BSCL2 Gene

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1. Normal Function

The *BSCL2* gene provides instructions for making a protein called seipin, whose function is unknown. Within cells, seipin is located in the membrane of a structure called the endoplasmic reticulum. The endoplasmic reticulum modifies newly produced proteins and also helps transport proteins, fats, and other molecules to specific sites either inside or outside the cell.

The *BSCL2* gene is active in cells and tissues throughout the body, particularly in nerve cells that control muscle movement (motor neurons) and in the brain. The gene is also active in fat-storing cells called adipocytes, which are the major component of fatty (adipose) tissue. Studies suggest that seipin plays a critical role in the development and function of adipocytes. In particular, seipin is involved in the development of lipid droplets, which are structures within these cells that store fat molecules.

2. Health Conditions Related to Genetic Changes

2.1. Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease

2.2. Congenital Generalized Lipodystrophy

At least 25 mutations in the *BSCL2* gene have been identified in people with congenital generalized lipodystrophy (also called Berardinelli-Seip congenital lipodystrophy) type 2. This rare condition is characterized by an almost total absence of adipose tissue and a very muscular appearance. A shortage of adipose tissue leads to multiple health problems, including high levels of fats called triglycerides circulating in the bloodstream (hypertriglyceridemia) and diabetes mellitus. In some cases, this form of the condition is also associated with intellectual disability, which is usually mild to moderate.

Most of the *BSCL2* gene mutations that cause congenital generalized lipodystrophy type 2 lead to the production of a nonfunctional version of the seipin protein or prevent cells from making any of this protein. A loss of functional seipin disrupts the normal development and function of adipocytes, including lipid droplets, which prevents fats from being stored normally in adipose tissue. The resulting lack of body fat underlies most of the signs and symptoms of congenital generalized lipodystrophy type 2. A loss of seipin function in the brain may help explain why intellectual disability can occur with this form of the condition.

2.3. Distal Hereditary Motor Neuropathy, Type V

At least two *BSCL2* gene mutations have been identified in people with distal hereditary motor neuropathy, type V, a progressive disorder that affects motor neurons in the spinal cord. It results in muscle weakness and affects movement of the hands and feet. The mutations that can cause this disorder each change a single protein building block (amino acid) in the seipin protein. In one mutation, the amino acid serine is replaced with the amino leucine at position 90 (written as Ser90Leu or S90L). In another, the amino acid asparagine is replaced with the amino acid serine at protein position 88 (written as Asn88Ser or N88S).

It is unclear how *BSCL2* gene mutations cause distal hereditary motor neuropathy, type V. These genetic changes probably alter the structure of seipin, causing it to fold into an incorrect 3-dimensional shape. Research findings indicate that misfolded seipin proteins build up in the endoplasmic reticulum. This accumulation likely damages and kills motor

neurons, which leads to muscle weakness.

2.4. Silver Syndrome

At least two mutations in the *BSCL2* gene, the N88S and S90L mutations described above, have been reported to cause Silver syndrome. This condition is characterized by muscle weakness and wasting in the hands and abnormal muscle stiffness (spasticity) in the legs. The mutations likely result in misfolded seipin proteins that accumulate within neurons, leading to cell damage and cell death. The loss of neurons causes muscle weakness and spasticity in people with Silver syndrome.

It is unclear how the same mutations in the *BSCL2* gene can cause Silver syndrome; distal hereditary motor neuropathy, type V; or another disorder called Charcot-Marie-Tooth syndrome in different people. People with Silver syndrome sometimes have family members with the same *BSCL2* gene mutation who have one of these other conditions.

3. Other Names for This Gene

- Berardinelli-Seip congenital lipodystrophy 2 (seipin)
- BSCL2_HUMAN
- GNG3LG
- seipin
- SPG17

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