Nager Syndrome

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Nager syndrome is a rare condition that mainly affects the development of the face, hands, and arms. The severity of this disorder varies among affected individuals.

Keywords: genetic conditions

1. Introduction

Children with Nager syndrome are born with underdeveloped cheek bones (malar hypoplasia) and a very small lower jaw (micrognathia). They often have an opening in the roof of the mouth called a cleft palate. These abnormalities frequently cause feeding problems in infants with Nager syndrome. The airway is usually partially blocked due to the micrognathia, which can lead to life-threatening breathing problems.

People with Nager syndrome often have eyes that slant downward (downslanting palpebral fissures), no eyelashes, and a notch in the lower eyelids called an eyelid coloboma. Many affected individuals have small or unusually formed ears, and about 60 percent have hearing loss caused by defects in the middle ear (conductive hearing loss). Nager syndrome does not affect a person's intelligence, although speech development may be delayed due to hearing impairment.

Individuals with Nager syndrome have bone abnormalities in their hands and arms. The most common abnormality is malformed or absent thumbs. Affected individuals may also have fingers that are unusually curved (clinodactyly) or fused together (syndactyly). Their forearms may be shortened due to the partial or complete absence of a bone called the radius. People with Nager syndrome sometimes have difficulty fully extending their elbows. This condition can also cause bone abnormalities in the legs and feet.

Less commonly, affected individuals have abnormalities of the heart, kidneys, genitalia, and urinary tract.

2. Frequency

Nager syndrome is a rare condition. Its prevalence is unknown. More than 75 cases have been reported in the medical literature.

3. Causes

More than half of cases of Nager syndrome are caused by mutations in the *SF3B4* gene. The cause of the remainder of cases is unknown; other genes are thought to be involved in the condition.

The *SF3B4* gene provides instructions for making the SAP49 protein, which is one piece of a complex called a spliceosome. Spliceosomes help process messenger RNA (mRNA), which is a chemical cousin of DNA that serves as a genetic blueprint for making proteins. The spliceosomes recognize and then remove regions from mRNA molecules that are not used in the blueprint (which are called introns).

The SAP49 protein may also be involved in a chemical signaling pathway known as the bone morphogenic protein (BMP) pathway. This signaling pathway regulates various cellular processes and is involved in the growth of cells. The SAP49 protein is particularly important for the maturation of cells that build bones and cartilage (osteoblasts and chondrocytes).

SF3B4 gene mutations that cause Nager syndrome prevent the production of functional SAP49 protein. Although the effect of this protein shortage is unknown, researchers suspect that it disrupts spliceosome formation, which may impair mRNA processing and alter the activity of genes involved in the development of several parts of the body. A loss of SAP49 may also impair BMP pathway signaling, leading to abnormal development of bones in the face, hands, and arms.

3.1. The Gene Associated with Nager Syndrome

- SF3B4

4. Inheritance

When caused by mutations in the *SF3B4* gene, Nager syndrome follows an autosomal dominant inheritance pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases result from new mutations in the gene and occur in people with no history of the disorder in their family. Less commonly, an affected person inherits the mutation from one affected parent. Autosomal dominant Nager syndrome may also be caused by mutations in other genes.

Nager syndrome can also be inherited in an autosomal recessive pattern, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of a mutated gene, but they typically do not show signs and symptoms of the condition. Nager syndrome is suspected to have an autosomal recessive inheritance pattern when unaffected parents have more than one affected child. The genetic cause in these families is unknown.

5. Other Names for This Condition

- acrofacial dysostosis 1, Nager type
- AFD1
- NAFD
- Nager acrofacial dysostosis
- Nager acrofacial dysostosis syndrome
- preaxial acrofacial dysostosis
- preaxial mandibulofacial dysostosis

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