RAI1 Gene

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retinoic acid induced 1

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1. Normal Function

The *RAI1* gene provides instructions for making a protein that is active in cells throughout the body, particularly nerve cells (neurons) in the brain. Located in the nucleus of the cell, the RAI1 protein helps control the activity (expression) of certain genes. Most of the genes regulated by RAI1 have not been identified. However, studies suggest that this protein controls the expression of several genes involved in daily (circadian) rhythms, such as the sleep-wake cycle. The RAI1 protein also appears to play a role in development of the brain and of bones in the head and face (craniofacial bones).

2. Health Conditions Related to Genetic Changes

2.1. Potocki-Lupski syndrome

Having an extra copy of the *RAI1* gene in each cell is thought to underlie many of the major features of Potocki-Lupski syndrome. This condition is characterized by delayed development, mild to moderate intellectual disability, behavioral problems including autism spectrum disorder (which affects social interaction and communication), sleep disturbances, and other health problems. The condition results from abnormal copying (duplication) of a small piece of the short (p) arm of chromosome 17 at position p11.2. In about two-thirds of affected individuals, the duplicated segment includes approximately 3.7 million DNA building blocks (base pairs), also written as 3.7 megabases (Mb). (A deletion of this segment causes Smith-Magenis syndrome, described below.) In the remaining one-third of cases, the duplication is larger or smaller, ranging from less than 1 Mb to almost 20 Mb. All of these duplications affect one of the two copies of chromosome 17 in each cell.

All of the duplications known to cause Potocki-Lupski syndrome contain the *RAI1* gene. Studies suggest that the duplication increases the amount of RAI1 protein, which disrupts the expression of genes that influence circadian rhythms. These changes may account for the sleep disturbances that occur with Potocki-Lupski syndrome. Too much RAI1 protein may also disrupt brain development, which could account for delayed development, intellectual disability, behavioral problems, and other neurological features of this condition. Development of the bones in the head and face may also be affected, leading to subtle facial differences in people with Potocki-Lupski syndrome.

2.2. Smith-Magenis syndrome

Researchers believe that a partial or total loss of function of the *RAI1* gene accounts for most of the signs and symptoms of Smith-Magenis syndrome. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, behavioral problems, and other abnormalities affecting many parts of the body.

In most people with Smith-Magenis syndrome, the condition results from a deletion of a small piece of chromosome 17 in each cell. Most often, this chromosome segment, located at 17p11.2, is the same one that is duplicated in Potocki-Lupski syndrome (described above). Occasionally the deletion is larger or smaller. All of the deletions affect one of the two copies of chromosome 17 in each cell.

All of the deletions known to cause Smith-Magenis syndrome contain the *RAI1* gene. Studies suggest that the deletion leads to a reduced amount of RAI1 protein in cells, which disrupts the expression of genes involved in circadian rhythms. These changes may account for the sleep disturbances that occur with Smith-Magenis syndrome. It is unclear how a loss of one copy of the *RAI1* gene leads to the other physical, mental, and behavioral problems associated with this condition.

A small percentage of people with Smith-Magenis syndrome have a mutation in the *RAI1* gene instead of a chromosomal deletion. Although these individuals have many of the major features of the condition, they are less likely than people with a deletion to have certain other features, including short stature, hearing loss, and heart or kidney abnormalities. It is likely that, in people with a deletion, the loss of other genes in the deleted region accounts for these additional signs and symptoms; the role of these genes is under study.

2.3. Yuan-Harel-Lupski syndrome

Having an extra copy of the *RAI1* gene in each cell is thought to underlie many of the major features of Yuan-Harel-Lupski (YUHAL) syndrome, which is characterized by multiple neurological problems. This condition results from duplication of a small piece of chromosome 17 in a region designated p12-p11.2. In YUHAL syndrome, the duplicated segments can range in size from 3.2 Mb to 19.7 Mb. These duplications affect one of the two copies of chromosome 17 in each cell.

The duplications that cause YUHAL syndrome all contain the *RAI1* gene and a nearby gene called *PMP22*; the segments may also contain additional genes. Some features of YUHAL syndrome, such as delayed development, behavioral and sleep problems, and unusual facial features, are similar to those of Potocki-Lupski syndrome (described above) and are likely caused by an extra copy of the *RAI1* gene. Other features of YUHAL syndrome, such as muscle weakness and decreased sensitivity to touch, heat, and cold in the lower legs and feet, likely result from an extra copy of the *PMP22* gene.

3. Other Names for This Gene

- KIAA1820
- RAI1_HUMAN
- SMCR
- SMS

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