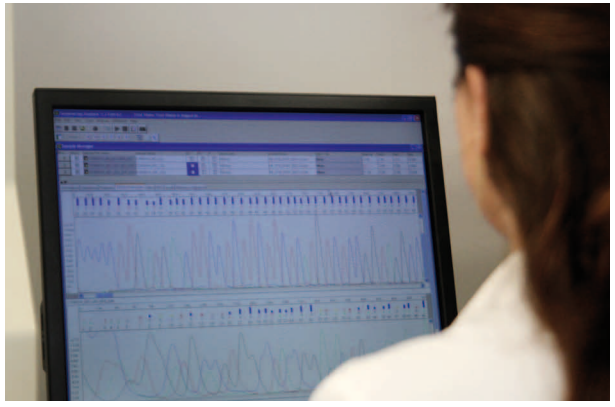


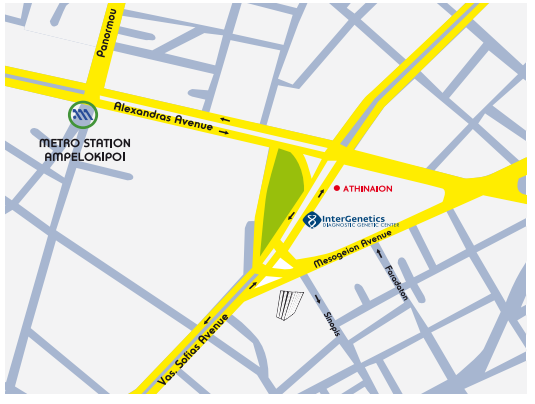
Why perform genomic analysis – whole exome sequencing

Currently, whole exome sequencing is useful:

1. for uncovering pathogenic mutations, for rare (or complex) common genetic disorders
2. for identifying pathogenic mutations, causing or predisposing for common genetic diseases, e.g. cancers, mental retardation (MR), autism
3. for detecting somatic mutations (mosaicism)

Today, whole exome sequencing is not useful:

1. for identifying common variants/ polymorphisms with unknown functional significance
2. for personal genomic profiling or for communicating predispositions and risks for common diseases



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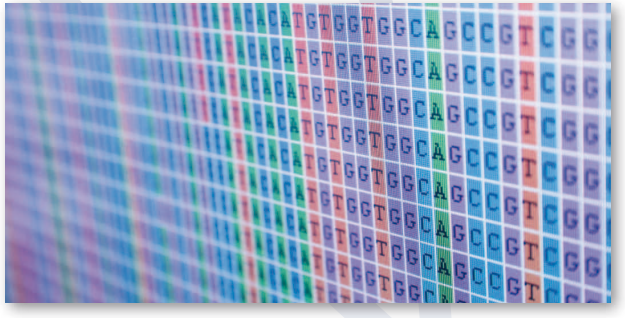
DIAGNOSTIC GENETIC CENTER

GENOMIC TESTING OF ALL HUMAN GENES

Whole Exome Sequencing with next generation sequencing



… the era of Genomic Medicine is... here and we follow closely…

- ✓ *we can now realize the cause for many complex and as yet undiagnosed genetic disorders*
- ✓ *our group has sucessfully completed the analysis by whole exome sequencing of numerous clinical cases, leading to the uncovering of the genetic cause for a variety of complex genetic diseases in affected adults, children and fetuses*

Basic information regarding whole exome sequencing

Sequence analysis of all known human genes (whole exome sequencing - WES), through new generation sequencing technologies (next generation sequencing - NGS) is the new genetic super- weapon, as it is theoretically in a position to uncover the molecular basis for any genetic disorder in an affected individual, which has not been diagnosed by other available conventional genetic testing options. This test is completely different from other types of currently known genetic testing, in terms of the number of genes that are analyzed simultaneously. Until now, classical approaches to the diagnosis of genetic diseases involved the investigation of specific targeted genes (1-5), considered to be associated with the observed phenotype. Now, this new powerful technology allows high-throughput analysis of all ~22,000 human genes (whole exome sequencing) or, alternatively, the simultaneous analysis of hundreds of genes (gene panels) associated with different categories of diseases with a genetic etiology.

Main concepts

Exome = the coding part of our genome = all known human genes. It includes ~22,000 genes, > 160,000 exons, covers ~40-50 Mb (40-50 million bases) and includes the analysis of intron-exon junctions (splice sites).

How is clinical whole exome sequencing performed and how long does the test take to be completed

The test is based on the method of next generation sequencing (NGS) and utilizes a special genome analyzer instrument together with complex and highly specialized software tools. The test is generally completed within 4-5 months.

When do we apply whole exome sequencing

The application of this highly specialized test is aimed at clinicians and their patients, who suffer from an as yet undiagnosed disease believed to have a genetic etiology. This does not mean that there must necessarily exist a prior family history of the disease, since in the case of recessive or sporadic disorders (being the majority of genetic diseases) there is usually only one affected family member.

Based on the published data up to date, the application of whole analysis has proven extremely useful for diagnosing the cause of neuro-developmental pediatric diseases, complex syndromes, undiagnosed neuromuscular disorders, autism, etc., and is particularly valuable in the management of oncological cases-cancers.

What are the limitations of the test

Due to the fact that we still do not understand the precise function of many human genes, as well as their interactions, it is possible to fail to reach a definitive diagnosis, especially in cases with ill-defined clinical symptoms.

The test is highly sensitive and complex. Therefore, the analysis and the clinical evaluation of the results should be performed by a highly skilled group of clinical and molecular geneticists, ensuring the maximum diagnostic validity for the patient and the family.

Genetic counseling

Proper clinical genetic assessment of each case and genetic counseling, both before and following the test, is essential in order to determine the appropriate strategy for laboratory testing and to interpret correctly the concepts of pathological and normal.