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NLM Citation: Jansen AC, Andermann E. Progressive Myoclonus Epilepsy, Lafora Type. 2007 Dec 28 [Updated 2019 Feb 21]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Progressive Myoclonus Epilepsy, Lafora Type

Synonyms: Lafora Body Disease, Lafora Disease

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Created: December 28, 2007; Updated: February 21, 2019.

Summary

Clinical characteristics

Progressive myoclonus epilepsy, Lafora type (also known as Lafora disease [LD]) is characterized by focal occipital seizures presenting as transient blindness or visual hallucinations and fragmentary, symmetric, or generalized myoclonus beginning in previously healthy individuals at age eight to 19 years (peak 14-16 years). Generalized tonic-clonic seizures, atypical absence seizures, atonic seizures, and focal seizures with impaired awareness may occur. The course of the disease is characterized by increasing frequency and intractability of seizures. Status epilepticus with any of the seizure types is common. Cognitive decline becomes apparent at or soon after the onset of seizures. Dysarthria and ataxia appear early while spasticity appears late. Emotional disturbance and confusion are common in the early stages of the disease and are followed by dementia. Most affected individuals die within ten years of onset, usually from status epilepticus or from complications related to nervous system degeneration.

Diagnosis/testing

The diagnosis of Lafora disease is established in a proband with characteristic neurologic findings and/or biallelic pathogenic variants in one of the two known causative genes, *EPM2A* or *NHLRC1*, identified on molecular genetic testing. On rare occasion skin biopsy to detect Lafora bodies is necessary to confirm the diagnosis.

Management

Treatment of manifestations: Medical treatment in combination with physical therapy and psychosocial support. Regular evaluation and readjustment are required as the disease progresses. Antiepileptic drugs are effective against generalized seizures, but do not influence the progression of cognitive and behavioral symptoms. Overmedication in treating drug-resistant myoclonus is a risk. Gastrostomy feedings can decrease the risk of aspiration pneumonia when disease is advanced.

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Surveillance: Clinical and psychosocial evaluation at three- to six-month intervals throughout the teenage years.

Agents/circumstances to avoid: Phenytoin; possibly lamotrigine, carbamazepine, and oxcarbazepine.

Genetic counseling

Lafora disease is inherited in an autosomal recessive manner. Heterozygotes (carriers) are asymptomatic and not at risk of developing the disorder. 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, prenatal testing for at-risk pregnancies, and preimplantation genetic testing are possible if the pathogenic variants in the family are known.

Diagnosis

Suggestive Findings

Progressive myoclonus epilepsy, Lafora type, also known as Lafora disease (LD), **should be suspected** in a previously healthy older child or adolescent (usually in the early teens) who has the following:

- Focal occipital seizures presenting as transient blindness or visual hallucinations
- Fragmentary, symmetric, or generalized myoclonus
- Generalized seizures including tonic-clonic seizures, absence seizures, or drop attacks
- Progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, ataxia, and, at later stages, spasticity and dementia
- Slowing of background activity, loss of α-rhythm and sleep features, and photosensitivity on early EEGs
- Periodic acid Schiff-positive intracellular inclusion bodies (Lafora bodies) on skin biopsy (see Clinical Description)
- Normal brain MRI at onset

Establishing the Diagnosis

The diagnosis of Lafora disease **is established** in a proband with characteristic neurologic findings and/or biallelic pathogenic variants in one of the genes listed in Table 1.

Skin biopsy can be performed in individuals with a clinical diagnosis of Lafora disease in whom no pathogenic variant can be identified on molecular genetic testing.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Lafora disease is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Lafora disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Lafora disease, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Serial single-gene testing. Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

Sequence analysis of *EPM2A* and *NHLRC1* may be performed in any order, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found. Because the clinical manifestations of LD caused by pathogenic variants in either gene are so similar, it is not possible to predict which gene will be involved in any given individual. Therefore, serial single-gene testing, while possible, is not the recommended approach.

A multigene panel that includes *EPM2A* and *NHLRC1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Lafora disease is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which genes are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Progressive Myoclonus Epilepsy, Lafora Type

Gene [1, 2]	Proportion of Lafora Disease Attributed to Pathogenic Variants in This Gene	Proportion of Pathogenic Variants [3] Detectable by Test Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
EPM2A	42% [6]	85%-90% [6]	10%-15% [6]
NHLRC1	58% [6]	>90% [6]	<10% [6]

1. Genes are listed alphabetically.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Turnbull et al [2016]

Skin Biopsy

Although molecular genetic analysis of *EPM2A* and *NHLRC1* represents the gold standard for confirming the diagnosis, skin biopsy remains a useful diagnostic tool in individuals with a clinical diagnosis of Lafora disease in whom no pathogenic variant can be identified.

In affected individuals, skin biopsy reveals 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 involves a risk of false negative results [Lesca et al 2010], 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].

Clinical Characteristics

Clinical Description

Age of onset. Lafora disease (LD) typically starts during childhood or adolescence (range: 8-19 years, peak 14-16 years), after a period of apparently normal development. Many affected individuals experience isolated febrile or nonfebrile convulsions in infancy or early 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 et al 2000b, Minassian 2002]. Intra- and interfamilial variability in age at onset is considerable [Gómez-Abad et al 2007, Lohi et al 2007].

Seizure types. The main seizure types in LD include myoclonic seizures and occipital seizures, although generalized tonic-clonic seizures, atypical absence seizures, atonic seizures, and focal seizures with impaired awareness 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 et al 2000b]. Not all visual hallucinations in individuals with LD are epileptic in origin, as some respond initially to antipsychotic, rather than antiepileptic, medications [Andrade et al 2005].

Progression. 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 while spasticity appears late. Emotional disturbance and confusion are common in the early stages of the disease and are followed by dementia. See Table 2 for a comparison of the findings at onset and later in the disease course.

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 [Turnbull et al 2016]. Variation by country in the care available for individuals with LD may influence longevity and disease complications.

Table 2. Clinical Findings of Progressive Myoclonus Epilepsy, Lafora Type

Evaluation Type	At Onset	Later in Disease Course
General physical examination, incl liver & spleen size	Normal	Normal
Neurologic examination, incl fundi & reflexes	Normal	Dysarthria, ataxia, spasticity; fundi remain normal
Mental state examination	Visual hallucinations, cognitive deficits, depressed mood, headaches	↑ hallucinations, agitation, & dementia w/predominantly frontal cognitive impairment affecting mainly performance ability & executive function
EEG	Normal or slow background, occipital discharges	Slow background, paroxysms of generalized irregular spike-wave discharges w/occipital predominance, & focal (especially occipital) abnormalities, loss of sleep features, marked photosensitivity
Visual, somatosensory, & auditory brain stem evoked potentials	High-voltage visual & somatosensory evoked potentials	Amplitudes may return to normal size; prolongation of brain stem & central latencies
Nerve conduction studies	Normal	Normal
MRI of the brain	Normal	Normal or atrophy [1]
Proton MR spectroscopy of the brain	Data not available	↓ NAA/creatine ratio in frontal & occipital cortex, basal ganglia, & cerebellum; ↓ NAA/myoinositol ratio in frontal gray & white matter; ↓ NAA/choline ratio in cerebellum [2]
Transcranial magnetic stimulation	Not applicable	Defective short intracortical inhibition: inhibition at ISI 6 ms & ISI 10 ms; defective long-interval cortical inhibition

Altindag et al [2009], Canafoglia et al [2010], Turnbull et al [2016]
ISI = interstimulus intervals; NAA = N-acetylaspartate
1. No significant correlation observed with disease evolution
2. At least two years after onset of symptoms

Genotype-Phenotype Correlations

Genotype-phenotype correlations are difficult to establish in LD due to the large number of pathogenic variants in both *EPM2A* and *NHLRC1*, as well as the frequent occurrence of compound heterozygotes in different combinations [Chan et al 2005, Gómez-Abad et al 2005].

Within an ethnic group of individuals sharing the same pathogenic variant the phenotype can be highly variable [Gómez-Abad et al 2007] or very similar [Turnbull et al 2008].

Intra- and interfamilial variability in age at onset is considerable, suggesting that genetic factors other than the *EPM2A* or *NHLRC1* pathogenic variants may influence the pathogenesis of LD [Gómez-Abad et al 2007, Lohi et al 2007]. The LD-associated gene products laforin and malin are known to interact with a diverse set of proteins, and variations in genes that code for these interacting proteins could contribute to variations in phenotype [Singh & Ganesh 2012]. It has indeed been demonstrated that a sequence variant in *PPP1R3C*, which codes for the protein PTG (protein targeting to glycogen), contributes to a milder course of LD [Guerrero et al 2011].

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

- A potential sub-phenotype consisting of childhood-onset learning disorder followed by epilepsy and neurologic deterioration has been associated with either pathogenic variants in exon 1 of *EPM2A* [Ganesh et al 2002a, Annesi et al 2004] or the p.Ile198Asn pathogenic variant located in an NHL protein-protein interaction domain of *NHLRC1* [Gómez-Abad et al 2005]. However, further study is needed to clarify whether this observation represents a true "sub-phenotype" or is the result of as-yet unknown genetic and/or environmental modifying factors [Lesca et al 2010].
- Some studies have indicated that individuals with pathogenic variants in *NHLRC1* have a slightly milder course than those with pathogenic variants in *EPM2A* [Gómez-Abad et al 2005, Franceschetti et al 2006, Singh et al 2006], while others found no difference in disease severity between the two [Traoré et al 2009, Brackmann et al 2011]. This observation may, at least in part, be due to the relatively common occurrence of the pathogenic variant p.Asp146Asn in *NHLRC1*, which is associated with an atypical milder form of LD consisting of a later onset of symptoms, longer disease course, and extended preservation of daily activities in all individuals reported to date. This pathogenic variant has never been reported in individuals with typical LD [Ferlazzo et al 2014, Lanoiselée et al 2014].

Nomenclature

Lafora disease (LD) is also referred to as myoclonic epilepsy of Lafora or progressive myoclonic epilepsy-2 (EPM2).

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 [Genton et al 2016].

Prevalence

Exact prevalence figures for LD are lacking; based on all published reports of LD-causing pathogenic variants, the overall global frequency is estimated at 4:1,000,000 individuals [Turnbull et al 2016].

LD occurs worldwide. While relatively rare in the nonconsanguineous 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].

Within the Italian and Japanese populations, pathogenic variants in *NHLRC1* are more common than pathogenic variants in *EPM2A*. Conversely, *EPM2A* pathogenic variants are more common in the Spanish and French populations. Within the Indian and Arab populations the distribution of pathogenic variants in the two genes is more or less even [Singh & Ganesh 2009, Lesca et al 2010].

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 [A Lehesjoki & R Kälviäinen, personal communication].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *EPM2A* or *NHLRC1*.

Differential Diagnosis

Early-onset Lafora body disease (OMIM 616640) is characterized by progressive myoclonus epilepsy and the presence of Lafora bodies in muscle but not in sweat glands. In contrast to typical Lafora disease (LD), early-onset LD presents at around age five years. Symptoms include dysarthria, myoclonus, and ataxia, which can be confused with late infantile-variant neuronal ceroid-lipofuscinosis. However, pathology reveals Lafora bodies instead of ceroid-lipofuscinosis. The disease course of early-onset LD is much more protracted than either infantile neuronal ceroid-lipofuscinosis or typical LD. Early-onset LD has been reported in one individual with homozygous pathogenic variants in *PRDM8*; inheritance is autosomal recessive [Turnbull et al 2012].

Although the occurrence of myoclonus and generalized tonic-clonic seizures in adolescence may raise the possibility of **juvenile myoclonic epilepsy** (OMIM 254770), the persistence of EEG background slowing and cognitive deterioration should raise the suspicion of a more severe epilepsy syndrome, such as progressive myoclonus epilepsy. Juvenile myoclonic epilepsy is caused by pathogenic variants in *EFHC1*; inheritance is autosomal dominant.

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

Careful ophthalmologic examination, including electroretinography, is useful in addressing the possibilities of neuronal ceroid-lipofuscinoses and **sialidosis types I and II** (OMIM 256550).

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.

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.

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

See Epilepsy, Progressive Myoclonic: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Lafora disease (LD), the following are recommended if they have not already been completed:

- Clinical evaluation
- Multidisciplinary evaluation of all aspects of development including concerns regarding behavior, intellectual ability, academic performance, neuropsychological skills, speech and language skills, motor skills, psychosocial skills, and impact on parents and sibs
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Management of LD consists of medical treatment in combination with physical therapy and psychosocial support. Regular evaluation and readjustment are required as the disease progresses.

Medical Treatment

In general, treatment recommendations for LD follow those of other PMEs [Michelucci et al 2016, Ferlazzo et al 2017]. Apart from an open-label trial with perampanel in ten individuals with LD, no specific clinical trials have been performed in LD.

Antiepileptic drugs (AEDs) have a clear effect against generalized seizures, sometimes controlling seizures for many months. Generalized seizures are rare in individuals who are treated, even years after disease onset. However, AEDs do not influence the progression of cognitive and behavioral symptoms.

- **First-line AEDs** include valproic acid and benzodiazepines.
  - Valproic acid is the traditional antiepileptic treatment for LD; because it is a broad-spectrum AED, it suppresses, for some time, the generalized tonic-clonic seizures and myoclonic jerks.
  - Benzodiazepines (clonazepam, clobazam, diazepam) 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. Some individuals may develop tolerance, requiring dose adjustment or switching to another benzodiazepine.
  - Because the myoclonus associated with LD may be drug resistant, overmedication may be a risk in individuals with LD.
- **Second-line AEDs** include levetiracetam, zonisamide, topiramate, and perampanel, although evidence is limited.
  - Common polytherapy combinations consist of valproic acid with perampanel, topiramate, zonisamide, or levetiracetam, and a benzodiazepine.
  - An open-label trial with add-on perampanel in ten individuals with LD showed significant reduction in seizures greater than 74% from baseline in four. Seven had major improvement in myoclonus. Three withdrew due to inefficacy or side effects. There was no improvement in disability or cognition [Goldsmith and Minassian 2016].
- **Third-line strategies** include primidone, phenobarbital, piracetam, and ethosuximide.

  There are two anecdotal reports on the use of vagal nerve stimulation in LD [Hajnsek et al 2013, Mikati & Tabbara 2017].
- **Emergency treatment** for severe aggravation with serial seizures or status epilepticus consists of intravenous benzodiazepines or loading with phenytoin. Phenytoin should not be kept as maintenance therapy after arrest of the status.

Physical Therapy

Physical therapy is recommended in order to maintain ambulation as long as possible, and to prevent pulmonary and orthopedic complications.

Psychosocial Support

Schooling. During early stages of the disease, it is recommended to maintain schooling and social life as much as possible, although time in school may progressively need to be reduced.

Family support. In addition to medical treatment, psychosocial support of the patient and the family are key and need to be evaluated and adjusted throughout the entire disease duration. This includes regular evaluation and discussion of management options, referral to patient organizations (see below), psychological support, and social services to assist with organization of care and administrative issues.

Support in Later Stages

As the disease progresses, generalized seizures become more frequent and myoclonus more disabling, requiring more intensive support in the home environment or through institutionalization, depending on availability of care and family preferences.

- Serial seizures or status epilepticus may require admission to critical care.
- 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 teen years.

Agents/Circumstances to Avoid

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

Anecdotal reports describe possible exacerbation of myoclonus with the following:

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

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to evaluation of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Due to the severity of the disorder, individuals with LD typically do not have children. However, in cases of mild LD with slow disease progression as reported with the p.Asp146Asn variant in *NHLRC1*, pregnancies could occur [Ferlazzo et al 2014]. The universal use of AEDs in individuals with LD, even when mild, warrant counseling regarding the potential consequences of fetal exposure to maternal anticonvulsant therapy.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

It is anticipated that with an improved understanding of the pathogenesis in LD, targeted treatments might become available in the future [Minassian 2016].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

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 (i.e., carriers of one *EPM2A* or *NHLRC1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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.
- Intrafamilial variability has been observed (see Genotype-Phenotype Correlations).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with LD would be obligate heterozygotes (carriers) for a pathogenic variant in *EPM2A* or *NHLRC1*. Because of the early onset and rapid deterioration, individuals with LD typically do not reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *EPM2A* or *NHLRC1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *EPM2A* or *NHLRC1* pathogenic variants in the family.

Carrier testing is also possible for the reproductive partners of known carriers; absence of a detectable *EPM2A* or *NHLRC1* pathogenic variant lowers the likelihood that the reproductive partner is a carrier but does not rule out this possibility.

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/preimplantation genetic 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 affected, are carriers, or are at risk of being carriers.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *EPM2A* or *NHLRC1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather

than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Chelsea's Hope Lafora Children Research Fund**
  chelseashope.org
- **American Epilepsy Society**
  aesnet.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com

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	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EPM2A	6q24.3	Laforin	EPM2A database	EPM2A	EPM2A
NHLRC1	6p22.3	E3 ubiquitin-protein ligase NHLRC1	NHLRC1 database	NHLRC1	NHLRC1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

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

254780	MYOCLONIC EPILEPSY OF LAFORA 1; MELF1
607566	EPM2A GLUCAN PHOSPHATASE, LAFORIN; EPM2A
608072	NHL REPEAT-CONTAINING PROTEIN 1; NHLRC1
620681	MYOCLONIC EPILEPSY OF LAFORA 2; MELF2

Molecular Pathogenesis

The mechanism by which pathogenic variants in either *EPM2A* or *NHLRC1* result in Lafora disease and the exact role of the Lafora bodies in the pathogenesis of LD have been the subject of intensive research efforts over the past few years.

Pathology in LD consists of the progressive formation of polyglucosans (insoluble glucose polysaccharides that precipitate and aggregate into concretized masses called Lafora bodies), resulting in neurodegeneration. Lafora bodies form in neuronal perikarya and in neuronal short processes (mostly dendrites). Lafora bodies in the neuronal processes are much smaller but they massively outnumber Lafora bodies in the perikarya. Extraneurally, Lafora bodies also form in heart, liver, and skeletal muscle, but cause no symptoms in these organs [Turnbull et al 2011].

A normal glycogen molecule contains up to 55,000 glucose units, yet remains soluble because its glucose chains are short (13 units), each chain is a branch of another, and the whole molecule is a sphere, the surface of which is composed of the hydrophilic ends of chains [Graham et al 2010]. This unique organization allows mammalian cells to store large amounts of carbohydrate energy in a soluble, rapidly accessible form. Without branching, glucose polymers 13 units or longer are poorly soluble and tend to precipitate and crystallize [Hejazi et al 2008]. Polyglucosans are malformed glycogen molecules. They have very long chains, insufficient branches, and a resultant lack of spherical organization. They are more similar to plant amylopectin or starch than to glycogen, and like these plant carbohydrates they are insoluble and they precipitate and accumulate [Minassian 2001].

Glycogen is synthesized through coordinated actions of glycogen synthase and glycogen branching enzyme – the former responsible for chain elongation, the latter for chain branching. Glycogen is digested by glycogen phosphorylase and glycogen debranching enzyme.

The current view on LD pathogenesis suggests that LD is predominantly caused by an impairment in chain-length regulation affecting only a small proportion of the cellular glycogen. The principal function of laforin (gene product of *EPM2A*) relevant to LD is mediated through malin (gene product of *NHLRC1)* and directed to preventing glycogen molecules with hyperextended chains. In the absence of either protein, some glycogen molecules at a time precipitate and gradually over time aggregate and amass into Lafora bodies, which, reaching a certain threshold profusion (at age ~14 years in humans), initiate and then drive the progressive myoclonus epilepsy [Nitschke et al 2017; Sullivan et al 2017].

EPM2A

Gene structure. *EPM2A* has four exons spanning 130 kb; they are alternatively spliced to form two major *EPM2A* transcripts [Minassian et al 1998, Serratosa et al 1999, Ganesh et al 2000, Gómez-Garre et al 2000]. NM_005670.3 represents the longer transcript and encodes the longer laforin isoform (a) of 331 amino acids. For a detailed summary of gene, transcript, and protein isoform information, see Table A, **Gene** and **Normal gene product**.

Pathogenic variants. To date, more than 70 different pathogenic variants in *EPM2A* have been reported in more than 100 families [Turnbull et al 2016]. An overview of the different pathogenic variants can be found in the Human Gene Mutation Database or the Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database [Ianzano et al 2005].

Pathogenic variants in *EPM2A* are scattered all along the coding regions of the gene, but also accumulate in discrete spots of high recurrence. The most common pathogenic variant is the nonsense c.721C>T variant, the so-called "Spanish" pathogenic variant, which accounts for approximately 17% of *EPM2A*-mediated LD. Its high prevalence is the result of both a founder effect and recurrent events [Gómez-Garre et al 2000, Ganesh et al 2002b]. Large deletions make up 10%-15% of *EPM2A* pathogenic variants, and the pathogenic c.512G>A variant accounts for approximately 8%.

Table 3. Pathogenic *EPM2A* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.512G>A	p.Arg171His	NM_005670.3 NP_005661.1
c.721C>T	p.Arg241Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *EPM2A* is known to encode two distinct proteins by differential splicing; a phosphatase active cytoplasmic isoform (a) (laforin, NP_005661.1) and a phosphatase inactive nuclear isoform (b)

(NP_001018051.1). Both isoforms of the laforin protein have unique C termini [Ganesh et al 2002c, Ianzano et al 2004]. The carboxyl terminal of isoform (b) targets laforin to the nucleus, a feature that is not shared by longer laforin isoform (a). Ianzano et al [2004] demonstrated that disturbances in the physiologic functions of laforin isoform (a) underlie the pathogenesis of LD, and isoform (b) cannot functionally substitute for laforin isoform (a). The common segment of the laforin isoforms consists of a carbohydrate-binding module and a dual-specificity protein phosphatase domain [Ganesh et al 2000].

Dubey et al identified three additional *EPM2A* splice variants with potential to code for five distinct proteins in alternate reading frames. The novel isoforms, when ectopically expressed in cell lines, show distinct subcellular localization and interact with and serve as substrates of malin (protein product of *NHLRC1*). Alternative splicing could possibly be one of the mechanisms by which *EPM2A* regulates the cellular functions of the proteins it codes for [Dubey et al 2012].

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 et al 2000b, Ganesh et al 2002b].

Laforin is conserved in all vertebrates; while it has been lost in the vast majority of lower organisms, it is an ancient protein that is conserved in a subset of protists and invertebrates that have undergone slower rates of molecular evolution and/or metabolize a carbohydrate similar to Lafora bodies. The laforin protein holds a unique place in evolutionary biology and has yielded insights into glucan metabolism and the molecular etiology of Lafora disease [Gentry & Pace 2009].

Abnormal gene product. Nonsense variants, insertions, and deletions in *EPM2A* are predicted to be functionally "null" and to have lost phosphatase activity. Missense variants in *EPM2A* also result in a lack of phosphatase activity in vitro, resulting in a "null" effect [Fernández-Sánchez et al 2003, Ganesh et al 2006]. Loss of phosphatase activity is not restricted to pathogenic variants located in the DSPD; it has also been observed for pathogenic variants affecting the CBD of *EPM2A* [Wang et al 2002, Fernández-Sánchez et al 2003]. It is likely that the missense variants 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 et al 2002a]. Missense variants also affect the subcellular localization of laforin [Ganesh et al 2002a, Mittal et al 2007] and disrupt the interaction of laforin with R5 and malin (protein product of *NHLRC1*) proteins that interact with laforin in vivo [Fernández-Sánchez et al 2003, Gentry et al 2005]. It is evident that not all aspects of the protein function have been tested for each missense variant, and that sensitive assays for checking the effect of pathogenic variants on protein function are yet to be developed [Singh & Ganesh 2009].

NHLRC1 (*EPM2B*)

Gene structure. *NHLRC1* 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 et al 2003b]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. To date, more than 70 pathogenic variants have been reported in more than 125 families. The majority are missense variants, although insertions, deletions, and nonsense variants have also been found. A heterozygous deletion of the entire *NHLRC1* gene has been reported in an Italian and a Serbian family [Lohi et al 2007]. An overview of pathogenic alleles in *NHLRC1* is available in the Human Gene Mutation Database or the Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database [Ianzano et al 2005].

- The missense variant c.205C>G, affecting the RING finger domain, is the most common variant in *NHLRC1* and accounts for approximately 15% of *NHLRC1* pathogenic variants. It is present in all affected

individuals of Portuguese origin and has been reported repeatedly in affected persons of Italian, French, and Spanish heritage [Chan et al 2003a, Gómez-Abad et al 2005, Franceschetti et al 2006, Lesca et al 2010]. The high prevalence of this pathogenic variant is also explained both by founder effect and recurrent mutation events [Chan et al 2003a, Gómez-Abad et al 2005, Franceschetti et al 2006].

- The c.468_469delAG pathogenic variant, involving the removal of two bases in the coding region, accounts for approximately 8% of *NHLRC1* pathogenic variants, and is by far the most common deletion. It has been identified in 14 individuals belonging to the same genetic isolate of tribal Oman. All shared a common haplotype, suggesting a founder effect [Turnbull et al 2008].
- Note: Whereas c.205C>G pathogenic variant is common in affected persons of Italian and Spanish heritage, both the c.205C>G and c.468_469delAG pathogenic variants have been identified in different ethnic groups, suggesting a recurrent mutation event; these two sites represent hot spots for *NHLRC1* pathogenic variants [Ganesh et al 2006].
- Missense pathogenic variant c.76T>A is prevalent in French-Canadian ethnic isolates [Chan et al 2003a, Singh et al 2006] and the shared chromosome 6p22 haplotype of these pedigrees suggested a founder effect [Chan et al 2003a].
- The c.436G>A variant has been reported in individuals with mild LD. The mean age at onset in individuals with this variant reported in the literature is 18 years; this variant is the only one reported with such late onset age [Ferlazzo et al 2014].

Table 4. *NHLRC1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.76T>A [1]	p.Cys26Ser	NM_198586.2 NP_940988.2
c.205C>G [1]	p.Pro69Ala	
c.436G>A	p.Asp146Asn	
c.593T>A	p.Ile198Asn	
c.468_469delAG [1]	p.Gly158ArgfsTer17	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Details in Pathogenic variants

Normal gene product. *NHLRC1* encodes E3 ubiquitin-protein ligase NHLRC1 (also known as malin), a 395-amino acid protein. Malin contains a zinc finger of the RING type and six NHL-repeat protein-protein interaction domains [Chan et al 2003b].

Abnormal gene product. Nearly all pathogenic variants in *NHLRC1* are predicted to result in the loss of function of malin [Chan et al 2003b, Gómez-Abad et al 2005, Singh et al 2005]. For more information, see Turnbull et al [2016].

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Chapter Notes

Author Notes

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Revision History

- 21 February 2019 (ha) Comprehensive update posted live
- 22 January 2015 (me) Comprehensive update posted live
- 3 November 2011 (me) Comprehensive update posted live
- 28 December 2007 (me) Review posted live
- 2 January 2007 (ea) Original submission

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