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## Progressive Myoclonus Epilepsy, Lafora Type

**Lafora Body Disease, Lafora Disease. Includes: EPM2A-Related Lafora Disease, NHLRC1-Related Lafora Disease**

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### Summary

**Disease characteristics.** Lafora disease (LD) is characterized by fragmentary, symmetric, or generalized myoclonus and/or generalized tonic-clonic seizures, visual hallucinations (occipital seizures), and progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, and ataxia beginning in previously healthy adolescents between ages 12 and 17 years. The frequency and intractability of seizures increase over time. Status epilepticus is common. Emotional disturbance and confusion are common at or soon after onset of seizures and are followed by dementia. Dysarthria and ataxia appear early; spasticity late. Most affected individuals die within ten years of onset, usually from status epilepticus or from complications related to nervous system degeneration.

**Diagnosis/testing.** Diagnosis is usually based on clinical and EEG findings and detection of two mutations in one of the two genes known to be associated with LD: *EPM2A* or *NHLRC1* (*EPM2B*). On rare occasion skin biopsy to detect pathognomonic Lafora bodies is necessary to confirm the diagnosis.

**Management.** *Treatment of manifestations:* Antiepileptic drugs (AEDs) are effective against generalized seizures. *Prevention of secondary complications:* Overmedication in treating drug-resistant myoclonus is a risk. Gastrostomy feedings can decrease the risk of aspiration pneumonia when disease is advanced. *Surveillance:* clinical and psychosocial evaluation at three- to six-month intervals throughout the teenage years. *Agents/circumstances to avoid:* phenytoin, and possibly carbamazepine, oxcarbazepine, and lamotrigine.

**Genetic counseling.** Lafora disease is inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal diagnosis for at-risk pregnancies are possible if the disease-causing mutations in the family are known.

### Diagnosis

#### Clinical Diagnosis

The diagnosis of Lafora disease (LD) is suspected in a previously healthy older child or adolescent (usually in the early teens) who has the following:

- Fragmentary, symmetric, or generalized myoclonus **and/or** generalized tonic-clonic seizures
- Visual hallucinations (occipital seizures)

- Progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, ataxia, and, at later stages, spasticity and dementia
- Slowing of background activity, loss of  $\alpha$ -rhythm and sleep features, and photosensitivity on early EEGs
- Periodic acid Schiff-positive intracellular inclusion bodies (Lafora bodies) on skin biopsy
- Normal MRI of the brain at onset

See Table 1.

Table 1. Clinical Evaluation of Lafora Disease

Evaluation Type	At Onset	Later in Disease Course
<b>General physical examination, including liver and spleen sizes</b>	Normal	Normal
<b>Neurologic examination, including fundi and reflexes</b>	Normal	Dysarthria, ataxia, spasticity; fundi remain normal
<b>Mental state examination</b>	Visual hallucinations (epileptic), depressed mood, cognitive deficits	Increased hallucinations, agitation, dementia
<b>EEG</b>	Normal or slow background, loss of $\alpha$ -rhythm and sleep features; photosensitivity is common	Slow background, paroxysms of generalized irregular spike-wave discharges with occipital predominance, and focal, especially occipital, abnormalities
<b>Visual, somatosensory, and auditory brain stem evoked potentials</b>	High-voltage visual and somatosensory evoked potentials	Amplitudes may return to normal size; prolongation of brain stem and central latencies
<b>Nerve conduction studies</b>	Normal	Normal
<b>MRI of the brain</b>	Normal	Normal or atrophy <sup>1</sup>
<b>Proton MR spectroscopy of the brain</b>	Reduced NAA/creatinine ratio in frontal and occipital cortex, basal ganglia, and cerebellum <sup>2</sup>	Reduced NAA/creatinine ratio in frontal and occipital cortex, basal ganglia, and cerebellum <sup>1</sup>

Minassian 2001, Minassian 2002, Villanueva et al 2006

1. No significant correlation observed with disease evolution

2. At least two years after onset of symptoms

## Testing

**Skin biopsy** reveals the pathognomonic Lafora bodies [Carpenter et al 1974, Carpenter & Karpati 1981] composed of starch-like polyglucosans, which are insufficiently branched and hence insoluble glycogen molecules. Lafora bodies are present in either eccrine duct cells or in apocrine myoepithelial cells.

Note: (1) Normal PAS-positive apical granules in secretory apocrine cells found in the axilla can be mistaken for Lafora bodies; thus, biopsy of skin outside the axilla and genital regions is favored, as eccrine duct cell Lafora bodies are unmistakable [Andrade et al 2003]. (2) Interpretation of findings on skin biopsy includes a risk of false negative results, especially in newly symptomatic individuals, and a risk of false positive results because of the difficulty in distinguishing Lafora bodies from normal PAS-positive polysaccharides in apocrine glands [Drury et al 1993, Andrade et al 2003].

## Molecular Genetic Testing

**Genes.** The two genes known to be associated with LD are *EPM2A* (locus name EPM2A) [Minassian et al 1998] and *NHLRC1* (also known as *EPM2B*; locus name EPM2B) [Chan, Young et al 2003].

- Gomez-Abad et al (2005) found mutations in 97% (75/77) of families with LD: *EPM2A* (70%) and *NHLRC1* (27%)
- Franceschetti et al (2006) found mutations in 21/22 (95%) of families with LD: *EPM2A* (22%) and *NHLRC1* (73%)
- Lohi et al (2006) found mutations in 88% (75/85) of families with LD: *EPM2A* (45%) and *NHLRC1* (43%)
- Singh et al (2006) found mutations in 84% (23/28) of families with LD: *EPM2A* (54%) and *NHLRC1* (34%)

These marked variations may be accounted for by ethnic differences or by chance variation and small sample size.

**Other loci.** Mutations in at least one other gene also cause LD. Chan, Omer et al (2004) described one family with three individuals with biopsy-verified LD and no identifiable mutation in either *EPM2A* or *NHLRC1*. Linkage and haplotype analyses excluded both loci from causative involvement in this family, providing indirect evidence for a third locus for LD. The findings were supported by an independent study [Singh et al 2005, Singh et al 2006].

### Clinical testing

- **Sequence analysis of the entire coding region.** Given the high allelic heterogeneity observed in LD, it is likely that the majority of the mutations arise as a single event and that only a very small proportion of mutant alleles can be predicted in certain populations (see [Molecular Genetics](#)).
  - ***EPM2A* and *NHLRC1*.** Studies of the combined mutation detection frequency of sequence analysis in *EPM2A* and *NHLRC1* reveal that between 88% and 97% of mutations in these two genes can be detected using sequence analysis alone [Gomez-Abad et al 2005, Franceschetti et al 2006, Lohi et al 2006].
- **Deletion analysis**
  - ***EPM2A* and *NHLRC1*.** The proportion of mutations in *EPM2A* and *NHLRC1* not detected by sequence analysis that are attributable to deletions is unknown.
  - Deletions should be suspected in affected individuals who have a single heterozygous mutation in one of the genes, and in patients who have an apparently homozygous mutation in one of the genes but the mutation is carried by only one parent.
  - In the one study to date specifically looking for deletions in three individuals with a single heterozygous mutation who were suspected to have deletions, Lohi et al (2007) found three deletions in three families, one in *EPM2A* and two in *NHLRC1*.

Table 2. Summary of Molecular Genetic Testing Used in Progressive Myoclonus Epilepsy, Lafora Type

Gene Symbol	Proportion of LD Attributed to Mutations in This Gene	Test Method	Mutation Detection Frequency by Test Method	Test Availability
<i>EPM2A</i>	22%-70%	Sequence analysis	88%-97% <sup>1</sup>	Clinical <b>Testing</b>
		Deletion analysis <sup>2</sup>	Unknown	
<i>NHLRC1</i> ( <i>EPM2B</i> )	27%-73%	Sequence analysis	88%-97% <sup>1</sup>	Clinical <b>Testing</b>
		Deletion analysis <sup>2</sup>	Unknown	

Test Availability refers to availability in the [GeneTests Laboratory Directory](#). *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the [GeneTests Laboratory Directory](#) by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. Includes data for mutation detection frequency for both *EPM2A* and *NHLRC1* [Chan, Young et al 2003; Gomez-Abad et al 2005; Franceschetti et al 2006; Lohi et al 2006; Singh et al 2006]

2. Identifies exonic and whole gene deletions

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click [here](#).

## Testing Strategy

**Confirmation of the diagnosis in a proband** requires **one** of the following:

- Detection of Lafora bodies on skin biopsy
- Identification of two mutations in either *EPM2A* or *NHLRC1*

Note: Although some evidence suggests that persons with *NHLRC1*-associated LD tend to live longer than those with *EPM2A*-associated LD [Gomez-Abad et al 2005, Franceschetti et al 2006], the clinical manifestations of LD caused by mutations in either gene are so similar that it is not possible to predict which gene will be mutated in any given individual.

**Carrier testing for at-risk relatives** requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing LD.

**Prenatal diagnosis** for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

## Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *EPM2A* or *NHLRC1*.

## Clinical Description

### Natural History

Lafora disease (LD) typically starts between ages 12 and 17 years, after a period of apparently normal development. Many affected individuals experience isolated febrile or nonfebrile convulsions in infancy or earlier in childhood. Intractable seizures rarely begin as early as age six years. In families with more than one affected child, clinical signs such as subtle myoclonus, visual hallucinations, or headaches are noted earlier in subsequent affected children than in the proband [Minassian, lanzano, Meloche et al 2000; Minassian 2002]. Intra- and interfamilial variability in age at onset is considerable [Gomez-Abad et al 2007, Lohi et al 2007].

The main seizure types in LD include myoclonic seizures and occipital seizures, although generalized tonic-clonic seizures, atypical absence seizures, and atonic and complex partial seizures may occur.

Myoclonus can be fragmentary, symmetric, or massive (generalized). It occurs at rest and is exaggerated by action, photic stimulation, or excitement. Both negative (loss of tone) and positive (jerking) myoclonus can occur. Myoclonus usually disappears with sleep. Trains of massive myoclonus with relative preservation of consciousness have been reported. Myoclonus is the primary reason for early wheelchair dependency. In the advanced stages of the disease, affected individuals often have continuous generalized myoclonus.

Occipital seizures present as transient blindness, simple or complex visual hallucinations, photomyoclonic or photoconvulsive seizures, or migraine with scintillating scotomata [Berkovic et al 1993; Minassian, lanzano, Meloche et al 2000].

The course of the disease is characterized by increasing frequency and intractability of seizures. Status epilepticus with any of the previously mentioned seizure types is common. Cognitive decline becomes apparent at or soon after the onset of seizures. Dysarthria and ataxia appear early; spasticity late. Emotional disturbance and confusion are common in the early stages of the disease and are followed by dementia.

By their mid-twenties, most affected individuals are in a vegetative state with continuous myoclonus and require tube feeding. Some maintain minimal interactions with the family such as a reflex-like smiling upon cajoling. Affected individuals who are not tube-fed aspirate frequently as a result of seizures; death from aspiration pneumonia is common.

Most affected individuals die within ten years of onset, usually from status epilepticus or from complications related to nervous system degeneration [Minassian 2002].

## Genotype-Phenotype Correlations

Genotype-phenotype correlations are difficult to establish in LD because compound heterozygotes in different combinations are common [Chan et al 2005, Gomez-Abad et al 2005]. Variation by country in the care available for individuals with LD may in part influence longevity and disease complications.

Also, intra- and interfamilial variability in age at onset is considerable, suggesting that genetic factors other than the *EPM2A* or *NHLRC1* mutations may influence the pathogenesis of LD [Gomez-Abad et al 2007, Lohi et al 2007].

To date, no correlations have been demonstrated between phenotype and mutation type (missense or truncating) or location of the mutation in the gene.

- Although a sub-phenotype consisting of childhood-onset learning disorder followed by epilepsy and neurologic deterioration has been associated with either mutations in exon 1 of *EPM2A* [Ganesh, Delgado-Escueta, Suzuki et al 2002; Annesi et al 2004] or the p.Ile198Asn mutation located in an NHL protein-protein interaction domain of *NHLRC1(EPM2B)* [Gomez-Abad et al 2005], these findings need to be replicated, expanded, and studied further in order to understand their relationship to the underlying pathophysiologic processes.
- Individuals with mutations in *NHLRC1* tend to live longer than those with mutations in *EPM2A* [Gomez-Abad et al 2005, Franceschetti et al 2006, Singh et al 2006]. This finding has been demonstrated repeatedly for persons with the *NHLRC1(EPM2B)* mutation p.Asp146Asn [Baykan et al 2005, Gomez-Abad et al 2005, Franceschetti et al 2006]. However, this does not apply to all persons with mutations in *NHLRC1*, as some may have extremely severe phenotypes.

## Nomenclature

Lafora disease is also referred to as myoclonic epilepsy of Lafora or progressive myoclonic epilepsy type 2.

The term progressive myoclonus epilepsy (PME) covers a large and varied group of diseases characterized by myoclonus, generalized tonic-clonic seizures, and progressive neurologic deterioration [Berkovic et al 1986].

## Prevalence

Exact prevalence figures for LD are not available.

LD occurs worldwide. Although relatively rare in the outbred populations of the United States, Canada, China, and Japan, LD is relatively common in the Mediterranean basin of Spain, France, and Italy, in restricted regions of central Asia, India, Pakistan, northern Africa, and the Middle East, in ethnic isolates from the southern United States and Quebec, and in other parts of the world with a high rate of consanguinity [Delgado-Escueta et al 2001].

In affected individuals, mutations in *NHLRC1* are more common than mutations in *EPM2A*. Mutations in *NHLRC1* are not very common in the general population in Japan or in countries surrounding the Adriatic Sea [Chan, Young et al 2003; Singh et al 2005; Franceschetti et al 2006; Singh et al 2006].

Note: LD has not been reported in Finland, where founder effects for a number of genetic disorders are common, and where EPM1 (Unverricht-Lundborg disease) has the highest prevalence [Lehesjoki A and Kalviainen R, personal communication].

## Differential Diagnosis

*For current information on availability of genetic testing for disorders included in this section, see [GeneTests Laboratory Directory](#). —ED.*

**Juvenile myoclonic epilepsy.** Although the occurrence of myoclonus and generalized tonic-clonic seizures in adolescence may raise the possibility of juvenile myoclonic epilepsy, the persistence of EEG background slowing and cognitive deterioration should raise the suspicion of a more severe epilepsy syndrome, such as PME.

Earlier age at onset, slower rate of disease progression, and absence of Lafora bodies on skin biopsy differentiates **EPM1 (Unverricht-Lundborg disease)** from Lafora disease (LD).

Careful ophthalmologic examination, including electroretinography, is useful in addressing the possibilities of **neuronal ceroid-lipofuscinoses** and **sialidosis**.

Cerebrospinal fluid concentration of lactate and titers of measles antibody can be helpful in dismissing the

possibility of **myoclonic epilepsy with ragged red fibers (MERRF)** and **subacute sclerosing panencephalitis (SSPE)**, respectively [Minassian 2001, Minassian 2002].

Visual hallucinations, withdrawal, and cognitive decline raise concerns of **schizophrenia**, which becomes less likely with the onset of convulsions and the appearance of an epileptiform EEG.

Magnetic resonance imaging excludes structural abnormalities, and posteriorly dominant irregular spike-wave discharges on EEG raise suspicion of LD.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Lafora disease (LD), the following are recommended:

- Clinical evaluation
- Evaluation of speech, walking, coordination, handwriting, school performance, and emotional status

### Treatment of Manifestations

Antiepileptic drugs (AEDs) have a major effect against generalized seizures, sometimes controlling seizures for many months. Generalized seizures are rare in individuals who are treated, even years after disease onset.

**Valproic acid** is the traditional antiepileptic treatment for LD because it is a broad-spectrum AED that controls both the generalized tonic-clonic seizures and myoclonic jerks.

**Clonazepam** can be used as an adjunctive medication for control of myoclonus, as in other forms of PME, although the literature does not provide clear evidence for its effect on myoclonus in LD.

**Zonisamide** has had a significant effect on both seizures and myoclonus in a small number of individuals with Unverricht-Lundborg disease and Lafora disease.

Both **piracetam** and **levetiracetam** have been effective, sustained, and well-tolerated as add-on treatment for myoclonus in progressive myoclonus epilepsy (PME) [Koskiniemi et al 1998, Genton et al 1999, Fedi et al 2001, Crest et al 2004]. Levetiracetam had a significant effect on myoclonus in two sisters with LD [Boccella et al 2003]. Lohi et al (2006) reported that levetiracetam exacerbated seizures while improving myoclonus in two persons with LD.

### Prevention of Secondary Complications

Overmedication is a risk with individuals with LD as a result of drug-resistant myoclonus.

Placement by percutaneous endoscopy of a gastrostomy tube for feeding can be helpful in decreasing the risk of aspiration pneumonia in individuals with advanced disease.

### Surveillance

Clinical and psychosocial evaluation should be performed at three- to six-month intervals throughout the teenage years.

### Agents/Circumstances to Avoid

As in other forms of progressive myoclonus epilepsies, the use of phenytoin should be avoided.

Anecdotal reports describe possible exacerbation of myoclonus with the following:

- Carbamazepine [Nanba & Maegaki 1999]
- Oxcarbazepine [Kaddurah & Holmes 2006]
- Lamotrigine [Cerinara et al 2004, Crespel et al 2005]

### Testing of Relatives at Risk

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Since the typical polyglucosan accumulations in LD result from alterations of proteins involved in the regulation of glycogen metabolism, the feasibility and tolerability of a long-term ketogenic diet in LD was studied in five individuals [Cardinali et al 2006]. Although the ketogenic diet was well tolerated and nutritional measures and laboratory findings remained stable, the ketogenic diet did not stop disease progression. However, given the considerable heterogeneity of the natural history of LD, the possibility that the ketogenic diet affects the natural history cannot be excluded. Larger studies are needed to further evaluate the utility of the ketogenic diet in treating LD.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) for access to information on clinical studies for a wide range of diseases and conditions.

## Other

**Genetics clinics**, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the [GeneTests Clinic Directory](#).

**See Consumer Resources** for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the [GeneTests Clinic Directory](#).*

## Mode of Inheritance

Lafora disease (LD) is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

### Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband.** Because of the early onset and rapid deterioration, individuals with LD typically do not reproduce.

**Other family members of a proband.** Sibs of the proband's parents are at a 50% risk of being carriers; first cousins of the proband have a 25% risk of being carriers.

## Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in an affected family member.

Carrier testing is also available to the reproductive partners of known carriers.

## Related Genetic Counseling Issues

**Family planning.** The optimal time for determination of genetic risk, clarification of carrier status, and discussion

of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or at risk of being carriers.

**DNA banking.** DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly appropriate for affected individuals in whom molecular genetic testing of *EPM2A* and *NHLRC1* identifies neither or only one mutation. See [Testing](#) for a list of laboratories offering DNA banking.

## Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see [Testing](#).

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

Table A. Progressive Myoclonus Epilepsy, Lafora Type: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	HGMD
<i>EPM2A</i>	6q24	Laforin	<a href="#">EPM2A</a>
<i>NHLRC1</i>	6p22.3	NHL repeat-containing protein 1	<a href="#">NHLRC1</a>

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, [click here](#).

Table B. OMIM Entries for Progressive Myoclonus Epilepsy, Lafora Type ([View All in OMIM](#))

<a href="#">254780</a>	MYOCLONIC EPILEPSY OF LAFORA
<a href="#">607566</a>	EPM2A GENE; EPM2A
<a href="#">608072</a>	NHL REPEAT-CONTAINING 1 GENE; NHLRC1

## Molecular Genetic Pathogenesis

The mechanism by which mutations in either *EPM2A* or *NHLRC1*(*EPM2B*) result in Lafora disease (LD) and the exact role of the Lafora bodies in the pathogenesis of LD require further study. Given the fact that defects in either laforin or malin lead to LD, it is presumed that these two proteins together regulate a critical pathway involved in neuronal function and that they act on a common substrate, either directly or indirectly.

Laforin-deficient mice show widespread neuronal degeneration and a phenotype that closely resembles human LD, suggesting that laforin is critical for neuronal survival and that some symptoms of LD are initiated by neuronal death [Ganesh, Delgado-Escueta, Sakamoto et al 2002]. Mouse models further suggest that LD is a primary neurodegenerative disorder that may utilize a non-apoptotic mechanism of cell death [Ganesh, Delgado-Escueta, Sakamoto et al 2002; Chan, Ackerley et al 2004].

In vitro and in vivo approaches have provided evidence for a laforin-mediated glycogen metabolic pathway regulating the generation and/or disposal of pathogenic polyglucosan inclusions, Lafora bodies [Fernandez-Sanchez et al 2003; Lohi, Ianzano et al 2005]. Proteins involved in this pathway are R5 (a regulatory subunit of protein phosphatase 1 that enhances glycogen accumulation), glycogen synthase (GS), glycogen synthase

kinase 3 (GSK3), malin, HIRIP5 (a cytosolic protein involved in iron metabolism), and EPM2AIP1 (a protein with unknown functions) [Ganesh et al 2003, Ianzano et al 2003].

Laforin specifically binds polyglucosans. When laforin is absent, polyglucosans accumulate, resulting in the formation of Lafora bodies [Chan, Ackerley et al 2004; Ganesh et al 2004]. This suggests that the role of laforin is to detect appearance of polyglucosan during glycogen synthesis and to initiate mechanisms to downregulate glycogen synthase (GS). Laforin was shown to interact with malin, an E3-ubiquitin ligase, which specifically polyubiquitinates its substrate on Lafora bodies [Lohi, Ianzano et al 2005]. This substrate could be GS, as malin also interacts with GS [Lohi, Ianzano et al 2005]. Based on these results, the Minassian group proposed that laforin, in response to appearance of polyglucosans, directs two negative-feedback pathways: polyglucosan-laforin-GSK3-GS to inhibit GS activity and polyglucosan-laforin-malin-GS to remove GS through proteasomal degradation [Lohi, Ianzano et al 2005]. However, the link between laforin and GSK3 remains unclear. Worby et al (2006) found no change in the phosphorylation status of GSK3 in the presence of laforin in western blots. This result was further confirmed by the absence of changes in the phosphorylation status of GSK3 in muscle tissue from laforin p.Cys266Ser mutant transgenic mice [Wang et al 2007] and in brain tissue from laforin-deficient mice [Tagliabracci et al 2007].

An alternative model for the development of polyglucosan bodies was proposed by Rodríguez de Córdoba, Guinovart, and colleagues [Solaz-Fuster et al 2007, Vilchez et al 2007], who showed that mouse neurons have the enzymatic machinery for synthesizing glycogen, but that it is suppressed by retention of muscle glycogen synthase (MGS) in the phosphorylated, inactive state. This suppression was ensured by a complex of laforin and malin. The laforin-malin complex caused proteasome-dependent degradation of both (1) the adaptor protein targeting to glycogen, PTG, which brings protein phosphatase 1 to MGS for activation, and (2) MGS itself. Enforced expression of PTG led to glycogen deposition in neurons and caused apoptosis. Therefore, the malin-laforin complex ensures inhibition of neuronal glycogen synthesis, even under intense glycogenic conditions. This may explain the formation of polyglucosan inclusions in Lafora disease, in which laforin or malin are absent or have lost their normal function.

It has been demonstrated that in plants, mutations in the starch excess 4 (SEX4) gene result in the accumulation of amylopectin, similar to the way loss of laforin leads to the accumulation of polyglucosans with formation of Lafora bodies in humans [Niittyta et al 2006, Gentry et al 2007]. In plants, human laforin can rescue the SEX4-mutated phenotype [Gentry et al 2007].

Studies in mice have shown that malin interacts with the glycogen debrancher enzyme amylo-1,6-glucosidase,4-alpha-glucanotransferase (AGL). Mutations in the AGL gene cause Cori disease or glycogen storage disease III [Cheng et al 2007].

## ***EPM2A***

**Normal allelic variants:** The *EPM2A* gene has four exons spanning 130 kb; they are alternatively spliced to form two major *EPM2A* transcripts [Minassian et al 1998, Serratos et al 1999, Ganesh et al 2000, Gomez-Garre et al 2000].

Several polymorphisms in *EPM2A* have been described [Gomez-Garre et al 2000; Minassian, Ianzano, Meloche et al 2000; Singh et al 2005]:

- Among the polymorphisms, 136G>C (p.Ala46Pro) is specific to the Japanese and Chinese populations [Ganesh et al 2001].
- The p.Gln55Lys substitution in *EPM2A* was found in two affected persons who were also heterozygous for a large deletion in *NHLRC1*, as well as in seven of 500 individuals without LD and in a person with adult-onset disease, always in the heterozygous state. To date, it remains unclear whether this change constitutes a rare benign SNP of no consequence, whether it may cause LD when homozygous, or whether it could predispose to *NHLRC1* deletion in certain situations [Lohi et al 2007].

**Pathologic allelic variants:** To date, at least 38 different mutations in *EPM2A* have been reported [Minassian et al 1998; Serratos et al 1999; Gomez-Garre et al 2000; Minassian, Ianzano, Delgado-Escueta et al 2000; Minassian, Ianzano, Menoche et al 2000; Ganesh, Delgado-Escueta, Suzuki et al 2002; Ki et al 2003; Annesi et al 2004; Ianzano et al 2004; Singh et al 2005; Lohi et al 2006]. These include 16 missense mutations, six nonsense mutations, six insertions of a few bases, seven deletions of a few bases, and three large deletions involving several kilobases [Ganesh et al 2006]. Two more mutations, a missense mutation and a deletion, have not been published but are listed in the Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database [Ianzano et al 2005].

Of all the types of mutations in *EPM2A* described to date, 42% represent missense mutations, and all the known

missense mutations target either the carbohydrate-binding domain (CBD) or the dual-specificity phosphatase domain (DSPD) of laforin [Ganesh et al 2006].

Except for the larger deletions, all the mutations are distributed evenly across the *EPM2A* gene. Exceptions are the high prevalence of the following:

- 721C>T (p.Arg241X) mutation in the Spanish population. Its high prevalence is the result of both a founder effect and recurrent events [Gomez-Garre et al 2000; Ganesh, Delgado-Escueta, Suzuki et al 2002].
- Homozygous deletion of exon 2 (Ex2-56Kbdel) in three Arab families, caused by a founder effect [Gomez-Abad et al 2007]. Haplotype analysis suggests that this *EPM2A* mutation arose many generations previously; thus it may be of importance for cases distributed more widely in the Middle East [Gomez-Abad et al 2007].

**Normal gene product:** The *EPM2A* gene encodes laforin, a 331-amino acid protein phosphatase. Laforin contains an N-terminal carbohydrate-binding domain (CBD), encoded mainly by exon 1, and a dual-specificity phosphatase domain (DSPD) spanning exons 3 and 4 [Minassian, Ianzano, Meloche et al 2000; Ganesh, Delgado-Escueta, Suzuki et al 2002;]. Both isoforms of the laforin protein have alternate C termini [Ganesh, Suzuki et al 2002]. The common segment consists of a carbohydrate-binding module and a dual-specificity protein phosphatase domain [Ganesh et al 2000]. Isoform A localizes at the rough endoplasmic reticulum. Isoform B localizes to the nucleus.

**Abnormal gene product:** Nonsense mutations, insertions, and deletions in *EPM2A* are predicted to be functionally 'null' and to have lost phosphatase activity. Missense mutations in *EPM2A* also result in a lack of phosphatase activity in vitro, resulting in a 'null' effect [Fernandez-Sanchez et al 2003, Ganesh et al 2006]. Loss of phosphatase activity is not restricted to mutations located in the DSPD; it has also been observed for mutations affecting the CBD of *EPM2A* [Wang et al 2002, Fernandez-Sanchez et al 2003]. It is likely that the missense mutations affect proper folding of the laforin protein, as illustrated by transfection experiments overexpressing missense mutants, which resulted in ubiquitin-positive cytoplasmic aggregates, suggesting that they were folding mutants destined for degradation [Ganesh et al 2000; Ganesh, Delgado-Escueta, Sakamoto et al 2002]. Missense mutations also affect the subcellular localization of laforin [Ganesh, Delgado-Escueta, Sakamoto et al 2002; Mittal et al 2007] and disrupt the interaction of laforin with R5 and malin, proteins that interact with laforin in vivo [Fernandez-Sanchez et al 2003; Gentry et al 2005].

Two laforin isoforms have unique C termini, produced by differentially spliced transcripts of the *EPM2A* gene [Ganesh, Suzuki et al 2002; Ianzano et al 2004]. The unique carboxyl terminal of isoform 2 targets laforin to the nucleus, a feature that is not shared by laforin isoform 1. Ianzano et al (2004) demonstrated that disturbances in the physiologic functions of laforin isoform 1 underlie the pathogenesis in LD, and isoform 2 cannot functionally substitute for laforin isoform 1.

### ***NHLRC1(EPM2B)***

**Normal allelic variants:** *NHLRC1(EPM2B)* is a single-exon gene spanning 1,188 base pairs that has all of the proposed features of the consensus sequence of a eukaryotic translational initiation site at its 5' end and two putative polyadenylation signals at its 3' end. Northern blot analysis indicates the presence of *NHLRC1* as two transcripts of 1.5 kb and 2.4 kb in all tissues examined, including specific subregions of the brain [Chan, Young et al 2003]. Six polymorphisms have been reported [Chan, Young et al 2003; Singh et al 2005].

**Pathologic allelic variants:** Forty-six mutations have been reported, the majority of which are missense mutations, although insertions, deletions, and nonsense mutations have also been found [Chan, Young et al 2003; Gomez-Abad et al 2005; Singh et al 2005; Franceschetti et al 2006; Singh et al 2006; Lohi et al 2007]. One additional mutation has been listed in the *Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database*. A heterozygous deletion of the entire *NHLRC1* gene has been reported in an Italian and a Serbian family [Lohi et al 2007].

- The missense mutation p.Pro69Ala, affecting the RING finger domain, is the most common mutation in *NHLRC1*. It is present in all affected individuals of Portuguese origin and has been reported repeatedly in affected persons of Italian and Spanish heritage [Chan, Bulman et al 2003; Gomez-Abad et al 2005; Franceschetti et al 2006]. The high prevalence of this mutation is also explained both by founder effect and recurrent mutation events [Chan, Bulman et al 2003; Gomez-Abad et al 2005; Franceschetti et al 2006].
- The p.Gly158fs mutation, involving the removal of two bases in the coding region (468-469delAG), is the second most common mutation in *NHLRC1* and is by far the most common deletion mutation.

Note: Although p.Pro69Ala mutation is common in affected persons of Italian and Spanish heritage, both the p.Pro69Ala and p.Gly158fs mutations have been identified in different ethnic groups, suggesting a recurrent mutational event, and these two sites represent hot spots for *NHLRC1* mutations [Ganesh et al 2006].

- Missense mutation p.Cys26Ser is prevalent in French-Canadian ethnic isolates [Chan, Bulman et al 2003; Singh et al 2006] and the shared chromosome 6p22 haplotype of these pedigrees suggested a founder effect [Chan, Bulman et al 2003]. To date, all but one French-Canadian individual were homozygous for the p.Cys26Ser mutation. This individual was heterozygous for two other *NHLRC1* mutations, but he was known to also have distant German and other European ancestry [Chan, Bulman et al 2003].

To date, this mutation has not been detected in non-French-Canadian families.

**Normal gene product:** The *NHLRC1* gene encodes malin, a 395-amino acid protein. Malin contains a zinc finger of the RING type and six NHL-repeat protein-protein interaction domains [Chan, Young et al 2003]. The presence of a RING finger predicts an E3 ubiquitin ligase function [Freemont 2000]. Malin colocalizes with laforin in the endoplasmic reticulum [Mittal et al 2007].

**Abnormal gene product:** See Ganesh et al (2006). Nearly all mutations in *NHLRC1* are predicted to result in the loss of function of malin [Chan, Young et al 2003; Gomez-Abad et al 2005; Singh et al 2005]. Malin is a single subunit E3 ubiquitin ligase involved in the ubiquitin-mediated proteolysis cascade [Gentry et al 2005; Lohi, lanzano et al 2005]. Malin also interacts with and ubiquitinates laforin, leading to its degradation [Gentry et al 2005]. Thus, one of the critical functions of malin is to regulate the cellular concentration of laforin by ubiquitin-mediated degradation, and missense mutations in *NHLRC1* associated with LD disrupt this function [Gentry et al 2005].

#### Animal models of Lafora disease

- **The *Epm2a* knockout mouse model of Lafora disease.** A mouse model using the knockout approach was generated by deleting the exon containing the PTP domain [Ganesh, Delgado-Escueta, Sakamoto et al 2002]. Homozygous null mutants were viable and showed Lafora bodies and signs of neurodegeneration as early as age two months. Only at age four months did the knockout mice begin to display an impaired behavioral response, followed at a later stage by myoclonic seizures, ataxia, and epileptiform activity on EEG. Generalized seizures did not occur. These findings illustrate that the accumulation of Lafora bodies precedes the onset of phenotypic abnormalities.
- **The transgenic mouse model of Lafora disease.** A transgenic mouse model of LD was generated by overexpressing laforin carrying a phosphatase inactivating point mutation (p.Cys266Ser) [Chan, Ackerley et al 2004]. This resulted in trapping laforin's normal yet unknown substrate and in the production of Lafora bodies in neurons, hepatocytes, and myocytes. The findings from this model regarding the localization of the laforin protein contributed significantly to the understanding of the physiologic role that laforin plays in LD. In brain, laforin resides in the neuronal somas and dendrites, similar to human disease. It localizes at the endoplasmic reticulum, but not directly on ribosomes. The model also showed that laforin preferentially binds polyglucosans in vivo and starch in vitro. Laforin is thus designed to detect polyglucosans and likely serves to initiate mechanisms to prevent their further accumulation or mechanisms to promote their removal [Chan, Ackerley et al 2004].
- **Canine model of Lafora disease.** Approximately 5% of miniature wirehaired dachshunds (MWHD) in the UK exhibit LD [Lohi, Young et al 2005]. The phenotype and the pathology observed in this breed of dog precisely replicates the symptoms observed in human LD, except for the later age of onset in dogs (age six years in dogs, equivalent to age ~40-45 years in humans). The genetic basis of LD in the MWHD consists of a coding dodecamer expansion mutation of the dog ortholog of *NHLRC1*. This mutation represents the first tandem repeat expansion mutation in any nonhuman species [Lohi, Young et al 2005].

#### Resources

See *Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.*—ED.

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### Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

### Suggested Readings

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### Chapter Notes

#### Author Notes

Web: [mni.mcgill.ca](http://mni.mcgill.ca)

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