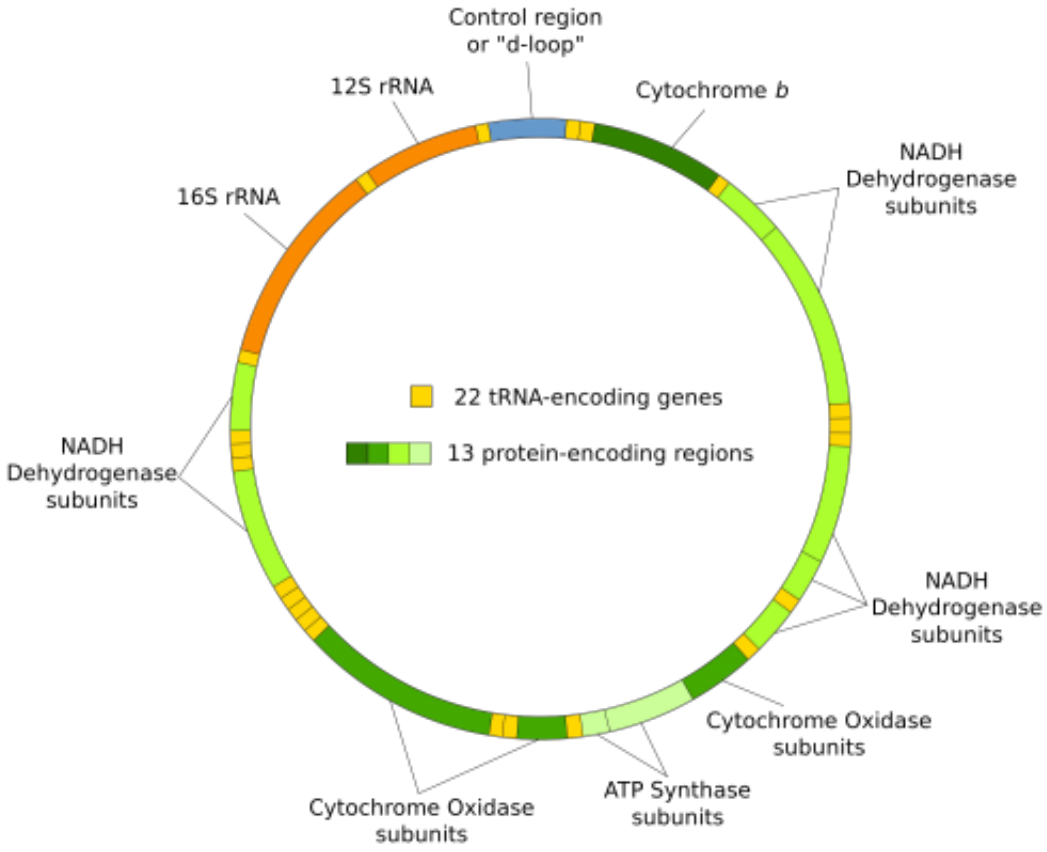
Gene behind long-recognized mitochondrial disease has highly varied effects

March 12 2019



Mitochondrial DNA. Credit: en.wikipedia.org

For more than two decades, mutations in a gene located in the DNA of mitochondria have been classified as a mitochondrial disease and linked to a particular set of symptoms. However, according to new findings

from researchers at Children's Hospital of Philadelphia (CHOP), mutations in this gene, which encodes an essential part of the mitochondrial motor known as ATP synthase that generates cellular energy, are much more variable than previously thought. This prompts the need to develop more precise clinical tests that can better determine the course of treatment for patients affected by mitochondrial disorder. The study was published online on February 14 in the journal *Human Mutation*.

Mitochondria are structures found within human and animal cells that are responsible for energy production. Mitochondria contain 37 genes encoded in their own DNA (mtDNA) that are separate from the DNA found inside the nucleus of the cell. Variations in more than 350 different genes located across both nuclear and mitochondrial DNA are responsible for causing mitochondrial diseases, which can typically cause more than 16 different symptoms in each patient and affect multiple organs.

Mutations in the mtDNA-encoded ATP synthase membrane subunit 6 gene (MT-ATP6) are found in between 10 and 20 percent of cases of Leigh syndrome, a progressive brain disorder long recognized as a form of mitochondrial disease, and another recognizable condition known as neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome.

"We went into this study wanting to look at the more than 200 reported cases of mitochondrial disease with a MT-ATP6 mutation to better understand the clinical presentation of its many variants," said study leader Rebecca Ganetzky, MD, an attending physician in the Mitochondrial Medicine Frontier Program at CHOP, and an assistant professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania. "Patients with an MT-ATP6 mutation not only vary significantly in what symptoms they develop, but there has also been extensive variability in biochemistry analyses of their cells and

tissues, making it difficult to apply any sort of universal diagnostic or treatment strategy for these patients."

Ganetzky and her colleagues reviewed all of the 218 published cases of MT-ATP6 mitochondrial disease to-date to assess their variants and compare those findings with clinical and biochemical features of the disease. The authors also presented a new clinical case series of 14 additional patients with MT-ATP6 variants of uncertain significance or relation to their medical problems.

What the researchers ultimately found was that despite those having one common mutation, this is a particularly heterogeneous disease in terms of the sequence variations and clinical symptoms that may occur. The study identified a total of 34 variants within the MT-ATP6 mutation, where surprisingly no single biochemical feature was shared by all individuals with these variants.

"This study provides an important point of reference for patients in whom MT-ATP6 variants are discovered in diagnostic testing, as we now recognize just how variable this disease may be," Ganetzky said. "We need to develop better ways to test for this disease, since the classical clinical syndromic presentations of NARP and Leigh syndrome are not sufficient to capture the problems present in all of these patients."

Ganetzky said that future studies are needed to systematically evaluate the functional significance for all of the MT-ATP6 variants. The authors recommend a multi-pronged approach to assessing biochemical diversity, including development of a common community resource of all gene variants along with their biochemical and clinical features. Additionally, a project supported by the National Institutes of Health is under way led by CHOP Mitochondrial Medicine Frontier Program executive director, Marni J. Falk, MD, to expertly curate MT-ATP6 variants that cause Leigh syndrome. CHOP also offers and continues to

investigate a variety of advanced testing techniques for mitochondrial disease, including those that will help better understand mitochondrial energy production effects in patients with MT-ATP6 variants.

More information: Rebecca D. Ganetzky et al, MT-ATP6 mitochondrial disease variants: Phenotypic and biochemical features analysis in 218 published cases and cohort of 14 new cases, *Human Mutation* (2019). DOI: 10.1002/humu.23723

Provided by Children's Hospital of Philadelphia