LARGE1 gene

LARGE xylosyl- and glucuronyltransferase 1

Normal Function

The protein produced from the *LARGE1* gene is found in a specialized structure within cells called the Golgi apparatus, where newly produced proteins are modified. The LARGE1 protein is involved in a process called glycosylation. Through this chemical process, sugar molecules are added to certain proteins. In particular, the LARGE1 protein adds chains of sugar molecules composed of xylose and glucuronic acid to a protein called alpha (α)-dystroglycan. Glycosylation is critical for the normal function of α -dystroglycan.

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, 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.

Health Conditions Related to Genetic Changes

Walker-Warburg syndrome

At least seven mutations in the *LARGE1* gene have been found to cause Walker-Warburg syndrome. This condition is the most severe form of a group of disorders known as congenital muscular dystrophies. Walker-Warburg syndrome causes skeletal muscle weakness and abnormalities of the brain and eyes. Because of the severity of the problems caused by this condition, affected individuals usually do not survive past early childhood.

LARGE1 gene mutations involved in Walker-Warburg syndrome prevent the normal glycosylation of α-dystroglycan. As a result, α-dystroglycan can no longer effectively anchor cells to the proteins and other molecules that surround them. Without functional α -dystroglycan to stabilize the muscle fibers, they become damaged as they repeatedly contract and relax with use. The damaged fibers weaken and die over time, which affects the development, structure, and function of skeletal muscles in people with Walker-Warburg syndrome.

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 a brain abnormality called cobblestone lissencephaly, in which the surface of the brain lacks the normal folds and grooves and instead appears bumpy and irregular. Less is known about the effects of *LARGE1* gene mutations on other parts of the body.

Other disorders

Mutations in the *LARGE1* gene are also involved in a less severe form of congenital muscular dystrophy known as congenital muscular dystrophy type 1D (MDC1D). This condition causes muscle weakness, brain abnormalities, and intellectual disability but does not affect the eyes. As in Walker-Warburg syndrome (described above), *LARGE1* gene mutations that cause MDC1D prevent the normal glycosylation of α-dystroglycan. It is unclear how mutations in this gene cause several different muscular dystrophies.

Other Names for This Gene

- acetylglucosaminyltransferase-like 1A
- acetylglucosaminyltransferase-like protein
- glycosyltransferase-like protein LARGE1
- KIAA0609
- LARGE
- LARGE_HUMAN
- like-acetylglucosaminyltransferase
- like-glycosyltransferase
- MDC1D
- MDDGA6
- MDDGB6

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of LARGE1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=9215[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28LARGE%5BTIAB%5D%29+OR+%28like-glycosyltransferase%5BTIAB%5D%29+AND+%28glycosylation%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ACETYLGLUCOSAMINYLTRANSFERASE-LIKE PROTEIN; LARGE1 (https://omim.org/entry/603590)
- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH IMPAIRED INTELLECTUAL DEVELOPMENT), TYPE B, 6; MDDGB6 (https://omim.org/entry/608840)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/9215)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=LARGE1[gene])

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Genomic Location

The *LARGE1* gene is found on chromosome 22 (https://medlineplus.gov/genetics/chromosome/22/).

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