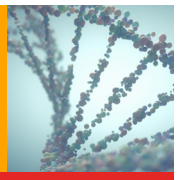
CGC genetics
a Unilabs company

Exome Sequencing



Information for health professionals

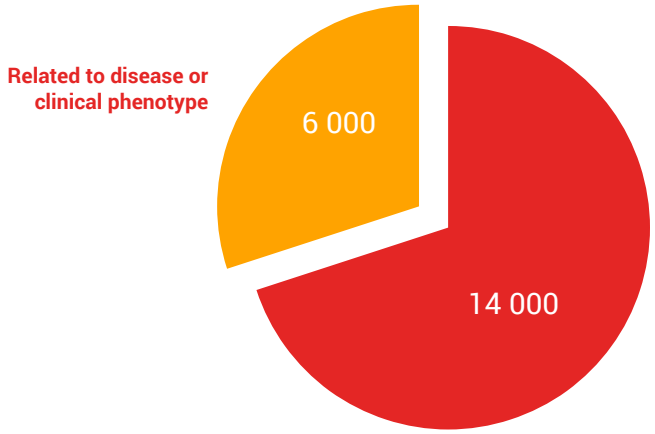
EXOME SEQUENCING

A POWERFUL DIAGNOSTIC TOOL A BREAKTHROUGH SOLUTION TO SOLVE MEDICAL DILEMMAS

Exome Sequencing by CGC Genetics combines the highest diagnostic yield availablae with the clinical interpretation and integration provided by our specialized Medical Team.

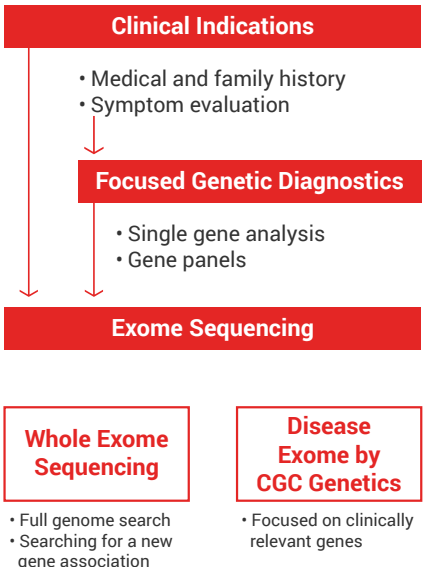
With Exome Sequencing, patients can be studied with a significantly reduced turnaround time and cost, when compared with previous sequential approach of single gene or gene panel sequencing.

CGC Genetics has available two Exome Sequencing options, to best fit patient's individual needs:



The entire human exome comprises over 20 000 genes

- **Whole Exome Sequencing**, which analyzes the entire exome by sequencing about 20 000 genes;
- **Disease Exome by CGC Genetics**, which analyzes >6 000 clinically relevant genes.



CLINICAL INDICATIONS FOR EXOME SEQUENCING:

- Undiagnosed genetic condition not identified with prior genetic testing
- Clinical phenotype that may overlap with several genetic disorders
- Clinical phenotype that does not correspond to any known genetic disorder
- Clinical phenotype which is unclear or complex and/or may involve multiple genes
- A genetic disorder for which no genetic testing is available, is suspected

WHOLE EXOME SEQUENCING – WES

Whole Exome Sequencing (WES) entails the sequencing of all genomic coding regions, i.e., the exons.

The goal is to obtain the highest possible amount of genetic information of a patient by searching genetic variants throughout the 20 000 genes that make up the exome.

Since this test yields many thousands of genetic variants to be analyzed CGC Genetics recommends WES TRIO, i.e., performing WES in both the patient and the parents. This way, it is possible that both parents serve as a reference for filtering benign variants, or ascertain the parent-of-origin for each variant, making WES an effective diagnostic method in detecting, e.g., recessive Mendelian diseases and de novo variants.

Variants may be either detected in genes related with defined clinical conditions or in genes whose association with disease has not been yet described.

Whole Exome Sequencing has an average depth of coverage of 100x. This entails a very thorough study of coding sequences analyzed with high diagnostic yield in most regions

WES ADVANTAGES:

- Maximum diagnostic yield currently available
- Clinical phenotype expansion through the identification of new genes with clinical significance
- Detection of new variants or gene associations not yet described
- Confirmation of possible variants by Sanger sequencing
- Solving complex diagnostic cases
- Report with clinical integration and interpretation

DISEASE EXOME BY CGC GENETICS

Disease Exome by CGC Genetics is the largest sequencing panel available which includes approximately >6 000 clinically relevant genes.

Disease Exome has a particular focus on coding regions (exons) and in flanking regions (splicing sites) and is based on the following databases:

1. Human Gene Mutation Database (HGMD) (www.hgmd.cf.ac.uk/ac/index.php)
2. Online Mendelian Inheritance in Man (OMIM) (www.omim.org)
3. GeneTests (www.genetests.org)

DISEASE EXOME ADVANTAGES:

- Targeted at clinically relevant genes;
- High diagnostic yield
- Confirmation of possible variants by Sanger sequencing
- Report with clinical integration and interpretation
- Useful in situations where only the patient sample is available

Disease Exome by CGC Genetics is designed to produce an average depth of coverage of 100x and minimum 20x in more than 95% of target regions.

MITOCHONDRIAL DNA TEST

In exome sequencing only nuclear DNA is analyzed, excluding mitochondrial DNA. Mitochondrial genome contains 37 genes involved in several mitochondrial disorders.

CGC Genetics offers a panel for detection of mitochondrial diseases, which includes full sequencing analysis by NGS of the whole mitochondrial genome.

METHODOLOGY

Next Generation Sequencing – NGS

Next Generation Sequencing (NGS) is the most advanced technology for sequencing analysis. In a single test, a gene, several genes (panel) or the whole exome are analyzed at a fraction of the time and cost than before.

This technology provided a breakthrough in genetic diagnostic yield, reducing turnaround time and cost.

1 › SAMPLE PREPARATION
DNA is extracted from provided samples.

2 › NGS LIBRARY PREPARATION AND TARGET ENRICHMENT
Library preparation with an exceptional target enrichment approach.

3 › ALIGNMENT AND VARIANT CALLING
Sequencing output is precisely aligned against a reference genome build. This will allow detection of variants and potential mutations.

4 › DATA ANALYSIS
Variants found by NGS are analyzed and classified in order to identify the ones that have or may have clinical significance. Variant classification is performed according to ACMG recommendations [1]

5 › VARIANT CONFIRMATION
At CGC Genetics all potential variations/mutations detected by NGS are reanalyzed and confirmed through Sanger sequencing. Employing two different methodologies into the detection of potentially harmful mutations provides robust clinical diagnostics, while eliminating possible artifacts and false positives.

6 › CLINICAL INTEGRATION AND REPORTING
Sequencing results are analyzed and interpreted by our highly qualified scientists and integrated by our clinical geneticists.

[1] Richards S et al., Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 2015, 17(5):405-24. DOI: 10.1038/gim.2015.30.

METHODOLOGY PROCESS

WORKFLOW

3-STEP PROCESS:

1. Clinical Request

Exome sequencing can be focused on the patient alone (Disease Exome by CGC Genetics) or the patient and both biological parents (Whole Exome Sequencing TRIO).

Patient clinical information is crucial to deliver a well-founded diagnostic approach.

2. Exome sequencing and variant confirmation

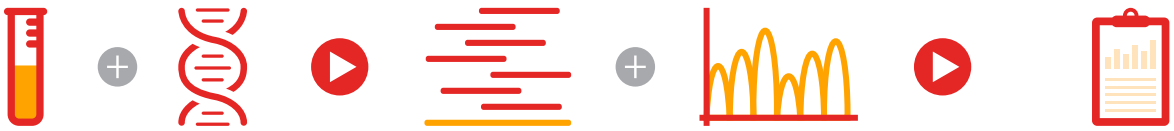
Exome sequencing uses Next Generation Sequencing (NGS) technology to perform sequencing analysis in a single test of WES TRIO or Disease Exome by CGC Genetics. Potential variants and/or disease-causing mutations are reanalyzed by Sanger sequencing, the gold standard of genetic diagnostics.

3. Clinical analysis and integrated reports

Clinical reports are always based on individual patient information and analyzed by experienced senior geneticists.

Integrated reports are sent directly to the requesting physician through our secure online portal.

Clinical request and sample preparation	Whole Exome Sequencing Disease Exome by CGC Genetics	Clinically integrated report



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