SOPHiA GENETICS™

SOPHIA DDM™ EXTENDED CARDIO SOLUTION

Getting to the heart of inherited cardiac disorders

The SOPHiA DDM™ Extended Cardio Solution (ExtCAS) is a genomic application that bundles a smart capture-based target enrichment kit with the analytical performance and advanced features of the SOPHiA DDM™ Platform.

Expertly designed, this solution targets 128 genes associated with the most prevalent inherited arrhythmias and cardiomyopathies.

SMART DESIGN

- Comprehensive application targeting 128 genes associated with cardiac disorders
- 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 due to the presence of homologous regions: *TTN* exons 172-197 and *FLNC* exon 47.

Discover the full power of your genomic data

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

SOPHiA DDM™ MaxCare Program
Assistance with assay set up for fast and worry-free transition to routine testing

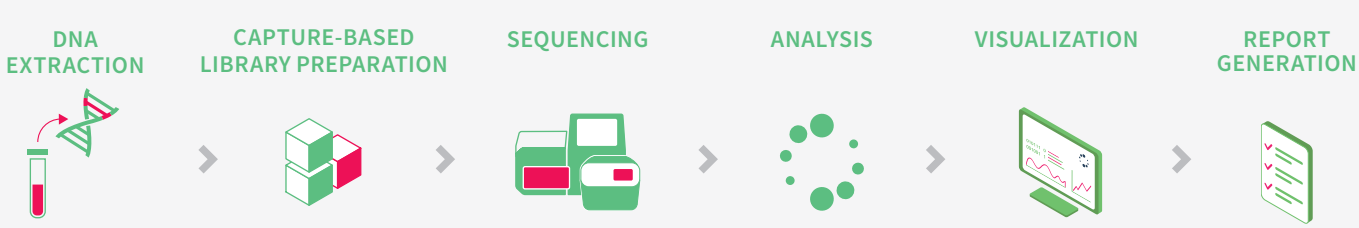
Data security policy
Compliance with national privacy laws, GDPR, HIPAA guidelines and applicable legislation

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

SOPHiA DDM™ Extended Cardio Solution

Streamlined workflow from DNA extraction to variant report generation

SOPHiA DDM™ Extended Cardio Solution (ExtCAS) provides straightforward library preparation workflow. A ready-to-sequence target-enriched library is 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 is compatible with Illumina and Thermo Fisher Scientific sequencing platforms. Sequencing output files are then analyzed by SOPHiA DDM™ Platform, 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

SOPHiA DDM™ ExtCAS covers the complete coding sequence (± 5bp of exon-flanking regions) of 128 genes related to arrhythmias and cardiomyopathies. 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*

Specifications

Parameter	Details
Sample source	Blood
DNA input requirement	200 ng
Target region	470 kb
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)
MiniSeq™	High Output Kit (2x150bp)	8
MiSeq®	v3 (2x300bp)	12
NextSeq® 500/550	Mid Output Kit v2 (2x125bp)	48
	High Output Kit v3 (2x150bp)	96*
Ion S5™	Ion 530	4
	Ion 540	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

SOPHiA DDM™ ExtCAS achieves 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.

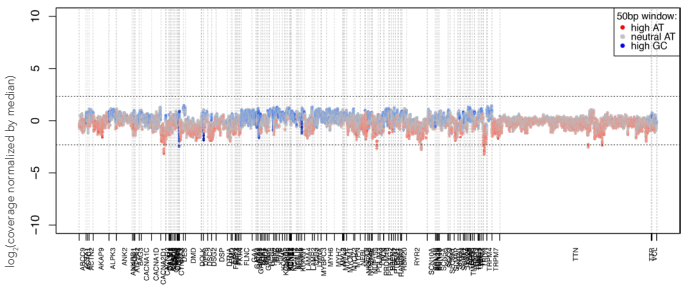


Figure 1: Coverage uniformity profile of a typical sample analyzed with SOPHiA DDM™ ExtCAS. The X-axis represents the genes included in SOPHiA DDM™ ExtCAS, and the Y-axis the $\log_2$ coverage normalized by the median. The closer the dots are to the 0 line, the more homogenous the reads are covering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

SOPHiA DDM™ Extended Cardio Solution

Advanced analytical performance

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

SOPHiA DDM™ Platform reaches advanced analytical performance:

	Observed
Sensitivity	100%
Specificity	99.99%
Accuracy	99.99%
Precision	98.68%
Repeatability	99.99%
Reproducibility	99.98%
Average on-target rate	89.60%
Coverage uniformity	99.84%
Average % of target region > 200x	99.96%

SOPHiA DDM™ ExtCAS performance metrics were calculated on 177 distinct confirmed variants in 9 distinct samples. 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™ Platform detects CNVs in all covered genes* at a resolution of 1 exon (Fig. 2). This analysis is performed using our proprietary algoritm MUSKAT™ by evaluating the coverage levels of the target regions across all samples within the same sequencing run. For each sample, SOPHiA DDM™ Platform 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 DDM™ Extended Cardio Solution 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 due to the presence of homologous regions: *TTN* exons 172-197 and *FLNC* exon 47.

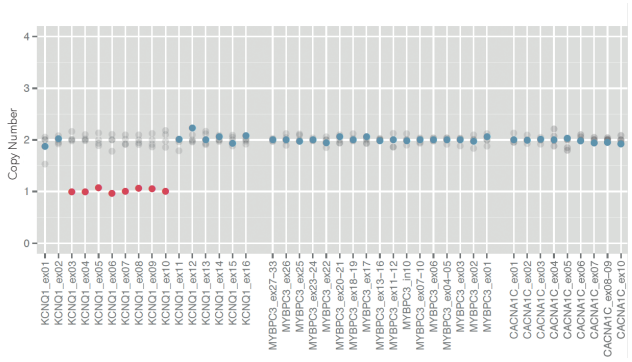
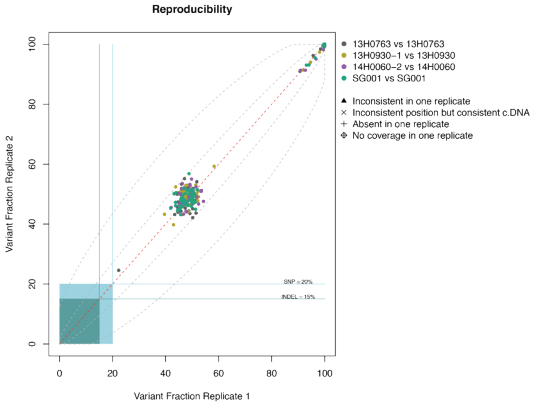


Figure 2: Normalized coverage levels of Copy Number status.
Plot shows the normalized coverage levels in a given sample (blue and red dots) compared to the reference coverage levels (grey dots). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence 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. SOPHiA DDM™ ExtCAS has been tested extensively, ensuring almost 100% repeatability and reproducibility (Fig.3), giving genomic experts confidence in their NGS sequencing.

3A



3B

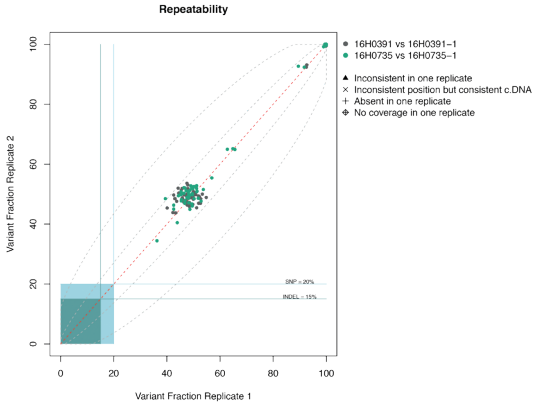


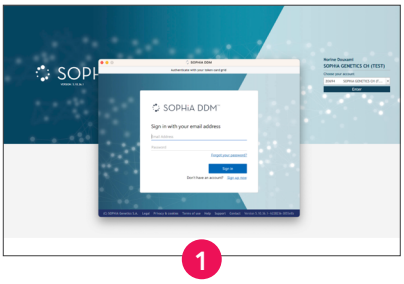
Figure 3: SOPHiA DDM™ ExtCAS reaches 99.98% reproducibility (3A) and 99.99% repeatability (3B). The variant fractions, depicted by the colored dots, are typically 0.5 (heterozygous) or 1.0 (homozygous), as expected for germline variants. The grey, dotted lines represent the 5% and 10% deviation from 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.

SOPHiA DDM™ Extended Cardio Solution

Integrated features for efficient variant prioritization and interpretation

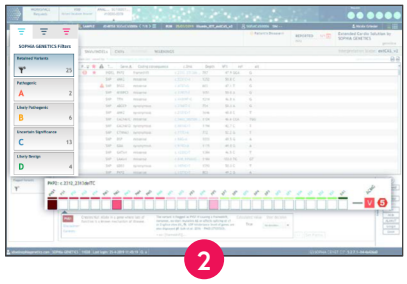
The SOPHiA DDM™ Platform features dual variant pre-classification, intuitive variant filters, and reporting functionalities to simplify data visualization and interpretation.

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.



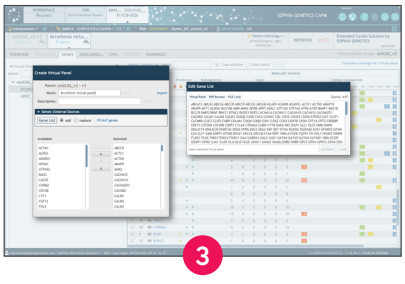
Secure and simple data upload

A 2-step login to SOPHiA DDM™ Platform allows direct upload of sequencing output files (FASTQ). All relevant information is automatically extracted and displayed, saving time and avoiding human error from manual insertion.



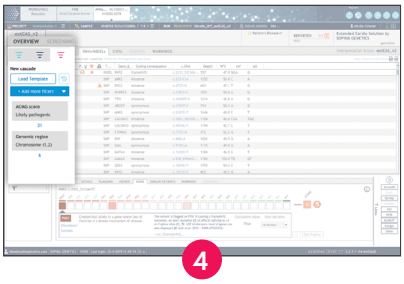
Dual variant pre-classification

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.



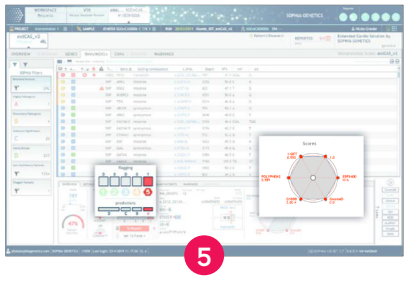
Phenotype-driven Virtual Panels

Virtual Panels are a time-saving feature of SOPHiA DDM™ Platform allowing direct selection of genes associated with phenotype (HPO). Users can also create and save Virtual Panels based on their practice.



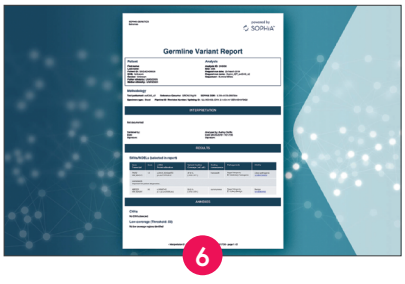
Cascading filters

Apply custom filtering options for quicker screening of relevant variants and save strategies for future analyses and inclusion in reports. These include frequency, coding consequences and predicted pathogenicity.



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).



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™ Platform, 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™ Platform 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 DDM™ Extended Cardio Solution is a comprehensive genomic application that characterizes germline variants associated with the most prevalent inherited arrhythmias and cardiomyopathies. It enables the assessment of 128 genes in a single assay by leveraging the advanced analytical power of SOPHiA DDM™ Platform. As a result, this solution offers 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.