BCS1L Gene

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BCS1 homolog, ubiquinol-cytochrome c reductase complex chaperone

genes

1. Normal Function

The *BCS1L* gene provides instructions for making a protein that functions in cell structures called mitochondria, which convert the energy from food into a form that cells can use. The BCS1L protein is critical for the formation of a group of proteins known as complex III. Specifically, BCS1L adds a component called Rieske Fe/S protein to the complex. In mitochondria, complex III performs one step of the multistep process known as oxidative phosphorylation, in which oxygen and simple sugars are used to create adenosine triphosphate (ATP), the cell's main energy source.

As a byproduct of its action in oxidative phosphorylation, complex III produces reactive oxygen species, which are harmful molecules that can damage DNA and tissues. The reactive oxygen species produced by complex III are thought to also play a role in normal cell signaling, particularly when levels of oxygen in the body are low (hypoxia).

Some researchers believe the BCS1L protein is involved in the breakdown (metabolism) of iron, although the mechanism is unknown.

2. Health Conditions Related to Genetic Changes

2.1. Björnstad Syndrome

At least six *BCS1L* gene mutations have been found to cause Björnstad syndrome, a condition characterized by a hair abnormality known as pili torti (or "twisted hair") and hearing loss. *BCS1L* gene mutations associated with this condition alter the BCS1L protein and impair its ability to interact with other proteins. These changes reduce BCS1L's ability to add the Rieske Fe/S protein to complex III. As a result, complex III is incomplete, and excess Rieske Fe/S protein builds up in mitochondria. The resulting decrease in complex III activity reduces oxidative phosphorylation to approximately 60 percent of normal.

Studies show that in people with Björnstad syndrome, complex III produces little or no reactive oxygen species; however, for unknown reasons, another protein complex involved in oxidative phosphorylation called complex I

produces excessive amounts of reactive oxygen species, even more than would be produced by normally functioning complex III. Researchers believe that tissues in the inner ears and hair follicles are particularly sensitive to reactive oxygen species and are damaged by the abnormal amount of these molecules, leading to the characteristic features of Björnstad syndrome. It is unclear if a lack of cellular energy due to the reduction of complex III function also contributes to the features of this condition.

2.2. GRACILE Syndrome

At least one mutation in the *BCS1L* gene can cause GRACILE syndrome, a severe condition that affects several body systems and is found almost exclusively in Finland. Affected infants are small at birth; they have kidney and liver problems and elevated levels of iron in the body. These infants do not survive more than a few months after birth.

The *BCS1L* gene mutation that causes GRACILE syndrome changes a single protein building block (amino acid) in the BCS1L protein. The amino acid serine is replaced by the amino acid glycine at position 78 (written as Ser78Gly or S78G). This alteration likely changes the shape of the protein, and the abnormal protein is broken down more quickly than the normal protein. What little protein remains is able to help form some complete complex III, although the amount is severely reduced, particularly in the liver and kidneys. As a result, complex III activity and oxidative phosphorylation are decreased in these organs in people with GRACILE syndrome. It is not clear why the liver and kidneys are specifically affected.

Researchers believe that impaired oxidative phosphorylation can lead to cell death by reducing the amount of energy available in the cell. Damage to the affected organs and tissues leads to many of the features of GRACILE syndrome. It is not clear why a change in the *BCS1L* gene leads to iron accumulation in people with this condition.

2.3. Mitochondrial complex III deficiency

Mitochondrial complex III deficiency can be caused by *BCS1L* gene mutations. When associated with mutations in this gene, the condition is most often characterized by problems with the liver (hepatopathy), kidneys (tubulopathy), and brain (encephalopathy). The *BCS1L* gene mutations associated with this condition alter the BCS1L protein and severely reduce the function of complex III. As in Björnstad syndrome, the loss of complex III function reduces production of reactive oxygen species from complex III but increases production from complex I. In addition, in *BCS1L*-related mitochondrial complex III deficiency, cells contain more mitochondria than normal, probably to compensate for the severe reduction in oxidative phosphorylation; this increase further elevates the production of reactive oxygen species to levels higher than those found in Björnstad syndrome. The loss of complex III function also reduces the amount of energy available in cells, much like in GRACILE syndrome. Damage to the kidneys, liver, and brain from reactive oxygen species and lack of available energy likely leads to the features of mitochondrial complex III deficiency.

2.4. Leigh syndrome

Leigh syndrome

3. Other Names for This Gene

- BC1 (ubiquinol-cytochrome c reductase) synthesis-like
- BCS1
- BCS1-like protein
- BCS1_HUMAN
- h-BCS1
- Hs.6719
- mitochondrial chaperone BCS1
- mitochondrial complex III assembly

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