Clues for Diagnosis of Genetic Epilepsy Syndrome in a Busy clinic

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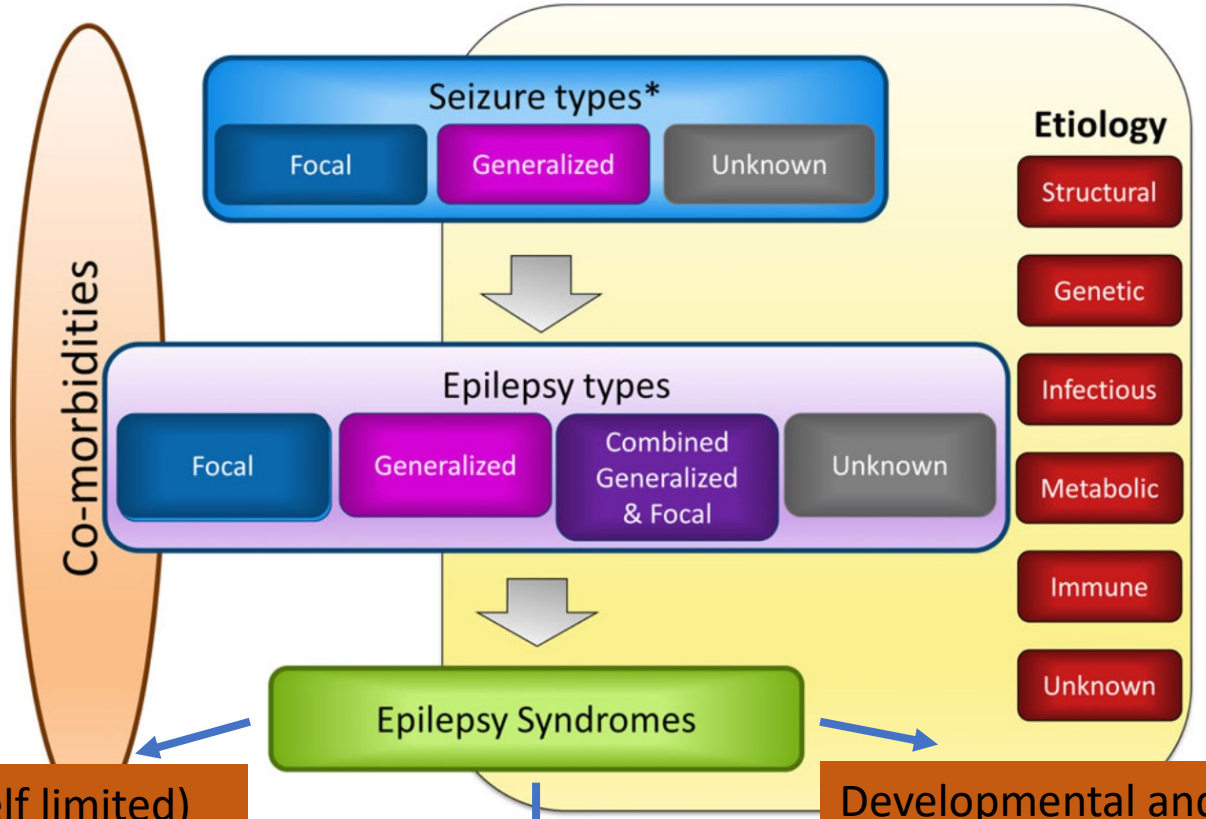
Outlines

- Why is giving the diagnosis of genetic epilepsy syndrome important?
- Clues of diagnosis:
  - History and physical exams
  - Laboratory
  - Neuroimaging
  - No treatment will be discussed

Genetic Epilepsy Syndrome



Focal epilepsy syndrome (self limited)

Developmental and epileptic encephalopathy

Generalized epilepsy syndrome (Genetics)

Scheffer IE et al, Epilepsia 2017

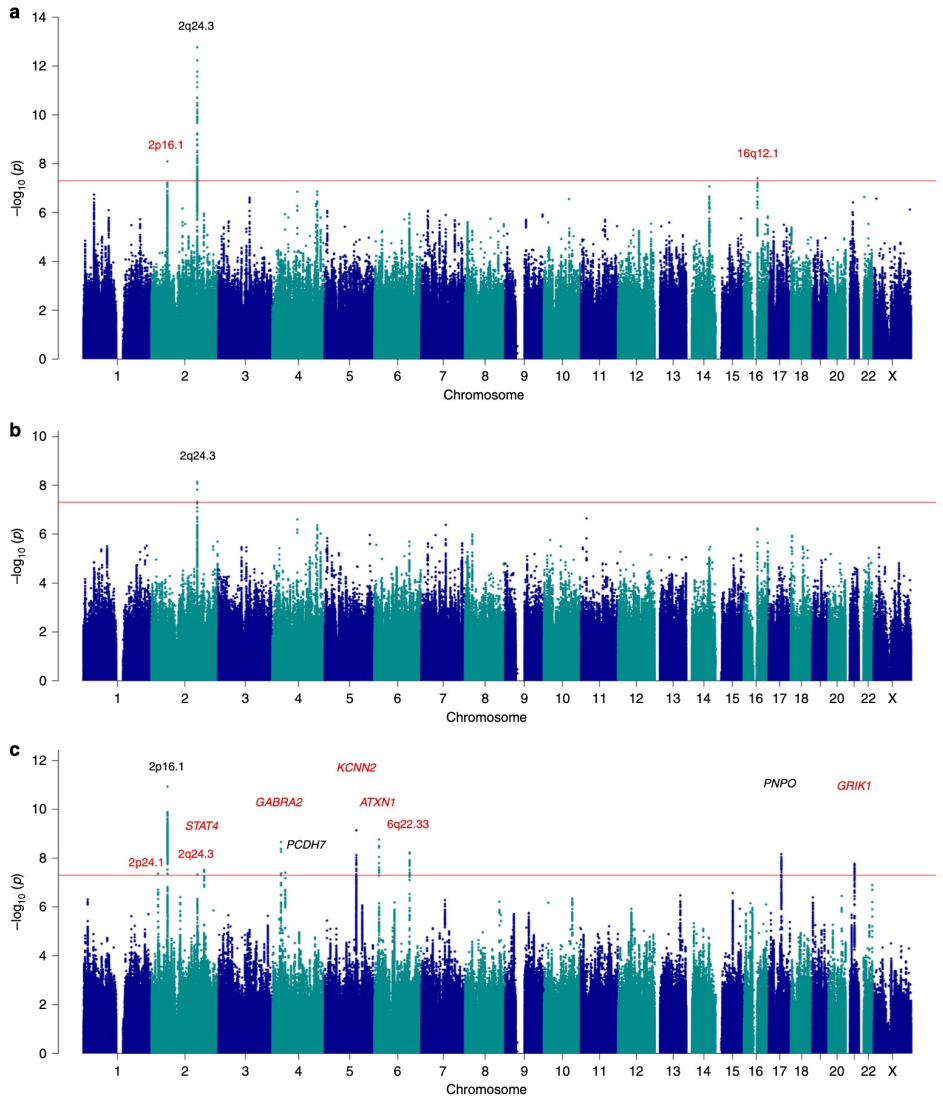
Genetic Epilepsy Syndrome

- “Genetic” does not mean inherited
- Clusters of features; seizure types, EEG findings, neuroimaging features that tend to occur together
- Often age dependent (onset and remission)
- Distinctive seizure triggers, diurnal variation, prognostic outcomes , comorbidities and treatment implications
- Does not have a one-to-one correlation with the etiologic diagnosis
- One epilepsy syndrome may have evolved from another epilepsy syndrome

Specchio N et al, Epilepsia 2022
Hirsch E etal, Epilepsia 2022

Genetic Epilepsy Syndromes

- The ILAE Consortium on Complex Epilepsies: mega-analysis identified 11 loci associated with GGEs
- Inherited or de novo mutations
- Different degrees of severity and a variety of clinical manifestations



Nature Communications (2018), 9:5269

Phenotype at most recent follow up, *n*	*n* (%) with a genetic cause identified	Genes implicated (*n*)
Epilepsy, 263		
DEE, 62		
West syndrome, 27	3/27 (11.1)	*CDKL5* (2), *DEPDC5*
Dravet syndrome, 11	11/11 (100)	*SCN1A* (11)
Other DEEs, 24	13/24 (54.1)	*PCDH19* (3), *CDKL5* (2), *KCNQ2* (2), *GABRA1*, *KCNT1*, *MECP2*, *SCN2A*, *SCN8A*, *STXBP1*
Alper-Huttenlocher syndrome, 1	1/1 (100)	*POLG*
Absences with eyelid myoclonia, 1	1/1 (100)	*CHD2*
Early onset absence epilepsy, 5	0/5	
Epilepsy with myoclonic-atonic seizures, 8	2/8 (25)	*STX1B*, *SLC6A1*
Familial focal epilepsy, 1	1/1 (100)	*DEPDC5*
Febrile seizures plus, 6	0/6	
Genetic epilepsy with febrile seizures plus, 2	1/2	*SCN1A*
Glut1 deficiency syndrome, 7	7/7 (100)	*SLC2A1* (7)
Myoclonic epilepsy of infancy, 3	0/3	
Panayioutopoulos syndrome, 1	0/1	
Self-limited familial infantile epilepsy, 5	5/5 (100)	*PRRT2* (5)
Self-limited infantile epilepsy, 27	11/27 (40.7)	*PRRT2* (10), *KCNQ2*
Self-limited familial neonatal seizures, 7	7/7 (100)	*KCNQ2* (5), *KCNQ3* (2)
Self-limited neonatal seizures, 1	1/1 (100)	*KCNQ2*
Unclassified myoclonic epilepsy, 5	0/5	
Unclassified generalized epilepsy, 10	1/10 (10)	*CACNA1A*
Unclassified focal epilepsy, 59	5/59 (8.5)	*DEPDC5* (2), *KCNA2*, *KCNQ2*, *PRRT2*
Unclassified focal and generalized epilepsy, 8	0/8	
Unclassified epilepsy, 44	6/44 (13.6)	*SLC6A1* (3), *COL4A1*, *PCDH19*, *PRRT2*
Not epilepsy, 80		
Febrile seizures only, 64	3/64 (4.7)	*SCN1A* (2), *KCNA2* (mosaic, 20)
Single episode of afebrile status, 10	0/10	
Single cluster of afebrile seizures in 24 h, 6	1/6 (16.7)	*CACNA1A*

Symonds JD et al, Brain 2019

SeLECTs

- Formerly called Benign Rolandic epilepsy, 7% of childhood epilepsy
- Age at onset 4-10 years, peaks around 7 years, male predominance
- Normal development and past medical history
- Normal neurological exam
- Seizure types: focal and focal to bilateral convulsions, 80% during sleep
- Seizure frequency: majority < 10 seizures in lifetime
- Resolved spontaneously by the age of 16 years

Berg AT et al, Epilepsia 2006
Camfield PR et al, Pediatr Nuerol 2014

SeLECTs

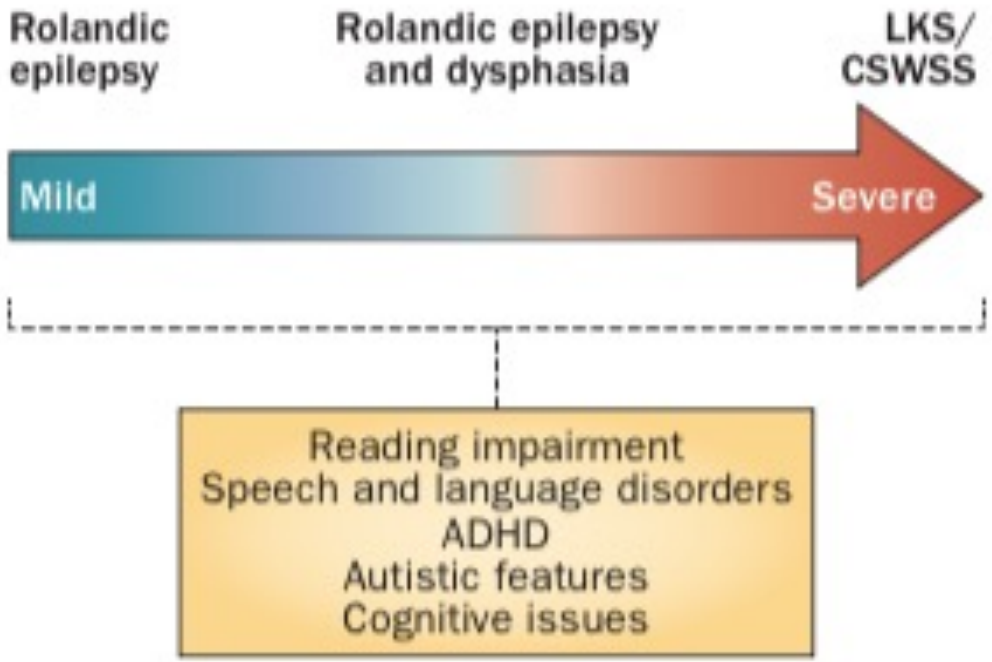
- Investigation
  - EEG: normal background with triphasic sharp waves with a transverse dipole, predominantly seen in drowsiness and sleep
  - MRI: Unremarkable, usually no need to do
  - Genetics: Complex inheritance, no pathologic gene variants found
- Differential diagnosis: D/EE SWAS, Focal seizures from structural abnormalities, FgX and other SeLFEs
- Treatment: Often not treat, CBZ*, OXC, VPA, LEV, BZD

Landau Kleffner syndrome

- Subtype of EE-SWAS
- Clinical manifestation:
  - Age at onset 3 to 8-year-old
  - Acquired epileptic aphasia/verbal agnosia, ADHD
  - Seizures: head drop, eye deviation/blinking, automatisms, GTC
  - Language disturbance
  - EEG: ESES with 1.5-2 Hz SW in 85% of slow wave sleep, maximal in the CT, absent of sleep architecture
- Etiology: ????structural lesions, Genetics (*GRIN2A*)

Lesca G et al, Epileptic Disord 2019

Epilepsy-aphasia spectrum

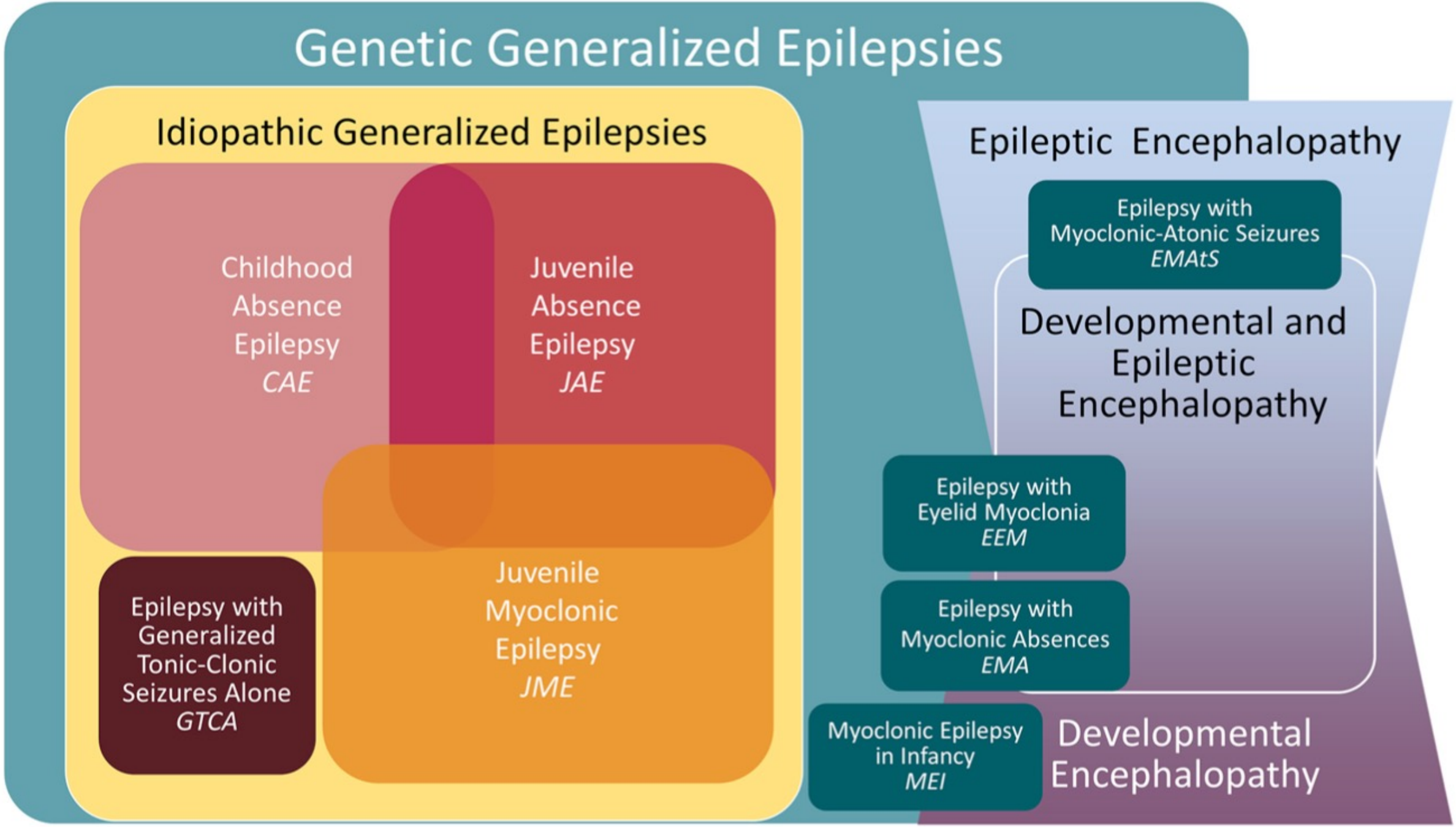


The spectrum of childhood focal epilepsies. Abbreviations: CSWSS, continuous spike and wave during slow-wave sleep syndrome; LKS, Landau–Kleffner syndrome ('acquired' epileptic aphasia). Original image courtesy of P. Szepetowski.

Table 1 Epileptic encephalopathy cohort screened for *GRIN2A* mutations

	Total *N*	*GRIN2A* mutations
Epilepsy-aphasia syndromes	44	4
Focal epilepsy, symptomatic focal epilepsy	50	0
Epileptic encephalopathies (other)	87	0
Infantile spasms	84	0
Epilepsy with myoclonic-atonic seizures	85	0
Symptomatic generalized epilepsies	85	0
Febrile infection-related epilepsy syndrome	12	0
Dravet syndrome	17	0
Lennox-Gastaut syndrome	34	0
Ohtahara syndrome	8	0
Epilepsy of infancy with migrating focal seizures	7	0
Progressive myoclonic epilepsies	6	0
Total	519	4

Nature Reviews Neurology 2013
Carvill LG et al, Nature Genetics 2013


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood Absence Epilepsy CAE
Juvenile Absence Epilepsy JAE
Juvenile Myoclonic Epilepsy JME
Epilepsy with Generalized Tonic-Clonic Seizures Alone GTCA
Epileptic Encephalopathy
Epilepsy with Myoclonic-Atonic Seizures EMAtS
Developmental and Epileptic Encephalopathy
Epilepsy with Eyelid Myoclonia EEM
Epilepsy with Myoclonic Absences EMA
Myoclonic Epilepsy in Infancy MEI
Developmental Encephalopathy

IGE

- The most common syndromes within the GGEs
- Polygenic inheritance with or without environmental factors
- Development is typically normal
- Clinical overlap
- EEG: generalized 2.5-5.5 Hz spike-wave, which may be activated by hyperventilation and photic stimulation
- ASMs, Na Ch blockers and VGB can exacerbate absence and myoclonic seizures

CAE

- CAE can evolve to the other IGE
- Almost 20% of school age children with epilepsy
- Age of onset 4-10 years, more common in girls
- Normal development and past medical history
- Normal neurological exam
- Seizure type: typical absence seizures, 3-20s
- EEG: 3-Hz GSW, fragments, ORIDA (30%), photic stimulations triggers GSW
- Children aged < 4 years, DDX: GLUT-1
- ASMs responsive, remits by early adolescence in 60%
- Genetic findings: *GABRG2, GABRA1, SLC2A1*, CNVs (intellectual disability)

Hirsch E et al, Epilepsia 2022

JME

- Most common adolescent and adult onset IGE, 10% in all epilepsies
- Age at onset 8-40 years, common 10-24 years
- 10 % evolved from CAE or JAE
- Seizure type: myoclonic seizures (after waking or being tired), GTC
- EEG: 3.5-5 Hz GSW, GPSW, Photosensitity (90%)
- Impairment of cognitive function can be seen
- Higher rates of anxiety and depression
- Treatment: Avoid Na channel blockers
- 80% recurrent rate after ASM withdrawal
- Genetic: rare pathogenic variants; *CACNB4, GABRA1, GABRD, EFHC1*

Hirsch E et al, Epilepsia 2022

EEM

- One of genetic generalized epilepsy syndrome of childhood
- “Jeavons syndrome”
- Triad: eyelid myoclonia with or without absence, induced by eye closure and photic stimulation
- DRE, GTC-controlled with ASMs
- Eyelid myoclonia is most prominent in awakening
- Age at onset is 6-8 years, female predominance
- Intellectual disability is seen
- Normal neurological exam

EEM

- No MRI required
- Genetics: shared genetic etiologies with IGE (CAE, JAE, JME and GTC alone)
- No single pathogenic gene variant

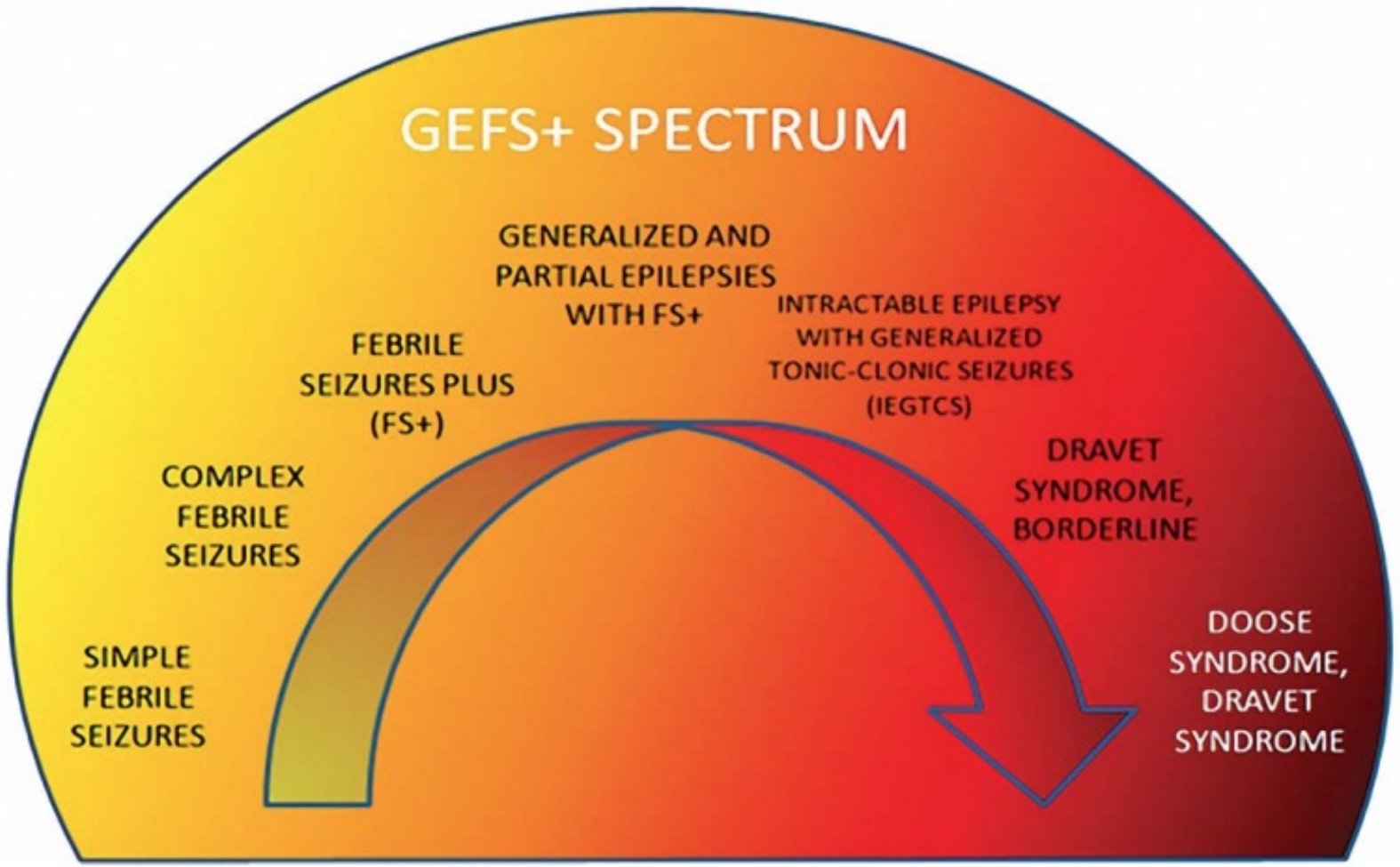
KCNQ2 encephalopathy

- The most common childhood onset genetic epilepsy
- LoF is related to a broad-spectrum neonatal onset epilepsy phenotypes
- Age at onset is in neonatal period, approximately 7 days
- EEG: Burst suppression (resolved around 2 months of age)
- Neuroimaging patterns: Basal ganglia and thalamic signal abnormalities, decreased WM volume
- Treatment: carbamazepine, phenytoin
- Prognostic outcomes: Varies

Micell F et al, Lancet 2022
Olson HE et al, Ann Neurol 2017

Epilepsy Syndromes related with FS

- Children with epilepsy syndromes can present with recurrent or prolonged FS
- Diagnosis of epilepsy syndromes is based on age of onset, seizure types, neurodevelopment, family history, EEG and genetic findings
- Early detection and management helps to improve prognostic outcomes and anti-seizure medication selection



Generalized epilepsy and febrile seizures plus spectrum and related phenotypes

Moya-Vilches JL and Devilat M, J Pediatr Epilepsy. 2014

Dravet Syndrome

- Sporadic
- Genetic mutations: *SCN1A*, SCN2A SCN3A SCN8A*
- Seizure onset occurs before the age of 1 year
- History of febrile status epilepticus
- Seizures are triggered by fever, vaccination, warm bath
- Seizure types: GTC, hemiconvulsions, myoclonic seizures, atypical absence, focal seizures
- Developmental delay → Developmental epileptic encephalopathy
- Gait abnormality

Dravet Syndrome

- Medical management
- Some anti-seizure medications (Na+Ch blockers) can be ineffective and have worse seizure outcomes
- RCT: Clobazam, Valproic acid and Stiripentol
- CBD and Fenfluramine show good efficacy in trials
- Early diagnosis and treatment helps to improve developmental outcomes

PCDH-19 related epilepsy

- First report in 1971, related to PCDH-19 mutations
- Predominantly in female with intellectual disability

Clinical features of PCDH-19 related epilepsy
Childhood onset epilepsy with or without fever Seizures can be focal or generalized
Cognitive impairment
Autistic spectrum disorders
Behavioral problems (ADHD, OCD, depression, schizophrenia, panic, aggression and self-injurious behavior etc.)

Debopam Samanta, Pediatr Neurol 2020

PCDH-19 related epilepsy VS Dravet syndrome

	PCDH19	Dravet
Age of seizure onset	Around 1-year-old	Around 6-month-old
Gender	Female	Both
Photosensitivity	Rare	Common
Status epilepticus	Less common	More common
Clusters of seizures	Common	Less common
Hemiclonic seizures	Rare	Common
Absence or myoclonic seizures	Rare	Common
Intellectual impairment	Variable	Common
Seizure remission after puberty	Common	Rare
Polyspikes in EEG	Rare	Common
Gait abnormalities	Rare	Crouch gait

Debopam Samanta, Pediatr Neurol 2020

LGS

- DRE with the onset before the age of 18 years (3-5 years), 1-2% of patients with epilepsy
- Evolve from other epilepsy syndrome, 20-30% from West syndrome
- Seizure types: Tonic seizures, atypical absence, atonic seizures
- Intellectual disabilities and behavioral problems
- Abnormal neurological examination
- EEG: diffuse slow spike waves (<2.5 Hz) with generalized fast activity
- MRI: structural lesions can be seen

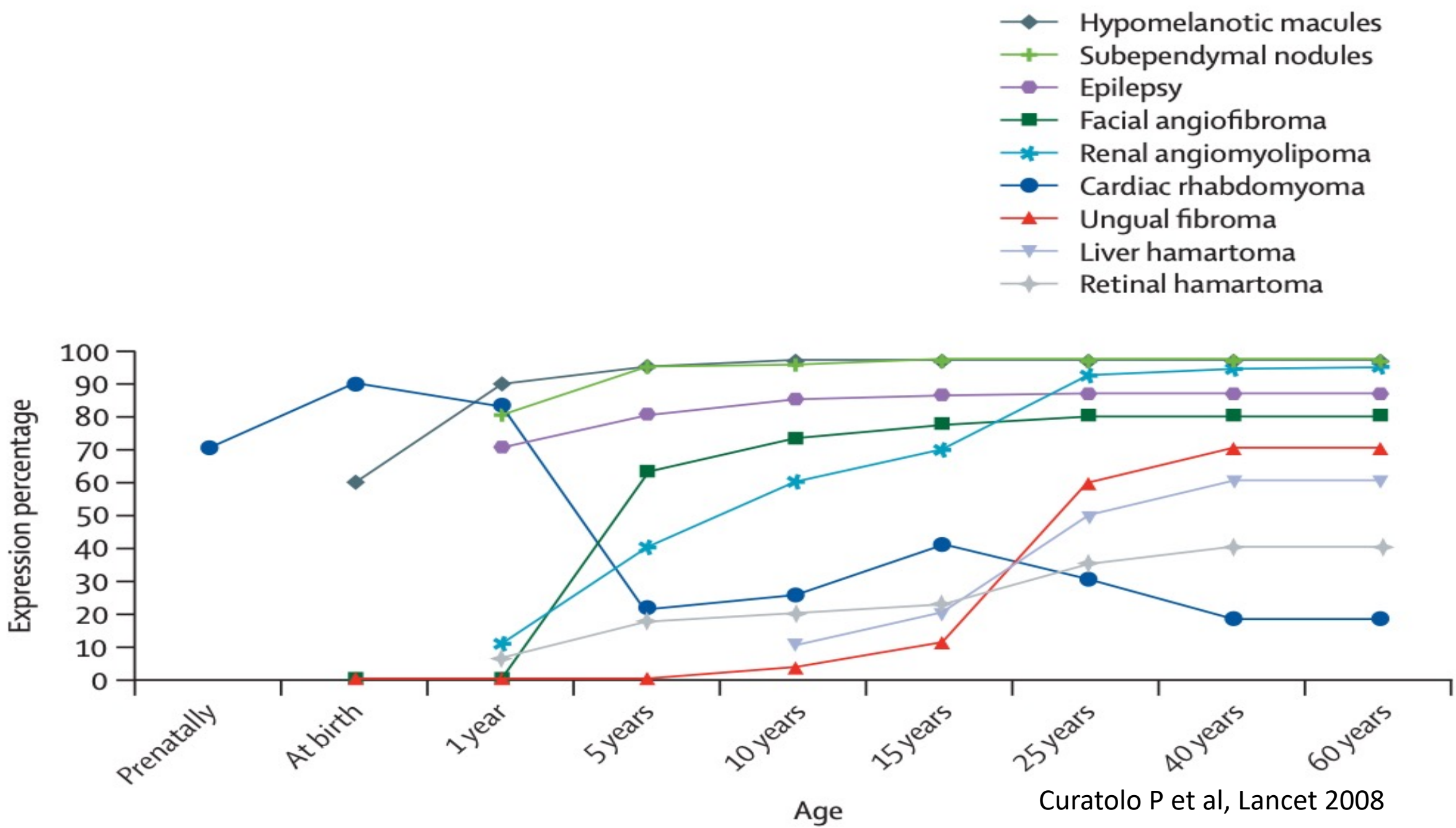
TSC

- Variable clinical phenotypes, affected 1:10000
- It is a disease of a lifetime
- Age-dependent expression of clinical manifestations
- Due to TSC1 or TSC2 mutations, 70% somatic, 30% germline (AD)
- Diagnosis criteria were firstly established in 1998
- The criteria were updated in 2012 for diagnosis, surveillance and management

TSC

- The majority of TSC patients harbor a TSC2 mutation that is associated with more severe clinical symptoms
- Patients with only phenotypes without TSC mutations have less severe clinical symptoms
- Brain and skin are affected in 90% of patients
- Cardiac rhabdomyoma indicated an 80% risk of TSC
- The most common neurological features are epilepsy, ASD and ID
- EEG before epilepsy onset becomes a standard of care

Sancak O et al, Eur J Hum Genet 2005
Slowinska M et al, Pediatr Neurol 2021



Curatolo P et al, Lancet 2008

Clinical criteria for diagnosis of TSC

Major Criteria	Minor Criteria
Hypomelanotic macules (≧3, ≧5mm)	“Confetti” skin lesions
Angiofibroma (≧3) or fibrous cephalic plaque	Dental enamel pits (≧2)
Ungual fibroma (≧2)	Intraoral fibroma (≧2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple retinal cysts
Cortical dysplasia	Nonrenal hamartomas
Subependymal nodules	
SEGA	***TSC2 or TSC1 mutations from DNA analysis
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis	
Angiomyolipoma (≧2)	

Northrub H et al, Pediatr Neurol. 2013

Neurological involvement in TSC

- Epilepsy is the most common, reported at 80-90% and is often DRE
- Typical onset is within the first 2-3 year of life
- One third developed epileptic spasms
- “TAND”
- Neuropsychiatric disorders are often underdiagnosed such as ASD, LD, ADHD and ID

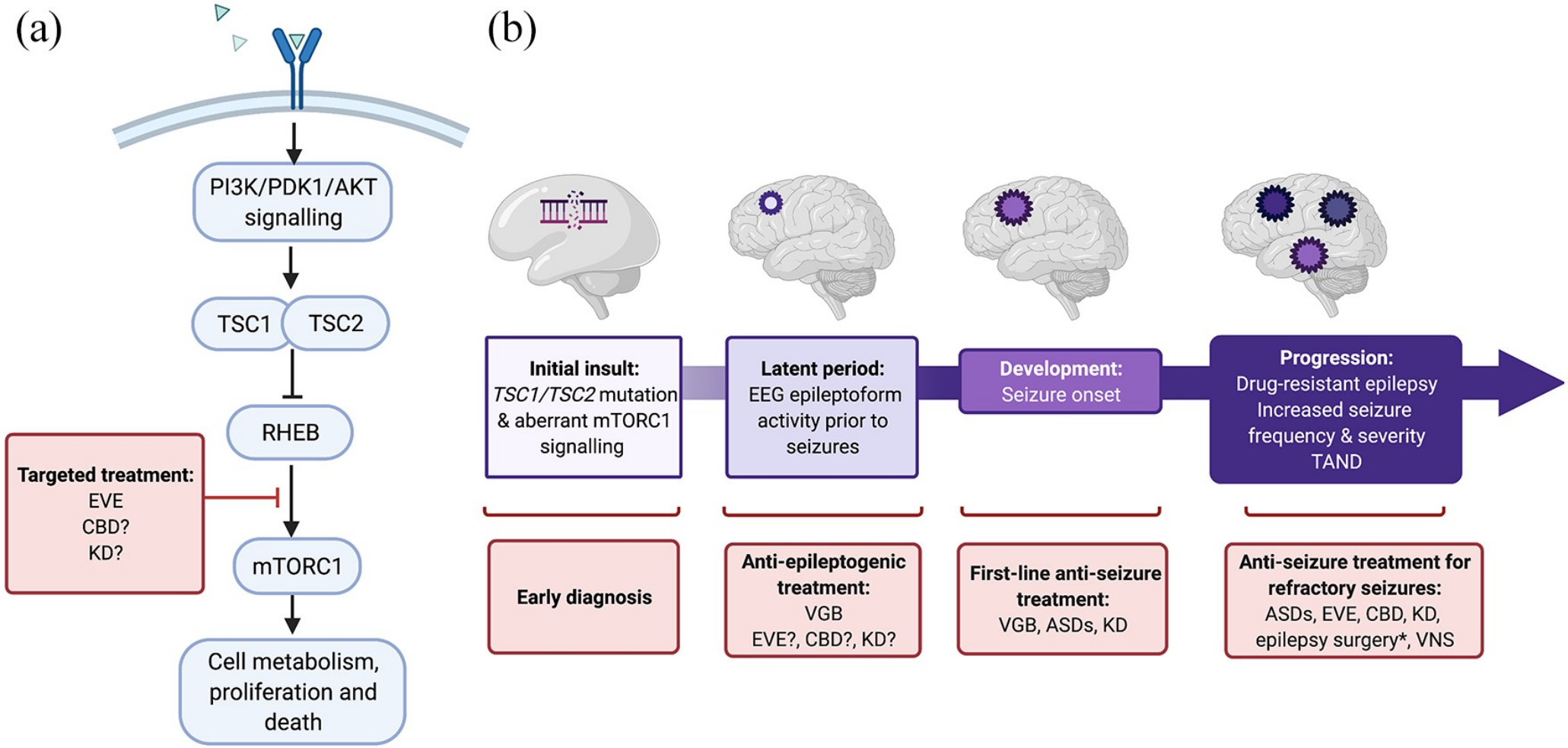
Table 1: Epilepsy Details

Number of patients with epilepsy	74
Median age of seizure onset (range)	12 months (0-168)
Initial seizure type	
Focal	49 (66%)
Generalized	4 (5%)
Epileptic spasms	19 (26%)
Unknown	2 (3%)
Infantile spasms	24 (32%)
Infantile spasms treatment	
Vigabatrin successful	18/21
Steroids successful	1/3
Status epilepticus	15 (20%)
Seizure-free at last follow-up	45 (61%)
Median duration seizure-free (range)	4.5 years (1-15)

Kingswood JC et al, Orphanet J Rare Dis. 2014
Curatolo P et al, Lancet Neurol. 2015

Wilbur C and Sanguansermsri C et al, Can J Neurol Sci. 2017

Treatment



Schubert-Bast S et al, Ther Adv Neurol Disord 2021

Treatment

Table 2: Epilepsy Surgery Population

Epilepsy surgery	19
Median age of seizure onset (range)	5 (0-22) months
Median age first surgery (range)	4.8 (1.1-15.6) years
Infantile spasms	8 (42%)
First surgery type	
Frontal resection	12
Parietal resection	2
Temporal resection	1
Multilobar resection	2
Total corpus callosotomy	2
Second surgery	4 (21%)
Frontal resection	2
Multilobar resection	1
Total corpus callosotomy	1
Seizure-free	9 (47%)
Median duration seizure-free (range)	2.5 (1-9) years

Wilbur C and Sanguansermsri C et al, Can J Neurol Sci. 2017