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My46 Trait Profile

Pelizaeus Merzbacher disease

Other Names: PLP1-related disorders

Pelizaeus-Merzbacher disease is a rare genetic condition that affects the white matter of the brain. It is caused by mutations in the PLP1 gene and makes the proteolipid protein 1 and DM20 proteins, both of which are found in myelin (i.e., the insulating cover around nerve cells).

Characteristics of Pelizaeus Merzbacher disease

Pelizaeus-Merzbacher disease (PMD) is a rare X-linked genetic condition, primarily affecting males, which results in changes in the white matter of the brain. As such, it falls into a class of white matter disorders called leukodystrophies. The classic form of PMD is characterized by back and forth movement of the eyes (nystagmus), low muscle tone (hypotonia) later developing into increased muscle tone (spasticity) with partial paralysis (paraparesis), tremors of the head and neck (titubation), uncoordinated movements (ataxia), and intellectual disability. Symptoms become apparent in the first months or years of life. Affected males may be able to walk with assisted devices, but this ability is often lost in late childhood or adolescence due to increasing spasticity. Most individuals with PMD are able to develop language and speech.

The classic form of the condition is typically slowly progressive with some individuals surviving through their 60s. However, the severity of PMD varies. The most severe form is called connatal PMD; symptoms are present at birth and death occurs usually by age 30, sometimes much earlier. The mildest form is called uncomplicated spastic paraplegia (SPG2). Males with SPG2 begin showing symptoms from 5 years of age to as late as their 20s-30s. Symptoms include a jerky (spastic) gait and problems with bladder control. However, affected individuals are able to walk and talk, and have normal cognition as well as a normal lifespan. Other forms of PMD, with symptoms falling between the connatal, classic, and SPG2 types, have been described. As such, it is better to think of the range of symptoms as part of a continuum rather than as separate conditions. Some people refer to this group of conditions collectively as PLP1-related disorders.

Diagnosis/Testing

Most individuals with PMD have a change or mutation in a gene called PLP1 that makes the proteolipid protein-1 and the DM20 protein, both of which are major components of central nervous system myelin.

About 50-70% of those with PMD have a duplication (extra copy) of the PLP1 gene and areas surrounding the gene. Rarely, an affected person will have a triplication (two extra copies) of the gene. The size of the duplication can vary from family to family and this can contribute to the variability in symptoms between families. The remainder of those with PMD/PLP1-related disorders have mutations that change the make-up of the protein (missense mutations), the length of the protein (nonsense mutations), or lead to the absence of protein (null mutations). To some extent, the type of mutation provides information about the expected severity of symptoms, but not completely. Genetic testing is needed to confirm a suspected clinical diagnosis of a PLP1-related disorder. The testing method used to look for gene duplications/triplications/whole gene deletions is different than the method used to look for small (point) mutations. Testing strategy should be guided in part by symptoms and by whether a mutation has been previously identified in the family.

Management/Surveillance

Management of PMD/PLP1-related disorders often includes medical care by neurologists, geneticists, physical therapists, orthopedic doctors, pulmonologists, and education specialists. Physical therapy and medication therapy can help manage spasticity; however sometimes surgery is needed to release joint contractures. Scoliosis is a concern; proper seating and physical therapy can help. Developmental assessments and early intervention are warranted in those whose symptoms include developmental delay.

Mode of inheritance

PMD is inherited in an X-linked recessive pattern. This means that in females, both copies of the PLP1 gene (i.e., one on each X chromosome) must have a mutation, whereas in males, only one copy of the PLP1 gene must have a mutation to be affected. A female with a mutation in one copy of the PLP1 gene is said to be a "carrier," and is typically not affected. However, a small proportion of carrier females have some signs of the condition; their symptoms are usually much milder than those of their affected male relative. Interestingly, the chance of having symptoms is higher in families with a mild mutation than in families with a mutation causing a severe form of the condition.

Another way in which a female may have symptoms is through skewed X-inactivation. Normally, one of a woman's two X chromosomes is randomly turned off in each cell of the body. In rare cases, skewed X-inactivation occurs causing the X chromosome with the PLP1 mutation to be always turned on. If this occurs, then a woman can have a PLP1-related disorder.

Risk to family members

The mutation causing the PLP1-related disorder may be inherited from the mother or it can be the result of a new (de novo) mutation in an affected child. If a mother is a carrier, each daughter has a 1 in 2 (50%) chance of being a carrier, and each son has a 1 in 2 (50%) chance of being affected.

Special considerations

A PMD-like condition, called hypomyelinating Pelizaeus-Merzbacher-like disease or PMLD1, has been described and is caused by mutations in a gene called GJC2. Unlike PMD, PMLD1 is inherited in an autosomal recessive pattern. As such, both males and females can be affected.

Resources

PMD Foundation
http://www.pmdfoundation.org/
Genetics Home Reference: Pelizaeus-Merzbacher disease
http://ghr.nlm.nih.gov/condition/pelizaeus-merzbacher-disease
United Leukodystrophy Foundation: Pelizaeus-Merzbacher
http://ulf.org/pelizaeus-merzbacher

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