VALUE PROPOSITION

Comprehensive pipeline for diagnosis of mitochondrial diseases using next-generation sequencing technology.

BACKGROUND

Mitochondria are cellular organelles, which are important for the normal functioning of cells, and are majorly involved in the production of energy. These organelles are therefore aptly termed the powerhouse of the cell. Mitochondria is composed of a double membrane and has a distinct and small circular genome with just over 16,000 bases. The small genome encodes for 37 genes. The mitochondria are peculiar in many ways. Its peculiar pattern of maternal inheritance also has been extensively used to understand human ancestry and migration. A single cell could also have multiple mitochondria, and some may be different from each other, in a few genetic variations: a phenomenon known as heteroplasmy. Apart from this, the human mitochondrial genome is also known to have a higher mutation rate, compared to the nuclear genome. Dysfunction of the mitochondrial genome, through genetic variations are well known to cause mitochondrial diseases. Mitochondrial diseases are of the most common genetic diseases, with an incidence of 1 in every 5000 births.

The group of disorders caused by the dysfunction of mitochondria are generally known as mitochondrial disorders and include mitochondrial myopathies, Leber's hereditary optic neuropathy (LHON), Leigh syndrome, Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP), Myoclonic Epilepsy with Ragged Red Fibers (MERRF) etc. Apart from these well-characterized diseases, recent studies have increasingly suggested mitochondrial variations and mitochondrial dysfunction to be associated with a number of disease conditions including neurological disorders such as Alzheimer’s disease and metabolic disorders such as type 2-diabetes mellitus.

The advent of next-generation sequencing (NGS) technology has offered a unique opportunity to sequence and annotate mitochondrial variations. Many recent studies have extensively used NGS approaches to identify mitochondrial variants and their associations with diseases. NGS also provides additional advantages including large depth coverage, which could be effectively used to map heteroplasmic variations. With the drastic drop in cost of DNA sequencing, it is possible that affordable mitochondrial sequencing could be effectively employed for patients suffering from mitochondrial disorders. The widespread application of NGS by clinicians is in part limited by the paucity of appropriate systematic computational pipelines for data analysis, which are easy to operate and provide clinical reports in easily interpretable formats.

The knowledge base encompasses a comprehensive pipeline, including experimental methodologies together with appropriate computational methods to sequence mitochondrial genome using next generation sequencing and appropriately analyze and interpret the data. This methodology has application in fast diagnosis of mitochondrial genomic variations and diseases associated with the variations. The overview of the knowledge base is summarized in Figure 1.

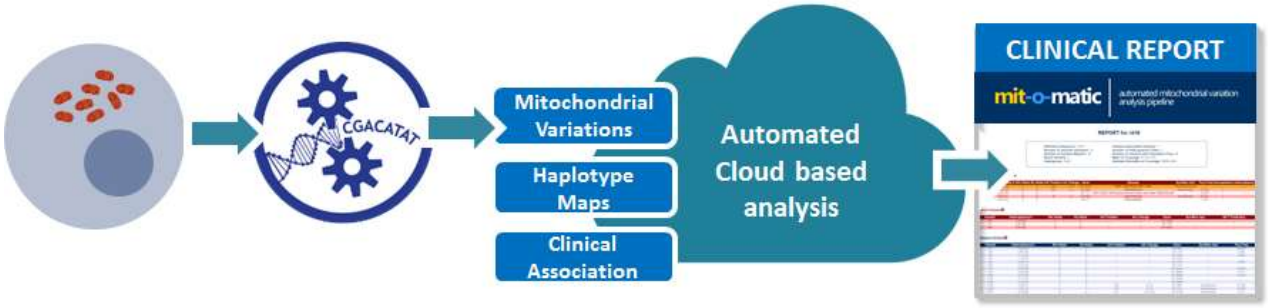

Figure 1. Schematic overview of the automated pipeline for analysis and annotation of mitochondrial variations using Next generation sequencing approach.

The commercial application of the knowledgebase would be in the following domains:

1) Fast and accurate diagnosis of mitochondrial genetic mutations with implications in
    a) Clinical diagnosis,
    b) Prenatal testing,
    c) Carrier status screening.

2) Systematic annotation of genetic mutations towards finding potential genetic associations with diseases/traits/phenotypes and understanding gene environment interactions and their effect on mitochondrial genetic variations in the research domain.

ADVANTAGES

1. Easy to use protocol for isolation of mitochondrial DNA.
2. Compatible with multiplexing on popular next generation sequencing platforms.
3. Automated-cloud based analysis approach through a user-friendly approach.
4. Extremely sensitive to detect heteroplasmy.

KNOWLEDGE BASE READINESS INDEX

Idea	Definition	Concept	Prototype	Validation	Demonstration	Development	Market Launch

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CSIR-Institute of Genomics & Integrative Biology (IGIB) is a premier Institute of Council of Scientific and Industrial Research (CSIR), engaged in research of national importance in the areas of genomics, molecular medicine, bioinformatics, proteomics and environmental biotechnology.

Interested companies are requested to send an EOI indicating their willingness to participate in further discussions by email ID: director@igib.res.in with copy to pbansal@igib.res.in, vinods@igib.res.in and s.sivasubbu@igib.res.in.