MBD5-Associated Neurodevelopmental Disorder

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MBD5-associated neurodevelopmental disorder (MAND) is a condition that affects neurological and physical development.

Keywords: genetic conditions

1. Introduction

Children with MAND have mild to severe intellectual disability and developmental delay. They often have poor coordination and do not walk until age 2 or 3. Their walking style (gait) is often unbalanced and wide-based. Language skills, both the production of speech and the ability to understand speech, are very limited in affected individuals. By age 2, most children with MAND develop recurring seizures (epilepsy). Most affected children have feeding problems due to weak muscle tone (hypotonia). Constipation also frequently occurs.

Sleep problems are common in MAND and include night terrors, waking frequently during the night, and waking early in the morning. As a result, many affected individuals are extremely tired during the day due to lack of sleep and poor-quality sleep. Most people with MAND have behavior problems similar to autism spectrum disorder, a developmental condition that affects communication and social interaction. They have a short attention span; perform repetitive hand movements (stereotypies), such as clapping, hand licking, and hand sucking; and grind their teeth.

People with MAND tend to have subtle facial features, including a broad forehead, thick and highly arched eyebrows, abnormalities of the outer ear, a short nose, a wide or depressed nasal bridge, downturned corners of the mouth, an upper lip that points outward (called a tented lip), and a full lower lip. Some affected individuals have mild skeletal abnormalities including small hands and feet, short fingers (brachydactyly), curved pinky fingers (fifth-finger clinodactyly), or a wide gap between the first and second toes (known as a sandal gap). Rarely, individuals with MAND have heart abnormalities.

2. Frequency

MAND is thought to be a rare disorder, although its prevalence is unknown. More than 100 affected individuals have been described in the scientific literature.

3. Causes

MAND is most often caused by a loss (deletion) or gain (duplication) of genetic material in a particular region of chromosome 2. These changes are also known either as 2q23.1 microdeletions or 2q23.1 microduplications. The missing or extra region varies in length from a few thousand to a few million DNA building blocks (base pairs) but always includes the *MBD5* gene. Less frequently, MAND is caused by mutations that affect only the *MBD5* gene. Because mutations in the *MBD5* gene and changes on chromosome 2 that involve this gene both cause MAND, researchers believe that *MBD5* gene changes underlie most of the signs and symptoms of the condition. Neurological features of the condition generally do not differ based on the genetic cause, although they can vary between individuals.

The *MBD5* gene provides instructions for a protein that likely regulates the activity (expression) of genes, controlling the production of proteins that are involved in neurological functions such as learning, memory, and behavior. The MBD5 protein also seems to play a role in the growth and division (proliferation) and maturation (differentiation) of various types of cells.

All of the genetic changes associated with MAND lead to an abnormal amount of MBD5 protein. *MBD5* gene mutations and deletions prevent one copy of the *MBD5* gene in each cell from producing any functional protein, which reduces the total amount of this protein in cells. A duplication leads to an increased amount of MBD5 protein. It is likely that any

changes in MBD5 protein levels impair its regulation of gene expression, leading to the uncontrolled production of certain proteins. Proteins that play a role in neurological functions are particularly affected, which helps explain why MAND impacts brain development and behavior. An increase or decrease in MBD5 protein disrupts gene expression that is normally well-controlled by this protein, which is likely why duplications and deletions involving the *MBD5* gene lead to the same signs and symptoms. The cause of the skeletal abnormalities and other non-neurological features of MAND is unclear. It is also unknown whether the loss or gain of other genes in chromosome 2 deletions or duplications contributes to the variable features of MAND.

3.1. The gene and chromosome associated with MBD5-associated neurodevelopmental disorder

- MBD5
- chromosome 2

4. Inheritance

MAND is considered an autosomal dominant condition because one copy of the altered chromosome 2 or *MBD5* gene in each cell is sufficient to cause the disorder. Most cases of MAND are not inherited but occur as random events during the formation of reproductive cells (eggs or sperm) in a parent of an affected individual. These cases occur in people with no history of the disorder in their family. In a small percentage of cases, people with MAND inherit the altered chromosome or gene from a parent with the condition.

5. Other Names for This Condition

- 2q23.1 microdeletion syndrome
- 2q23.1 microduplication syndrome
- MAND
- MBD5 haploinsufficiency

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