Genetics in Epilepsy

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Introduction

- First epilepsy gene was discovered in 1995.
- Although there is much that we do not understand we can now make genetic diagnoses and use these to influence treatment decisions.
- Most (but not all) single gene epilepsies present in childhood and are diagnosed by Pediatric Neurologists.
- However, many children transition to adult services
- In some cases, a diagnosis may not have been made.

Practical Guide to Diagnosing Genetic Epilepsy

- Taking a History
  - Ask older relatives
- Ask specifically about Febrile Seizures (particularly important in diagnosing Genetic Epilepsy with Febrile Seizures)
  - Prolonged nature, hemiclonic component

- Age of Onset of Seizure:
  - Early onset Absence Epilepsy starting at age < 4 years is concerning for SLC2A1 mutations.
  - Seizures in Autosomal Dominant Nocturnal Frontal Lobe epilepsy start before age 20 years.
- Birth History
  - In a recent study 58% of adults with intellectual disability and epilepsy, who had previously been thought to have a known historic cause for epilepsy such as perinatal trauma were found to have a genetic diagnosis. [1]

*1. The genetic landscape of intellectual disability and epilepsy in adults and the elderly: a systematic genetic work-up of 150 individuals. Genet Med 2021;**23**:1492–7.doi:10.1038/s41436-021-01153-6 pmid:http://www-ncbi-nlm-nih-gov.foyer.swmed.edu/pubmed/33911214*

Specific Scenarios

- Developmental and Epileptic Encephalopathies
  - Present in childhood and are associated with severe epilepsy and cognitive & behavior impairment
  - Most of the times the cause is de novo genetic mutations
  - There are over 100 genes associated with epileptic encephalopathies
  - Epilepsy gene panels or whole exome/genome sequencing are the standard diagnostic clinical tests for patients with developmental and epileptic encephalopathies and should be requested if not already done so

Important Developmental and Epileptic Encephalopathies

Syndrome	Age at onset	Clinical features / Pointers	Genetics
Dravet syndrome	First year of life, typically around 6 months	Seizures associated with fever (especially hemiclonic, or status epilepticus) common at onset. Multiple seizure types in the first year: hemiclonic, myoclonic and focal seizures with status epilepticus. Development delay is usually apparent in second year and usually moderate to severe intellectual impairment. Seizures (and fever sensitivity) persist throughout life but frequency may decrease. Higher risk of sudden unexpected death in epilepsy. Motor problems ('crouching' gait) and decline in mobility, behavioural problems and swallowing difficulties feature in adulthood.[58] Sodium channel antiseizure medications can make seizures worse. Treatment options include fenfluramine, cannabidiol and ketogenic diet.[8 59 60]	>80% have pathogenic *SCN1A* variants.[61] Other genes associated with similar phenotype include *GABRA1, GABRG2, HCN1, KCNA2, SCN1B*.[62]
Early infantile epileptic encephalopathy Ohtahara syndrome	0–3 months	Frequent intractable seizures, tonic seizures. Consider early myoclonic encephalopathy if myoclonic seizures predominate. A structural brain cause is common. Also, metabolic as well as genetic causes. Can evolve to West or Lennox–Gastaut syndrome. Normally severe developmental delay. Abnormal EEG with burst suppression can evolve to hypsarrhythmia.[12]	*STXBP1* (most common maybe 10%) others include *SCN2A, STXBP1* and *KCNQ2*.[12]
Epilepsy of infancy with migrating focal seizures	First year of life, typically 0–6 months	Rare and severe with focal seizures migrating between hemispheres. Most have severe developmental problems after onset of seizures. EEG can be normal initially, slowing with time, ictal changes correlate with seizures.[12 63]	Genes include *KCNT1* (30%), *SCN2A, SCN1A, PLCB1, TBC1D24* and *CHD2*.[63]
West syndrome	First year of life, typically around 6 months	Infantile spasms at onset with EEG hypsarrhythmia. Structural (tuberous sclerosis) and metabolic causes as well as genetic causes. Corticosteroids, vigabatrin and the ketogenic diet can be useful. Can evolve to Lennox-Gastaut syndrome.	Genes include *CDKL5, ARX, SPTAN1* and *STXBP1*
Epileptic encephalopathy with continuous spike-and-wave during sleep	Childhood onset, typically 4–5 years.	Progressive cognitive decline is prominent and is associated with characteristic EEG abnormality of continuous slow spike and wave in slow sleep. Seizures can remit but cognitive impairment can persist. A spectrum including Landau-Kleffner syndrome (milder phenotype with prominent aphasia)	*GRIN2A*
'Metabolic' developmental and epileptic encephalopathies (DEE)		Rare but potentially treatable genetic metabolic problems that can present as a developmental and epileptic encephalopathy include: guanidinoacetate methyltransferase (GAMT) deficiency—DEE phenotype, low serum creatinine can be a clue, check plasma and urine creatine, creatinine and guanidinoacetate. MR spectroscopy can be diagnostic. Oral creatine supplementation and dietary manipulation can cause dramatic improvements.[64] Pyridoxine dependent epilepsy (PDE) typically has a neonatal onset with drug resistant epilepsy and a developmental and epileptic encephalopathy phenotype that responds to high doses of pyridoxine. Elevated plasma and urinary concentrations of alpha-aminoadipic semialdehyde.[65]	*GAMT* (GAMT deficiency)—recessive *ALDH7A1* (PDE)—recessive

Specific Scenarios

Progressive Myoclonic Epilepsy (PME):

- Rare, autosomal recessive
- Characterized by progressive myoclonic seizures, cognitive decline and ataxia
- Typically present in childhood or early adolescence
- Consider PME in a case of Juvenile Myoclonic Epilepsy with progressive (particularly action-induced) myoclonus. Or with ataxia and/or worsening cognition.
- It is now possible to get a genetic diagnosis for at least 70% of progressive myoclonic epilepsies.[2]

*2. Courage C , Oliver KL , Park EJ , et al . Progressive myoclonus epilepsies-Residual unsolved cases have marked genetic heterogeneity including dolichol-dependent protein glycosylation pathway genes. Am J Hum Genet 2021;**108**:722–38.doi:10.1016/j.ajhg.2021.03.013 pmid:http://www-ncbi-nlm-nih-gov.foyer.swmed.edu/pubmed/33798445*

Progressive Myoclonic Epilepsies (PME)

Syndrome	Clinical features/pointers	Genetics
Unverricht–Lundborg disease	Most common and mildest of the progressive myoclonic epilepsies. Progressive and disabling action myoclonus. *Cascade* seizures with increasingly intense myoclonus. Occasional generalised tonic-clonic seizures. Photosensitivity common.[14 78] Preserved cognition until relatively late distinguishes from other progressive myoclonic epilepsies. Geographical variation in prevalence (Baltic myoclonus). Avoid sodium-channel blocking drugs.	*CSTB* (dodecamer nucleotide repeats)
Neuronal ceroid lipofuscinosis	This is a group of neurodegenerative lysosomal storage disorders. Common cause of childhood dementia. Prominent cognitive decline and visual failure, also cerebellar atrophy myoclonus and other seizures. Genetically heterogeneous, currently at least 14 genes, age at onset useful to classify. Other diagnostic tests for example, skin biopsy can be useful.[14 79]	Loci: CLN1-14 Genes: *PPT1, TPP1, CLN3, DNAJC5, CLN5, CLN6, MFSD8, CLN8, CTSD, ATP13A2, CTSF, KCTD7*
Lafora disease	Adolescent onset in otherwise normal people. Headaches, myoclonus, occipital seizures, visual hallucinations. Biopsy can reveal Lafora bodies (polyglucosan inclusions). Progressive dementia and death usually 10 years after onset.[14 80 81]	*EPM2A, NHLRC1, PRDM8*
Others	Myoclonic epilepsy with ragged-red fibres—see **table 2**. Sialidosis is a lysosomal storage disorder with 'cherry red spots' seen on funduscopy as well as visual decline, ataxia and dysmorphia (sialidosis type 2). Spinal muscular atrophy associated with progressive myoclonus epilepsy is caused by acid ceramidase deficiency and has typically distal lower motor neurone weakness.	MERRF (mitochondrial) Sialidosis: *NEU1*, SMA-PME: *ASAH1*

Specific Scenarios

- Malformations of Cortical Development:
  - Common cause of intractable epilepsy
  - Diagnosed with an MRI brain
  - Have a genetic cause
  - Recommended genetic investigations include a chromosomal microarray and a malformations of cortical development gene panel
  - Some are due to mosaic mutations (e.g, focal cortical dysplasia and hemimegalencephaly).
  - Causative mosaic mutations may be present only in the brain and either absent or rare in other body tissues and need more targeted testing.

Common Cortical Malformations

Phenotype	Description	Genetics
Periventricular nodular heterotopia	Grey matter along the ventricular walls unilaterally or bilaterally. Can occur as part of another disorder.[17] Can be caused by *FLNA* mutations (X-linked) which increase risk of systemic complications including heart, lung and gastrointestinal disease. *FLNA* disease mostly affects females as usually lethal in males.[82]	Numerous *copy number variants* and single gene mutations (including *FLNA*)
Polymicrogyria	Overfolding and abnormal cortical lamination. MR scan of brain shows apparent cortical thickening with irregular cortical surface and 'stippled' grey-white junction.[83] Genetic and congenital causes. Congenital cytomegalovirus infection accounts for around 30% of cases (suspect if additional microcephaly, congenital hearing loss, intracranial calcification). Can be associated with peroxisomal disorders (additional leukoencephalopathy) check plasma very-long-chain fatty acids.[17]	Copy number variants including 22q11.2 and 1p36 deletions and many single gene mutations including *GRIN1, WDR62, PIK3CA* and *PIK3R2*
Lissencephaly spectrum	'Smooth brain', absent or reduced gyri. The spectrum encompasses agyria, pachygyria and subcortical band heterotopia.[17 84] Mostly genetic causes, MR brain scan findings/patterns can strongly predict genotype.	Include *LIS1, DCX, TUBG1, TUBA1A, ARX*[17]
Subcortical band heterotopia	Part of the lissencephaly spectrum. A band of grey matter separated from the cortex and lateral ventricles by zones of grey matter.[17]	*LIS1* (*PAFAH1B1*), *DCX*
Subcortical heterotopia	Heterotopic grey matter within the white matter between cortex and lateral ventricles. Less common to find genetic cause.[17 85]	Mostly recessive, include *GPSM2, EML1 TUBB, KATNB1* or CENP)[17 85]
Tubulinopathies	Microtubules are important for neurodevelopment and mutations in tubulin genes can cause a range of malformations of cortical development, including pachygyria, polymicrogyria and microlissencphaly.[86] Additional features include dysmorphic basal ganglia, 'hooked' frontal horns in the ventricles, agenesis of the corpus callosum and cerebellar and brainstem hypoplasia. Each tubulin gene is associated with a predominant phenotype.[17 86]	Include *TUBA1A, TUBB2A, TUBB2B, TUBB3, TUBB4A, TUBB* and *TUBG1*
Focal cortical dysplasia	Focal irregularities of cortical morphology and thickness. Indistinct grey-white boundary. Can be subtle and occur as part of tuberous sclerosis. Overlap with familial focal epilepsy with variable foci (FFEVF) (**table 2**)—consider if familial epilepsy.	mTOR pathway genes including *TSC1, TSC2, MTOR*, GATOR1 complex genes including *DEPDC5, NPRL2 NPRL3.*

Specific Scenarios: Tuberous Sclerosis

- Tuberous sclerosis complex is characterized by multiple benign tumors in the skin, brain and other organ systems with various clinical features and presentations.
- Cutaneous manifestations (hypopigmented macules, angiofibromas, shagreen patches and forehead fibrous plaques) and neuropsychiatric problems occur in >90% of patients.
- Epilepsy occurs in around 80% of cases, tends to be early onset and can be severe.
- De novo (80%) and familial (autosomal dominant) mutations in *TSC1* and *TSC2* occur in over 90% of tuberous sclerosis cases and cause an overactivation of the mTOR pathway.
- As well as antiseizure medications, including cannabidiol and vigabatrin, treatment options include mTOR inhibitors such as Everolimus, the ketogenic diet and surgery.

Clinical Scenarios where genetic testing is indicated

- Developmental and epileptic encephalopathies
- Epilepsy with intellectual disability and/or other neurodevelopmental disorder
- Individual or family phenotype suggesting genetic cause
- Features suggesting mitochondrial disease
- Progressive myoclonic epilepsies
- Malformations of cortical development
- Early onset < 3 years
- Drug Resistant Epilepsy of unknown cause

Treatment and Prognosis

- Obtaining a genetic diagnosis can inform treatment options:
  - sodium channel blocking drugs should be avoided in Dravet syndrome caused by *SCN1A* loss of function mutations
  - ketogenic diet may improve outcomes for people with *SLC2A1* mutations
  - sodium valproate can cause severe hepatotoxicity in *POLG* deficiency.
  - human leucocyte antigen (HLA) genotype can influence the risk of severe adverse drug reactions and HLA genotyping might be considered before starting carbamazepine treatment (HLA-B*1502 for certain Asian ethnicities and HLA-A*3101 for Japanese, Korean and European ethnicity)

Targeted Therapies for Monogenic Epilepsies

- One of the best-known examples of genetic disease that responds to a specialized diet is *GLUT1* deficiency syndrome (*GLUT1-DS*), a syndrome that often provokes global developmental delay, movement disorders, and epilepsy, associated with low glucose in the cerebrospinal fluid (CSF) or hypoglycorrhachia.
- Caused by variants in *SLC2A1* which encodes the type 1 glucose transporter located in the blood-brain barrier

- The use of ketogenic diet for other genetic epilepsies has expanded beyond the well-known application for GLUT1-DS.
- Two brothers with newly-identified disease-causing variants in phosphatidyl inositol glycan A (*PIGA*) resulting in X-linked recessive multiple congenital anomalies-hypotonia-seizures syndrome (MCAHS2) who had poorly controlled seizures on multiple anti-seizure medications (ASMs) were able to achieve seizure freedom with the ketogenic diet.
- Discontinuation of the diet led to seizure recurrence. This case report was the first to note a prompt seizure response with initiation of ketogenic diet in *PIGA*-associated early-onset epileptic encephalopathy

- *Joshi C, Kolbe DL, Mansilla MA, Mason S, Smith RJH, Campbell CA. Ketogenic diet – a novel treatment for early epileptic encephalopathy due to PIGA deficiency. Brain Dev. (2016) 38:848–51. doi: 10.1016/j.braindev.2016.04.004*

Targeted Therapies for Monogenic Epilepsies

- Diet and Vitamins

Gene	Epilepsy syndrome	Suggested precision medicine	Therapeutic rationale	Status as precision medicine
ALDH7A1	Vitamin B6-deficient epilepsy	Pyridoxine, lysine-restricted diet	Impairment of lysine breakdown	Established (11)
CAD	DEE	Uridine	Disruption of pyrimidine metabolism	Established (15)
Folate cycle genes: FOLR-1, MTHFR, DHFR, PCFT	Cerebral folate transporter deficiency (ataxia and refractory myoclonic epilepsy)	Folinic acid, 5-methyltetrahydrofolate	Supplementation of active metabolite missing in folate cycle	Established (13, 14)
*PIGA**	X-linked recessive multiple congenital anomalies – hypotonia – seizures syndrome (MCAHS2), epileptic encephalopathy	Ketogenic diet	Unclear	Potential (10)
PNPO	Vitamin B6 – deficient epilepsy	Pyridoxal-5-phosphate	Supplementation of deficiency	Established (12)
PLPBP	Vitamin B6 – deficient epilepsy	Pyridoxine, pyridoxal-5-phosphate	Supplementation of deficiency	Established (92)
SLC2A1 (GLUT1)	*GLUT1* deficiency syndrome	Ketogenic diet	Alternate energy source	Established (8, 9)

*Indicates the current absence of a molecular or genetic rationale for this particular therapy.

Ion Channel Modulators

- Many genetic epilepsies stem from mutations in genes encoding voltage-gated ion channels and are generally referred to as “channelopathies.”
- Focus on Sodium and Potassium channelopathies

Precision Therapy for Channelopathies

- Sodium Channelopathies:
- In order of population prevalence, *SCN1A, SCN2A*, and *SCN8A* are most commonly associated with epilepsy.

Precision Therapy for Channelopathies

- *SCN1A* mutations are associated with various forms of seizures and epilepsies on a wide spectrum of severity, including “isolated” febrile seizures as well as Dravet syndrome (DS), a developmental and epileptic encephalopathy of poor prognosis.
- Eighty percent of DS cases are associated with loss-of-function (LOF) mutations in *SCN1A* particularly in inhibitory interneurons.
- Precision therapy for DS involves avoidance of sodium channel blockers (e.g., carbamazepine, lamotrigine), as they can worsen symptoms in some patients.
- And the use of agents that enhance GABAergic neurotransmission (e.g., clobazam)
- Fenfluramine, cannabidiol, and stiripentol have all been found to provide clinical benefit for this severe epilepsy syndrome in randomized clinical trials

Potassium Channelopathies

- 4-aminopyridine is a potassium channel blocker that can antagonize Gain of Function (GOF) defects in the *KCNA2* gene that causes an epileptic encephalopathy.
- In a study of n-of-1 trials in nine different centers, nine of 11 patients showed improvement in seizure burden, gait, ataxia, alertness, and cognition after starting 4-aminopyridine.
- Because of these findings, it seems a promising tailored treatment for KCNA2-encephalopathy caused by GOF variants.

Potassium Channelopathies

- Pathogenic variants in *KCNT1*, also encoding a potassium channel, are responsible for a broad phenotypic spectrum that include autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), early-onset epileptic encephalopathy (EOEE), and epilepsy of infancy with migrating focal seizures (EIMFS) in neonates and infants, which are often refractory to conventional ASMs.
- Initial studies suggested that *KCNT1*-related epilepsy caused by a GOF variant responds to quinidine, a sodium and potassium channel blocker mostly used as an anti-arrhythmic.
- However, subsequent clinical experience found that it was mostly ineffective in early-onset EE.
- A subsequent study of patients with *KCNT1*-related epilepsy noted a > 50% seizure reduction in 20% of patients, and with only a few achieving transient seizure freedom.
- While quinidine has had mixed results for this monogenic epilepsy syndrome, its robust efficacy in patients with specific variants in *KCNT1* does give hope that it may become standard therapy for those specific variant.
- Till then, *KCNT1* serves as an important reminder that, despite strong biomolecular evidence suggesting a certain therapy (e.g., ion channel modulation), the road to a successful therapy can sometimes be more complex than initially expected.

Precision Therapies for Channelopathies

Gene	Epilepsy syndrome	Suggested precision medicine	Therapeutic rationale	Status as precision medicine
KCNA2	DEE	4-aminopyridine	Reducing current amplitudes	Potential (43)
KCNQ2	DEE	Sodium channel blockers, retigabine, gabapentin	Selective potassium channel Kv7 opener (retigabine), potassium channel Kv7 activator (gabapentin)	- Sodium channel blockers – established (44) - Retigabine – potential (47) - Gabapentin – potential (48)
KCNT1	Epilepsy of infancy with migrating focal seizures, nocturnal frontal lobe epilepsy	- Quinidine - ASO	- Potassium channel blockade in GOF variants - Gene silencing	- Quinidine – potential (7, 49) - ASO – potential (86)
PRRT2	Benign familial infantile epilepsy, paroxysmal kinesigenic dyskinesia	Sodium channel blocker	Failure of neurotransmission	Potential (64, 65)
SCN1A	Dravet syndrome	- Avoid sodium channel blockers - Stiripentol - Fenfluramine - Cannabidiol - ASO	Loss of function of NaV1.1 sodium channels	- Avoidance of sodium channel blockers – established (1, 6) - Stiripentol – established (35) - Fenfluramine – potential (36) - Cannabidiol – established (16, 37) - ASO – hypothetical (84)
SCN2A	Ohtahara syndrome, early encephalopathy	Sodium channel blockers	Gain of function of NaV1.2 channel	Potential (31)
SCN8A	DEE	- Sodium channel blockers - ASO		- Sodium channel blockers – potential (42) - ASO – hypothetical (85)

Repurposing Established Medications

- **Protocadherin 19 Female Epilepsy:**
- patients with PCDH19-FE have been found to have lower levels of allopregnanolone, it has been theorized that replacement of that hormone with a synthetic analog, ganaxolone, which acts as a human neurosteroid, could be therapeutic
- Stiripentol has also been found to be beneficial as an adjunctive ASM in PCDH19-FE

- **PRRT2-Related Epilepsy**
- *PRRT2* disease-causing variants are among the most common genetic causes of epilepsy
- Precision medicine therapy for *PRRT2*-related seizures with carbamazepine came from the common genetics shared between Paroxysmal Kinesigenic Dyskinesia (PKD) and the infantile seizures.
- PKD had been treated effectively for years with carbamazepine and once it was understood that *PRRT2* variants explained both PKD and familial infantile seizures, carbamazepine and oxcarbazepine were used effectively for *PRRT2*-related infantile seizures

Repurposing Established Medications

Gene	Epilepsy syndrome	Suggested precision medicine	Therapeutic rationale	Status as precision medicine
*ARX**	Epileptic-dyskinetic encephalopathy	Valproic acid, estradiol	Unclear	Hypothetical (94, 95)
CACNA1A	Absence epilepsy with ataxia, DEE	- Aminopyridine (LOF) - Flunarizine (GOF)	Compensation in synaptic transmission (aminopyridine) calcium channel blockade (flunarizine)	Aminopyridine, flunarizine – potential (96)
CHRNA4/B2/A2	Sleep-related hypermotor epilepsy	Nicotine	Desensitization of nicotinic acetylcholine receptors	Established (66)
*FRRS1L**	DEE	Sulthiame	Unclear	Potential (67)
GABRB3	Lennox-Gastaut syndrome	Vinpocetine	Sodium channel modulation	Potential (68)
GABRG2	EE	Stiripentol	Increase GABA-A receptor activity	Hypothetical (97)
GRIN1/2A/2B/2D	Epilepsy with centrotemporal spikes, Landau-Kleffner syndrome, DEE	- NMDA receptor antagonists (memantine, dextromethorphan) - Ketamine (GOF) - Serine (LOF)	Modulation at the NMDA receptor	Potential (62, 63, 98)
*PCDH19**	DEE	- Ganaxolone - Stiripentol	- Compensation for altered steroidogenesis - Unclear	- Ganaxolone – potential (57, 99) - Stiripentol – potential (61)
*SLC13A5**	DEE	Stiripentol	- Unclear	Hypothetical (100)

**Indicates the current absence of a molecular or genetic rationale for this particular therapy.*

New Targeted Therapies on the Market

- **Rett Syndrome:**
- Caused by MECP2 mutation.
- Rett syndrome occurs worldwide in one of every 10,000 female births and is even rarer in boys.
- There are an estimated 5,000-10,000 girls with Rett syndrome in America.
- Most are under 20 years of age, although life expectancy is now around 50.
- Severe impairments affecting nearly every aspect of life, including the ability to speak, walk, eat and breathe as well as epilepsy.
- Key features: Speech Regression, Stereotypic hand wringing, clapping tapping and/or mouthing, loss of purposeful hand movement, impaired or absent mobility.

- Trofinetide/Daybue:
- FDA approved for treatment of Rett Syndrome in children and adults aged 2 years and older.
- It is a synthetic analog of tripeptide glycine-proline-glutamate (GPE), a cleavage product of insulin-like growth factor-1 (IGF-1)
- Exact mechanism of action is unknown

- Treatment with DAYBUE demonstrated statistically significant improvement compared to placebo on both co-primary efficacy endpoints, as measured by the change from baseline in Rett Syndrome Behaviour Questionnaire (RSBQ) total score (p=0.018) and the Clinical Global Impression-Improvement (CGI-I) scale score (p=0.003) at week 12.
- The RSBQ is a caregiver assessment that evaluates a range of symptoms of Rett syndrome including vocalizations, facial expressions, eye gaze, hand movements (or stereotypies), repetitive behaviors, breathing, night-time behaviors and mood.
- The CGI-I is a global physician assessment of whether a patient has improved or worsened.
- In the study, the most common side effects were diarrhea (82%) and vomiting (29%).

Thank You