OPA1 Gene

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1. Introduction

The *OPA1* gene provides instructions for making a protein that is found in cells and tissues throughout the body. The OPA1 protein is active in the inner membrane of cell structures called mitochondria, which are the energy-producing centers in cells. Mitochondria are dynamic structures that change shape through processes called fission (splitting into smaller pieces) and fusion (combining pieces). Changes in shape are necessary for mitochondrial function and the production of new mitochondria. The OPA1 protein helps to regulate the shape of mitochondria by playing a key role in the fusion process.

The OPA1 protein is also involved in a process that takes place in mitochondria called oxidative phosphorylation, from which cells derive much of their energy. Additionally, the OPA1 protein plays a role in the maintenance of the DNA within mitochondria, called mitochondrial DNA (mtDNA), and in controlled cell death (apoptosis).

2. Health Conditions Related to Genetic Changes

2.1. Optic atrophy type 1

At least 240 mutations in the *OPA1* gene have been found to cause optic atrophy type 1. This condition typically results in vision loss beginning in childhood that worsens over time. Affected individuals may also have problems with color vision, particularly distinguishing between shades of blue and green.

Most of the *OPA1* gene mutations that cause optic atrophy type 1 create a premature stop signal in the instructions for making the OPA1 protein. As a result, an abnormally small protein is produced, which is likely to be unstable and broken down quickly. The most common mutation that causes optic atrophy type 1 in individuals of Danish ancestry results in an abnormally small protein by deleting one DNA building block (nucleotide) in the *OPA1* gene (written as 2826delT).

OPA1 gene mutations that cause optic atrophy type 1 lead to problems in mitochondrial function. The mitochondria become misshapen and disorganized and have reduced energy-producing capabilities. The maintenance of mtDNA may also be impaired, resulting in mtDNA mutations that also contribute to mitochondrial dysfunction. Cells that contain these poorly functioning mitochondria are more susceptible to apoptosis. In particular, cells within the retina called retinal ganglion cells die over time. Specialized extensions of retinal ganglion cells, called axons, form the optic nerves, so when retinal ganglion cells die, the optic nerves break down (atrophy) and cannot transmit visual information to the brain. As the optic nerves atrophy, vision worsens, leading to the signs and symptoms of optic atrophy type 1.

While the OPA1 protein is found in cells throughout the body, retinal ganglion cells appear to be particularly sensitive to the effects of *OPA1* gene mutations. These cells have especially high energy requirements that make them more likely to malfunction and die when there are changes in mitochondrial function and decreases in energy production.

2.2. Other disorders

About 20 percent of individuals with mutations in the *OPA1* gene have the vision problems characteristic of optic atrophy type 1 (described above) with other health problems. Some *OPA1* gene mutations cause a condition called optic atrophy type 1 and deafness, which results in both vision loss and hearing loss.

OPA1 mutations can also cause a condition known as autosomal dominant optic atrophy (ADOA)-plus syndrome. ADOA-plus syndrome involves vision and hearing loss, weakness in the muscles that control eye movement (progressive external ophthalmoplegia), difficulty with balance and coordination (ataxia), disturbances in the nerves used for muscle movement and sensation (motor and sensory neuropathy), and skeletal muscle weakness (myopathy).

The most severe condition cause by *OPA1* gene mutations is Behr syndrome, which is characterized by neurological problems that begin by early childhood. Individuals with Behr syndrome develop optic atrophy, brain dysfunction (encephalopathy), loss of sensation and weakness in the limbs (peripheral neuropathy), difficulty coordinating movements (ataxia), feeding and digestive difficulties, and developmental delay.

The features of these conditions are likely caused by the loss of cells in multiple tissues due to poor mitochondrial function. It is unclear why *OPA1* gene mutations affect only the eyes in individuals with optic atrophy type 1 but have more widespread effects in others. Researchers speculate that some *OPA1* gene mutations lead to the production of an altered protein that interferes with the function of the normal protein produced from the non-mutated copy of the gene, further impairing OPA1 protein function.

While optic atrophy type 1 and ADOA-plus syndrome are caused by *OPA1* gene mutations in one copy of the gene in each cell, individuals with Behr syndrome have mutations in both copies of the *OPA1* gene in each cell. Alterations in both copies of the gene drastically reduce the amount of functional OPA1 protein, which likely leads to the severe signs and symptoms of Behr syndrome.

3. Other Names for This Gene

- dynamin-like 120 kDa protein, mitochondrial
- FLJ12460
- KIAA0567
- MGM1
- mitochondrial dynamin-like GTPase
- NPG
- NTG
- OPA1_HUMAN

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