RAB18 deficiency

Description

RAB18 deficiency causes two conditions with similar signs and symptoms that primarily affect the eyes, brain, and reproductive system. These two conditions, called Warburg micro syndrome and Martsolf syndrome, were once thought to be distinct disorders but are now considered to be part of the same disease spectrum because of their similar features and shared genetic cause.

Warburg micro syndrome is the more severe condition. Individuals with this condition have several eye problems from birth, including clouding of the lenses of the eyes (cataracts), abnormally small eyes (microphthalmia), and small corneas (microcornea). The lens is a structure at the front of the eye that helps focus light, and the cornea is the outer covering of the eye. In addition, the pupils of the eyes may be abnormally small (constricted), and they may not enlarge (dilate) in low light. Individuals with Warburg micro syndrome also have degeneration of the nerves that carry visual information from the eyes to the brain (optic atrophy). The eye problems impair vision in affected individuals.

People with Warburg micro syndrome have severe intellectual disability and other neurological features due to problems with growth and development of the brain. Affected individuals have delayed development and may never be able to sit, stand, walk, or speak. They usually have weak muscle tone (hypotonia) in infancy. By early childhood, they develop muscle stiffness (spasticity) and joint deformities (contractures) that restrict movement in the legs. The muscle problems worsen (progress) to include the arms and lead to paralysis of all four limbs (spastic quadriplegia). Eventually, breathing may be impaired. The brain abnormalities can contribute to vision problems (cortical visual impairment). Individuals with Warburg micro syndrome may also have recurrent seizures (epilepsy).

Some people with Warburg micro syndrome have reduced production of the hormones that direct sexual development (hypogonadotropic hypogonadism). The shortage of these hormones impairs normal development of reproductive organs. Affected males may have a small penis (micropenis) or undescended testes (cryptorchidism). Affected females may have underdeveloped internal genital folds (labia minora) or a small clitoris or vaginal opening (introitus).

Martsolf syndrome affects the same body systems as Warburg micro syndrome but is usually less severe. Individuals with Martsolf syndrome have cataracts, microphthalmia,

and small pupils. They have milder optic atrophy and cortical visual impairment than people with Warburg micro syndrome. Intellectual disability is mild to moderate in people with Martsolf syndrome. While language and motor skills, such as sitting and walking, are delayed, affected individuals usually acquire them. Hypotonia is common in infants with Martsolf syndrome, although spasticity worsens more slowly than in individuals with Warburg micro syndrome, and it usually affects only the legs and feet. Hypogonadotropic hypogonadism can also occur in individuals with Martsolf syndrome.

Neither Warburg micro syndrome nor Martsolf syndrome affect the life expectancy of affected individuals.

Frequency

RAB18 deficiency is rare; its exact prevalence is unknown. Warburg micro syndrome is more common than Martsolf syndrome.

Causes

RAB18 deficiency is caused by mutations in the *RAB3GAP1*, *RAB3GAP2*, *RAB18*, or *TBC1D20* gene. *RAB3GAP1* gene mutations are the most common cause of Warburg micro syndrome, although mutations in any of the genes can result in this condition. Mutations that cause Warburg micro syndrome completely eliminate the production or function of the protein produced from the gene. Martsolf syndrome is caused by mutations in the *RAB3GAP2* gene or rarely the *RAB3GAP1* gene. Mutations that result in Martsolf syndrome reduce but do not eliminate protein function.

The *RAB18* gene provides instructions for making the RAB18 protein. The *RAB3GAP1*, *RAB3GAP2*, and *TBC1D20* genes provide instructions for making proteins that regulate the activity of this protein. The RAB3GAP1 and RAB3GAP2 proteins interact to form a complex that turns on RAB18. In contrast, the TBC1D20 protein turns off RAB18.

When turned on, RAB18 regulates the movement of substances between compartments in cells and the storage and release of fats (lipids) by structures called lipid droplets. The protein also appears to play a role in a process called autophagy, which helps clear unneeded materials from cells.

Mutations in the *RAB18*, *RAB3GAP1*, *RAB3GAP2*, or *TBC1D20* gene are thought to disrupt RAB18 function. However, it is unclear why an absence or shortage (deficiency) of normal RAB18 activity leads to eye problems, brain abnormalities, and other features of Warburg micro syndrome or Martsolf syndrome.

Learn more about the genes associated with RAB18 deficiency

- RAB18
- RAB3GAP1
- RAB3GAP2
- TBC1D20

Inheritance

RAB18 deficiency 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.

Other Names for This Condition

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Martsolf syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0796037/)
- Genetic Testing Registry: Warburg micro syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5442005/)

Genetic and Rare Diseases Information Center

- Cataract-intellectual disability-hypogonadism syndrome (https://rarediseases.info.nih.gov/diseases/3406/index)
- Micro syndrome (https://rarediseases.info.nih.gov/diseases/5534/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- MARTSOLF SYNDROME 1; MARTS1 (https://omim.org/entry/212720)
- WARBURG MICRO SYNDROME 1; WARBM1 (https://omim.org/entry/600118)
- WARBURG MICRO SYNDROME 3; WARBM3 (https://omim.org/entry/614222)
- WARBURG MICRO SYNDROME 2; WARBM2 (https://omim.org/entry/614225)
- WARBURG MICRO SYNDROME 4; WARBM4 (https://omim.org/entry/615663)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28RAB18+deficiency%5BTIAB%5D%29+OR+%28Warburg+micro+syndrome%5BTIAB%5D%29+OR+%28Martsolf+syndrome%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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