Walker-Warburg Syndrome

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Contributor: Bruce Ren

Walker-Warburg syndrome is an inherited disorder that affects development of the muscles, brain, and eyes. It is the most severe of a group of genetic conditions known as congenital muscular dystrophies, which cause muscle weakness and wasting (atrophy) beginning very early in life. The signs and symptoms of Walker-Warburg syndrome are present at birth or in early infancy. Because of the severity of the problems caused by Walker-Warburg syndrome, most affected individuals do not survive past age 3.

Keywords: genetic conditions

1. Introduction

Walker-Warburg syndrome affects the skeletal muscles, which are muscles the body uses for movement. Affected babies have weak muscle tone (hypotonia) and are sometimes described as "floppy." The muscle weakness worsens over time.

Walker-Warburg syndrome also affects the brain; individuals with this condition typically have a brain abnormality called cobblestone lissencephaly, in which the surface of the brain lacks the normal folds and grooves and instead develops a bumpy, irregular appearance (like that of cobblestones). These individuals may also have a buildup of fluid in the brain (hydrocephalus) or abnormalities of certain parts of the brain, including a region called the cerebellum and the part of the brain that connects to the spinal cord (the brainstem). These changes in the structure of the brain lead to significantly delayed development and intellectual disability. Some individuals with Walker-Warburg syndrome experience seizures.

Eye abnormalities are also characteristic of Walker-Warburg syndrome. These can include unusually small eyeballs (microphthalmia), enlarged eyeballs caused by increased pressure in the eyes (buphthalmos), clouding of the lenses of the eyes (cataracts), and problems with the nerve that relays visual information from the eyes to the brain (the optic nerve). These eye problems lead to vision impairment in affected individuals.

2. Frequency

Walker-Warburg syndrome is estimated to affect 1 in 60,500 newborns worldwide.

3. Causes

Walker-Warburg syndrome can be caused by mutations in at least a dozen genes. The most commonly mutated genes were discovered first, including *POMT1*, *POMT2*, *CRPPA*, *FKTN*, *FKRP*, and *LARGE1*. Mutations in these genes are found in about half of individuals with Walker-Warburg syndrome. Other genes, some of which have not been identified, are also involved in development of this condition.

The proteins produced from the genes listed above and others involved in Walker-Warburg syndrome modify a protein called alpha (α)-dystroglycan; this modification, called glycosylation, is required for α-dystroglycan to function. The α-dystroglycan protein helps anchor the structural framework inside each cell (cytoskeleton) to the lattice of proteins and other molecules outside the cell (extracellular matrix). In skeletal muscles, the anchoring function of glycosylated α-dystroglycan helps stabilize and protect muscle fibers. In the brain, it helps direct the movement (migration) of nerve cells (neurons) during early development.

Mutations in the genes associated with Walker-Warburg syndrome prevent glycosylation of α-dystroglycan, which disrupts its normal function. Without functional α-dystroglycan to stabilize muscle cells, muscle fibers become damaged as they repeatedly contract and relax with use. The damaged fibers weaken and die over time, leading to progressive weakness of the skeletal muscles.

Defective α-dystroglycan also affects the migration of neurons during the early development of the brain. Instead of stopping when they reach their intended destinations, some neurons migrate past the surface of the brain into the fluid-filled space that surrounds it. Researchers believe that this problem with neuronal migration causes cobblestone lissencephaly in children with Walker-Warburg syndrome. Less is known about the effects of the gene mutations in other parts of the body, including the eyes.

Because Walker-Warburg syndrome involves a malfunction of α-dystroglycan, this condition is classified as a dystroglycanopathy.

3.1 The genes associated with Walker-Warburg syndrome

- CRPPA
- FKRP
- FKTN
- LARGE1
- POMT1
- POMT2

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- cerebroocular dysplasia-muscular dystrophy syndrome
- Chemke syndrome
- COD-MD syndrome
- HARD syndrome
- hydrocephalus, agyria, and retinal dysplasia
- MDDGA
- muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A
- muscular dystrophy-dystroglycanopathy [with brain and eye anomalies], type A
- Walker-Warburg congenital muscular dystrophy

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