Whole Exome Sequencing

Decoding genetic insights with WES

MEDICOVER GENETICS

WHAT IS MEDICOVER GENETICS **WHOLE EXOME SEQUENCING ANALYSIS**?

Medicover Genetics **Whole Exome Sequencing** (**WES**) analysis is a comprehensive genetic test that examines the coding regions (exons) of approximately **20,000 genes**. While exons represent only 1-2% of the human genome, 85% of all known disease-causing mutations are located in exonic regions[1]. Accurate detection of the disease-causing mutation can lead to improved clinical management and beneficial therapies, reducing or relieving the patient's symptoms and benefiting their quality of life. Through WES analysis, diagnosis can be achieved faster, avoiding extensive, costly and lengthy serial testing.

COMPLETE COVERAGE: MITOCHONDRIAL GENOME

Testing of the mitochondrial genome along with WES analysis

Primary mitochondrial disorders develop due to mutations either in the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA). They **can manifest at any age** and are characterized by:

- diverse clinical phenotype
- complex clinical presentation
- multi-system involvement

The mtDNA mutation's type and size, localization, and the level of heteroplasmy (presence of two or more mtDNA populations within a cell) determine disease penetrance. The marked clinical variation observed in patients with mitochondrial disorders makes diagnosis **extremely challenging**.

Analysis of all 37 genes of the mitochondrial genome, in addition to WES, will facilitate reaching a diagnosis faster and possibly avoid the need for invasive skeletal muscle biopsies. Our Postnatal WES + Mitochondrial Genome analysis:

- detects low levels of heteroplasmy
- covers single nucleotide variants (SNVs), small insertions and deletions (INDELs) and copy number variants (CNV)

WHO IS MEDICOVER GENETICS **WES ANALYSIS** FOR?

- Individuals with a heterogeneous disease manifesting with broad, atypical and complex symptoms
- Individuals who remain unresponsive to treatment for presumed diagnosis
- Individuals who have exhausted other available testing options without achieving a diagnosis
- Individuals who may have a rare genetic condition
- Individuals who have a suspected genetic disorder for which analysis with other testing methods may not exist or be as accurate
- Individuals suspected of having a mitochondrial disease, such as:
  - a multisystem disorder, muscle weakness, cardiomyopathy, visual problems or hearing loss, among others
  - a positive family history of a mitochondriopathy
- Fetuses with sonographic abnormalities, when other testing has yielded nondiagnostic or negative results

1. Rabbani, Bahareh, et al. "The Promise of Whole-Exome Sequencing in Medical Genetics." Journal of Human Genetics, vol. 59, no. 1, 2013, pp. 5–15

MEDICOVER GENETICS **WES ANALYSIS** OPTIONS

For all WES analysis tests, data analysis can be provided in the following formats:

PRIMARY
FASTQ sequencing files

SECONDARY
VCF files

TERTIARY
VCF with annotation & classification files

CLINICAL REPORT
Variant filtering and clinical interpretation performed by interdisciplinary team of scientific experts with CAP/CLIA credentials

WES ANALYSIS TESTS:

POSTNATAL WES

SAMPLE:
Buccal swab or DNA

TURNAROUND TIME:
2-3 weeks (Primary, Secondary, Tertiary)
4-6 weeks (Clinical Report)

POSTNATAL WES + MITOCHONDRIAL GENOME

SAMPLE:
Buccal swab or DNA

TURNAROUND TIME:
2-3 weeks (Primary, Secondary, Tertiary)
4-6 weeks (Clinical Report)

PRENATAL WES

SAMPLE:
DNA from chorionic villus sampling or amniocentesis & buccal swab(s) from parent(s)

TURNAROUND TIME:
2 weeks (Primary, Secondary, Tertiary)
2-3 weeks (Clinical Report)

TESTING OPTIONS:

 Single (patient only)

 Duo (patient + 1 family member)

 Trio (patient + 2 family members)

Analysis of family members, preferably of biological parents, along with the patient's sample allows for a more efficient clinical evaluation as it increases the potential for identifying a disease-causing variant and accurately determining its inheritance.

WHY RECOMMEND MEDICOVER GENETICS **WES ANALYSIS?**

- Assesses coding regions of almost 20,000 genes, increasing the chances of **identifying causative mutations** and **rare disorders**.
- **Provides genetic insight** on symptoms, potential complications and disease progression.
- Presents a patient-focused approach that can **shorten the diagnostic process**.
- **Supports clinicians** in providing an accurate diagnosis, and improving clinical management of patients.

CASE STUDY

11-day-old male infant presenting with facial dysmorphic features, atrial septal defect (ASD) and ventricular septal defect (VSD).
Healthcare team referred the infant for WES analysis, as per ACMG guidelines[2]. Trio analysis was selected.

Medicover Genetics WES analysis results

- A pathogenic, **de novo**, heterozygous mutation at exon 8 of the **FGFR2 gene**, associated with the patient's symptoms
- A pathogenic, X-linked, **maternally inherited**, hemizygous mutation at exon 8 of the **G6PD gene**. This mutation is the most common cause of chronic, drug-, food- or infection-induced hemolytic anemia and is a **risk factor for neonatal sepsis**, especially in males.

According to the patient's clinical and genetic findings, the healthcare team can accurately provide a diagnosis for the affected infant and an optimal clinical management plan which **takes into consideration the triggers and complications of both disorders**. Genetic counseling for future family planning is also recommended for this family.

- The simultaneous identification of the 2 distinct mutations would not have been possible without WES analysis.
- The trio analysis provided the inheritance of the variants identified without the need for subsequent parental testing.

SPECIFICATIONS & **COVERAGE**

Medicover Genetics WES analysis provides **increased depth of coverage**. The test examines **adjacent non-coding sequence**, and **provides deep**, **uniform coverage** even across GC-rich regions. Medicover Genetics applies a **robust bioinformatic pipeline** and variant calling software for precise result analysis and interpretation.

MUTATIONS COVERED

WES analysis screens for SNVs, small INDELs, and CNVs

ON-TARGET RATE

>95%

MEDIAN READ DEPTH

100x

COVERAGE

>97% over 20x

'We strongly recommend exome sequencing or genome sequencing as a first-tier or second-tier test [...] for patients with one or more congenital anomalies prior to one year of age or for patients with developmental delay/intellectual disability with onset prior to 18 years of age.' [2]

2. Manickam, Kandamurugu, et al. "Exome and Genome Sequencing for Pediatric Patients with Congenital Anomalies or Intellectual Disability: An Evidence-Based Clinical Guideline of the ACMG." Genetics in Medicine, vol. 23, no. 11, 2021, pp. 2029–2037

BENEFITS OF MEDICOVER GENETICS **WES ANALYSIS**

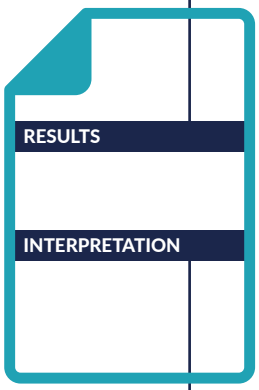
SAFE
Non-invasive sample collection*

ACCURATE
>95% on-target rate

EXTENSIVE
Examination of ~20,000 genes

BENEFICIAL
Can shorten the diagnostic process

WHAT WILL THE **REPORT** TELL ME?



CLINICALLY SIGNIFICANT VARIANT DETECTED

A pathogenic or likely pathogenic genetic variant has been identified in a gene or genes associated with the clinical characteristics provided.

NO CLINICALLY SIGNIFICANT VARIANT DETECTED

No disease-causing genetic variant related to the clinical characteristics provided has been identified in the genes tested.

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)

A genetic change has been detected, but it is currently unknown whether that change is associated with a genetic disorder.

SECONDARY FINDINGS

Pathogenic variants in specific genes recommended by ACMG† guidelines can be reported upon request.

Summary of the results and recommendations

Variant re-evaluation can be requested by healthcare providers at defined timeframes.

*Exception: prenatal WES
†American College of Medical Genetics and Genomics

HOW TO ADMINISTER THE **WES ANALYSIS** TEST?

Recommend WES analysis to your patient

Collect the sample(s)

Send the sample(s) to **Medicover Genetics**

The sample(s) will be analyzed at **Medicover Genetics** laboratories

Results will be sent to you

MORE **QUESTIONS**?

If you have additional questions or concerns, please contact us at **info.genetics@medicover.com**

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MKT-WES-DR-EN-V3.1