

EPM2A Gene

Subjects: **Genetics & Heredity**

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EPM2A, laforin glucan phosphatase

genes

1. Normal Function

The *EPM2A* gene provides instructions for making a protein called laforin. 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.

Studies suggest that laforin has multiple functions within cells. To carry out these functions, laforin interacts with several other proteins, including malin (which is produced from the *NHLRC1* gene). These proteins are part of complex networks that transmit chemical signals and break down unneeded or abnormal proteins. Additionally, laforin may act as a tumor suppressor protein, which means that it keeps cells from growing and dividing in an uncontrolled way.

Laforin and malin likely play 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 laforin and malin may prevent a potentially damaging buildup of glycogen in tissues that do not normally store this molecule, such as those of the nervous system.

2. Health Conditions Related to Genetic Changes

2.1 Lafora progressive Myoclonus Epilepsy

More than 50 mutations in the *EPM2A* gene have been identified in people with Lafora progressive myoclonus epilepsy. Many of these mutations change single protein building blocks (amino acids) in the laforin protein. Other mutations delete or insert genetic material in the *EPM2A* gene. Almost all mutations in this gene prevent cells from producing any laforin or lead to the production of a nonfunctional version of the protein.

It is unclear how mutations in the *EPM2A* gene lead to the major features of Lafora progressive myoclonus epilepsy. Studies suggest that a loss of laforin 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 laforin 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.

3. Other Names for This Gene

- epilepsy, progressive myoclonus type 2, Lafora disease (laforin)
- epilepsy, progressive myoclonus type 2A, Lafora disease (laforin)
- EPM2
- EPM2A_HUMAN
- laforin
- LD
- LDE
- MELF

References

1. Chan EM, Ackerley CA, Lohi H, Ianzano L, Cortez MA, Shannon P, Scherer SW, Minassian BA. Laforin preferentially binds the neurotoxic starch-like polyglucosans, which form in its absence in progressive myoclonus epilepsy. *Hum Mol Genet*. 2004 Jun 1;13(11):1117-29.
2. Ganesh S, Agarwala KL, Ueda K, Akagi T, Shoda K, Usui T, Hashikawa T, Osada H, Delgado-Escueta AV, Yamakawa K. Laforin, defective in the progressive myoclonus epilepsy of Lafora type, is a dual-specificity phosphatase associated with polyribosomes. *Hum Mol Genet*. 2000 Sep 22;9(15):2251-61.
3. Garyali P, Siwach P, Singh PK, Puri R, Mittal S, Sengupta S, Parihar R, Ganesh S. The malin-laforin complex suppresses the cellular toxicity of misfolded proteins by promoting their

degradation through the ubiquitin-proteasome system. *Hum Mol Genet.* 2009 Feb 15;18(4):688-700. doi: 10.1093/hmg/ddn398.

4. Girard JM, Lê KH, Lederer F. Molecular characterization of laforin, a dual-specificity protein phosphatase implicated in Lafora disease. *Biochimie.* 2006 Dec;88(12):1961-71.

5. Liu R, Wang L, Chen C, Liu Y, Zhou P, Wang Y, Wang X, Turnbull J, Minassian BA, Liu Y, Zheng P. Laforin negatively regulates cell cycle progression through glycogen synthase kinase 3beta-dependent mechanisms. *Mol Cell Biol.* 2008 Dec;28(23):7236-44. doi: 10.1128/MCB.01334-08.

6. Liu Y, Wang Y, Wu C, Liu Y, Zheng P. Deletions and missense mutations of EPM2A exacerbate unfolded protein response and apoptosis of neuronal cells induced by endoplasm reticulum stress. *Hum Mol Genet.* 2009 Jul 15;18(14):2622-31. doi: 10.1093/hmg/ddp196.

7. Minassian BA, Lee JR, Herbrick JA, Huijzen J, Soder S, Mungall AJ, Dunham I, Gardner R, Fong CY, Carpenter S, Jardim L, Satishchandra P, Andermann E, Snead OC3rd, Lopes-Cendes I, Tsui LC, Delgado-Escueta AV, Rouleau GA, Scherer SW. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet.* 1998 Oct;20(2):171-4.

8. Serratosa JM, Gómez-Garre P, Gallardo ME, Anta B, de Bernabé DB, Lindhout D, Augustijn PB, Tassinari CA, Malafosse RM, Topcu M, Grid D, Dravet C, Berkovic SF, de Córdoba SR. A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). *Hum Mol Genet.* 1999 Feb;8(2):345-52.

9. Singh S, Ganesh S. Lafora progressive myoclonus epilepsy: a meta-analysis of reported mutations in the first decade following the discovery of the EPM2A and NHLRC1 genes. *Hum Mutat.* 2009 May;30(5):715-23. doi: 10.1002/humu.20954. Review.

10. Solaz-Fuster MC, Gimeno-Alcañiz JV, Ros S, Fernandez-Sánchez ME, García-Fojea B, Criado García O, Vilchez D, Dominguez J, García-Rocha M, Sanchez-Piris M, Aguado C, Knecht E, Serratosa J, Guinovart JJ, Sanz P, Rodriguez de Córdoba S. Regulation of glycogen synthesis by the laforin-malin complex is modulated by the AMP-activated protein kinase pathway. *Hum Mol Genet.* 2008 Mar 1;17(5):667-78.

11. Tagliabuoni VS, Turnbull J, Wang W, Girard JM, Zhao X, Skurat AV, Delgado-Escueta AV, Minassian BA, Depaoli-Roach AA, Roach PJ. Laforin is a glycogen phosphatase, deficiency of which leads to elevated phosphorylation of glycogen in vivo. *Proc Natl Acad Sci U S A.* 2007 Dec 4;104(49):19262-6.

12. Vilchez D, Ros S, Cifuentes D, Pujadas L, Vallès J, García-Fojea B, Criado-García O, Fernández-Sánchez E, Medraño-Fernández I, Domínguez J, García-Rocha M, Soriano E, Rodríguez de Córdoba S, Guinovart JJ. Mechanisms suppressing glycogen synthesis in neurons and its demise in progressive myoclonus epilepsy. *Nat Neurosci.* 2007 Nov;10(11):1407-13.

13. Worby CA, Gentry MS, Dixon JE. Laforin, a dual specificity phosphatase that dephosphorylates complex carbohydrates. *J Biol Chem.* 2006 Oct 13;281(41):30412-8.

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