CENTOGENE
THE RARE DISEASE COMPANY

Whole Genome Sequencing

CentoGenome®

It's Covered

CentoGenome®
Whole Genome Sequencing

Establishing a rapid and reliable diagnosis for rare and neurodegenerative diseases can present a significant challenge, even for the most skilled physicians. However, with the latest advancements in technology, the utilization of Whole Genome Sequencing (WGS) as a first-line diagnostic test, and our deepening understanding of genetic factors, this challenge is now more manageable than ever before.

CENTOGENE's enhanced WGS solution, CentoGenome®, stands as one of the world's most comprehensive tools for diagnosing rare and neurodegenerative diseases – providing unparalleled genome coverage and diagnostic power in a single test. This cutting-edge solution combines superior technology driven by a streamlined CE-IVD bioinformatics pipeline and medical expert-based interpretation using the CENTOGENE Biodatabank. CentoGenome can detect nearly all variant types, from sequence variants to more complex variations such as structural variants, Copy Number Variations (CNVs), Uniparental Disomy (UPD), and repeat expressions, as well as CNVs associated with Spinal Muscular Atrophy (SMA) and disease-causing variants associated with Gaucher Disease (GD) and susceptibility to *GBA1*-related Parkinson's Disease (PD). With CentoGenome, you can significantly reduce time and resources to deliver a rapid and reliable diagnosis and identification of treatment options for your patients.

The CENTOGENE Advantage

Advanced Technology for Greater Insights

By implementing Polymerase Chain Reaction (PCR)-free technology, CentoGenome significantly reduces bias and provides high-quality sequence information for difficult-to-sequence genetic regions – enabling greater insights into coding, regulatory, and intronic regions

Integrated Variant Reclassification & Confirmatory Testing for a Life-Long Commitment

As a world leader and trusted partner, CENTOGENE provides a free-of-charge and proactive diagnosis confirmation and variant reclassification when necessary

Superior Performance for Enhanced Disease Coverage

CentoGenome leverages advanced data analysis through our CE-IVD bioinformatics pipeline and medical expert-based interpretation, powered by the CENTOGENE Biodatabank, to deliver superior variant detection

Unparalleled Genome Coverage and Diagnostic Power

CentoGenome is your first-line diagnostic tool — delivering a high diagnostic yield for genetically-linked diseases.[1–3]

Key Features and Performance

Uniform Genome Coverage	• Highly uniform and nearly complete coverage of the nuclear genome (>20,000 genes) and complete mitochondrial genome (37 genes) • >97% of the genome covered at ≥10x
Advanced and Sensitive Variant Detection	• Detection of SNVs, InDels, SVs, including small CNVs up to cytogenomic-level changes, and mtDNA with heteroplasmy ≥15% • Sensitivity: - SNVs and InDels (≤50 bp) 99.9% - CNVs >95% • Specificity of >99.9% is guaranteed for all reported variants* • UPD detection** for the well-known clinically relevant chromosomal regions: 6q24, 7, 11p15.5, 14q32, 15q11q13, 20q13, and 20 • Repeat expansion detection** in 23 well-known genes associates with neurological diseases: *AR*, *ATN1*, *ATXN1*, *ATXN2*, *ATXN3*, *ATXN7*, *ATXN8OS*, *ATXN10*, *CACNA1A*, *CNBP*, *CSTB*, *C9orf72*, *DMPK*, *FMR1*, *FXN*, *HTT*, *JPH3*, *NOP56*, *PABPN1*, *PHOX2B*, *PPP2R2B*, *PRNP*, and *TBP*
Enhanced Detection of Variants Associated to SMA & GD / PD* **	• Spinal Muscular Distrophy (SMA): *SMN1* / *SMN2* CNV analysis • Gaucher Disease (GD) / Parkinson's Disease (PD): *GBA1* including conversion analysis with its pseudogene *GBAP1*
Technical Details	• Genome is enzymatically fragmented and libraries are generated using Illumina DNA PCR-Free Library Prep kit, with 100 – 110 Gb of sequencing data generated for each patient • Illumina paired-end Next Generation Sequencing (NGS) technology (2x150 bp) • Nuclear genome aligned to Genome Reference Consortium Human Build 37 (GRCh37/hg19) • Mitochondrial genome aligned to revised Cambridge Reference Sequence (rCRS) of the Human Mitochondrial DNA (NC_012920)

SNVs: single nucleotide variants; **InDels:** small insertions/deletions; **SVs:** Structural variants; **CNVs:** copy number variations; **UPD:** uniparental disomy; **mtDNA:** mitochondrial DNA

* Variants with low quality and / or unclear zygosity are confirmed by orthogonal methods: SNVs and InDels by Sanger sequencing; CNVs by Multiplex Ligation-Dependent Probe Amplification (MLPA), Quantitative Polymerase Chain Reaction (qPCR), or Chromosomal Microarray (CMA). Internal confirmatory testing using an orthogonal method is also guaranteed when necessary for reported variants associated with repeat expansion diseases, UPD, *SMN1* / *SMN2* CNVs, and conversion events between *GBA1* and *GBAP1*, respectively by Fragment Length Analysis (FLA), CMA, MLPA, and qPCR

** Screening of UPD is performed using an in-house algorithm for Mendelian Inheritance Errors (MIE) to detect Runs of Homozygosity (ROH) for the well-known clinically relevant chromosomal regions . Screening of repeat expansions is performed by the ExpansionHunter.

*** SMA screening is performed using SMN Caller algorithm to detect *SMN1* / *SMN2* CNVs. *GBA1* screening is performed using Gauchian algorithm to detect recombination events affecting the region encompassing exons 9-11 (NM_000157.3), a region which has the highest homology to *GBAP1*

Tailored Testing and Life-Long Diagnostic Support

We offer flexible testing options and additional services tailored to your patient's needs, paired with life-long diagnostic support via a free-of-charge and proactive reclassification program.

Options & Additional Services

Testing Design*		• Solo, Duo, Trio, and PLUS • Mitochondrial genome analysis is performed only for the index patient and maternal samples
Testing Solutions	**CentoGenome**	• WGS for postnatal diagnostic testing of rare and neurodegenerative diseases • TAT: ≤ 20 business days
	CentoGenome MOx**	• Multiomics single-test solutions integrating WGS with biochemical testing and / or RNA-seq for splicing variants • CentoGenome MOx 1.0 and 2.0 for postnatal testing of rare and neurodegenerative diseases • CentoGenome MOx 1.0 TAT: ≤ 20 business days • CentoGenome MOx 2.0 TAT: ≤ 35 business days
	CentoGenome Prenatal***	• WGS for prenatal diagnostics (ongoing pregnancy) when fetus structural abnormalities detected on ultrasound or a diagnosis cannot be obtained using routine prenatal methods • Expedited and prioritized testing, and includes cell culture and maternal cell contamination (MCC) analysis • TAT: ≤ 15 business days
	CentoGenome POC***	• WGS for diagnostic testing of product of conception (pregnancy loss) in cases of intrauterine fetal demise or stillbirth to better understand cause of fetal loss and risk for recurrence, or when a diagnosis cannot be obtained using routine methods • Includes cell culture and MCC analysis • TAT: ≤ 20 business days
	CentoGenome Variants	• WGS raw and processed data (files in FASTQ, BAM, and VCF format along with filtered and annotated variant files in XLS format) for further research available • Free of charge for download via CentoPortal for a period of 30 days • TAT: ≤ 20 business days
Additional Options	**FAST Processing**	• ≤ 15 business days (not applicable with CentoGenome MOx 2.0)
	Free of Charge Raw Data	• For all testing solutions with medical reports, raw and processed data (files in FASTQ, BAM, and VCF format, along with filtered and annotated variant file in XLS format) are available • This data can be downloaded via CentoPortal free of charge for a period of 30 days
Life-long diagnostic support****		• Proactive variant-level reclassification; reclassification report issued at no extra cost • Case-level reanalysis for uncertain/negative results (e.g., new clinical information, one-year intervals) at an affordable cost

TAT: Turnaround time

* **Solo**: only the affected index patient is tested; **Duo**: index patient and affected or unaffected family member are tested; **Trio**: index patient and two family members, affected or unaffected, are tested; **PLUS**: additional family member beyond Trio is tested

** More details about our Multiomic Solutions at centogene.com/diagnostics/mox

*** WGS-based mitochondrial genome analysis and screening for UPD, repeat expansions, *SMN1* / *SMN2* CNVs and *GBA1* gene conversion is not offered due to technical limitations. More details about Prenatal Testing: centogene.com/diagnostics/our-tests/prenatal-testing

**** Case reanalysis is available only for orders with original sequencing data from August 2020 onwards. More details about Variant Reclassification Program: centogene.com/diagnostics/benefits-of-genetic-testing/variant-reclassification-program

Best-in-Class Medical Reporting and Advanced Insights

A team of highly trained medical experts interpret the data and verify every medical report. We perform internal confirmatory testing free of charge using orthogonal methods if applicable and use the CENTOGENE Biodatabank to confirm results and validate variant pathogenicity.

Medical Reports and Extra Expertise Insights

Main Findings	• Diagnostic findings related to patient's phenotype • Optional research findings* related to patient's phenotype providing information on potential diagnoses
Potential Relevant Findings	• Findings not directly related to patients' phenotype that might be clinically relevant to help close diagnostic gaps • List of variants for the index patient related to disorders with no apparent overlap with the described phenotype and/or variants with a zygosity inconsistent with the expected mode of inheritance
Secondary Findings*	• Optional findings unrelated to patients' phenotypes • Medically actionable variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines available for all tested individuals
Carriership Findings*	• Optional carriership status findings, not related to patients' phenotype but potentially clinically relevant for family planning, are provided upon request for both index and non-index individuals, except for fetuses of ongoing pregnancies • A list of sequence variants classified as pathogenic or likely pathogenic in the CENTOGENE Biodatabank for selected genes associated with recessive severe and early-onset Mendelian diseases is reported
Extra Disease Confirmation & Insights	• Internal confirmatory testing by an orthogonal method for reported variants when necessary • Extra insights supported by the CENTOGENE Biodatabank are used to confirm results and provide evidence about the pathogenicity of the variants found

* Please note that for testing index patients of in: 1) prenatal diagnostics (ongoing pregnancy), research, secondary, and carriership findings are not reported; 2) products of conception diagnostics (pregnancy loss), secondary findings are not reported.

For more information about our medical reporting, please visit centogene.com/reporting; more details about our carriership findings reported in our WGS at centogene.com/carriership

References
1 Data on file at CENTOGENE
2 Bertoli-Avella et al. 2020, PMID: 32860008
3 Cheema et al. 2020, PMID: 33083013

For More Information
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MAmaterial-361_V6.0_V4eng_May2024