Genetic Testing for Epilepsy: Progressive Myoclonic Epilepsy Panel Sequence Analysis and Exon-Level Deletion/Duplication Testing of 18 Genes

Panel Gene List: CLN3, CLN5, CLN6, CLN8, CSTB, CTSD, CTSF, DNAJC5, EPM2A, FOLR1, GOSR2, KCNC1, KCTD7, MFSD8, NHLRC1, PPT1, SCARB2, TPP1

Clinical Features:

The progressive myoclonic epilepsies (PME) are a group of rare inherited disorders characterized by seizures, myoclonus, and progressive neurological degeneration. Patients may also exhibit cerebellar ataxia, dementia, neuropathy, and myopathy. Myoclonic and generalized tonic-clonic seizures are most common, although absence, atypical absence, tonic, and focal seizures may occur.[1] Myoclonus in PME occurs separately from seizures. It may be focal or segmental and is often asymmetric and arrhythmic. Myoclonic jerks are often precipitated by posture, action, or stimuli such as sound, light, or touch, and they are most apparent on the face and distal extremities.[1,2] The symptoms of PME typically begin in adolescence or childhood and the outcome is generally severe; however, the age-of-onset, rate of progression, and associated features depend on the PME subtype. Lafora disease, Unverricht-Lundborg disease, and neuronal ceroid lipofuscinoses are three well-characterized subtypes of PME.[1,2] More recently, pathogenic variants in genes such as KCNC1, KCTD7, SCARB2, GOSR2, and FOLR1 have been identified in patients with PME, and the full clinical phenotype associated with some of these disorders is still being defined.

Lafora disease (LD) is characterized by the presence of Lafora bodies, which are Schiff-positive polyglucosan inclusion bodies found in neurons, skeletal muscle, and other tissues.[1,2] Individuals with Lafora disease typically exhibit dysarthria, ataxia, and visual hallucinations due to occipital seizures, in addition to the typical features of PME. LD typically onsets between 12-17 years, although in rare cases intractable seizures have occurred as young as 6 years of age.[3] Over time, seizures become more frequent and are increasingly difficult to control. Most patients die within 10 years of diagnosis, often from status epilepticus.[1,2,3]

Unverricht-Lundborg disease (EPM1) causes stimulus-sensitive myoclonus and tonic-clonic seizures typically beginning between 6-15 years of age.[1,2,4] Myoclonic jerks increase in frequency during the first 5-10 years after diagnosis and are often intractable.[4] Tonic-clonic seizures may also increase in frequency in the early stages of the disease but later respond to antiepileptic drugs.[4] The disease progression is slow, with incoordination and dysarthria developing over time. With supportive treatment, lifespan is normal in most cases.[4]

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited lysosomal storage disorders resulting in PME often associated with visual loss.[1,2,5] The NCLs have been subdivided based on age of presentation and clinical features. Infantile NCL typically causes myoclonic jerks, seizures, deceleration of head growth, retinal blindness and developmental delay between 6-24 months. Late-infantile NCL (LINCL) is characterized by epilepsy, developmental regression, ataxia, and visual impairment beginning between 2-4 years of age. Juvenile NCL (JNCL or Batten disease) usually presents between 4-10 years of age with rapidly progressive visual loss and epilepsy. Adult-onset NCL (ANCL or Kufs disease) typically begins around age 30 with progressive myoclonic epilepsy, behavioral abnormalities, dementia, ataxia, and pyramidal/extrapyramidal signs. Northern epilepsy is characterized by tonic-clonic or complex-partial seizures beginning between ages 2-10 years and also results in intellectual disability and motor dysfunction.

Inheritance Pattern/Genetics:

The Progressive Myoclonic Epilepsy Panel at GeneDx includes sequencing and deletion/duplication analysis of 18 genes causing PME. Specifically, the panel includes genes known to cause Lafora disease, Unverricht-Lundborg disease, the neuronal ceroid lipofuscinoses, and other genetic progressive myoclonic epilepsies. Note that this test may not detect the dodecamer repeat expansion that accounts for ~90% of all CSTB variants causing Unverricht-Lundborg disease. These disorders are all inherited in an autosomal recessive manner with the exception of the KCNC1 and DNAJC5 (CLN4B) gene, which are associated with autosomal dominant disorders. The function of many of the proteins is unknown, although NHLRC1 is involved in axonal and dendritic transport in neurons, KCNC1 is a voltage-gated potassium channel that plays a role in enabling high-frequency neuronal firing, and PPT1 and TPP1 are involved in the breakdown of long-chain fatty acids and small peptide hormones, respectively.[1,5,18]

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic

variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

If clinically appropriate, if the Progressive Myoclonic Epilepsy Panel is negative, sequencing and deletion/duplication analysis of the remaining genes on the Comprehensive Epilepsy Panel is available as a separate test.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Progressive Myoclonic Epilepsy Panel depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below.

Epilepsy Type	Gene	Protein	Inh	Diagnostic Yield in Selected Population(s)
Lafora disease	EPM2A	Laforin	AR	53% Lafora disease[3]
	NHLRC1 (EPM2B)	NHL repeat-containing protein 1 (malin)	AR	40% Lafora disease[3]
Neuronal Ceroid Lipofuscinoses (NCL)	PPT1 (CLN1)	Palmitoyl-protein thioesterase 1	AR	98% PPT1 deficiency[7]
	TPP1 (CLN2)	Tripeptidyl-peptidase 1	AR	95% TPP1 deficiency[8]
	CLN3	Battenin	AR	92% Juvenile NCL[9]
	DNAJC5 (CLN4B)	DnaJ homolog subfamily C member 5	AD	25% Kufs disease[10,11]
	CLN5	Ceroid-lipofuscinosis neuronal protein 5	AR	94% Finnish late-infantile NCL[5]; Otherwise rare

Epilepsy Type	Gene	Protein	Inh	Diagnostic Yield in Selected Population(s)
	CLN6	Ceroid-lipofuscinosis neuronal protein 6	AR	Rare[5]
	MFSD8 (CLN7)	Major facilitator superfamily domain-containing protein 8	AR	Rare[5]
	CLN8	Ceroid-lipofuscinosis neuronal protein 8	AR	100% Finnish Northern epilepsy[5]; Otherwise rare
	CTSD (CLN10)	Cathepsin D	AR	Rare[5]
	CTSF (CLN13)	Cathepsin D	AR	Rare[5]
	KCTD7 (CLN14)	BTB/POZ domain-containing protein KCTD7	AR	Rare[12]
Unverricht-Lundborg disease (EPM1)	CSTB*	Cystatin-B	AR	~10% of Unverricht-Lundborg disease[4]
SCARB2-associated PME	SCARB2 (EPM4)	Lysosome membrane protein 2	AR	~7% progressive myoclonic epilepsy[13]l Unknown in action myoclonus-renal failure syndrome[14]
GOSR2-associated PME	GOSR2 (EPM6)	Golgi SNAP receptor complex member 2	AR	Rare[15,16]
Cerebral folate deficiency	FOLR1	Folate receptor alpha	AR	Rare[17]
KCNC1-associated myoclonus epilepsy and ataxia (MEAK)	KCNC1	Potassium voltage-gated channel subfamily C member 1	AD	Rare[18]

* The dodecamer repeat expansion that accounts for ~90% of all CSTB mutations may not be detectable by this

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