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### Researchers from Dino Ferrari Centre in Milan discover a novel mechanism of mitochondrial disease opening the way to the development of future therapies.

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#### **The Mitochondrial Disulfide Relay System Protein GFER Is Mutated in Autosomal Recessive Myopathy with Cataract and Combined Respiratory Chain Deficiency**

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Mitochondria are small organelles present within every cell of human organism. Most of the energy used by our body is produced in a complex series of chemical reactions performed inside the mitochondrial respiratory chain. The respiratory chain is made of four multienzymatic complexes whose proteins are synthesized on the basis of instructions derived from mitochondrial DNA and several genes belonging to nuclear genome.

A defect in mitochondrial activity, reducing the oxidative metabolism, leads to the impairment of the energetic levels of cells, tissues and whole organs defining a pathological state commonly indicated as “mitochondriopathy.”

This term refers to heterogeneous clinical presentations which affect specific cellular types or, more often, several systems with the impairment of various parts of the nervous and sensorineural system, endocrinous apparatus, heart, liver and gastrointestinal apparatus. Some of the most severe syndromes so far described are: Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke (MELAS), Mitochondrial Encephalopathy with Ragged Red Fibers (MERRF), Kearns-Sayre Syndrome (KSS), Pearson’s Syndrome, the infantile onset Leigh’s and Alpers’s syndromes, Mitochondrial NeuroGastroIntestinal Encephalopathy (MNGIE), Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoparesis (SANDO) and Mitochondrial DNA Depletions Syndromes (MDS).

Muscular tissue and brain are often severely struck in mitochondrial encephalomyopathies due to their great energetic requirements.

Frequency of these disorders has been only partially estimated in some populations. A recent study performed in United Kingdom has identified potentially pathogenic mutations in mitochondrial DNA in one child on 200 live births. Adding mutations in nuclear genes encoding for mitochondrial factors, we can say that mitochondrial disorders are relatively common in the general population.

Despite the great advances obtained in the comprehension of the genetic basis of mitochondrialopathies, the molecular causes of most of these disorders (especially the ones with infantile onset and a severe progression) remain unknown.

Analyzing DNA samples from a family where three of the five children are affected by a mitochondrial myopathy with congenital cataract and combined respiratory chain deficiency, the research group lead by professor Giacomo Comi at Dino Ferrari Centre (University of Milan, Foundation IRCCS Ospedale Maggiore Policlinico Mangiagalli and Regina Elena) has discovered that this disease is caused by mutations in GFER (growth factor, augmenter of liver regeneration ERV1 homolog) gene.

The protein encoded by this gene is localized in the intermembrane mitochondrial space and it has a fundamental role in the import process into mitochondria of several essential proteins rich in cysteins. Among these proteins, there are many factors involved in assembly of the respiratory chain complexes but also molecules relevant to detoxification pathways such as CCS, the copper chaperone of superoxide dismutase 1 (SOD1) whose mutations are causative of a form of familial amyotrophic lateral sclerosis).

Researchers have found that GFER is less abundant in cells derived from patients than from healthy subjects: the low amount of mutated proteins cannot sustain an efficient import of the aforementioned proteins, impairing the biochemical pathway known as "Mitochondrial Disulfide Relay System" and leading to the energetic deficit observed in tissues from affected children.

For the first time this import process into intermembrane mitochondrial space is directly involved in the pathogenesis of a human disease. It is likely that furthers studies on GFER and other proteins involved in this mechanism will improve our comprehension of other mitochondrial and neurodegenerative disorders. This study unravels a novel mechanism of mitochondrial disease never explored so far in man: its analysis will contribute to the development of therapeutic strategies for the treatment of this class of diseases.