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The Role of Mutations on *NAGA* Gene in Schindler Syndrome

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Abstract

Schindler syndrome is an inherited genetic disorder that mainly causes neurological problems. Schindler's syndrome is caused by a mutation in the *NAGA* gene, which is located in the long arm of chromosome 22 as 22q13.2. Amniocentesis or chorionic villus sampling can be used to screen for the disease before birth. After birth, urine tests, along with blood tests and skin biopsies can be used to diagnose Schindler disease. Genetic testing is also always an option, since different forms of Schindler disease have been mapped to the same gene on chromosome 22; though different changes (mutations) of this gene are responsible for the infantile- and adult-onset forms of the disease. The Genetic testing Registry can be used to acquire information about the genetic tests for this condition.

Keywords: Schindler syndrome • Genetic disorder • *NAGA* gene • Kanzaki disease

Introduction

Schindler disease, also known as Kanzaki disease and alpha-N-acetylgalactosaminidase deficiency is a rare disease found in humans. This lysosomal storage disorder is caused by a deficiency in the enzyme alpha-*NAGA* (alpha-N-acetylgalactosaminidase), attributable to mutations in the *NAGA* gene on chromosome 22, which leads to excessive lysosomal accumulation of glycoproteins. A deficiency of the alpha-*NAGA* enzyme leads to an accumulation of glycosphingolipids throughout the body. This accumulation of sugars gives rise to the clinical features associated with this disorder. Schindler disease is an autosomal recessive disorder, meaning that one must inherit an abnormal allele from both parents in order to have the disease.

Literature Review

Generalities of Schindler syndrome

Schindler syndrome is an inherited genetic disorder that mainly causes neurological problems. Three types of Schindler syndrome have been identified, including type I (neonatal form and most severe), type II (adult and milder form), and type III, which is the median between type I and type II [1] (Figure 1).

Clinical signs and symptoms of Schindler's syndrome

As mentioned, three types of Schindler syndrome have been identified so far. Schindler syndrome type 1, also known as neonatal form, is the most severe form of this syndrome. Babies with Schindler's syndrome type 1 appear healthy at birth, but at 8 to 15 months of age, they begin to lose learned skills (developmental regression) and delay the development of new daily life skills. As the disease progresses, people with type 1 syndrome also experience blindness and seizures, and eventually lose awareness of their surroundings and do not respond appropriately. People with Schindler's syndrome type 1 usually die in childhood [2].

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Schindler's syndrome type 2 is also known as Kanzaki disease, which is milder than type 1 syndrome and is most commonly seen in adulthood. Affected individuals may develop mild cognitive impairment and hearing loss due to inner ear abnormalities (sensory hearing loss). They may experience feelings of weakness and inability due to neurological problems that connect the brain and spinal cord to muscles and sensory cells (peripheral nervous system). Large clusters of blood vessels that form small, dark red spots on the skin (angiocratoma) are characteristic of this form of Schindler's syndrome [3].

Schindler's syndrome is type 3, intermediate between type 1 (severe) and type 2 (mild). Affected individuals may show signs and symptoms at birth, including growth retardation, seizures, large and weak heart muscle (cardiomyopathy), and large liver (hepatomegaly). In other cases, people with this type of disorder in early childhood show behavioral problems with some of the characteristics of autism spectrum disorders. Autism spectrum disorders are characterized by impaired communication and social skills [4].

Etiology of Schindler Syndrome

Schindler's syndrome is caused by a mutation in the *NAGA* gene, which is located in the long arm of chromosome 22 as 22q13.2. This gene provides the instructions for the synthesis of the enzyme alpha N-acetyl galactosaminidase. This enzyme works on lysosomes, which are the parts of cells that digest and recycle materials [5]. Within lysosomes, this enzyme helps break down complexes called glycoproteins and glycolipids, which are made up of sugar molecules attached to specific proteins and fats. In particular, alpha N-acetyl galactosaminidase helps remove a molecule called alpha N-acetyl galactosamine from the sugars in these complexes (Figure 2).

Mutations in the *NAGA* gene interfere with the ability of the enzyme alpha-N-acetyl galactosaminidase and disrupt its role in the breakdown of glycoproteins and glycolipids [6]. As a result, these substances accumulate in the lysosomes, leading the cells to malfunction, and eventually, the cells die. Cellular damage to the nervous system and other tissues and organs of the body leads to the signs and symptoms of Schindler syndrome (Figure 3).

Schindler's syndrome follows an autosomal recessive inherited pattern. Therefore, two copies of the mutated *NAGA* gene (one from the father and the other from the mother) are required to cause this syndrome, and the chance

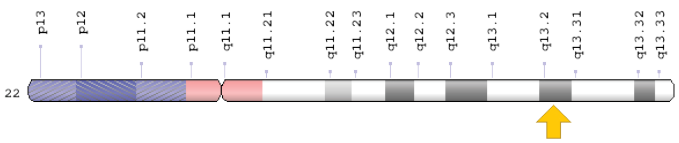

Figure 1. Schematic view of chromosome 22 where the *NAGA* gene is located in the long arm of this chromosome as 22q13.2.

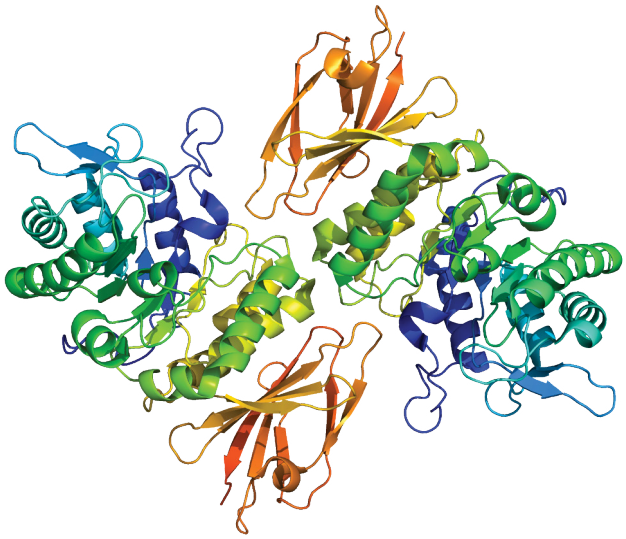

Figure 2. Schematic of the closed structure of the alpha-N-acetyl galactosaminidase enzyme.

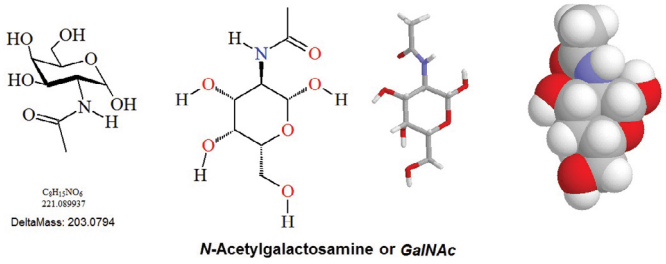

Figure 3. Schematic of the cyclic structure of the GalNAc enzyme.

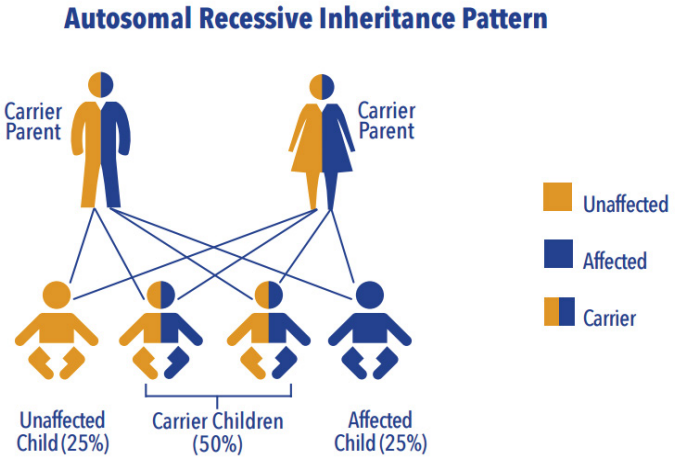

Figure 4. Schematic of the autosomal recessive inherited pattern followed by Schindler syndrome.

of having a child with this autosomal recessive syndrome is 25% for each possible pregnancy [7] (Figure 4).

Frequency of Schindler Syndrome

Schindler's syndrome is a very rare genetic disorder that has only been reported in the medical literature [8].

Diagnosis of Schindler Syndrome

Schindler's syndrome is diagnosed based on the clinical findings of some patients and some pathological and neurological tests. The most accurate way to diagnose this syndrome is to test molecular genetics for the *NAGA* gene to check for possible mutations [9].

Treatment options for Schindler's Syndrome

The treatment and management strategy for Schindler's syndrome is symptomatic and supportive. Treatment may be performed with the efforts and coordination of a team of specialists including a pediatrician, a pediatric neurologist, a physical therapist, an audiologist, a cardiologist, a liver specialist, and other health care professionals. There is no effective treatment for this syndrome and all clinical measures are taken to alleviate the suffering of the patients. Genetic counseling is also essential for all parents who want a healthy baby [10,11].

History of Schindler Syndrome

Schindler syndrome was first reported in 1988 by Dr. Detlev Schindler and then more fully described by Japanese physician and biochemist Dr. Hiro Kanzaki in 2006.

Discussion and Conclusion

Infants with Schindler disease tend to die within 4 years of birth; therefore, treatment for this form of the disease is mostly palliative. However, Type II Schindler disease, with its late onset of symptoms, is not characterized by neurological degeneration. There is no known cure for Schindler disease, but bone marrow transplants have been trialed, as they have been successful in curing other glycoprotein disorders. Babies with Schindler's syndrome type 1 appear healthy at birth, but at 8 to 15 months of age, they begin to lose learned skills (developmental regression) and delay the development of new daily life skills. Schindler's syndrome is caused by a mutation in the *NAGA* gene, which is located in the long arm of chromosome 22 as 22q13.2. This gene provides the instructions for the synthesis of the enzyme alpha N-acetyl galactosaminidase. Treatment may be performed with the efforts and coordination of a team of specialists including a pediatrician, a pediatric neurologist, a physical therapist, an audiologist, a cardiologist, a liver specialist, and other health care professionals.

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