



The Role of Genetic Mutations in Genes *MLC1* & *HEPACAM* in Van der Knaap Syndrome

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Abstract

People with this syndrome also have Leukoencephalopathy, which is a white-matter brain disorder. White matter contains nerve fibers that are covered by a fatty substance called myelin. Myelin insulates the nerve fibers and promptly transmits nerve fibers. More than half of the people with this condition have recurrent seizures (epilepsy). Despite the wide range of brain disorders, people with this condition usually have mild to moderate intellectual disabilities. The mutation in the *MLC1* gene, which is based on the long arm of chromosome number 22, is 22q13.33, leading to van der Knaap syndrome in the type 1 neoplasm. This forms 75% of all cases.

Keywords: Van der knaap syndrome; Genetics mutations; *MLC1*; *HEPACAM* genes; Astroglial cells

Overview of Van der Knaap Syndrome

The van der knaap syndrome, also known as megalino spinal leukoplasty, with subcortical cysts [1], is a genetic disorder that affects brain development and function. People with this condition usually have a large megalencephaly that is known to be at birth or during the first year of life. Megalencephaly leads to an increase in the size of the head (macrocephaly) [2,3].

Symptoms of Van der Knaap Syndrome

People with this syndrome also have Leukoencephalopathy, which is a white-matter brain disorder. White matter contains nerve fibers that are covered by a fatty substance called myelin. Myelin insulates the nerve fibers and promptly transmits nerve fibers. In the van der Knaap syndrome, myelin swells and contains full-fluid bags (vauxol). Over time, swelling decreases and myelin begins to die (atrophy). People with this condition may develop cysts in the brain; because these cysts form in the brain called the cerebral cortex, they are therefore called subcortical cysts. These cysts can grow in size and number.

Brain abnormalities in people with tubeless neoplasm disturb muscle use, resulting in motor problems. Sufferers typically experience spasticity and lack of coordination and balance of movements (ataxia). The ability to walk among those affected by this syndrome is very different. Some people lose their ability to walk in life very quickly and need wheelchairs, while other people are able to go to puberty. A minor trauma of the head can disturb most of the movements and may lead to coma. The affected person may also suffer from dystrophy, repeated movements of the organs (atheosis), difficulty in swallowing (dysphagia) and dysarthria.

More than half of the people with this condition have recurrent seizures (epilepsy). Despite the wide range of brain disorders, people with this condition usually have mild to moderate intellectual disabilities.

There are three types of van der Knaap syndrome in the nape, which are characterized by their symptoms and the genetic cause. Types 1 and 2A have different genetic causes but are almost identical in symptoms and symptoms. Types 2A and 2B have a similar genetic cause, but signs and symptoms of type 2B improve after one year. After recovery, people with type 2B usually develop cancer and may have intellectual disorientation.

Etiology of Van der Knaap Syndrome

The mutation in the *MLC1* gene, which is based on the long arm of chromosome number 22, is 22q13.33, leading to van der knaap syndrome in the type 1 neoplasm. This forms 75% of all cases [4]. The *MLC1* gene provides guidelines for protein production, which is found mainly in the brain.

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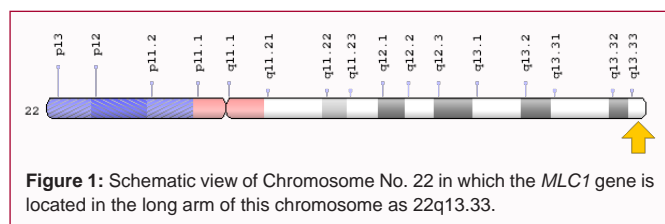


Figure 1: Schematic view of Chromosome No. 22 in which the *MLC1* gene is located in the long arm of this chromosome as 22q13.33.

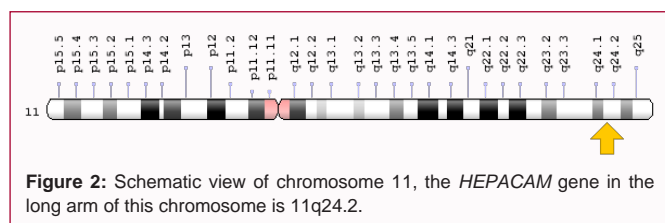


Figure 2: Schematic view of chromosome 11, the *HEPACAM* gene in the long arm of this chromosome is 11q24.2.

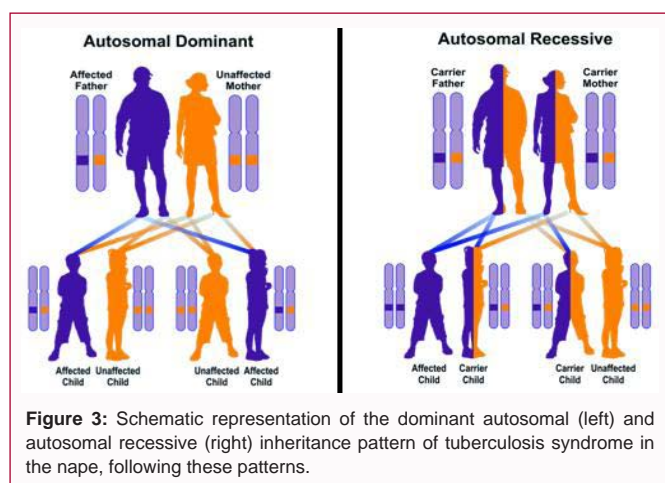


Figure 3: Schematic representation of the dominant autosomal (left) and autosomal recessive (right) inheritance pattern of tuberculoma syndrome in the nape, following these patterns.

The *MLC1* protein is found in astroglial cells, a special form of brain cells called glial cells. Glial cells maintain other neurons. The *MLC1* protein acts in a movement that connects adjacent astroglial cells to each other. The role of the *MLC1* protein in the cellular connection is unknown, but research suggests that it can control the flow of fluids in cells or the ability to connect cells to each other (cell adhesion) (Figure 1).

The mutation in the *HEPACAM* gene, which is based on 11q24.2 in the long arm of chromosome 11, leads to a tuberculoma syndrome in the type 2A and 2B neoplasms. These types together make up 20% of all cases of van der Knaap syndrome. The *HEPACAM* gene provides instructions for protein synthesis called GlialCAM [5-7]. This protein acts mainly in the brain, especially in glial cells. GlialCAM binds to other GlialCAM proteins or the *MLC1* protein and directs them to cellular connections. The performance of GlialCAM in cellular connection is not clear.

Most mutations in the *MLC1* gene change the structure of the *MLC1* protein or prevent the production of this protein, leading to a lack of *MLC1* protein in astroglial cell transplantation. *HEPACAM* gene mutations lead to a protein that is unable to transfer the GlialCAM and *MLC1* proteins to the cells. It is still unknown how the lack of *MLC1* or GlialCAM in cellular interactions in the brain causes impairment in brain growth and function and causes symptoms of van der Knaap syndrome.

Approximately 5% of people with van der Knaap syndrome have not identified the mutation in the *MLC1* gene or *HEPACAM*. In these

people, the cause of the disorder is unknown (Figure 2).

All cases of van der Knaap syndrome in the nap after mutations in the *MLC1* gene (type 1) and some cases of mutations in the *HEPACAM* gene (type 2A) follow the autosomal recessive pattern of heredity. Therefore, to create these types of van der Knaap syndrome in nephews, two versions of the mutated genes *MLC1* and *HEPACAM* (one of the father and the other of the mother) are needed and the chance of having a child with this syndrome in autosomal recessive state, for each pregnancy the probability is 25%.

Van der Knaap syndrome 2B follows the dominant autosomal pattern. Therefore, to produce this type of syndrome, a gene mutation of *HEPACAM* (parent or parent) is required and the chance of having a child with this syndrome in the dominant autosomal state is 50% for each possible pregnancy. Most cases of type 2B are caused by new mutations (*de novo*) in the *HEPACAM* gene that occurs in the formation of reproductive cells (eggs or sperm) or in the embryo's early growth. These occur in people who do not have a history of family dysfunction.

Frequency of Van der Knaap Syndrome

Van der Knaap syndrome is a rare genetic disorder whose frequency is not known in the world. So far, more than 150 cases of this syndrome have been reported from around the world in medical literature (Figure 3).

Diagnosis of Van der Knaap Syndrome

Van der Knaap syndrome is detected based on the clinical and clinical findings of the patients and some pathologic and neurological tests. The most accurate method for detecting this syndrome is the molecular genetic testing for the *MLC1* and *HEPACAM* genes to investigate the presence of possible mutations.

Treatment Routes in Van der Knaap Syndrome

The strategy of treatment and management of this syndrome is symptomatic and supportive. Treatment may be done by a team of experts, including a neurologist, orthopedic specialist, physician specialist physician, and other health care professionals. There is no

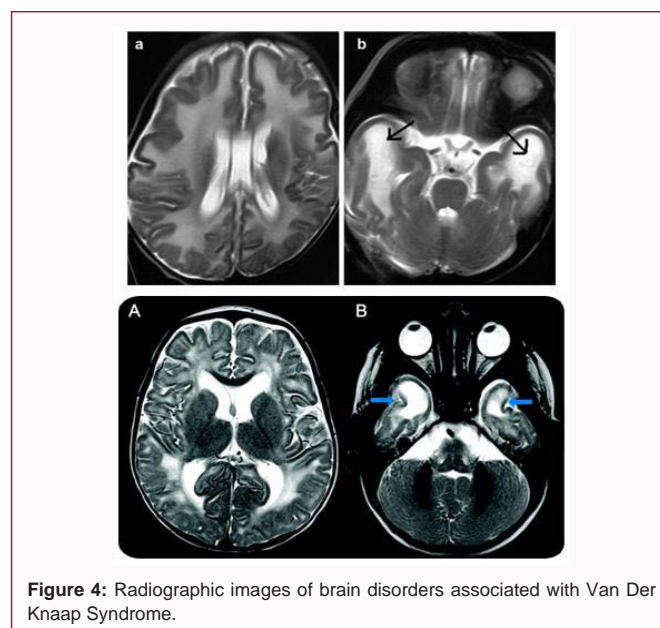


Figure 4: Radiographic images of brain disorders associated with Van Der Knaap Syndrome.

reliable treatment for this syndrome, and all clinical measures are designed to reduce the suffering of the sufferers. Genetic counseling is also needed for all parents who want a healthy baby (Figure 4).

Discussion and Conclusion

Brain abnormalities in people with tubeless neoplasm disturb muscle use, resulting in motor problems. Sufferers typically experience spasticity and lack of coordination and balance of movements (ataxia). The ability to walk among those affected by this syndrome is very different. Some people lose their ability to walk in life very quickly and need wheelchairs, while other people are able to go to puberty. A minor trauma of the head can disturb most of the movements and may lead to coma. The affected person may also suffer from dystrophy, repeated movements of the organs (atheosis), difficulty in swallowing (dysphagia) and dysarthria. The mutation in the *HEPACAM* gene, which is based on 11q24.2 in the long arm of chromosome 11, leads to a tuberculosis syndrome in the type 2A and 2B neoplasms. These types together make up 20% of all cases of van der Knaap syndrome. The mutation in the *MLC1* gene, which is based on the long arm of chromosome number 22, is 22q13.33, leading to van der Knaap syndrome in the type 1 neoplasm. There is no reliable treatment for this syndrome, and all clinical measures are designed to reduce the suffering of the sufferers.

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