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Clotilde Roussille

[clotilde.roussille@univ-angers.fr](mailto:clotilde.roussille@univ-angers.fr)

Tel. : 02.44.68.85.11

## ■ Leber hereditary optic neuropathy: discovery of a mechanism of blindness development and a new therapeutic lead.

**A team from the French laboratory of Integrated Neurovascular and Mitochondrial Biology (University of Angers/ Inserm/ CNRS) from the Mitochondrial Medicine Research Centre (MMRC), gathering researchers and physicians from the University and Hospital of Angers, has just discovered a new pathological mechanism of blindness development in patients with Leber hereditary optic neuropathy. The study has been published in *Brain*.**

### Main scientific investigators :

*Pascal Reynier and Guy Lenaers*

The Leber hereditary optic neuropathy (LHON) causes the degeneration of optic nerves that manifests as a sudden severe alteration of vision in young adults, occurring in a few weeks or months.

It is the most frequent genetic disease that concerns mitochondria, the "power plants" of our cells. It affects 1 person in 30,000 in Europe, thus more than 2,000 people in France.

Although it is known that this vision pathology is triggered by mutations in the mitochondrial DNA that are transmitted by the mother, the actual data on the pathological mechanism cannot explain the incomplete penetrance of the disease, since only 1 man out of 2, and 1 woman out of 5, with one of the LHON mutations will actually become blind.

The MitoLab team from the French laboratory of Integrated Neurovascular and Mitochondrial Biology (University of Angers/ Inserm/ CNRS), with the Hospital of Angers, work on the physio-pathological causes of this disease for many years and ensure a clinical and molecular diagnosis of the patients within the reference national center of rare mitochondrial diseases.

In collaboration with another research team from Angers (SOPAM Oxidative stress and metabolic pathologies - Inserm / University of Angers), the researchers have used a state-of-the-art technology: metabolomics with mass spectrometry to analyze simultaneously a large amount of small molecules (sugars, amino-acids, fats,...) present in our cells, allowing to characterize in details the diseases by defining their metabolic signature.

In the study published in *Brain* on September 16<sup>th</sup>, the comparison of patients with a LHON mutation to control individuals, revealed a novel key characteristic of the disease: a stress from the endoplasmic reticulum, a peculiar compartment of our cells, where lipids and proteins are synthesized.

This discovery, which was made possible thanks to the active support of patient associations, brings two major innovations for the management of the disease.

Firstly, the cell stress has been noticed only in symptomatic patients, and could therefore be considered as a biomarker for the actual risk of developing blindness.

Secondly, it paves the way for new therapeutic perspectives with treatments targeting the endoplasmic reticulum stress, so as to potentially reduce the risk of sudden loss of sight in patients with LHON.

*\*Patient associations: Fondation Visio, UNADEV and Ouvrir les Yeux*

### **About MMRC/ PREMMi**

The Mitochondrial Medicine Research Centre (MMRC/PREMMi), based in Angers, France gathers all the local laboratories involved in mitochondrial investigations, hence creating a scientific dynamic for the emergence of a unique, international-sized, mitochondrial medicine consortium.

The MMRC/PREMMi strategy consists in transferring the knowledge and skills acquired on mitochondrial inherited rare diseases to common diseases involving mitochondrial dysfunction (Alzheimer, Parkinson, cancer, diabetes, cardio-vascular diseases, aging).

One of the main challenges in mitochondrial medicine is to identify therapeutic pathways targeting mitochondria in many diseases for which there is no treatment yet available.

The MMRC/PREMMi program favors the reinforcement of collaborations between plant and metazoan life sciences research axes. From this alliance, new therapeutic molecules should be identified to generating tomorrow's medicine for common diseases with a mitochondrial deficit.

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