NFU1 Gene

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NFU1 iron-sulfur cluster scaffold

genes

1. Introduction

The *NFU1* gene provides instructions for making a protein involved in the formation of molecules called iron-sulfur (Fe-S) clusters. These clusters are attached to certain other proteins and are required for their proper function.

Two versions (isoforms) of the NFU-1 protein are produced from the *NFU1* gene. One version is found in cellular structures called mitochondria. Mitochondria are the energy-producing centers of cells. In these structures, several proteins carry out a series of chemical steps to convert the energy in food into a form that cells can use. Many of the proteins involved in this process require Fe-S clusters to function, including protein complexes called complex I, complex II, and complex III.

Fe-S clusters are also required for another mitochondrial protein to function; this protein is involved in the modification of additional proteins that aid in energy production in mitochondria, including the pyruvate dehydrogenase complex and the alpha-ketoglutarate dehydrogenase complex. This modification is also critical to the function of the glycine cleavage system, a set of proteins that breaks down a protein building block (amino acid) called glycine when levels become too high.

The other version of the NFU-1 protein is found in the fluid-filled space inside the cell (the cytoplasm). While this protein is likely involved in Fe-S cluster formation in the cytoplasm, the role of this isoform is not well understood.

2. Health Conditions Related to Genetic Changes

2.1. Multiple mitochondrial dysfunctions syndrome

Mutations in the *NFU1* gene can cause multiple mitochondrial dysfunctions syndrome. This severe condition is characterized by impairment of more than one mitochondrial function, such as reduced activity of complex I, II, or III, pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, or the glycine cleavage system. Affected infants often have severe brain dysfunction (encephalopathy) and elevated levels of a chemical called lactic acid in the body (lactic acidosis). These babies usually do not survive past infancy.

NFU1 gene mutations lead to production of an altered NFU-1 protein that is likely broken down quickly. Although some mutations affect both isoforms of the NFU-1 protein, loss of the mitochondrial version appears to be responsible for the condition. The lack of mitochondrial NFU-1 protein impairs Fe-S cluster formation. Consequently, proteins affected by the presence of Fe-S clusters, including those involved in energy production and glycine breakdown, cannot function normally. Reduced activity of complex I, II, or III, pyruvate dehydrogenase, or alpha-ketoglutarate dehydrogenase leads to potentially fatal lactic acidosis, encephalopathy, and other signs and symptoms of multiple mitochondrial dysfunctions syndrome. In some affected individuals, impairment of the glycine cleavage system leads to a buildup of glycine (hyperglycinemia).

3. Other Names for This Gene

- CGI-33
- HIRA-interacting protein 5
- HIRIP
- HIRIP5
- iron-sulfur cluster scaffold protein
- MMDS1
- Nfu
- NFU1 iron-sulfur cluster scaffold homolog, mitochondrial
- NFU1 iron-sulfur cluster scaffold homolog, mitochondrial isoform 1
- NFU1 iron-sulfur cluster scaffold homolog, mitochondrial isoform 2
- NFU1 iron-sulfur cluster scaffold homolog, mitochondrial isoform 3
- NFU1_HUMAN
- NifU
- NifU-like C-terminal domain containing
- NIFUC

References

1. Cameron JM, Janer A, Levandovskiy V, Mackay N, Rouault TA, Tong WH, Ogilvie I,Shoubridge EA, Robinson BH. Mutations in iron-sulfur cluster scaffold genes NFU1 and BOLA3 cause a fatal deficiency of multiple respiratory chain and 2-oxoaciddehydrogenase enzymes. Am J Hum Genet. 2011 Oct 7;89(4):486-95. doi:10.1016/j.ajhg.2011.08.011.
2. Invernizzi F, Ardissone A, Lamantea E, Garavaglia B, Zeviani M, Farina L,Ghezzi D, Moroni I. Cavitating leukoencephalopathy with multiple mitochondrialdysfunction syndrome and NFU1 mutations. Front Genet. 2014 Nov 20;5:412. doi:10.3389/fgene.2014.00412.
3. Mayr JA, Feichtinger RG, Tort F, Ribes A, Sperl W. Lipoic acid biosynthesisdefects. J Inherit Metab Dis. 2014 Jul;37(4):553-63. doi:10.1007/s10545-014-9705-8.
4. Navarro-Sastre A, Tort F, Stehling O, Uzarska MA, Arranz JA, Del Toro M,Labayru MT, Landa J, Font A, Garcia-Villoria J, Merinero B, Ugarte M,Gutierrez-Solana LG, Campistol J, Garcia-Cazorla A, Vaquerizo J, Riudor E,Briones P, Elpeleg O, Ribes A, Lill R. A fatal mitochondrial disease isassociated with defective NFU1 function in the maturation of a subset ofmitochondrial Fe-S proteins. Am J Hum Genet. 2011 Nov 11;89(5):656-67. doi:10.1016/j.ajhg.2011.10.005.
5. Rouault TA. Biogenesis of iron-sulfur clusters in mammalian cells: newinsights and relevance to human disease. Dis Model Mech. 2012 Mar;5(2):155-64.doi: 10.1242/dmm.009019. Review.