

The Role of Genetics Mutations in Genes EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5 in Induce Leukoencephalopathy with Vanishing White Matter Syndrome

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Abstract

LVWM syndrome is a progressive genetic disorder that affects the brain and spinal cord (central nervous system). In most cases, people with LVWM syndrome do not reveal any symptoms of birth defects. Children with this syndrome delay the development of motor skills such as sitting and walking. The LVWM syndrome is based on the mutation of the EIF2B1 gene, which is based on 12q24.31 in the long arm of chromosome 12, and the EIF2B2 gene, which is located in the long arm of Chromosome 14, which is 14q24.3, has the EIF2B3 gene in the short arm of chromosome 1 of 1p34.1, the EIF2B4 gene, which is based on the short arm of chromosome number 2, is positioned as 2p23.3, and the EIF2B5 gene, which is based on the long arm of chromosome number 3, is based on 3q27.1.

Keywords: LVWM syndrome, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5 genes, Brain disorders.

GENERALIZED LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

LVWM syndrome is a progressive genetic disorder that affects the brain and spinal cord (central nervous

system). This impairment results in the loss of white matter in the central nervous system, which includes myelin-bound neural fibers. Myelin is a white, fatty substance that insulates and protects nerves¹.

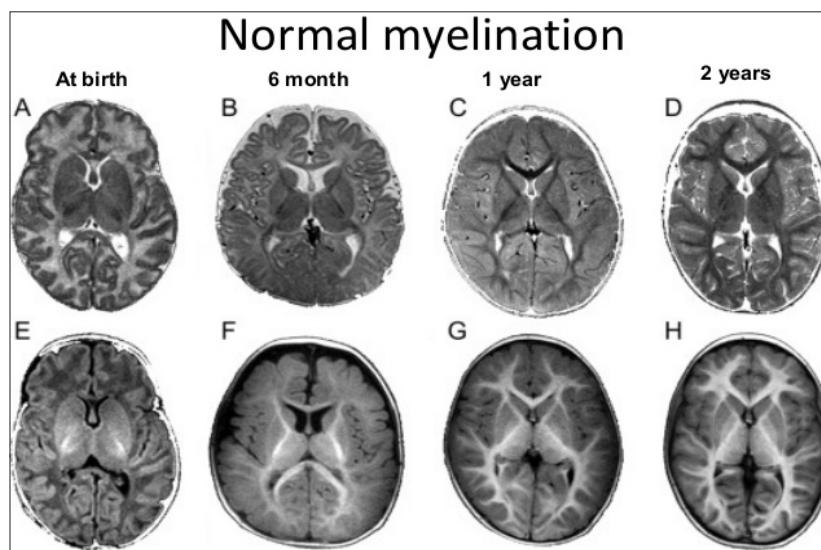


Fig 1. Radiological picture of normal human brain malignancy at different degrees of age.

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SYMPTOMS OF LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

In most cases, people with LVWM syndrome do not reveal any symptoms of birth defects. Children with this syndrome delay the development of motor skills such as sitting and walking. Early in childhood, most

people develop motor symptoms such as abnormal muscle stiffness (spasticity) and lack of coordination of movements (ataxia). In addition, in some cases severe mental impairment may also be present. Some women with LVWM syndrome may have an abnormal development of ovaries (ovarian destruction)¹.

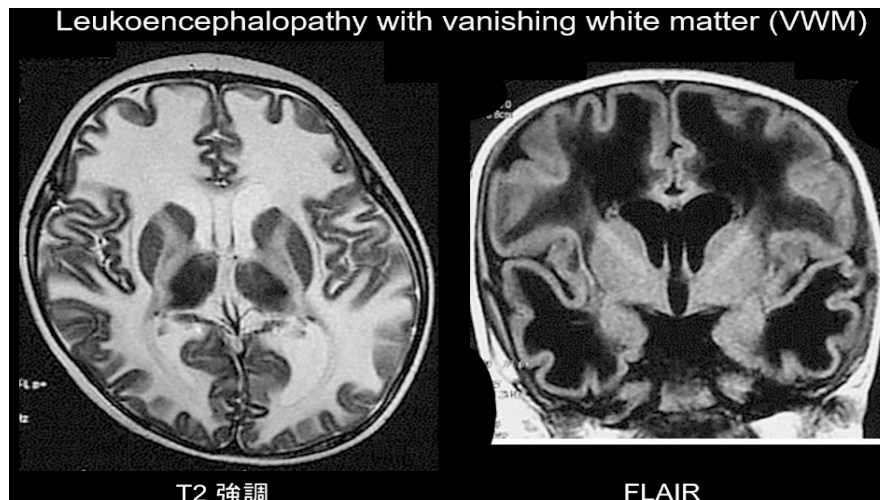


Fig 2. Radiological image of the human brain with LVWM syndrome.

It is worth noting that the most common symptoms of LVWM syndrome begin in childhood, but some severe forms of the syndrome also appear at birth. Mild forms of the syndrome begin in adolescence or adolescence, and behavioral and psychological problems are usually the first sign of the syndrome. Some women with mild LVWM syndrome in their adolescence show ovarian dysfunction and this disorder is known as ovarian lactic dysfunction¹.

ETIOLOGY OF LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

The LVWM syndrome is based on the mutation of the EIF2B1 gene, which is based on 12q24.31 in the long arm of chromosome 12, and the EIF2B2 gene, which is located in the long arm of Chromosome 14, which

is 14q24.3, has the EIF2B3 gene in the short arm of chromosome 1 of 1p34.1, the EIF2B4 gene, which is based on the short arm of chromosome number 2, is positioned as 2p23.3, and the EIF2B5 gene, which is based on the long arm of chromosome number 3, is based on 3q27.1. All these genes provide instructions for the synthesis of 5 protein subunits called eIF2B. The eIF2B protein helps regulate the total synthesis of protein in the cell by interacting with another protein called eIF2. The eIF2 protein is referred to as a primer factor, since it initially involves protein synthesis. Adequate regulation of protein synthesis is necessary to ensure that the correct level of protein for the cell is available to cope with changing conditions. For example, cells need to synthesize proteins much faster, whether they are multiplying, or at rest¹.

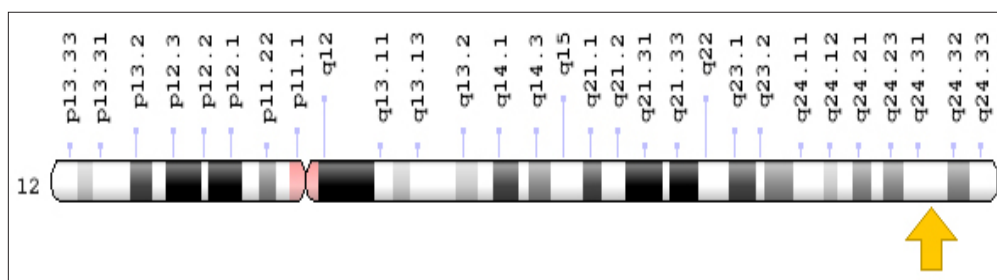


Fig 3. Schematic view of chromosome 12, whose EIF2B1 gene is located in the long arm of this chromosome 12q24.31.

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The mutation in all of the five genes results in the loss of eIF2B protein function in a variety of ways, of which about 65% of these mutations occur in the EIF2B5 gene. For example, these mutations may interfere with

the ability of one of the eIF2B protein subunits to form a single complex, or interfere with the eIF2B protein with the eIF2 protein, in which case the initiator factor will not function properly².

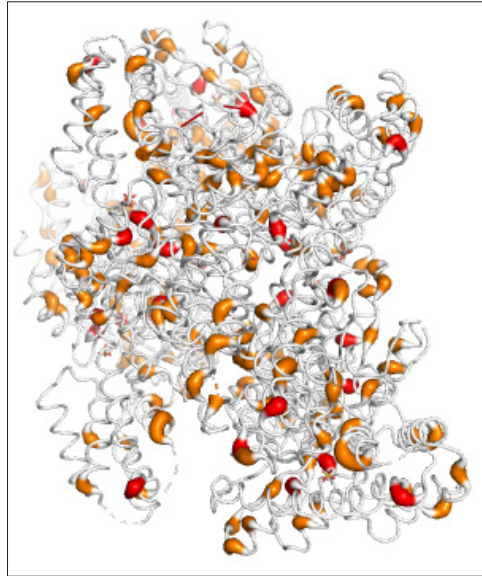


Fig 4. A schematic of the EIF2B1 protein packet structure.

Losing a portion of the eIF2B function will make the body's ability to regulate protein synthesis and counteract the changes in conditions and stress, making it more difficult. Researchers believe that

white matter cells (myelin) may be particularly affected by stress-induced abnormal response and produce signs and symptoms of LVWM syndrome³.

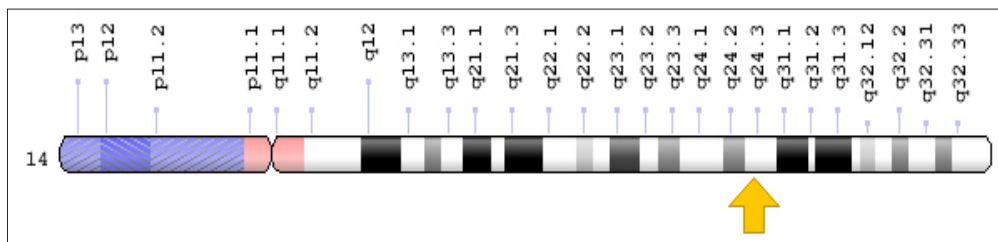


Fig 5. Schematic view of chromosome number 14, in which the EIF2B2 gene is located in the long arm of this chromosome as 14q24.3.

LVWM syndrome follows an autosomal recessive hereditary pattern. Therefore, in order to create this syndrome, two versions of the mutated genes are needed: EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5

(one parent and one mother), and the chance of having a child with this syndrome in an autosomal recessive state, for each pregnancy the probability is 25%⁴.

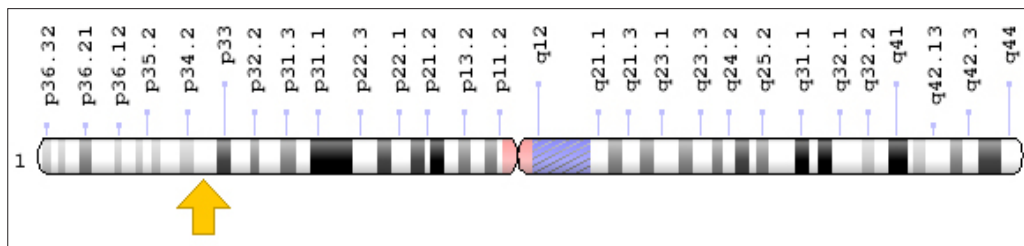


Fig 6. Schematic view of chromosome number 1, in which the EIF2B3 gene is based on the short arm of this chromosome as 1p34.1.

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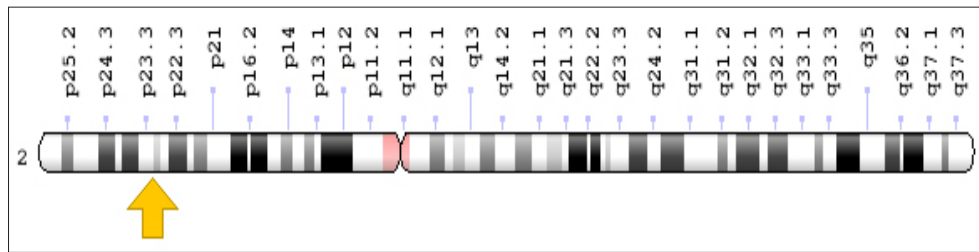


Fig 7. Schematic view of chromosome number 2, in which the EIF2B4 gene is based on the short arm of this chromosome 2p23.3.

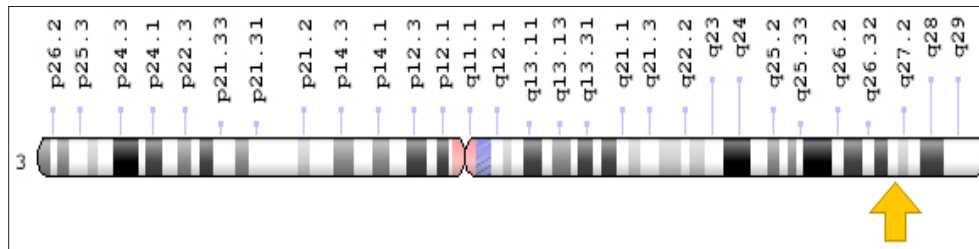


Fig 8. Schematic view of chromosome number 3 where the EIF2B5 gene is located in the long arm of this chromosome at 3q27.1.

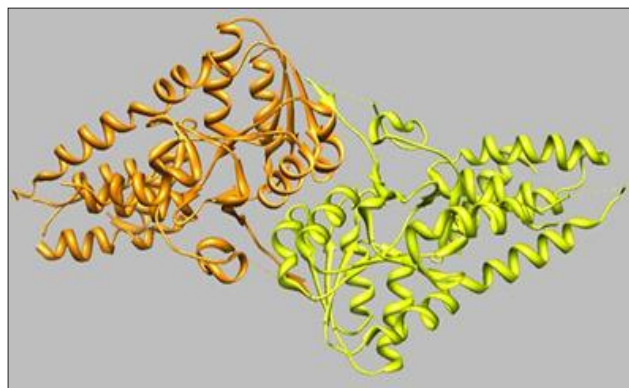


Fig 9. Schematic of the eIF2B protein packet structure.

FREQUENCY OF LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

LVWM syndrome is a genetic disorder whose frequency is not known in the world. Although this syndrome is a rare disorder, it appears to be one of the most common hereditary diseases affecting the white matter (myelin) in the brain⁵.

DIAGNOSIS OF LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

LVWM syndrome is diagnosed based on the clinical and clinical findings of the patients and some pathologic and neurological tests. The most accurate diagnostic method for this syndrome is the molecular genetic testing for EIF2B1, EIF2B2, EIF2B3, EIF2B3,

EIF2B4, and EIF2B5 genes to investigate the presence of possible mutations⁶.

TREATMENT PATHWAYS FOR OF LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER SYNDROME (LVWM)

The LVWM syndrome treatment and management strategy is symptomatic and supportive. Treatment may be done by a team of experts, including a neurologist, orthopedic specialist, physical medicine specialist, gynecologist, reproductive biology specialist, psychiatrist, and other health care professionals. There is no standard treatment for this syndrome and all clinical measures are needed to reduce the suffering of the infected person. Genetic counseling is also important for all parents who want a healthy baby^{7,8,9,10,11,12}.

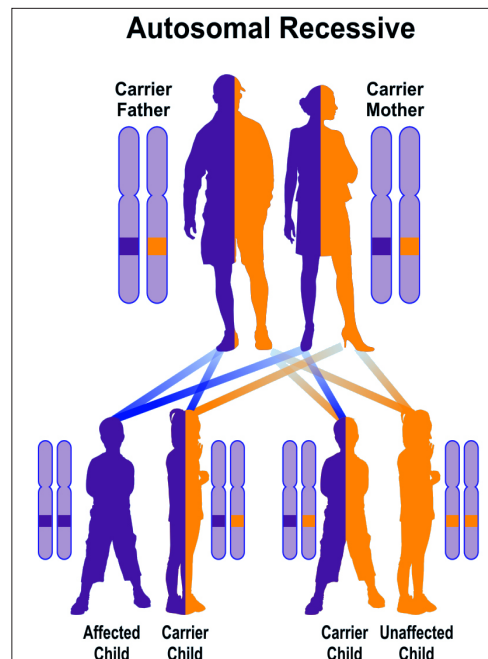


Fig 10. Schematic view of an autosomal recessive hereditary pattern that also follows the LVWM syndrome.

DISCUSSION AND CONCLUSION

LVWM syndrome is a progressive genetic disorder that affects the brain and spinal cord (central nervous system). In most cases, people with LVWM syndrome do not reveal any symptoms of birth defects. Children with this syndrome delay the development of motor skills such as sitting and walking. The LVWM syndrome is based on the mutation of the EIF2B1 gene, which is based on 12q24.31 in the long arm of chromosome 12, and the EIF2B2 gene, which is located in the long arm of Chromosome 14, which is 14q24.3, has the EIF2B3 gene in the short arm of chromosome 1 of 1p34.1, the EIF2B4 gene, which is based on the short arm of chromosome number 2, is positioned as 2p23.3, and the EIF2B5 gene, which is based on the long arm of chromosome number 3, is based on 3q27.1. There is no standard treatment for this syndrome and all clinical measures are needed to reduce the suffering of the infected person.

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