CentoMito™
Mitochondrial diseases
Physician information
Helping your patients and their families to make decisions about therapy and screening options.

Caring for people through reliable genetic testing.

Thinking about tomorrow, today.
Bridging genetic testing and medical expertise in mitochondrial disease diagnostics

CENTOGENE is a global leader in the diagnostics of rare genetic diseases and holds multiple international accreditations (ISO, CAP, CLIA) meeting the highest standards for diagnostic testing and reporting. Our experience combined with our medical competence and scientific expertise allows the application of state-of-the-art technologies and the development of a unique, multi-ethnic mutation database, CentoMD®. This database helps you detect the right genotype/phenotype correlation as well as provide differential diagnostic approaches.

Over the past years, CENTOGENE has analyzed thousands of mitochondrial disease patients from all over the world. This medical expertise enables CENTOGENE to provide you with reliable interpretation results. We will assist you in elucidation the factor contributing to disease frequency, thus providing new insights into the genetics, pathophysiology, and therapeutic options for mitochondrial diseases.

In this brochure CENTOGENE provides you with an explanation of the different technologies that can be used to perform molecular diagnostics for mitochondrial diseases.

Contact us today to gain further insight into your rare genetic disease.

Prof. Arndt Rolfs
Chief Executive Officer
What are mitochondrial diseases?
Mitochondrial diseases are genetic conditions that occur when mitochondria are failing to produce energy for cells. Genetic mutations in the mitochondrial genome, or nuclear genes encoding proteins functioning inside mitochondria, are causing developmental, neurological, muscular and cognitive disabilities with symptoms including poor growth, loss of muscle coordination, muscle weakness and pain, seizures, vision and/or hearing loss, gastrointestinal issues, learning disabilities and organ failure.

Mitochondrial disorders are estimated to affect 1 in 4,000 people.
To date, there is NO treatment and NO cure for mitochondrial diseases.

The most common types of mitochondrial myopathy are (see fig. 1 on page 6-7):

- Kearns-Sayre syndrome (KSS)
- Leigh’s syndrome and maternally inherited Leigh’s syndrome (MILS)
- Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)
- Myoclonus epilepsy with ragged red fibers (MERRF)
- Neuropathy, ataxia and retinitis pigmentosa (NARP)
- Pearson syndrome
- Chronic progressive external ophthalmoplegia (CPEO)
- Myogastrointestinal encephalomyopathy (MNGIE)
What are the major symptoms of mitochondrial diseases?

Mitochondrial DNA disease commonly affects multiple different organs, with symptoms including:
(also see fig. 1 on page 6-7)
› Loss of movement control, muscle weakness
› Neurological problems, seizures
› Developmental delay, learning disabilities
› Visual and/or hearing problems
› Heart, liver or kidney disease
› Gastrointestinal disorders
› Diabetes

How do we inherit mitochondrial diseases?

Only the mother’s mitochondrial DNA is passed on to the next generation. Cells contain hundreds of mitochondria, and each mitochondrion contains several copies of mitochondrial DNA, which contains the information for making mitochondrial proteins. When different mutations are present in all mitochondria in the same organism, this state is called ‘homoplasmy’ and when it is present in some mitochondria but not others, it’s called ‘heteroplasmcy’. At CENTOGENE we use complex new techniques able to identify levels of heteroplasmy in the patients affected with mitochondrial disorders.

Mitochondrial diseases are rarely inherited in an X-linked or autosomal dominant pattern. A combination of chromosomal and mitochondrial errors has also been reported to cause mitochondrial myopathy, in particular myogastrointestinal encephalomyopathy (MNGIE).
Fig. 1: Mitochondrial diseases and most characteristic and major symptoms

- Hypotonia
- Seizures
- Liver failure
- Renal tubulopathy

- SANDO
  - Sensory axonal neuropathy
    - Sensory and cerebellar ataxia
    - Epilepsy
    - Dysarthria, and/or myopathy

- Myoclonus
- Seizures
- Cerebellar ataxia
- Myopathy
- Dementia
- Optic atrophy
- Bilateral deafness
- Peripheral neuropathy
- Spasticity
- Multiple lipomata

- Sideroblastic anemia
- Pancytopneia
- Exocrine pancreatic failure
- Renal tubular defects

Alpers-Huttenlocher syndrome

Ataxia neuropathy syndromes

Myoclonic epilepsy with ragged-red fibers (MERRF)

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)

- Stroke-like episodes
- Seizures and/or dementia
- Ragged-red fibers and/or lactic acidosis
- Diabetes mellitus
- Cardiomyopathy
- Bilateral deafness
- Pigmentary retinopathy
- Cerebellar ataxia

Leigh syndrome

Pearson syndrome

Mitochondrial diseases
Leber hereditary optic neuropathy (LHON)

- Peripheral neuropathy
- Ataxia
- Pigmentary retinopathy
- Basal ganglia lucencies
- Abnormal EEG
- Sensorimotor neuropathy

Kearns-Sayre syndrome (KSS)

- Early onset hypotonia
- Feeding difficulties
- Respiratory difficulties
- Cardiomyopathy
- Toni-Fanconi-Debre syndrome
- Pigmentary retinopathy
- CSF protein >1g/L
- Cerebellar ataxia
- Heart block
- Bilateral deafness
- Myopathy
- Dysphagia
- Diabetes mellitus
- Hypoparathyroidism
- Dementia

Infantile myopathy and lactic acidosis

- Early onset hypotonia
- Feeding difficulties
- Respiratory difficulties
- Cardiomyopathy
- Toni-Fanconi-Debre syndrome

Myoclonic epilepsy myopathy sensory ataxia (MEMSA)

- Myopathy Seizures
- Cerebellar ataxia
- Dementia
- Peripheral neuropathy
- Spasticity

Chronic progressive external ophthalmoplegia (CPEO)

- External ophthalmoplegia
  - Bilateral ptosis
  - Mild proximal myopathy
- Subacute painless
- Bilateral visual failure (males:females: 4:1)
- Onset 24 years
- Dystonia
- Cardiac pre-excitation

Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)

- Peripheral neuropathy
  - Ataxia
  - Pigmentary retinopathy
- Basal ganglia lucencies
- Abnormal EEG
- Sensorimotor neuropathy

Diseases
What causes mitochondrial diseases?

- Mutations of nuclear genes, localized in the nucleus of the cell can cause recessive or dominantly inherited mitochondrial diseases
- Mutations in mitochondrial DNA (mtDNA)
- Mutations in both nuclear genes and mtDNA
- Sporadic mutations, mostly deletions of large parts of the mitochondrial DNA toxic substances or some drugs can trigger mitochondrial disease

Why is genetic testing for mitochondrial diseases needed?

Mitochondrial diseases are difficult to diagnose and they can present symptoms long after birth. To improve the quality of life for adults and children affected by mitochondrial diseases, it is important to establish a diagnosis as soon as possible by using genetic testing.

Who should be tested for mitochondrial diseases?

- Individuals with clinical symptoms characteristic of a specific mitochondrial disorder
- Individuals with any progressive multisystem disorder of unknown etiology
- Individuals with multiple complex neurologic features or a single neurological symptom with other system involvement
- Children presenting with lactic acidosis
What type of test results can be expected?

- **Positive result** - Indicates that a previously characterized disease-causing mutation was identified. This result can help the physician to assess the risk of experiencing certain symptoms and indicate the best way of treating the disease. A positive result may also identify family members at risk for having the mutation and carrier testing may be recommended.

- **Negative result** - Does not necessarily rule out a mitochondrial disorder, and the patient should be managed according to clinical symptoms. Possible reasons for a negative result could be that the patient (a) may have a mutation in a gene not covered by the testing panel, or (b) has a mutation which is not detectable by the test performed, or (c) does not have a mitochondrial disorder.

- **Variant of unknown clinical significance (VUS)** - Indicates that we have identified a change in the DNA, which is not known to be associated with a disorder. To clarify the clinical significance of such a variant, testing other family members may be helpful.
Why is genetic testing for mitochondrial diseases needed?

**Major symptoms**
- Poor growth, developmental delays
- Loss of muscle coordination, muscle weakness
- Neurological symptoms, seizures
- Visual and/or hearing problems
- Learning disabilities, mental retardation
- Heart, liver, or kidney disease
- Gastrointestinal disorders, severe constipation
- Respiratory disorders
- Diabetes
- Increased risk of infection
- Thyroid dysfunction
- Dementia

**Metabolic findings**
- Increased serum lactate and pyruvate
- Abnormal lactate/pyruvate ratio
- Abnormal liver enzymes and ammonia
- Increased creatine kinase
- Abnormal urine organic acids
- Abnormal Krebs cycle intermediates

**Positive family history**

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**Fig. 2:**
Diagnostic algorithm for mitochondrial diseases at CENTOGENE
Testing of other family members

VUS

Carrier testing for family members, prenatal and pre-implantive testing, genetic counselling

Positive result

CentoMito™ comprehensive

WES

Positive result

WGS

Negative result

Positive result

Negative result
What tests for diagnostics of mitochondrial diseases are offered by CENTOGENE?

CENTOGENE has designed special gene panels for mitochondrial disease diagnostics:

**CentoMito™ comprehensive** includes the following genes:

- AARS2; AASS; ABAT; ABCB6; ABCB7; ABCD1ABCD3; ACACA; ACAD8; ACAD9; ACADM; ACADS; ACADSB; ACADVL; ACAT1; ACO2; ACOX1; ACSF3; ACSL4; ADCK3; ADCK4; AFG3L2; AGK; AGXT; ALIM1; AK2; ALAS2; ALDH1A1; ALDH2; ALDH3A2; ALDH4A1; ALDH5A1; ALDH6A1; ALDH7A1; AMACR; AMT; APOPT1; ATIC; ATP5A1; ATP5E; ATP7B; ATPAF2; ATXN2; AUH; BAX; BCKDHA; BCKDHB; BCKDK; BCL2; BCS1L; BOLA3; BRIP1; BTD; C10orf2; C12orf65; CA5A; CASP8; CAT; CHCHD10; C10orf2; CLPB; CLPP; COA5; COA6; COASY; COMT; COQ2; COQ4; COQ6; COQ9; COX10; COX14; COX15; COX20; COX4I2; COX6A1; COX6B1; COX7B; CPOX; CPS1; CPT1A; CPT1C; CPT2; CRBN; CYB5A; CYB5R3; CYC1; CYCS; CYP11A1; CYP11B1; CYP12A1; CYP12B1; CYP27A1; CYP27B1; D2HGDH; DARS2; DBT; DECR1; DGUOK; DHCR24; DHODH; DHTKD1; DIABLO; DLAT; DLD; DMGDH; DMPK; DNA2; DNAJC19; DNA1L1; EARS2; ECHS1; EHHADH; ELAC2; EPHX2; ETPA; ETFB; ETFDH; ETHE1; FARS2; FASTKD2; FBXL4; FECH; FH; FKBP10; FOXRED1; FTH1; FXN; GARS; GATM; GCDH; GDAP1; GFER; GFM1; GFM2; GK; GLDC; GLRX5; GLUD1; GLYCTK; GPI; GPT2; GPX1; GRHPR; GSR; GTPBP3; HADH; HADHA; HADHB; HARS2; HAX1; HCCS; HIBCH; HINT1; HK1; HLCS; HMBS; HMGCL; HMGCS2; HOA1; HSD17B10; HSD17B4; HSD3B2; HSPA9; HSD1; HTRA2; IARS2; IBA57; IDH2; IDH3B; ISCA2; ISCU; IVD; KARS; KIF1B; KRT5; L2HGDH; LARS2; LIAS; LIPT1; LONP1; LRPRRC; LRM3; LRM4; LRM7; MAAO; MAOB; MARS2; MCCC1; MCCC2; MCEE; MFN2; MGME1; NICU1; MIP; MLH1; MLYCD; MAA; MMAB; MMACHC; MMADHC; MOCS1; MPC1; MPV17; MRPL3; MRPL44; MRPS16; MRPS22; MSRB3; MTFMT; MTO1; MTPAP; MTRR; MUT; MUTHY; NADK2; NAGS; NARS2; NDUFA1; NDUFA10; NDUFA11; NDUFA12; NDUFA4; NDUFA9; NDUFAF1; NDUFAF2; NDUFAF3; NDUFAF4; NDUFAF5; NDUFAF6; NDUFA11; NDUFB3; NDUFB9; NDUFS1; NDUFS2; NDUFS3; NDUFS4; NDUFS6; NDUFS7; NDUFS8; NDUFV1; NDUFV2; NFU1; NNT; NTHL1; NUBPL; OAT; OGDH; OGG1; OPA1; OPA3; OTC; OXCT1; P4HB; PAM16; PANK2; PARK7; PC; PCCA; PCCB; PCK2; PDHA1; PDHB; PDK3; PDP1; PDSS1; PDSS2; PDX1; PET100; PEX11B; PHYH; PINK1; PRL3; PNPLA8; PNPO; PNPT1; POLG; POLG2; PPM1K; PPOX; PRODH; PTGS1; PTRF; PTRH2; PTS; PUS1; PYCR1; PYCR2; QDPR; RARS; RARS2; RDH11; RECQL4; RMND1; RNASEH1; RNASEL; RPIA; RPL35A; RPS14; RRMB2; SARDH; SARS2; SCO1; SCO2; SCP2; SDHA; SDHAF1; SDHAF2; SDHB; SDHC; SDHD; SECISBP2; SERAC1; SFXN4; SLC16A1; SLC19A3; SLC25A1; SLC25A12; SLC25A13; SLC25A15; SLC25A19; SLC25A20; SLC25A22; SLC25A3; SLC25A38; SLC25A4; SLC25A46; SLC37A4; SLC9A6; SNAP29; SOD1; SOD2; SPG7; SPR; SPTLC2; STAR; STOM; SULCL1A2; SULCL1G1; SUGCT; SUOX; SURF1; TACO1; TARS2;
TCIRG1; TIMM44; TIMM8A; TK2; TMEM126A; TMEM70; TMLHE; TPI1; TPK1; TRMU; TRNT1; TSFM; TTC19; TUBB3; TUFM; TXNRD2; TYMP; UNG; UQCC2; UQCRB; UQRC2; UQCRQ; VARS2; WDR81; XPNPEP3; YARS2 and complete mitochondrial genome.

By targeting nuclear encoded genes, as well as mitochondrial encoded genes this panel provides a comprehensive test for patients with mitochondrial deficiency as evident from the analysis of biopsy material or a suspicion of mitochondrial disease based on patient’s symptoms. CentoMito™ Comprehensive covers the entire mitochondrial genome (100% coverage at >1000x) along with 372 nuclear genes related to the mitochondrial diseases (mean coverage of 120x, with >94% of bases covered at ≥20x).

CentoMito™ Comprehensive includes sequence analysis of 372 nuclear encoded mitochondrial proteins and complete mitochondrial genome, with detection of heteroplasmy down to 15%.

CENTOGENE is also offering:

CentoMito™ Genome, that includes all mitochondrial genes: MT-ND1, MT-ND2, MT-CO1, MT-CO2, MT-ATP8, MT-ATP6, MT-CO3, MT-ND3, MT-ND4L, MT-ND4, MT-ND5, MT-ND6, MT-CYB, MT-TF, MT-RNR1, MT-TV, MT-RNR2, MT-TL1, MT-TI, MT-TQ, MT-TM, MT-TW, MT-TA, MT-TN, MT-TC, MT-TY, MT-TS1, MT-TD, MT-TK, MT-TG, MT-TR, MT-TH, MT-TS2, MT-TL2, MT-TE, MT-TT, MT-TP.

At CENTOGENE we need only 1mL EDTA blood or 2µg DNA for the analysis of either the mitochondrial diseases panel or the CentoMito™ Comprehensive panel.

Turnaround time for CentoMito™ Genome is 20 days, for CentoMito™ Comprehensive <45 days.
How can mitochondrial diseases be treated?

There are no cures for mitochondrial diseases, but treatment can help reduce symptoms or delay or prevent the progression of the disease. Only with a diagnosis obtained by means of genetic testing we can suggest the best fitting therapy or management for the affected patients.

- Physiotherapy can help to maintain function and muscle fatigue can be improved by regular gentle exercise
- A good diet, including adequate vitamin and supplements intake (for example creatine, L-carnitine and coenzyme Q10) and the avoidance of obesity are important
- Problems with breathing require treatment with occasional or permanent ventilator support
- Certain drugs may affect mitochondrial function, and it is generally recommended avoiding those drugs and alcohol
- Diabetes can be treated with insulin
- Drugs to treat seizures and headaches can be prescribed
- Specialists may be required to treat vision, hearing, speech and swallowing difficulties as necessary
Countries sending samples to CENTOGENE

Samples
- > 2000
- 501 – 2000
- 101 – 500
- 51 - 100
- < 50
- < 50
Please visit our website for more information:

www.centogene.com

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