Metabolism and Neurology

Set Up Program
Assistance with assay set up for fast and worry-free transition to routine testing

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

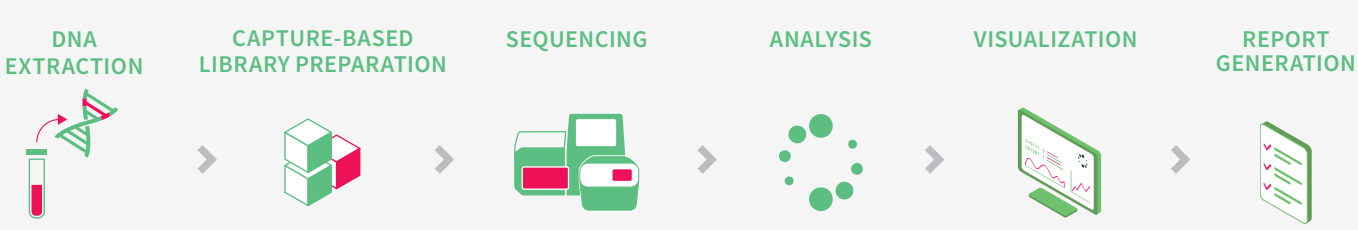
SOPHiA GENETICS' community
Anonymized and safe knowledge sharing among experts worldwide

Cardio Solutions

Streamlined workflow from DNA extraction to variant report generation

Cardio and Extended Cardio Solutions (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 sequencing platforms. Sequencing output files are then analyzed by SOPHiA DDM™, which adapts to the specifics of each sequencer, ensuring advanced analytical performance. Finally, results are displayed on the platform for streamlined interpretation and generation of a comprehensive variant report.



Relevant gene content

CAS covers the complete coding sequence (± 25bp of exon-flanking regions) of 31 genes, and ExtCAS the complete coding sequence (± 5bp of exon-flanking regions) of 128 genes related to arrhythmias and cardiomyopathies. ExtCAS was 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 regions, 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*

CAS: **31 relevant genes**
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 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 and precise CNV detection.

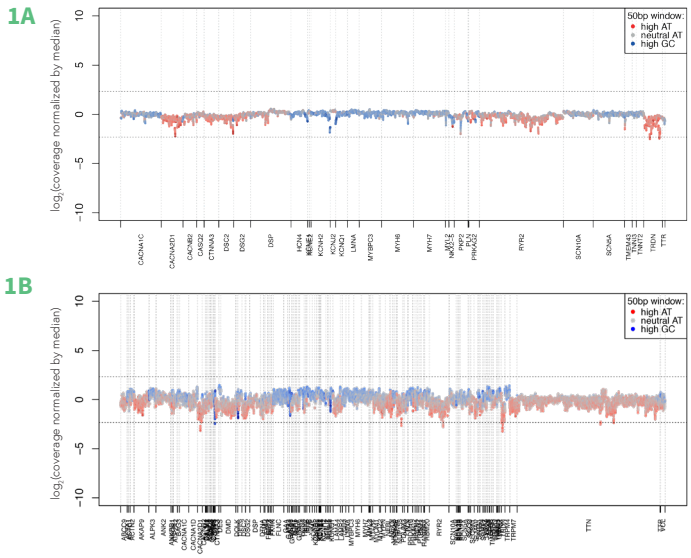


Figure 1: Coverage uniformity profile of a typical sample analyzed with CAS (1A) and ExtCAS (1B). The X-axis represents the genes included in CAS (1A) and ExtCAS (1B), and the Y-axis the $\log_2$ coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are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

Advanced analytical performance

SOPHiA DDM™ analyzes complex NGS data by detecting, annotating and pre-classifying SNVs, Indels and CNVs in all the genes covered by the solutions in a single experiment.

SOPHiA DDM™ 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%

CAS performance metrics were calculated on 114 distinct confirmed variants in 41 distinct samples. ExtCAS performance metrics were calculated on 177 distinct confirmed variants in 9 distinct samples. In both cases, sequencing was performed using the MiSeq® instrument.

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 DDM™ detects CNVs in all covered 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 DDM™ 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 simultaneous detection of SNVs, Indels and CNVs in a single experiment. 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 CNV detection in ExtCAS due to the presence of homologous regions: *TTN* exons 172-197 and *FLNC* exon 47.

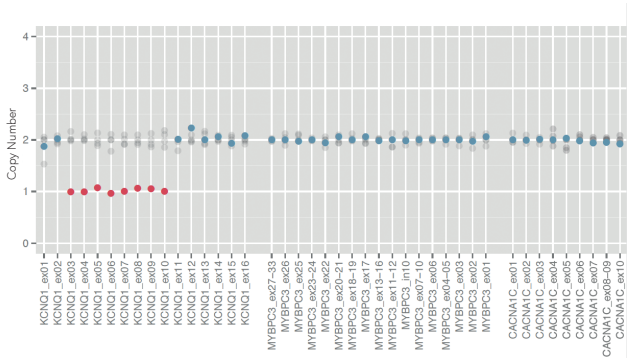
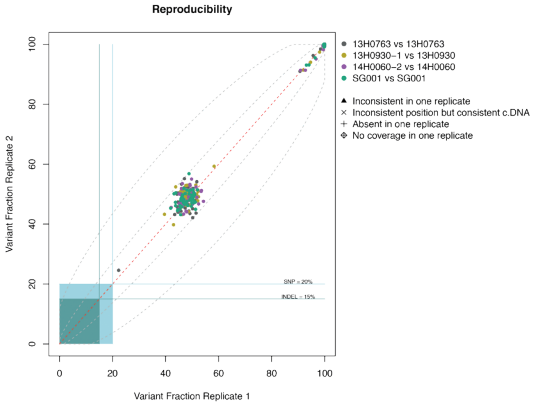


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and red dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence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

Very high repeatability and reproducibility

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

3A



3B

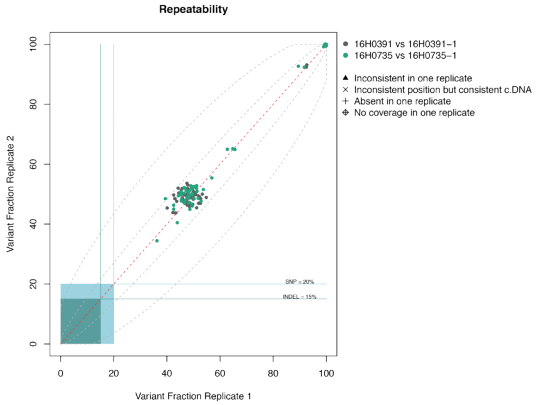


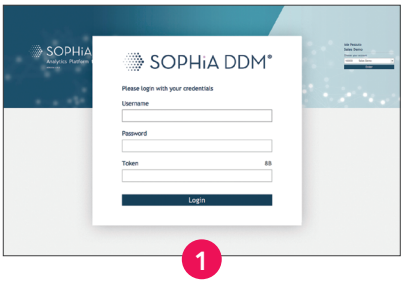
Figure 3: ExtCAS reaches 99.98% reproducibility (3A) and 99.99% repeatability (3B). The variant fractions, depicted by the colored dots, are typically 0.5 (heterozygous) or 1.0 (homozygous), as expected for germline variants. The grey, dotted lines represent the 5% and 10% deviation from identity (diagonal = red dashed line). The blue and green squares represent the low variant fraction cut-off (SNP=20%, Indel=15%). In 3A, the replicated samples show an almost perfect match in variant fractions between 2 separate runs. In 3B, the replicated samples show almost perfect match in variant fraction between the 2 replicates in the same run. Data on File.

Cardio Solutions

Integrated features for efficient variant prioritization and interpretation

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

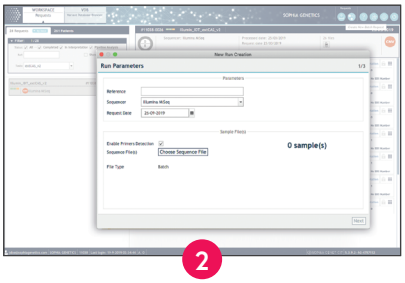
The platform enables researchers to explore and interpret genomic variants and also to report significant findings. Users can also have access to Alamut Visual Plus™, a full-genome browser that integrates numerous curated genomic and literature databases, guidelines, and missense and slicing predictors, enabling a deeper variant exploration.



1

Secure login

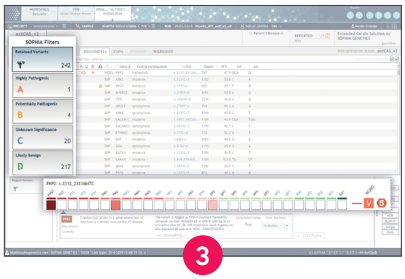
Access to SOPHiA DDM™ is restricted to registered users only. Log in features a 2-step verification procedure.



2

Quick and simple data upload

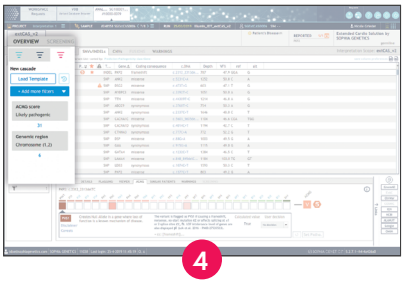
Once sequencing output files are uploaded, all relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



3

Dual variant pre-classification

Detected variants are displayed by variant type (SNVs, Indels and CNVs). Users can easily visualize an overview of major variants pre-classified through machine learning-based pathogenicity classes and ACMG scores.



4

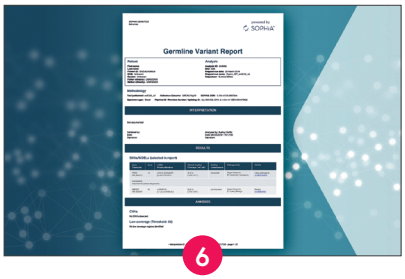
Cascading filters

Apply custom filtering options for quicker screening of relevant variants and save strategies for future analyses and inclusion in reports.

5

Variant flagging

Users can flag the pathogenicity of variants. Flagging decisions are greatly supported by the shared knowledge of the SOPHiA GENETICS 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.

SOPHiA GENETICS' 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.

Guarantee 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 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 DDM™. As a result, these solutions globally offer a streamlined and standardized workflow, that can be easily implemented by any healthcare institution.

References:
[1]Mademont-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.
[2]Mademont-Soler I, Pinsach-Abuin ML, Riuró H, et al. Large genomic imbalances in Brugada syndrome. PLoS ONE. 2016;11: e0163514.

For Research Use Only. Not for use in diagnostic procedures.