U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Lehesjoki AE, Kälviäinen R. Progressive Myoclonic Epilepsy Type 1. 2004 Jun 24 [Updated 2020 Jul 2]. 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 Myoclonic Epilepsy Type 1

Synonyms: EPM1, Unverricht-Lundborg Disease (ULD)

Anna-Elina Lehesjoki, MD, PhD[1] and Reetta Kälviäinen, MD, PhD[2]

Created: June 24, 2004; Updated: July 2, 2020.

Summary

Clinical characteristics

Progressive myoclonic epilepsy type 1(EPM1) is a neurodegenerative disorder characterized by onset from age six to 15 years, stimulus-sensitive myoclonus, and tonic-clonic epileptic seizures. Some years after the onset, ataxia, incoordination, intentional tremor, and dysarthria develop. Individuals with EPM1 are cognitively mostly within the normal range, but show emotional lability and depression. The epileptic seizures are usually well controlled by anti-seizure medication, but the myoclonic jerks are progressive, action activated, and treatment resistant, and can be severely disabling.

Diagnosis/testing

The diagnosis of EPM1 is established in a proband with suggestive findings and either biallelic abnormal CCC-CGC-CCC-GCG dodecamer repeat expansions in *CSTB* or compound heterozygosity for a *CSTB* dodecamer repeat expansion and a *CSTB* sequence variant (i.e., single-nucleotide variant or indel) identified by molecular genetic testing.

Management

Treatment of manifestations: Symptomatic pharmacologic and rehabilitative management, including psychosocial support, are the mainstay of care; valproic acid, the first drug of choice, diminishes myoclonus and the frequency of generalized seizures; clonazepam, approved by FDA for the treatment of myoclonic seizures, is an add-on therapy; high-dose piracetam is used to treat myoclonus; levetiracetam, brivaracetam, and perampanel appear to be effective for both myoclonus and generalized seizures. Topiramate and zonisamide may also be used as add-on therapy.

Surveillance: Lifelong clinical follow up including evaluation of drug treatment and rehabilitation.

Author Affiliations: 1 Folkhälsan Research Center and University of Helsinki, Helsinki, Finland; Email: anna-elina.lehesjoki@helsinki.fi. 2 Kuopio Epilepsy Center, Kuopio University Hospital, Member, EpiCARE ERN, University of Eastern Finland, Kuopio, Finland; Email: reetta.kalviainen@kuh.fi.

Agents/circumstances to avoid: Phenytoin aggravates neurologic symptoms or even accelerates cerebellar degeneration; sodium channel blockers (carbamazepine, oxcarbazepine), GABAergic drugs (tiagabine, vigabatrin), and gabapentin and pregabalin may aggravate myoclonus and myoclonic seizures.

Genetic counseling

EPM1 is inherited in an autosomal recessive manner. 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 both *CSTB* pathogenic variants in a family are known, carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

The diagnosis of progressive myoclonic epilepsy type 1 (EPM1) **is suspected** in a previously healthy child age six to 15 years who manifests the following:

- Involuntary, action-activated myoclonic jerks AND/OR generalized tonic-clonic seizures
- Photosensitive, generalized spike-and-wave and polyspike-and-wave paroxysms on EEG
- Abnormal EEG (always abnormal, even before the onset of manifestations). The background activity is labile and may be slower than normal. Photosensitivity is marked.
- A gradual worsening of the neurologic manifestations (myoclonus and ataxia), difficulties running, playing sports, using stairs
- Normal brain MRI

Establishing the Diagnosis

The diagnosis of EPM1 disease **is established** in a proband with suggestive findings and either biallelic abnormal CCC-CGC-CCC-GCG dodecamer repeat expansions in *CSTB* or compound heterozygosity for a *CSTB* dodecamer repeat expansion and a *CSTB* sequence variant (i.e., single-nucleotide variant or indel) identified by molecular genetic testing (see Table 1).

Note: Pathogenic dodecamer repeat expansions in *CSTB* **cannot be detected** by sequence-based multigene panels, exome sequencing, or genome sequencing.

Repeat sizes

- **Normal.** 2 to 3 dodecamer repeats
- **Uncertain significance.** 12-17 dodecamer repeats (unstable, but not clinically characterized)
- **Pathogenic (full penetrance).** ≥30 dodecamer repeats

Note: The dodecamer repeat sequence is CCC-CGC-CCC-GCG. Repeats of 4-11 and 18-29 have not been observed.

Molecular genetic testing relies on targeted analysis to characterize the number of *CSTB* CCC-CGC-CCC-GCG dodecamer repeats (see Table 7).

Table 1. Molecular Genetic Testing Used in Progressive Myoclonic Epilepsy Type 1

Gene [1]	Method [2, 3]	Proportion of Probands with a Pathogenic Variant Detectable by Method
CSTB	Targeted analysis for the dodecamer expansion	~90% [4, 5]
	Sequence analysis [6]	~10% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Table 7 for specific methods to characterize the number of dodecamer (CCC-CGC-CCC-GCG) repeats in *CSTB*.
3. Sequence-based multigene panels, exome sequencing, and genome sequencing cannot detect pathogenic repeat expansions 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. Lalioti et al [1997], Joensuu et al [2008]
6. ~99% in Finnish individuals [Joensuu et al 2008]

Clinical Characteristics

Clinical Description

In more than half of individuals with progressive myoclonic epilepsy type 1 (EPM1) the first manifestation is involuntary myoclonic jerks [Kälviäinen et al 2008, Hyppönen et al 2015]. The myoclonic jerks are action activated and stimulus sensitive and may be provoked by light, physical exertion, and stress. They occur predominantly in the proximal muscles of the extremities and are asynchronous; they may be focal or multifocal and may generalize to a series of myoclonic seizures or even status myoclonicus (continuous myoclonic jerks involving a semi-loss of consciousness).

During the first five to ten years, the symptoms/myoclonic jerks characteristically progress and about one third of affected individuals become severely incapacitated (wheelchair bound). Although the myoclonic jerks are disabling and resistant to therapy, the individual usually learns to tolerate them over time, if psychosocial support is good and depression not too severe.

In almost half of individuals, the first manifestation is tonic-clonic seizures. There may also be absence, psychomotor, and/or focal motor seizures. Epileptic seizures, infrequent in the early stages of the disease, often increase in frequency during the ensuing three to seven years. Later they may cease entirely with appropriate anti-seizure medication. In rare cases, tonic-clonic seizures do not occur.

Neurologic findings initially appear normal; however, experienced observers usually note recurrent, almost imperceptible myoclonus, especially in response to photic stimuli or other stimuli (threat, clapping of hands, nose tapping, reflexes) or to action (movements made during neurologic examination) or to cognitive stimuli (task demanding cognitive and psychomotor processing). Some years after the onset, ataxia, incoordination, intentional tremor, and dysarthria develop.

Cognitive performance, especially memory, is mostly within the normal range. However, affected individuals may exhibit poor performance in time-limited tests dependent on motor functions.

The disease course is inevitably progressive; however, the rate of deterioration – especially in terms of walking capacity – appears to vary even within the same family. Generalized tonic-clonic seizures are usually controlled with treatment, but myoclonic jerks may become severe, appear in series, and inhibit normal activities [Magaudda et al 2006, Hyppönen et al 2015]. Myoclonic jerks may also be subcortical in origin and therefore difficult to control [Danner et al 2009]. The individual becomes depressed and progression ensues. Education is often interrupted because of emotional, social, and intellectual problems.

In the past, life span was shortened; many individuals died eight to 15 years after the onset of disease, usually before age 30 years. With better pharmacologic, physiotherapeutic, and psychosocial supportive treatment, life expectancy is comparable to controls up to age 40 years, but is poorer over the long term. Death occurs mainly due to respiratory infections [R Kälviäinen, personal communication].

Genotype-Phenotype Correlations

Individuals with pathogenic variants in *CSTB* usually develop similar disease manifestations. There is evidence that correlation exists between the length of the expanded dodecamer repeat and the age of onset or disease severity [Hyppönen et al 2015]. However, disease severity also varies among affected individuals within a family with apparently similar repeat-size expansions.

Moreover, EPM1 resulting from compound heterozygosity for a dodecamer repeat expansion and a sequence variant (i.e., single-nucleotide variant or indel) often presents with earlier age of onset, more severe myoclonus, and seizures that may be drug resistant [Koskenkorva et al 2011, Canafoglia et al 2012]. It has been also suggested that compound heterozygosity causes a more severe EPM1 phenotype in affected males than females, but the numbers are small [Assenza et al 2017].

Recently, homozygous stop-codon and frameshift pathogenic variants in *CSTB* were associated with infantile-onset progressive disorders with unexplained severe developmental delay, microcephaly, and hypomyelination [Mancini et al 2016, O'Brien et al 2017).

Nomenclature

Progressive myoclonic epilepsy type 1 (EPM1) was originally referred to as Baltic myoclonus (or Baltic myoclonic epilepsy) and Mediterranean myoclonus. EPM1 is known to occur worldwide, and thus these toponyms are misleading and should no longer be used.

Prevalence

EPM1 has the highest incidence among the progressive myoclonic epilepsies (PMEs), a term that includes a large and varied group of diseases characterized by stimulus-sensitive myoclonus, epilepsy, and progressive neurologic deterioration.

EPM1 occurs worldwide. Prevalence is increased in certain populations:

- The North African countries of Tunisia, Algeria, and Morocco, where exact prevalence figures are not available
- Finland, where its prevalence (2:100,000) is higher than anywhere else in the world [R Kälviäinen, personal communication]. The incidence in Finland is estimated at 1:20,000 births.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CSTB*.

Differential Diagnosis

At the onset of progressive myoclonic epilepsy type 1 (EPM1), juvenile myoclonic epilepsy (JME) (OMIM PS254770) – which has a more favorable outcome – should be considered as a diagnostic alternative. Individuals with JME have a normal neurologic examination and undisturbed background of the EEG.

Other disorders to consider in the differential diagnosis of EPM1 are summarized in Table 2.

Table 2. Genes of Interest in the Differential Diagnosis of Progressive Myoclonic Epilepsy Type 1

Gene(s)	Disorder	MOI	Clinical Characteristics of Differential Diagnosis Disorder	
			Overlapping w/EPM1	Distinguishing from EPM1
EPM2A *NHLRC1*	PME, Lafora type	AR	• PME • Focal occipital seizures & fragmentary, symmetric, or generalized myoclonus beginning in previously healthy individuals	• Later onset (age 8-19 yrs); rapid disease progression; death ~10 yrs after diagnosis • Prior to the availability of molecular genetic testing, histologic findings on skin biopsy established the diagnosis.
GOSR2	EPM6 (OMIM 614018)	AR	• Early-onset ataxia (average age 2 yrs) followed by action myoclonus & seizures later in childhood • Independent ambulation lost in 2nd decade	Earlier onset; scoliosis (develops by adolescence)
KCNC1	EPM7 (OMIM 616187)	AD	• Resembles EPM1 at disease onset [1] • Presents at age 6-15 yrs w/myoclonus (sometimes reported as tremor) • The later disease course is characterized by moderate-to-severe incapacitating myoclonus, infrequent tonic-clonic seizures, ataxia, & mild (if any) cognitive decline.	EPM7 & EPM1 have a remarkably similar clinical presentation. EPM7 may have a somewhat more severe progression than EPM1 in its early phases.
MT-TF *MT-TI* *MT-TK* *MT-TL1* *MT-TP*	MERRF	Mat	• PME • Onset usually in childhood, after normal early development	• Brain MRI often shows brain atrophy & basal ganglia calcification. • Muscle biopsy typically shows RRF.
SCARB2	Action myoclonus - renal failure syndrome	AR	Typically presents at ages 15-25 yrs; may present w/neurologic symptoms (e.g., tremor, action myoclonus, seizures, ataxia) [2]	May present w/proteinuria that progresses to renal failure

AD = autosomal dominant; AR = autosomal recessive; Mat = maternal; MERRF = myoclonic epilepsy with ragged red fibers; MOI = mode of inheritance; PME = progressive myoclonic epilepsy; RRF = ragged red fibers

1. Muona et al [2015]

2. Action myoclonus - renal failure syndrome typically comprises a continuum of two major (and ultimately fatal) manifestations: progressive myoclonic epilepsy and renal failure; however, in some instances, the kidneys are not involved. Neurologic manifestations can appear before, simultaneously, or after the renal manifestations.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with progressive myoclonic epilepsy type 1 (EPM1), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with EPM1

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment of myoclonus, incl myoclonus at rest, w/action, & in response to stimuli	Use standardized UMRS.
	Seizure type & frequency	Obtain baseline EEG before initiation of anti-seizure therapy (when EEG is most characteristic).
	Cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades & smooth pursuit)	Use standardized scale to establish baseline for ataxia (SARA, ICARS, or BARS).
Musculoskeletal / Activities of daily living	By physical medicine & rehab/OT/PT	To assess gross motor & fine motor skills, gait, ambulation, need for adaptive devices, need for ongoing PT/OT
Speech	For those w/dysarthria: speech & language eval	Consider referral to speech & language pathologist.
Cognitive	Neuropsychologist	Cognitive eval to establish baseline
Psychiatric	Psychiatrist	Evaluate as needed for depression & supportive therapy.
Development / School performance	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/ language eval • Evaluation for special education
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of EPM1 to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent and patient organizations; • Need for social work involvement for parental support; • Need for home nursing referral.	To facilitate peer support for patients & families

BARS = Brief Ataxia Rating Scale; ICARS = International Cooperative Ataxia Rating Scale; MOI = mode of inheritance; OT = occupational therapist/therapy; PT = physical therapist/therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMRS = Unified Myoclonus Rating Scale

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with EPM1

Manifestation/Concern		Treatment	Considerations/Other
Myoclonus	**Pharmacologic**	Valproic acid	First drug of choice; diminishes myoclonus & frequency of generalized seizures
		Clonazepam	FDA-approved for treatment of myoclonic seizures; used as add-on therapy [1]
		High-dose piracetam	Useful in treatment of myoclonus [2]
		Levetiracetam, brivaracetam, [3] perampanel [4]	Appears effective for both myoclonus & generalized seizures
		Topiramate & zonisamide	May be used as add-on therapies
		N-acetylcysteine	Variable results [5]
		Vagus nerve stimulation	Reduces seizures & significantly improves cerebellar function on neurologic exam [6]
	Other	Avoid extreme stimuli (lights, noises, stress).	
Seizures		Anti-seizure medication	
Activities of daily living (ADL)		PT/OT	• PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function [1] • OT to optimize ADL (incl use of adaptive devices, e.g., weighted eating utensils & dressing hooks) • Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, motorized chairs). • Home adaptations to prevent falls (e.g., grab bars, raised toilet seats) & improve mobility (e.g., ramps to accommodate motorized chairs)
Developmental delay / Intellectual disability		See Developmental Delay / Intellectual Disability Management Issues.	
Dysarthria		Speech & language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia		Feeding therapy programs to improve nutrition & dysphagia & reduce aspiration risk	• Video esophagram may help define best food consistency. • Education re strategies to mitigate aspiration • PEG tube in advanced cases
Weight		Nutrition assessment	• Consider nutritional & vitamin supplementation to meet dietary needs. • Avoid obesity, which can exacerbate difficulties w/ambulation & mobility.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family support & resources	Psychotherapy, peer support	

OT = occupational therapy; PEG = percutaneous endoscopic gastrostomy; PT = physical therapy

1. Shahwan et al [2005]
2. Koskiniemi et al [1998]
3. Kälviäinen et al [2016]
4. Crespel et al [2017]
5. Edwards et al [2002]
6. Smith et al [2000]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for school-age individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Surveillance

Table 5. Recommended Surveillance for Individuals with EPM1

System/Concern	Evaluation	Frequency
Myoclonus	Severity of myoclonus using UMRS	At least annually
Seizures	Seizure type & frequency	

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Cerebellar involvement	Clinical eval	Per symptom progression
Dysarthria	Need for alternative communication method or speech therapy	
Dysphagia	Assess aspiration risk & feeding methods	
Weight / Nutritional status	• Monitor BMI. • Consult a nutritionist • High-calorie supplementation	
Activities of daily living	Clinically to evaluate rehab plan	At least annually
School performance	Interview	
Cognitive/Psychiatric	Evaluate mood, signs of psychosis, & cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms
Family support & resources	Interview	Annually

BMI = body mass index; UMRS = Unified Myoclonus Rating Scale

Agents/Circumstances to Avoid

Phenytoin should be avoided, as it has been found to have aggravating side effects on the associated neurologic symptoms, and may even accelerate cerebellar degeneration [Eldridge et al 1983].

Sodium channel blockers (carbamazepine, oxcarbazepine, phenytoin) and **GABAergic drugs** (tiagabine, vigabatrin) as well as **gabapentin** and **pregabalin** should in general be avoided as they may aggravate myoclonus and myoclonic seizures [Medina et al 2005].

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

Progressive myoclonic epilepsy type 1 (EPM1) 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., presumed to be carriers of one *CSTB* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a *CSTB* pathogenic variant and allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If each parent is known to be heterozygous for a *CSTB* pathogenic variant, each sib of an affected individual has at conception 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.
- A sib who inherits biallelic *CSTB* pathogenic variants is likely to have clinical manifestations similar to those of the proband; however, intrafamilial clinical variability may be observed (particularly if affected family members have compound heterozygous *CSTB* pathogenic variants; see Genotype-Phenotype Correlations).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Unless an individual's reproductive partner has EPM1 or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *CSTB*.
- Because of the low carrier rate in the general population, the risk that an affected individual would have children with a carrier is extremely low except in certain populations (see Prevalence).

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

Carrier Detection

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

Carrier testing for the reproductive partners of a known carrier is possible. Primarily, targeted testing for the dodecamer repeat expansion should be done, and if it remains negative, sequencing of *CSTB* should be considered.

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.

Prenatal Testing and Preimplantation Genetic Testing

Once both *CSTB* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for EPM1 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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.

- **National Library of Medicine Genetics Home Reference**
  Unverricht-Lundborg disease
- **American Epilepsy Society**
  www.aesnet.org
- **EpiCARE: a European Reference Network for rare and complex epilepsies**
  www.epi-care.eu
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.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 Myoclonic Epilepsy Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CSTB	21q22.3	Cystatin-B	CSTB database	CSTB	CSTB

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 Myoclonic Epilepsy Type 1 (View All in OMIM)

254800	MYOCLONIC EPILEPSY OF UNVERRICHT AND LUNDBORG
601145	CYSTATIN B; CSTB

Molecular Pathogenesis

CSTB encodes cystatin B, an inhibitor of several papain-family cysteine proteases, cathepsins. Cystatin B interacts with histones and cathepsin L in the nucleus where it could regulate cathepsin L activity [Čeru et al 2010].

Cstb-deficient knockout mice display a phenotype similar to the human disease with progressive ataxia and myoclonic seizures [Pennacchio et al 1998]. The mice show early microglial activation and inflammation, preceding clinical onset of myoclonus [Tegelberg et al 2012, Okuneva et al 2015, Okuneva et al 2016]. In addition, altered GABAergic signaling with subsequent loss of GABA inhibition have been reported in *Cstb*-deficient knockout mice, suggesting a mechanism for latent hyperexcitability resulting in myoclonus and seizures [Franceschetti et al 2007, Buzzi et al 2012, Joensuu et al 2014].

Impaired redox homeostasis has been reported as a pathophysiologic mechanism in *Cstb*-deficient knockout mice with cystatin-B-cathepsin B signaling dysregulation being a critical mechanism coupling oxidative stress to neuronal degeneration and death [Lehtinen et al 2009].

Mechanism of disease causation. Loss of function. Dodecamer repeat expansion results in a significantly reduced amount of *CSTB* mRNA: 5%-10% of the expression found in controls [Joensuu et al 2007]. Other disease-associated variants also result in loss of cystatin-B function and some are associated with total lack of intracellular cystatin B [Joensuu et al 2007, Joensuu et al 2008].

Table 6. *CSTB* Technical Considerations

Technical Issue	Comment [Reference]
Sequence of repeat	CCC-CGC-CCC-GCG
Methods to detect expanded allele (See Table 7.)	Southern blotting [Lalioti et al 1997] & PCR for expanded repeat analysis [Joensuu et al 2007] have been described.
Somatic instability	There is no evidence for substantial somatic instability of the expanded repeat.
Germline instability	Expanded repeats show some instability in germline transmissions, w/both contractions & expansions implied. No tendency for expansion in successive generations has been reported.

Methods to characterize *CSTB* CCC-CGC-CCC-GCG repeats. Due to the technical challenges of detecting and sizing *CSTB* CCC-CGC-CCC-GCG repeat expansions, multiple methods may be needed to rule out or detect CCC-CGC-CCC-GCG repeat expansion (see Table 7). Repeats in the normal range (2-3) are detected by traditional PCR. However, detection of apparent homozygosity for a normal repeat by traditional PCR does not rule out the presence of an expanded repeat, thus, testing by a specific PCR method for expansion detection or Southern blotting is required.

Table 7. Methods to Characterize *CSTB* CCC-CGC-CCC-GCG Repeats

Interpretation of CCC-CGC-CCC-GCG Repeat Number	Expected Results by Method	
	Conventional PCR	Expanded repeat analysis [1]
Normal: 2-3	Detected [2]	Expansions can be detected, & repeat size can be approximated [3, 4]
Pathogenic (full penetrance): ≥30	Not detected	

1. Methods to detect and approximate the size of expanded repeats include long-range PCR sized by gel or capillary electrophoresis and Southern blotting. The upper limit of repeat size detected will vary by assay design, laboratory, sample, and/ or patient due to competition by the normal allele during amplification.
2. Detection of an apparently homozygous repeat does not rule out the presence of an expanded repeat; thus, testing by expanded repeat analysis is required to detect a repeat expansion.
3. Southern blotting [Lalioti et al 1997] and a specific PCR protocol [Joensuu et al 2007] for the CCC-CGC-CCC-GCG repeat expansion have been described
4. Precise sizing of repeats is not necessary as clinical utility for determining the exact repeat number has not been demonstrated.

Table 8. Notable *CSTB* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Repeat Range
NM_000100.4	c.-179_-190CCCCGCCCCGCG[2_3]	--	Normal variants
	c.-179_-190CCCCGCCCCGCG[12_17]	--	Uncertain significance
	c.-179_-190CCCCGCCCCGCG[30_?]	--	Full-penetrance

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.

Chapter Notes

Author History

Reetta Kälviäinen, MD, PhD (2007-present)
Marja-Leena Koskiniemi, MD, PhD; University of Helsinki (2004-2007)
Anna-Elina Lehesjoki, MD, PhD (2004-present)

Revision History

- 2 July 2020 (bp) Comprehensive update posted live
- 26 November 2014 (me) Comprehensive update posted live
- 18 June 2009 (me) Comprehensive update posted live
- 18 September 2007 (cd) Revision: sequence analysis available on a clinical basis
- 12 February 2007 (me) Comprehensive update posted live
- 24 June 2004 (me) Review posted live
- 6 February 2004 (ael) Original submission

References

Literature Cited

Assenza G, Benvenga A, Gennaro E, Tombini M, Campana C, Assenza F, Di Pino G, Di Lazzaro V. A novel c132-134del mutation in Unverricht-Lundborg disease and the review of literature of heterozygous compound patients. Epilepsia. 2017;58:e31–5. PubMed PMID: 27888502.

Buzzi A, Chikhladze M, Falcicchia C, Paradiso B, Lanza G, Soukupova M, Marti M, Morari M, Franceschetti S, Simonato M. Loss of cortical GABA terminals in Unverricht-Lundborg disease. Neurobiol Dis. 2012;47:216–24. PubMed PMID: 22538221.

Canafoglia L, Gennaro E, Capovilla G, Gobbi G, Boni A, Beccaria F, Viri M, Michelucci R, Agazzi P, Assereto S, Coviello DA, Di Stefano M, Rossi Sebastiano D, Franceschetti S, Zara F. Electroclinical presentation and genotype-phenotype relationships in patients with Unverricht-Lundborg disease carrying compound heterozygous CSTB point and indel mutations. Epilepsia. 2012;53:2120–7. PubMed PMID: 23205931.

Čeru S, Konjar Š, Maher K, Repnik U, Križaj I, Benčina M, Renko M, Nepveu A, Žerovnik E, Turk B, Kopitar-Jerala N. Stefin B interacts with histones and cathepsin L in the nucleus. J Biol Chem. 2010;285:10078–86. PubMed PMID: 20075068.

Crespel A, Gelisse P, Tang NP, Genton P. Perampanel in 12 patients with Unverricht-Lundborg disease. Epilepsia. 2017;58:543–7. PubMed PMID: 28166365.

Danner N, Julkunen P, Khyuppenen J, Hukkanen T, Könönen M, Säisänen L, Koskenkorva P, Vanninen R, Lehesjoki AE, Kälviäinen R, Mervaala E. Altered cortical inhibition in Unverricht-Lundborg type progressive myoclonus epilepsy (EPM1). Epilepsy Res. 2009;85:81–8. PubMed PMID: 19321308.

Edwards MJ, Hargreaves IP, Heales SJ, Jones SJ, Ramachandran V, Bhatia KP, Sisodiya S. N-acetylcysteine and Unverricht-Lundborg disease: variable response and possible side effects. Neurology. 2002;59:1447–9. PubMed PMID: 12427904.

Eldridge R, Iivanainen M, Stern R, Koerber T, Wilder BJ. "Baltic" myoclonus epilepsy: hereditary disorder of childhood made worse by phenytoin. Lancet. 1983;2:838–42. PubMed PMID: 6137660.

Franceschetti S, Sancini G, Buzzi A, Zucchini S, Paradiso B, Magnaghi G, Frassoni C, Chikhladze M, Avanzini G, Simonato M. A pathogenetic hypothesis of Unverricht-Lundborg disease onset and progression. Neurobiol Dis. 2007;25:675–85. PubMed PMID: 17188503.

Hyppönen J, Äikiä M, Joensuu T, Julkunen P, Danner N, Koskenkorva P, Vanninen R, Lehesjoki AE, Mervaala E, Kälviäinen R. Refining the phenotype of Unverricht-Lundborg disease (EPM1): a population-wide Finnish study. Neurology. 2015;84:1529–36. PubMed PMID: 25770194.

Joensuu T, Kuronen M, Alakurtti K, Tegelberg S, Hakala P, Aalto A, Huopaniemi L, Aula N, Michellucci R, Eriksson K, Lehesjoki AE. Cystatin B: mutation detection, alternative splicing and expression in progressive myclonus epilepsy of Unverricht-Lundborg type (EPM1) patients. Eur J Hum Genet. 2007;15:185–93. PubMed PMID: 17003839.

Joensuu T, Lehesjoki AE, Kopra O. Molecular background of EPM1-Unverricht-Lundborg disease. Epilepsia. 2008;49:557–63. PubMed PMID: 18028412.

Joensuu T, Tegelberg S, Reinmaa E, Segerstråle M, Hakala P, Pehkonen H, Korpi ER, Tyynelä J, Taira T, Hovatta I, Kopra O, Lehesjoki AE. Gene expression alterations in the cerebellum and granule neurons of Cstb(-/-) mouse are associated with early synaptic changes and inflammation. PLoS One. 2014;9:e89321. PubMed PMID: 24586687.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kälviäinen R, Khyuppenen J, Koskenkorva P, Eriksson K, Vanninen R, Mervaala E. Clinical picture of EPM1-Unverricht-Lundborg disease. Epilepsia. 2008;49:549–56. PubMed PMID: 18325013.

Kälviäinen R, Genton P, Andermann E, Andermann F, Magaudda A, Frucht SJ, Schlit AF, Gerard D, de la Loge C, von Rosenstiel P. Brivaracetam in Unverricht-Lundborg disease (EPM1): results from two randomized, double-blind, placebo-controlled studies. Epilepsia. 2016;57:210–21. PubMed PMID: 26666500.

Koskenkorva P, Hyppönen J, Aikiä M, Mervaala E, Kiviranta T, Eriksson K, Lehesjoki AE, Vanninen R, Kälviäinen R. Severer phenotype in Unverricht-Lundborg disease (EPM1) patients compound heterozygous for the dodecamer repeat expansion and the c.202C>T mutation in the CSTB gene. Neurodegener Dis. 2011;8:515–22. PubMed PMID: 21757863.

Koskiniemi M, Van Vleymen B, Hakamies L, Lamusuo S, Taalas J. Piracetam relieves symptoms in progressive myoclonus epilepsy: a multicentre, randomised, double blind, crossover study comparing the efficacy and safety of three dosages of oral piracetam with placebo. J Neurol Neurosurg Psychiatry. 1998;64:344–8. PubMed PMID: 9527146.

Lalioti MD, Scott HS, Buresi C, Rossier C, Bottani A, Morris MA, Malafosse A, Antonarakis SE. Dodecamer repeat expansion in cystatin B gene in progressive myoclonus epilepsy. Nature. 1997;386:847–51. PubMed PMID: 9126745.

Lehtinen MK, Tegelberg S, Schipper H, Su H, Zukor H, Manninen O, Kopra O, Joensuu T, Hakala P, Bonni A, Lehesjoki A-E. Cystatin B deficiency sensitizes neurons to oxidative stress in progressive myoclonus epilepsy, EPM1. J Neurosci. 2009;29:5910–5. PubMed PMID: 19420257.

Magaudda A, Ferlazzo E, Nguyen VH, Genton P. Unverricht-Lundborg disease, a condition with self-limited progression: long-term follow-up of 20 patients. Epilepsia. 2006;47:860–6. PubMed PMID: 16686650.

Mancini GM, Schot R, de Wit MC, de Coo RF, Oostenbrink R, Bindels-de Heus K, Berger LP, Lequin MH, de Vries FA, Wilke M, van Slegtenhorst MA. CSTB null mutation associated with microcephaly, early developmental delay, and severe dyskinesia. Neurology. 2016;86:877–8. PubMed PMID: 26843564.

Medina MT, Martinez-Juarez IE, Duron RM, Genton P, Guerrini R, Dravet C, Bureau M, Perez-Gosiengfiao KT, Amador C, Bailey JN, Chaves-Sell F, Delgado-Escueta AV. Treatment of myoclonic epilepsies of childhood, adolescence, and adulthood. Adv Neurol. 2005;95:307–23. PubMed PMID: 15508934.

Muona M, Berkovic SF, Dibbens LM, Oliver KL, Maljevic S, Bayly MA, Joensuu T, Canafoglia L, Franceschetti S, Michelucci R, Markkinen S, Heron SE, Hildebrand MS, Andermann E, Andermann F, Gambardella A, Tinuper P, Licchetta L, Scheffer IE, Criscuolo C, Filla A, Ferlazzo E, Ahmad J, Ahmad A, Baykan B, Said E, Topcu M, Riguzzi P, King MD, Ozkara C, Andrade DM, Engelsen BA, Crespel A, Lindenau M, Lohmann E, Saletti V, Massano J, Privitera M, Espay AJ, Kauffmann B, Duchowny M, Møller RS, Straussberg R, Afawi Z, Ben-Zeev B, Samocha KE, Daly MJ, Petrou S, Lerche H, Palotie A, Lehesjoki AE. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. Nat Genet. 2015;47:39–46. PubMed PMID: 25401298.

O'Brien A, Marshall CR, Blaser S, Ray PN, Yoon G. Severe neurodegeneration, progressive cerebral volume loss and diffuse hypomyelination associated with a homozygous frameshift mutation in CSTB. Eur J Hum Genet. 2017;25:775–8. PubMed PMID: 28378817.

Okuneva O, Körber I, Li Z, Tian L, Joensuu T, Kopra O, Lehesjoki AE. Abnormal microglial activation in the Cstb(-/-) mouse, a model for progressive myoclonus epilepsy, EPM1. Glia. 2015;63:400–11. PubMed PMID: 25327891.

Okuneva O, Li Z, Körber I, Tegelberg S, Joensuu T, Tian L, Lehesjoki A-E. Brain inflammation is accompanied by peripheral inflammation in Cstb-/- mice, a model for progressive myoclonus epilepsy. J Neuroinflammation. 2016;13:298. PubMed PMID: 27894304.

Pennacchio LA, Bouley DM, Higgins KM, Scott MP, Noebels JL, Myers RM. Progressive ataxia, myoclonic epilepsy and cerebellar apoptosis in cystatin B-deficient mice. Nat Genet. 1998;20:251–8. PubMed PMID: 9806543.

Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurol. 2005;4:239–48. PubMed PMID: 15778103.

Smith B, Shatz R, Elisevich K, Bespalova IN, Burmeister M. Effects of vagus nerve stimulation on progressive myoclonus epilepsy of Unverricht-Lundborg type. Epilepsia. 2000;41:1046–8. PubMed PMID: 10961635.

Tegelberg S, Kopra O, Joensuu T, Cooper JD, Lehesjoki AE. Early microglial activation precedes neuronal loss in the brain of the Cstb-/- mouse model of progressive myoclonus epilepsy, EPM1. J Neuropathol Exp Neurol. 2012;71:40–53. PubMed PMID: 22157618.

License