

## **New hope for mitochondrial disorders**

New Delhi, March 31 (India Science Wire): Efforts to find a treatment for mitochondrial disorders is set to get a major boost with a team of researchers at the Department of Biotechnology's National Institute of Immunology (DBT-NII) figuring out a way to tackle autosomal dominant progressive external ophthalmoplegia (adPEO), which is a widely prevalent mitochondrial disorder.

Mitochondrial genetic disorders refer to a group of conditions that affect the mitochondria, the structures in the body cells that are responsible for making energy. People with these conditions can be of any age with almost any affected body system. However, the brain, muscles, heart, liver, nerves, eyes, ears and kidneys are the organs and tissues most commonly affected. Symptom severity can also vary widely.

Mitochondrial genetic disorders can be caused by changes (mutations) in either the mitochondrial DNA or nuclear DNA that lead to dysfunction of the mitochondria and inadequate production of energy. Those caused by mutations in mitochondrial DNA are transmitted by maternal inheritance, while those caused by mutations in nuclear DNA may follow an autosomal dominant, autosomal recessive or X-linked pattern of inheritance. Treatment varies based on the specific type of condition and the signs and symptoms present in each person.

In the new study, the researchers at NII focused on autosomal dominant progressive external ophthalmoplegia (adPEO) as it is one of the most common Mitochondrial disorders. The disorder occurs when there is a problem in the replication and removal of mismatches in the mitochondrial DNA. In healthy mitochondria, a protein called Polymerase Gamma carries out these two vital functions. It consists of a single catalytic subunit, Polymerase GammaA, which complexes with two identical subunits of the accessory factor, Polymerase GammaB. Polymerase Gamma has to move inside the mitochondria to do its work.

So far, the dogma was that the transport into mitochondria was determined by a peptide called Mitochondrial Localization Signal (MLS). The new study has extended the present knowledge. The researchers have found that along with MLS, a process called ubiquitylation, also decides whether Polymerase Gamma A will optimally enter the mitochondria. The study also zeroed in on another protein called MITOL, which is present on the outer membrane of the mitochondria, was behind the ubiquitylation of Polymerase GammaA. The team also determined the site on the Polymerase GammaA that gets ubiquitylated by MITOL.

On further study, the researchers found that Polymerase GammaA in 50% of the tested adPEO patients was highly ubiquitylated. However it was possible to reverse the process of ubiquitylation either by removing MITOL itself or by genetically modifying the site Polymerase GammaA in adPEO patients that gets highly ubiquitylated by MITOL. Speaking to India Science Wire, the leader of the team, Dr. Sagar Sengupta, said, "It will be interesting to test in future whether the reactivation of Polymerase Gamma A can actually be carried out in the patients using mitochondrial genome editing techniques".

The research findings have been published in the journal PLoS Biology. The research team includes Mansoor Hussain, Aftab Mohammed, Shabnam Saifi, Aamir Khan, Ekjot Kaur, Swati, Priya and Himanshi Agarwal, besides Dr. Sengupta.

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