NHLRC1 gene

NHL repeat containing E3 ubiquitin protein ligase 1

Normal Function

The *NHLRC1* gene provides instructions for making a protein called malin. Although this protein is active in cells throughout the body, it appears to play a critical role in the survival of nerve cells (neurons) in the brain.

Malin is part of the cell machinery that breaks down (degrades) unwanted proteins within cells. The protein tags damaged and excess proteins with a molecule called ubiquitin, which serves as a signal to degrade these proteins. This process, which is known as the ubiquitin-proteasome system, acts as the cell's quality control system by disposing of damaged, misshapen, and excess proteins. This system also regulates the level of proteins involved in several critical cell activities such as the timing of cell division and growth. Malin belongs to a group of proteins in the ubiquitin-proteasome system called E3 protein-ubiquitin ligases.

Malin targets several proteins for degradation, including laforin (which is produced from the *EPM2A* gene). The interaction between malin and laforin likely plays a critical role in regulating the production of a complex sugar called glycogen. Glycogen is a major source of stored energy in the body. The body stores this sugar in the liver and muscles, breaking it down when it is needed for fuel. Researchers believe that malin and laforin may prevent a potentially damaging buildup of glycogen in tissues that do not normally store this molecule, such as those of the nervous system.

Health Conditions Related to Genetic Changes

Lafora progressive myoclonus epilepsy

More than 45 mutations in the *NHLRC1* gene have been identified in people with Lafora progressive myoclonus epilepsy. Many of these mutations change single protein building blocks (amino acids) in the malin protein. Other mutations delete or insert genetic material in the *NHLRC1* gene. Almost all mutations in this gene prevent cells from producing any malin or lead to the production of a nonfunctional version of the protein.

The most common *NHLRC1* gene mutation replaces the amino acid proline with the amino acid alanine at position 69 in the malin protein (written as Pro69Ala or P69A).

This mutation has been found in many affected individuals of Portuguese, Italian, and Spanish heritage. The second most common *NHLRC1* gene mutation replaces the amino acid glycine with a premature stop signal in the instructions for making malin (written as Gly158Ter or G158X). This mutation has been seen in affected individuals from several different ethnic groups.

It is unclear how mutations in the *NHLRC1* gene lead to the major features of Lafora progressive myoclonus epilepsy. Studies suggest that a loss of malin prevents cells from regulating the production of glycogen. As a result, distinctive clumps called Lafora bodies form within many types of cells. Lafora bodies are made up of an abnormal form of glycogen (called polyglucosan) that cannot be broken down and used for fuel. Instead, polyglucosans build up to form clumps that can damage cells. Neurons appear to be particularly vulnerable to this type of damage. Although Lafora bodies are found in many of the body's tissues, the signs and symptoms of Lafora progressive myoclonus epilepsy are limited to the nervous system.

Researchers are uncertain how a loss of functional malin contributes to the formation of Lafora bodies. However, a lack of this protein ultimately results in the death of neurons, which interferes with the brain's normal functions. The degeneration of neurons likely underlies the seizures, movement abnormalities, intellectual decline, and other neurological problems seen with Lafora progressive myoclonus epilepsy.

Other Names for This Gene

- bA204B7.2
- EPM2B
- MALIN
- MGC119262
- MGC119264
- MGC119265
- NHL repeat containing 1
- NHLC1_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of NHLRC1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=378884[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28NHLRC1%5BTIAB%5D%29+OR+%28EPM2B%5BTIAB%5D%29+OR+%28malin%5BTIAB%5D%29%29+A

ND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- NHL REPEAT-CONTAINING PROTEIN 1; NHLRC1 (https://omim.org/entry/608072)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/378884)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=NHLRC1[gene])

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Genomic Location

The *NHLRC1* gene is found on chromosome 6 (https://medlineplus.gov/genetics/chromosome/6/).

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