Mowat-Wilson Syndrome

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Mowat-Wilson Syndrome

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Abstract

Mowat-Wilson syndrome (MWS) is a rare genetic disorder that causes systemic deficiencies and abnormalities during development. Common presentations of this disorder include Hirschsprung disease (HSCR), intellectual disability, delayed development, distinctive facial features, microcephaly, epilepsy, and heart defects. MWS is likely underdiagnosed, especially in patients who do not display HSCR. Prognosis for MWS depends on the severity and presence of congenital anomalies, and few patients have been reported to live into early adulthood. Therapy may also be required to control seizures, while occupational and speech therapy may help with delayed psychomotor development which is prevalent in all patients. MWS is caused by a pathogenic variant of the ZEB2 gene that follows an autosomal dominant pattern of inheritance. A mutation of the ZEB2 gene suggests that the myelination process may represent a potential therapeutic target. Current treatments focus on symptoms; however, a potential therapeutic target may focus on the effects the mutation has on gene expression.

Facial Features: Narrow triangular chin, deep set large eyes, broad nasal bridge, saddle nose, rounded nasal tip, open mouth, full or everted lower lip, posteriorly rotated ears, and large uplifted ear lobes with a central depression.

Nervous System: Seizures, intellectual disability, dysphagia

Musculoskeletal System: Microcephaly, short stature, slender body type, calcaneovalgus deformity.

Cardiovascular System: Congenital heart defects: abnormalities in pulmonary arteries and/or valves

Genitourinary System: Renal abnormalities, in male's hypospadias and cryptorchidism.

Digestive System: Hirschsprung disease (HSCR) and constipation

Brain Structure Deformities: Cerebral atrophy, underdeveloped hippocampus, and deformities of the temporal and frontal lobes.

MWS is a genetic mutation affecting the ZEB2 gene located on chromosome 2. Mutations range from missense to deletions or insertions. MWS follows an autosomal dominant pattern of inheritance, one abnormal gene will cause this syndrome. Occurring de novo, neither parent is seen to have any mutation.

Etiology

MWS is a genetic disorder caused by mutations in the ZEB2 gene. The ZEB2 gene is located on chromosome 2 and is involved in the development of multiple organ systems, including the nervous and musculoskeletal systems. The gene is responsible for producing a protein that regulates gene expression, and mutations in this gene can lead to a variety of physical and developmental abnormalities.

Clinical Description

Common Clinical Features

- Microcephaly
- Congenital Heart Defects
- Micrognathia
- Hearing Disorders
- Hirschsprung Disease
- Growth Retardation
- CNS
- Developmental delays
- Autoimmune disorders
- Hypothyroidism
- Diabetes mellitus
- Mental retardation
- Microcephaly
- Hypotonia
- Epilepsy
- Seizures
- Dystonia
- Dysphagia
- Dysarthria
- Intestinal dysmotility
- Neurologic anomalies
- Other congenital anomalies

Figure 2. Common Clinical Features

Prognosis/Management

Prognosis depending on severity of congenital anomalies
No cure, only treatments for symptoms
Surgery/physical therapy for somatic symptoms (including heart, intestinal, and vascular defects)
Speech therapy and Supportive Care
Pharmaceuticals for constipation, GERD, and seizures

Unresolved Questions

- Other genes are involved in the agenesis of corpus callosum?
- Cause of de novo mutations?
- How are symptoms connected to deletion/mutations of ZEB2?
- Comprehensive picture of ZEB2 regulatory elements.

References