SOPHiA GENETICS™

EXOME SOLUTIONS

From data to insights to confident care

The SOPHiA DDM™ Exome Solutions include two genomic applications, Clinical and Whole Exome, that both combine a capture-based target enrichment kit with the analytical capabilities and advanced features of the SOPHiA DDM™ Platform.

Expertly designed, these applications provide comprehensive coverage of multiple types of genomic variants in up to 19,425 genes, enabling data-informed decision making.

SMART KIT DESIGN

- High affinity probe design, ensuring high on-target rate and coverage uniformity throughout the target regions
- Whole Exome Solution v2: Targeting 19,425 genes and the entire mitochondrial genome
- Clinical Exome Solution v3: Targeting 4,727 genes, the entire mitochondrial genome, and ~ 200 non-coding variants with known pathogenicity in deep introns/enhancer/promoter genes
- Automated workflow available on leading liquid handling robots for high-throughput library preparation for optimal cost per sample

SOPHiA DDM™ PLATFORM

- Advanced analytical performance (i.e. >99% sensitivity and precision)
- High-confidence calling of SNVs and Indels
- Efficient CNV detection available for:
  - 97% of covered genes
- Intuitive features for simplified data visualization and interpretation
- Customizable report
- Secure storage of anonymized data

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
Dedicated 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

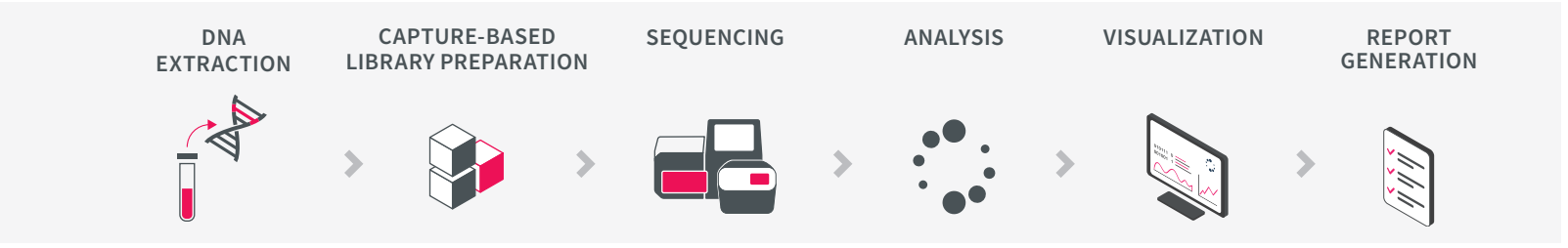
SOPHiA GENETICS™ community
Anonymized and safe knowledge sharing among experts worldwide

Exome Solutions

Streamlined workflow from DNA extraction to variant report generation

SOPHiA DDM™ Exome Solutions provide a straightforward library preparation workflow. Ready-to-sequence target-enriched libraries are generated in just 2 working days, starting from 200 ng 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

SOPHiA DDM™ Clinical Exome Solution v3 covers the coding regions (±5bp of intronic regions) of 4,727 genes*, the entire mitochondrial genome, and ~ 200 non-coding variants with known pathogenicity in deep introns/enhancers/promoters associated with rare and inherited disorders (probe footprint of 16 Mb). SOPHiA DDM™ Whole Exome Solution v2 covers 19,425 genes and the entire mitochondrial genome, enabling an exome-wide investigation. Probe design is highly optimized to guarantee a high on-target reads percentage and coverage uniformity even in GC-rich regions, including the first exon. For specific needs, the gene content can be customized.

*Complete list of genes available upon request.

Smart kit specifications

Parameter	Details
Sample source	Blood
DNA input requirement	200 ng
Target region	16 Mb (Clinical Exome)
	34 Mb (Whole Exome)
Hands-on library preparation time	8 hours

Sequencing and multiplexing recommendations

Sequencers	Flow Cell / Ion Chip Kit	Recommended samples per run (for >50x coverage depth)	
		Clinical Exome	Whole Exome
Illumina NovaSeq™ 6000	SP	48 (per lane)	12
	S1	96 (per lane)	24 (per lane)
	S2	NA	56 (per lane)
Illumina HiSeq® 2500	High Output (2x125bp)	NA	6 (per lane)
	Rapid Run Mode (2x150bp)	NA	3 (per lane)
Illumina NextSeq® 500/550	Mid Output Kit v2 (2x150bp)	16	3
	High Output Kit v2 (2x150bp)	48	12

Extremely uniform coverage

SOPHiA DDM™ Exome Solutions achieve very high on-target rates, which ensure reliable coverage uniformity values across all the target regions, even in GC-rich regions (Fig. 1).
Equal read coverage is of crucial importance for the precise identification of multiple types of variations, including CNVs.

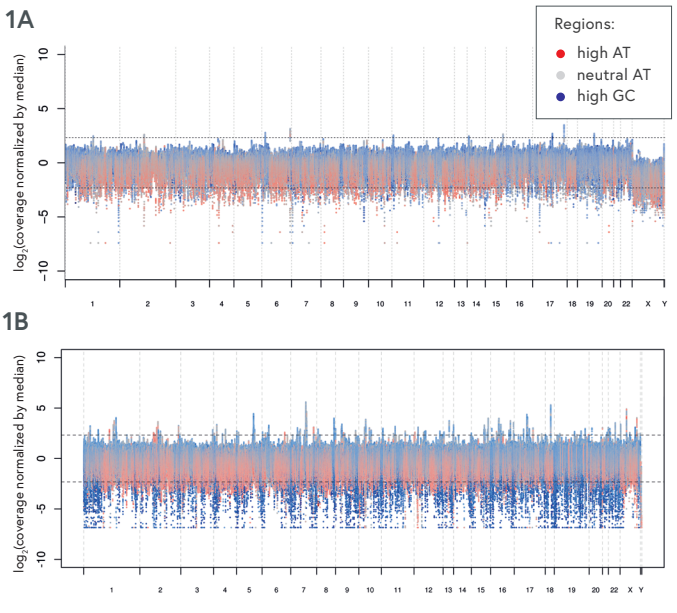


Figure 1: Coverage uniformity profile of a typical sample analyzed with SOPHiA DDM™ Clinical Exome Solution v2 (1A) and Whole Exome Solution v1 (1B). Comparable results are observed with SOPHiA DDM™ Clinical Exome Solution v3 and Whole Exome Solution v2 (data not shown). The X-axis represents the chromosomic positions targeted by each application 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.

Exome Solutions

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 applications, in a single experiment.

**CNV detection is available for 97% of the covered genes*

Analysis time from FASTQ files	
SOPHiA DDM™ Clinical Exome Solution v3	6 hours
SOPHiA DDM™ Whole Exome Solution v2	Overnight

Analysis time may vary depending on the number of samples multiplexed and server load.

	Clinical Exome Solution v3	Whole Exome Solution v2
Sensitivity for SNVs/Indels	>99%†	>99%¶
Sensitivity for CNVs 2-4 exons‡	>98%‡	>99%ᵅ
Sensitivity for mitochondrial SNVs/Indels	>99%	100%
Precision for SNVs/Indels	>99%	99%¶
Average on-target rate		>95%
Coverage uniformity	>99%	>99%
Average % of target region with depth >20x	>99%	>99%

†SNV and Indel performance metrics are based on more than 6,100 variants. There were 16.25M reads per sample. Sequencing was performed using an Illumina NextSeq® instrument.
‡Analytical performance for CNVs was calculated on 80 CNVs, sequenced using an Illumina NextSeq® instrument.
§Sensitivity for mitochondrial SNVs/Indels was calculated on 96 variants (93 SNPs and 3 Indels), sequenced using an Illumina NextSeq® instrument.
¶Performance metrics are based on high confidence regions in 4 reference samples, with 80M reads per sample. Sequencing was performed using an Illumina NextSeq® 550 instrument (300 bp read length).
ᵅAnalytical performance for CNVs was calculated from 4 samples, with 80M reads per sample. Sequencing was performed using an Illumina NovaSeq® instrument.

Sensitive CNV calling

Copy Number Variations (CNVs) play an important role in a broad range of genetic disorders[1]. Accurate CNVs detection via exome-based profiling can result in increased analytical yield. However, classical extended exome application settings render the detection of CNVs very difficult due to the extended target regions and the increased depth of sequencing needed to reliably identify CNVs.

SOPHiA DDM™ detects CNVs* at a resolution of 2-5 exons (Fig. 2) in both applications. 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.

**Accurate CNV calling requires at least 8 co-captured samples*

Thanks to its accuracy, the use of both applications reduces the need for additional assays by allowing the simultaneous detection of SNVs, Indels and CNVs. The result is a fast, nimble and cost-effective workflow.

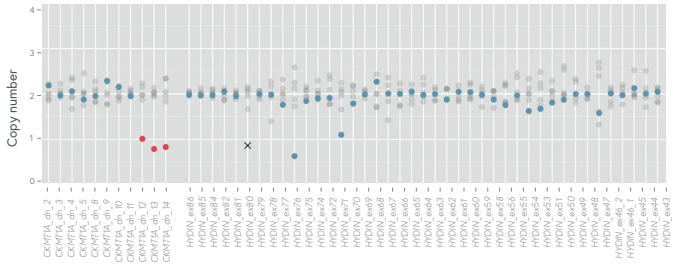


Figure 2: Example of normalized coverage levels of Copy Number status for SOPHiA DDM™ Clinical Exome Solution v2 on the SOPHiA DDM™ Platform. 90% sensitivity of CNV detection was observed in two consecutive regions (exons) with 40 million fragments (80 million reads). Comparable results are observed with SOPHiA DDM™ Clinical Exome Solution v3 (data not shown). Blue dots correspond to target regions without CNVs, red dots to deletions. Solid dots represent high-confidence CNV predictions.

Full coverage of the mitochondrial genome by the SOPHiA DDM™ Exome Solutions

The SOPHiA DDM™ Exome Solutions' panel design and sophisticated algorithms address the unique challenges associated with the mitochondrial genome, such as the high and variable amount of mitochondrial DNA and heteroplasmy, to provide coverage uniformity and to accurately and confidently identify mitochondrial variants in a streamlined analytical workflow. The applications provide coverage of the entire mitochondrial genome, with 100% sensitivity for mitochondrial SNVs/Indels down to 5% variant frequency (Fig. 3).

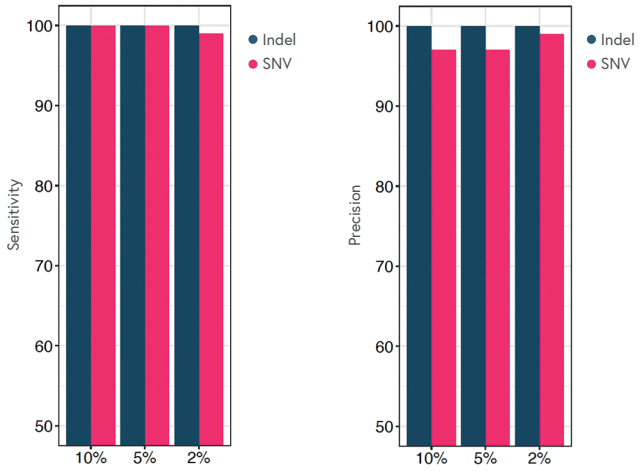
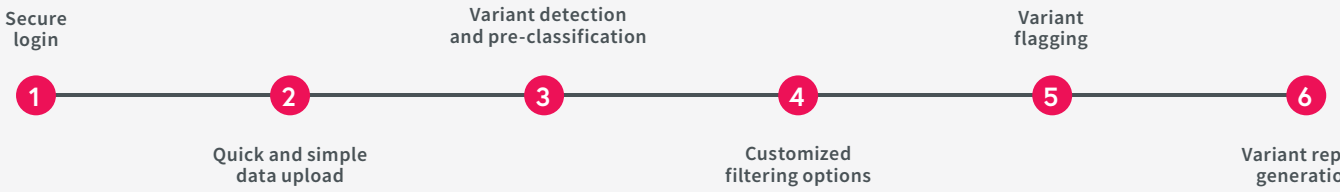


Figure 3: Sensitivity and precision of mitochondrial analysis for the SOPHiA DDM™ Clinical Exome Solution v3 on the SOPHiA DDM™ Platform, according to expected variant frequency. Metrics were calculated on 96 variants (93 SNPs and 3 Indels), sequenced using an Illumina NextSeq® instrument (data on file).

Exome Solutions

Integrated features for efficient variant visualization and interpretation

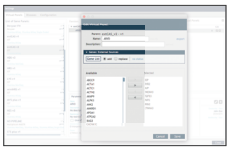
The SOPHiA DDM™ Platform enables clinical researchers to explore and interpret genomic variants and report significant findings. The Platform uses complete GRCh38/hg38-based analytics for variant annotation, performs comprehensive transcript annotation with MANE, and features variant prioritization options to streamline interpretation and help reduce turnaround time.



Dual-Variant Pre-Classification

Improve assessment of variant pathogenicity.

SOPHiA DDM™ assesses variant pathogenicity using machine learning- and ACMG-based ranking. SOPHiA DDM™ automatically gathers and collates information from various sources (such as population frequencies, *in silico* scores, disorder-specific data, splicing predictors, and databases on protein domains, loss of function and repetitive regions) to evaluate pathogenicity and rate variants as A: pathogenic, B: likely pathogenic, C: uncertain significance, or D: likely benign.



Virtual Panels

Limit interpretation to a subset of genes for quicker screening of relevant variants.

SOPHiA DDM™ offers direct access to the Human Phenotype Ontology (HPO) and Online Mendelian Inheritance in Man (OMIM®) databases to filter genes associated with specific disorders.

Cascading Filters

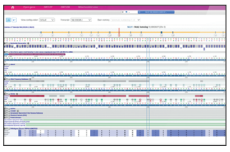
Easily filter variants to streamline interpretation of datasets.

This functionality enables users to quickly create and edit combinations of filters based on population frequency, ACMG score, ClinVar pathogenicity, genomic regions and many more criteria. Filter cascades can be saved, re-used, and included in reports.

Familial Variant Analysis (trio-analysis)

Identify the causative variant(s) responsible for a proband's phenotype through analysis of parental samples.

This feature filters according to mode of inheritance, such as autosomal recessive, compound heterozygosity, autosomal dominant, X-linked, and de novo variations.



Alamut™ Visual Plus

Explore variants on a genomic scale.

Through SOPHiA DDM™, you 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.

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

SOPHiA DDM™ Exome Solutions are comprehensive genomic applications enabling the detection of multiple types of variants associated with rare and inherited disorders. They enable the assessment of up to 19,425 genes in a single assay by leveraging the advanced analytical power of SOPHiA DDM™. As a result, these applications globally offer a streamlined and standardized workflow that can be easily implemented by any healthcare institution.

References:
[1] *Pfundt R., et al. Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders. Genet Med. 2017 Jun;19(6):667-675. doi: 10.1038/gim.2016.163. Epub 2016 Oct 27.*