Myoclonic epilepsy of Lafora

D'Eustachio, P., Pederson, B.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 71

This document contains 1 pathway and 2 reactions (see Table of Contents)
Myoclonic epilepsy of Lafora

Stable identifier: R-HSA-3785653

Diseases: glycogen storage disease

Lafora disease is a progressive neurodegenerative disorder with onset typically late in childhood, characterized by seizures and progressive neurological deterioration and death within ten years of onset. Recessive mutations in EPM2A (laforin) and NHLRC1 (malin) have been identified as causes of the disease. The disease is classified here as one of glycogen storage as EPM2A (laforin) and NHLRC1 (malin) regulate normal glycogen turnover and defects in either protein are associated with the formation of Lafora bodies, accumulations of abnormal, insoluble glycogen molecules in tissues including brain, muscle, liver, and heart (Ramachandran et al. 2009; Roach et al. 2012). Consistent with a central role for glycogen accumulation in the disease, reduced (Turnbull et al. 2011) or absent (Pederson et al. 2013) glycogen synthase activity prevents Lafora Disease in mouse models.

Type 2A disease. EPM2A (laforin) associated with cytosolic glycogen granules, normally catalyzes the removal of the phosphate groups added rarely but consistently to growing glycogen molecules (Tagliabracci et al. 2011). Defects in this catalytic activity lead to the formation of phosphorylated glycogen molecules that are insoluble and that show abnormal branching patterns (Minassian et al. 1998, Serratosa et al. 1999, Tagliabracci et al. 2011).

Type 2B disease. NHLRC1 (malin) normally mediates polyubiquitination of EPM2A (laforin) and PPP1R3C (PTG). The two polyubiquitinated proteins are targeted for proteasome-mediated degradation, leaving a glycogen-glycogenin particle associated with glycogen synthase. In the absence of NHLRC1 activity, EPM2A and PPP1R3C proteins appear to persist, associated with the formation of abnormal, stable glycogen granules (Lafora bodies) (Chan et al. 2003; Gentry et al. 2005). In NHLRC1 knockout mice PPP1R3C levels are unchanged rather than increased, suggesting that NHLRC1 does not target PPP1R3C for degradation. However, EPM2A protein levels are increased in this knockout consistent with NHLRC1’s pro-
posed role (DePaoli-Roach et al. 2010).

**Literature references**


**Editions**

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Defective EPM2A does not dephosphorylate phosphoglycogen (type 2A disease)

Location: Myoclonic epilepsy of Lafora

Stable identifier: R-HSA-3791349

Type: transition

Compartments: cytosol

Diseases: glycogen storage disease

EPM2A (laforin) associated with cytosolic liver- and muscle-form glycogen granules normally catalyzes the hydrolytic removal of the small numbers of phosphate groups incorporated into glycogen (Minassian et al. 1998, Serratosa et al. 1999, Tagliabracci et al. 2011). Defects in EMP2A (laforin) are the cause of the commonest form of Lafora disease. The three missense mutant forms of EPM2A (laforin) annotated here are examples of the disease-associated EPM2A alleles that have been described (Fernandez-Sanchez et al. 2003).

Literature references


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Defective NHLRC1 does not ubiquitinate EPM2A (laforin) and PPP1R3C (PTG) (type 2B disease)

Location: Myoclonic epilepsy of Lafora
Stable identifier: R-HSA-3797226
Type: transition
Compartments: cytosol
Diseases: glycogen storage disease

NHLRC1 (malin) mediates the ubiquitination of EPM2A (laforin) and PPP1R3C (PTG) associated with cytosolic liver- and muscle-form glycogen granules (Gentry et al. 2005). Defects in NHLRC1 (malin) are the cause of the second commonest form of Lafora disease (Roma-Mateo et al. 2012). The two missense mutant forms of NHLRC1 (malin) annotated here are examples of the disease-associated NHLRC1 alleles that have been described (Chan et al. 2003).

Literature references


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