Who & When: Epilepsy That is Unexplained

Pathologic variants resulting in epilepsy cause a variety of changes that can be broadly classified into the following categories

Cause/Indication	Definition/Description	Examples
Channelopathies	Channelopathies are diseases that develop because of defects in ion channels caused by either genetic or acquired factors. Mutations in genes encoding ion channels, which impair channel function, are the most common cause of channelopathies.	• Sodium channels: SCN1A, SCN2A, SCN8A, SCN8A, SCN3A. • Potassium channels: KCNQ2, KCNQ3M, KCNT1, KCNA2. • Calcium channels: CACNA1A, CACNA2D2, CACNA2D1, CACNA1H, CACNA1G. • Nicotinic acetylcholine receptor channels: CHRNA4, CHRNB2, CHRNA2. • GABA and Glutamatergic channels: GABRA1, GABRA2, GABRA5, GABRB1, GABRB2, GABRB3, GABRG2, and GABBR2, GRIN2A. • Sodium-potassium ATPase pump channels: ATP1A3, ATP1A2, ATP1A1. • Other channels: CLC (chloride channels), HCN (hyperpolarization-activation cyclic nucleotide-gated), TRP (transient receptor potential).
Childhood onset epilepsy including severe forms of childhood epilepsy	< 3-year-old	
Drug-resistant epilepsy, especially of unknown cause	Generalized and focal epilepsies in the absence of other reported clinical features	
Family history of epilepsy in two first-degree family members	Individual or family phenotype that suggests a known genetic cause	
Malformations of cortical development	A variety of genetic disorders or mutations that lead to failure of normal cortical migration. Several commonly described malformations include periventricular nodular heterotopia, polymicrogyria, lissencephaly spectrum, subcortical band heterotopia, tubulinopathies, and focal cortical dysplasia	• GATOR1 complex (i.e., DEPDC5, NPRL2, and NPRL3) underline focal cortical dysplasia's. • mTOR pathway are PTEN, AKT3, and PIK3CA, which can cause megalencephaly spectrum disorders and cortical dysplasias. • Cortical malformations can be seen with TUB1A (polymicrogyria), LIS1(lissencephaly and pachygyria), ARX (lissencephaly and pachygyria), and COL4A1 (porencephaly, schizencephaly, and hemorrhage) among others. • Absence or partial agenesis of corpus callosum.
Metabolic disorders	Conditions that affect any aspect of metabolism. Metabolic disorders may be acquired or genetic; features suggesting mitochondrial disease may be a hint.	• GLUT1 deficiency is caused by pathogenic variants in the SLC2A1 gene, resulting in several epilepsy phenotypes including infantile seizures, early onset absence epilepsy, myoclonic-astatic epilepsy, and focal epilepsy. • Pyridoxine-dependent (ALDH7A1mutation) and pyridoxal-5′-phosphate-dependent (PNPO mutation) epilepsies are infantile intractable epilepsies that respond to replacement of pyridoxine (vitamin B6) or pyridoxal-5′-phosphate, respectively. • Lysosomal storage disorders can cause several phenotypes, including epilepsy.
Neurodegeneration	Conditions that affect any aspect of metabolism. Metabolic disorders may be acquired or genetic; features suggesting mitochondrial disease may be a hint.	• Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is caused by a mutation in the TPP1 gene and results in a progressive neurologic disease including language delays, epilepsy, motor difficulty, ataxia, and blindness. • Progressive myoclonic epilepsies.

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Other neurologic findings		• Dyskinesias, ataxia, hemiplegic migraine, intellectual disability, neurodevelopmental comorbidities (autism, 9 duplications, cerebral palsy, etc.).
Syndromic disorder	Often present in the neonatal period with clear dysmorphology	• Dravet, Lennox Gastaut, developmental and epileptic encephalopathies (DEEs), Wolf–Hirschhorn (deletion of chromosome 4p), trisomy 18, trisomy 13, trisomy 21, Angelman syndrome, DiGeorge syndrome (22q11.2 deletion), SCN2A, 15q duplication, DEPDC5, GRIN2A, TSC, etc.
Unexplained epilepsy	Epilepsy is considered unexplained when— according to history, physical examination, imaging, and other standard evaluations— the cause of seizures cannot be attributed to a structural, metabolic, infectious, immunological, or other acquired etiology such as trauma or stroke.	
Populations with reduced access to testing	• Individuals from underserved communities are less likely to receive genetic testing, suggesting this might be due to the lack of provider awareness of when genetic testing is indicated or the process for procurement. • In the past, individuals from underserved populations were less likely to be referred for genetic testing even when indicated based on established guidelines. • Studies have shown that individuals from underserved populations may be less likely to utilize genetic services once referred. This may be due to high out- of- pocket costs and increased appointments to procure counseling, testing, and results. Members of minoritized groups have been at increased risk in prior literature.	