CENTOGENE

THE RARE DISEASE COMPANY

CentoXome®

FUTURE'S KNOWLEDGE APPLIED TODAY


More genetic information
requires cutting-edge
interpretation techniques

Whole Exome Sequencing

For some patients, the combination of symptoms does not allow the clinician to pinpoint a potential diagnosis. Therefore, ordering genetic testing becomes complex and might involve a stepwise diagnostic strategy, which often significantly increases costs. Furthermore, a delayed diagnosis may have a dramatic impact on the patient's quality of life.

Most of the disease-causing mutations (about 85%) detected to date are located in the exonic regions of genes. Exons are the segments of DNA which encode for proteins.

CentoXome®, CENTOGENE's whole exome sequencing service, offers a fast and cost-effective one-step solution which involves sequencing the entire coding region or exons, examining thousands of genes simultaneously.

When is whole exome sequencing required?

WES is especially recommended for patients with:

HETEROGENEOUS PHENOTYPES:

- Intellectual disability / developmental delay
- Cardiomyopathy
- Epilepsy
- Muscular dystrophy
- Ataxia
- Neuropathy
- Deafness
- Retinitis pigmentosa
- Bone disease
- Metabolic disorder
- Short stature
- Complex dysmorphia
- Other heterogeneous phenotypes; i.e. may be caused by a large number of genes

FULLY UNCLEAR PHENOTYPES:

- The physician cannot provide any plausible diagnosis for the cause of the symptoms; the interpretation of the genetic data is more complex

Clinical information is crucial

One consequence of whole exome sequencing is the increased amount, complexity and variety of results that need to be interpreted. It is therefore of utmost importance to obtain specific and detailed clinical information from the index patient and the parents (TRIO) when performing exome sequencing.

Withholding any clinical or medical information – including your patient's family history – may impact test results and their interpretation. **Missing clinical information** could lead to **not reporting genetic variants** which might be **relevant for the patient**.

For the variants that have not yet been described or for diseases not characterized in detail, there may be problems in understanding the exact mode of inheritance or consequence in the patient. In these circumstances, there is always a given risk that the results may lead to findings of uncertain significance which might require further follow up in the future.

Whole exome sequencing at CENTOGENE

CentoXome® transfers complex data and findings into a comprehensive medical report.

SEQUENCING OF ALL EXONS

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END-TO-END BIOINFORMATICS ANALYSIS OF RAW DATA

›

VALIDATION OF SEQUENCING RESULTS

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WORLD-CLASS CLINICAL REPORTS

Services tailored to your patients´ needs:

CentoXome® PLATINUM

- Express turnaround time of 15 business days
- Prenatal testing possible

CentoXome® GOLD

- Turnaround time of 30 business days

Statistical Data

TEST METHOD	DESCRIPTION	LIKELIHOOD OF DETECTING A SPECIFIC MUTATION*	INFORMATION CONTENT
HOTSPOT TESTING	Testing only for the most frequent mutations	~99.9%	SINGLE BASE PAIR
SANGER SEQUENCING	Gold standard of genetic testing	~99.9%	0.2 – 5 KB
NGS PANEL	Allows multiple genes to be analyzed in parallel	~96.1%	20 – 400 KB
NGS PANEL PLUS	Allows multiple genes to be analyzed in parallel; gene patchup included	~99.1%	20 – 400 KB
NGS PANEL GENOMIC	Powered by WGS, allows multiple genes to be analyzed in parallel with increased coverage	~99.1%	200 – 500 MB
WHOLE EXOME SEQUENCING	Analyzes the coding part of thousands of genes simultaneously	~93.2%	~60 MB
WHOLE GENOME SEQUENCING	Analyzes the whole genome	~97.6%	~3.2 GB

*within the targeted region

LIKELIHOOD OF DETECTING A MUTATION: Refers to the probability to identify a mutation in the analyzed region of the DNA. The scores depicted combine how well the target is covered and the sensitivity of the method in detecting any point mutation.

INFORMATION CONTENT: Amount of information captured by a given technique. It scales linearly with the size of the region that is being probed for the respective test.

Reporting your results

High-quality reporting is a key essential for building a partnership of trust. Our philosophy is more than just producing technical data. The extensive interpretation of clinical data delivered with our comprehensive medical reports includes differential diagnostic approaches as well as a detailed interpretation of key findings.

WHAT DOES OUR REPORTING INVOLVE?

- Clinical information evaluation
- Detailed method description
- Clear results of identified variants following international best-practice guidelines

  (Council of Medical Specialty Societies, American College of Medical Genetics)
- Comprehensive medical interpretation with differential diagnostic approaches, if applicable
- References to publications supporting the medical and scientific results
- Recommendations for follow-up analyzes for specific diseases
- Coverage report of genes relevant to the patient's phenotype

All identified variants undergo medical validation

Based on the standard clinical guidelines, only variants detected in genes with well characterized clinical implication in human diseases are considered. From these, all **relevant variants** related to the phenotype of the patient are **mentioned in the report**.

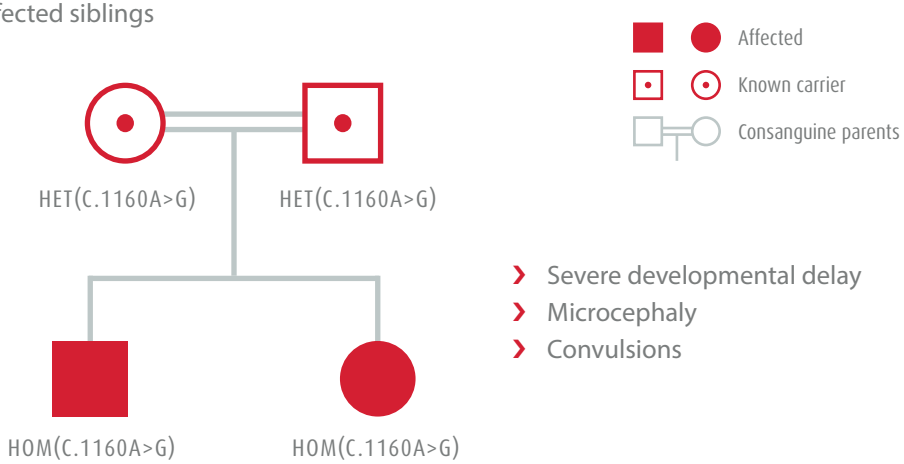
Pathogenicity of the variant(s) is discussed in light of the clinical information provided. Further diagnostic steps are recommended based on the clinical picture of the patient and family history for the disorder. Disease-associated polymorphisms with well-established clinical significance for the individual disease phenotype(s) are also reported.

As knowledge on variant frequencies dramatically increases year by year, re-evaluation of variants is an important step in improving our understanding of disease pathogenicity. To strengthen this variant curation process, CENTOGENE has created **CentoMD®**, **a mutation database that includes detailed clinical information, frequency, geographic origin, and classification of variants**. Re-evaluation of negative cases is encouraged after a period of 6 months or when new relevant clinical data is available.

Asparagine synthetase deficiency - CASE STUDY

PEDIGREE AND CLINICAL DATA

CentoXome® performed on two affected siblings



- Severe developmental delay
- Microcephaly
- Convulsions

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- Microcephaly
- Convulsions

DIAGNOSTIC PROCEDURE

- Microcephaly, intractable seizures and severe developmental delay are highly heterogeneous; a large number of genes are associated with each of the symptoms
- The exome was sequenced at an average coverage of 124X
- 51,318 variants were identified
- End-to-end bioinformatics analysis, variant priorization, found that both patients shared a previously unreported homozygous mutation in exon 10 of the asparagine synthetase (ASNS) gene (c.1160A>G[p.Tyr377Cys]); the parents were also confirmed to be carriers of this mutation
- Medical evaluation and a literature search confirmed this mutation as a deleterious mutation that causes low CSF and plasma asparagine in both patients

Services tailored to your patient´s needs:

FEATURES	CENTOXOME® PLATINUM	CENTOXOME® GOLD
TAT	15 business days	30 business days
COVERAGE DEPTH	Coverage of 100x, with approx. 97% of targeted bases covered >10x	
PRENATAL TESTING	✓	✗

Please visit our website
for more information:

www.centogene.com

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V5.4eng_January2019