SMCHD1 Gene

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1. Normal Function

The *SMCHD1* gene provides instructions for making a protein that is involved in regulating gene activity by altering the structure of DNA. Specifically, the SMCHD1 protein is associated with DNA methylation, which is the addition of methyl groups (consisting of one carbon atom and three hydrogen atoms) to DNA molecules. The addition of methyl groups is associated with the turning off (silencing) of genes, so regions of DNA with many methyl groups (hypermethylated regions) tend to have fewer genes that are turned on (active).

The SMCHD1 protein is involved in a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than egg cells. X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. The SMCHD1 protein appears to be involved in the hypermethylation of certain areas of DNA called CpG islands, although the mechanism is unclear. This hypermethylation is critical for inactivation of the X chromosome. The SMCHD1 protein then remains attached (bound) to the inactive X chromosome to help keep it inactivated.

The SMCHD1 protein also plays a role in hypermethylation of a region near the end of chromosome 4 called D4Z4. This region consists of 11 to more than 100 repeated segments, each of which is about 3,300 DNA building blocks (3.3 kb) long. The segment closest to the end of chromosome 4 contains a gene called *DUX4*. Because the D4Z4 region is hypermethylated, the *DUX4* gene is silenced in most adult cells and tissues. Little is known about the function of the protein produced from the *DUX4* gene; it appears to help control the activity of other genes.

The SMCHD1 protein appears to play a role in normal development of the nose, eyes, and other structures of the head and face and seems to be involved in repairing damaged DNA. However, little is known about its roles in these processes.

2. Health Conditions Related to Genetic Changes

2.1. Bosma arhinia microphthalmia syndrome

At least nine *SMCHD1* gene mutations have been found to cause Bosma arhinia microphthalmia syndrome (BAMS). Individuals with this rare condition have an abnormally small or absent nose (arhinia), unusually small eyes (microphthalmia), and a shortage of certain hormones that direct sex development (hypogonadotropic hypogonadism).

The gene mutations involved in BAMS change single protein building blocks (amino acids) in the SMCHD1 protein. Researchers are unsure how these changes affect the protein's function and lead to the developmental problems characteristic of BAMS. *SMCHD1* gene mutations may lead to abnormal silencing of genes involved in development of the head and face. Problems with nasal development may affect gonadotropin-releasing hormone (GnRH) neurons, which are nerve cells that control the release of reproductive hormones. GnRH neurons originate in the developing nose and then move to the brain. Impaired development of these neurons could explain hypogonadotropic hypogonadism in affected individuals.

Some family members of individuals with BAMS have milder symptoms, such as a reduced sense of smell (anosmia), arhinia without other features of BAMS, or less severe abnormalities of the nose. Researchers suspect that additional genetic factors contribute to the severity of the symptoms, although these factors are not yet known.

2.2. Facioscapulohumeral muscular dystrophy

Dozens of mutations in the *SMCHD1* gene have been found to cause facioscapulohumeral muscular dystrophy, a disorder characterized by muscle weakness and wasting (atrophy) that worsens slowly over time. Two forms of the disorder have been described: type 1 (FSHD1) and type 2 (FSHD2). Changes in the *SMCHD1* gene appear to play a role in both types.

SMCHD1 gene mutations cause most cases of FSHD2. These mutations reduce the amount of SMCHD1 protein available to silence the D4Z4 region. This region has fewer methyl groups than usual (hypomethylation), which is associated with impaired silencing of the *DUX4* gene in cells and tissues where it is usually turned off, such as adult muscle cells. However, hypomethylation of the D4Z4 region results in facioscapulohumeral muscular dystrophy only when it occurs in people who also have at least one copy of chromosome 4 that is described as "permissive." A "permissive" chromosome 4 has a functional region of DNA known as a pLAM sequence located next to the *DUX4* gene. The pLAM sequence is necessary for the production of the DUX4 protein. (Conversely, a "non-permissive" chromosome 4 does not contain a functional pLAM sequence, preventing the production of any DUX4 protein.) Researchers believe that the DUX4 protein influences the activity of other genes, particularly in muscle cells. However, it is unknown how the presence of this protein damages or destroys these cells, leading to progressive muscle weakness and atrophy.

Studies suggest that mutations in the *SMCHD1* gene can increase the severity of disease in people with the other type of facioscapulohumeral muscular dystrophy, FSHD1. FSHD1 results when the D4Z4 region is abnormally shortened (contracted), containing between 1 and 10 repeats instead of the usual 11 to 100 repeats. Researchers suspect that the combination of a contracted D4Z4 region and a *SMCHD1* gene mutation causes the D4Z4 region to have even fewer methyl groups attached, which allows the *DUX4* gene to be highly active. In people with both genetic changes, the overactive gene leads to severe muscle weakness and atrophy.

2.3. Other disorders

SMCHD1 gene mutations have also been found in individuals with arhinia without other features of BAMS (described above), which is referred to as isolated arhinia. Researchers are working to understand why some people with mutations in this gene develop only arhinia and others have additional abnormalities.

3. Other Names for This Gene

- KIAA0650
- SMC hinge domain-containing protein 1
- structural maintenance of chromosomes flexible hinge domain-containing protein 1

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