Idiopathic Generalised Epilepsies

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Outline

- History: how did we get here?,
- Idiopathic Generalised epilepsies within context of Genetic Generalised Epilepsies
- Diagnostic criteria

Edouard Hirsch

2005-2009 Commission Report
Epilepsia 2010;51:676-685

SPECIAL REPORT

Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009

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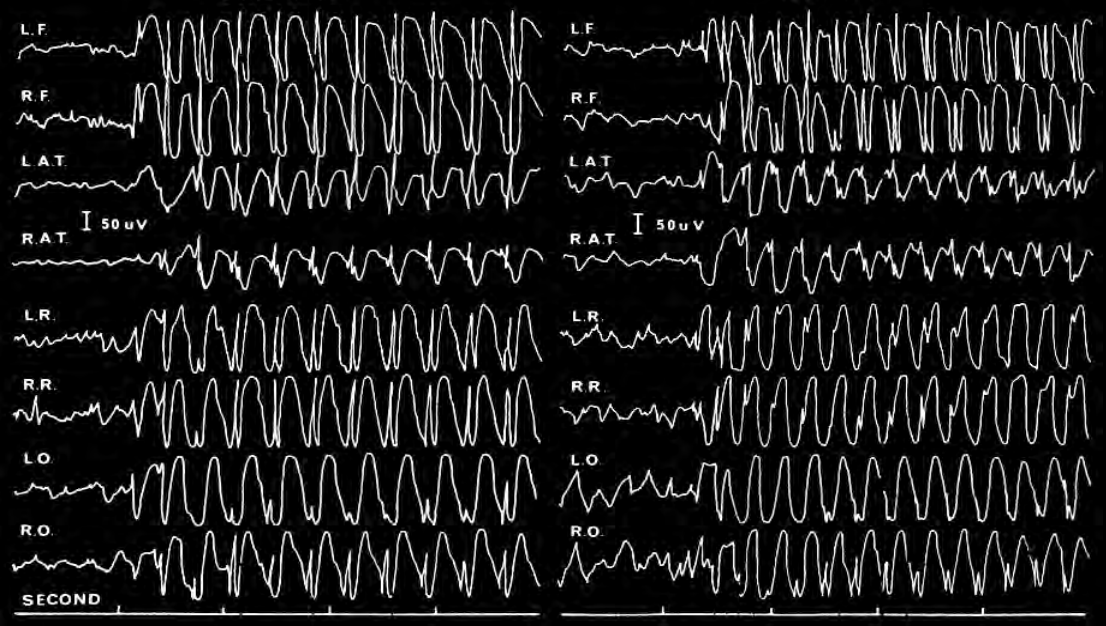
The term idiopathic was defined in the 1989 document:
'There is no underlying cause other than a possible hereditary predisposition…….
defined by age-related onset, clinical and electrographic characteristics, and a presumed genetic etiology.'

- highly pharmacoresponsive
- spontaneously remit during a predictable age range ……. unaccompanied by other consequences or disabilities, *although this is clearly not the case, as a variety of subtle cognitive and behavioral disorders are seen in association with these epilepsies.*

How do we know the Generalized Epilepsies are genetic?

Twins of William Lennox, 1950

Constance - Absence, onset 6 y - Kathryn



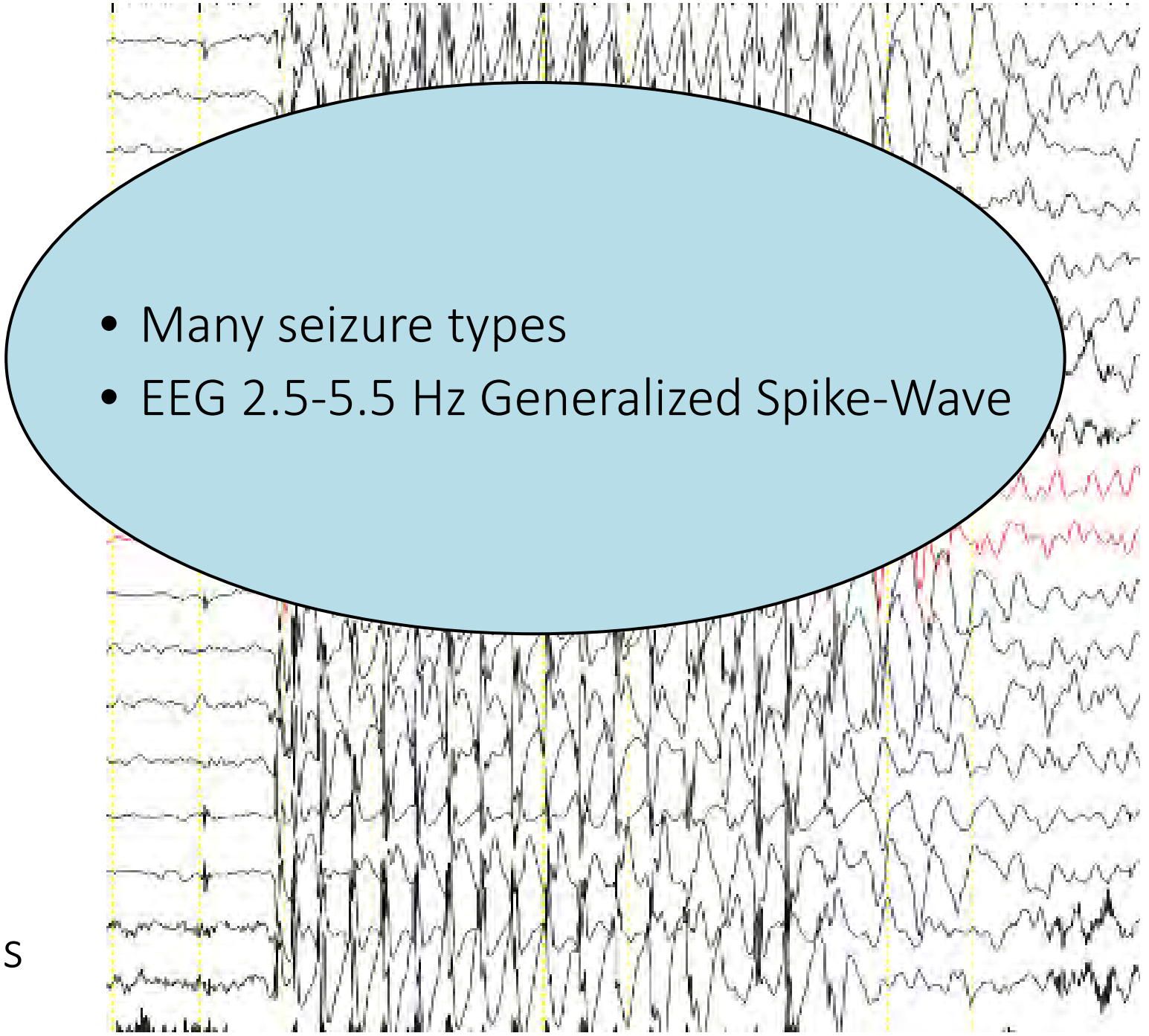
3 Hz Generalized Spike-Wave

2003: Seizure free since teenage

Courtesy of Ingrid Scheffer

Genetic Generalized Epilepsies

- Presumed genetic aetiology
- Broad group of patients
- Common and rare syndromes



- Many seizure types
- EEG 2.5-5.5 Hz Generalized Spike-Wave

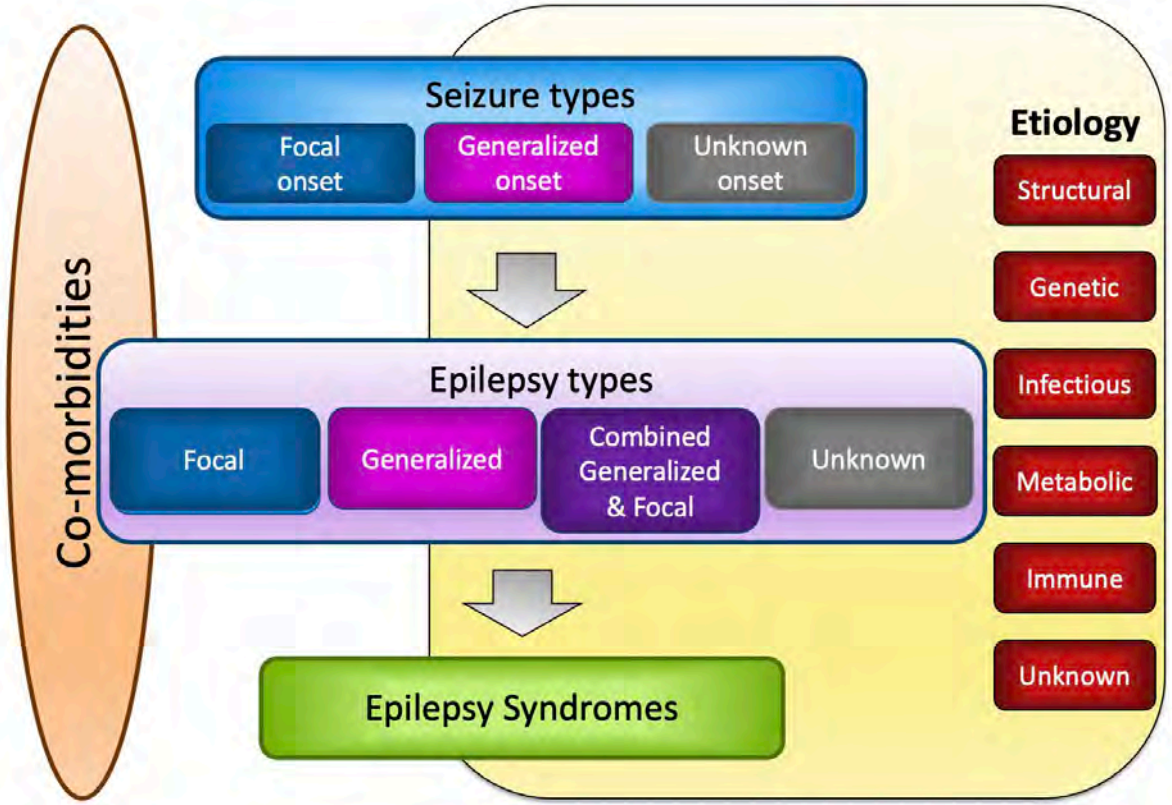
INTERNATIONAL LEAGUE AGAINST EPILEPSY

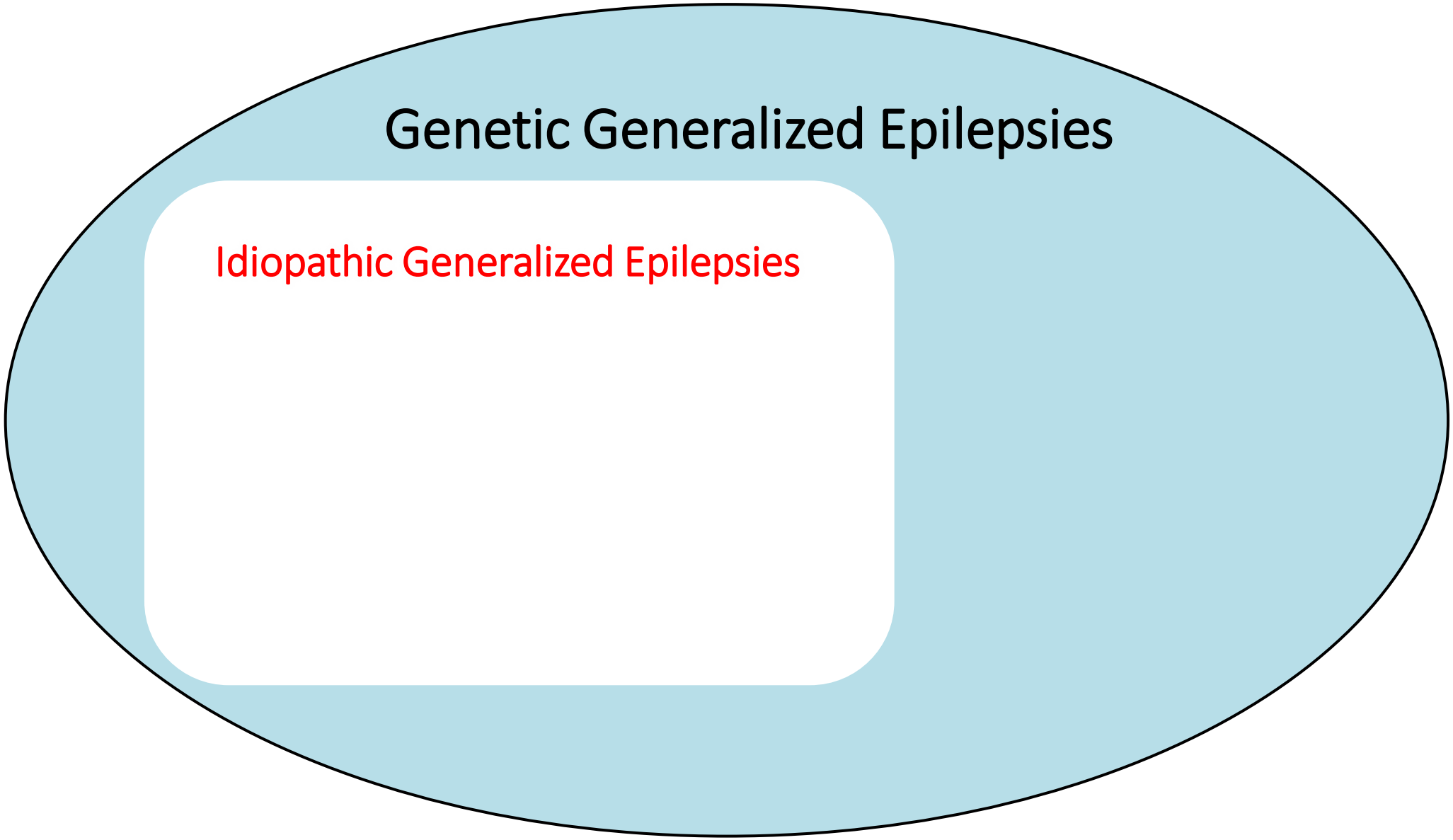
ILAE POSITION PAPER

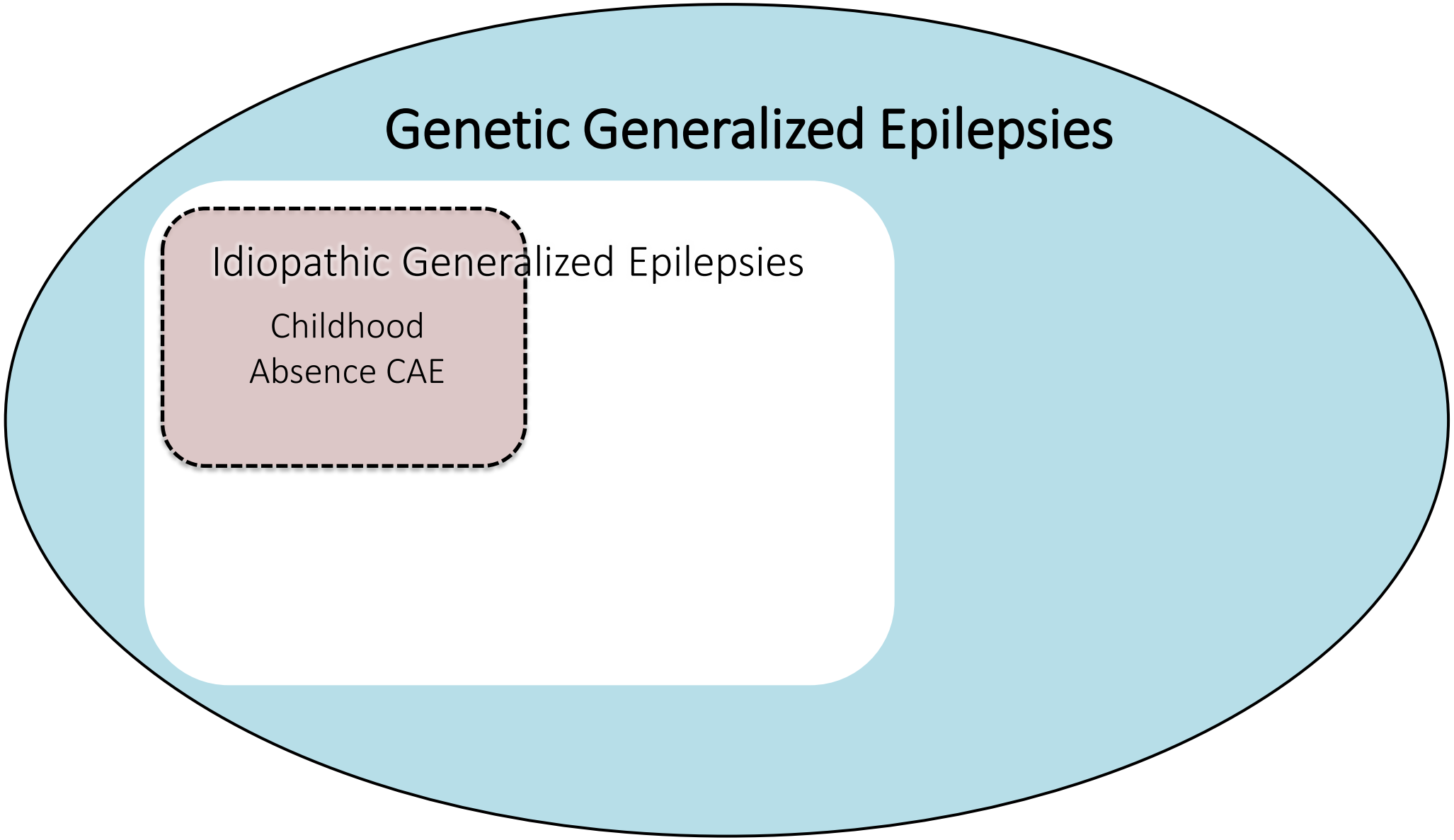
ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

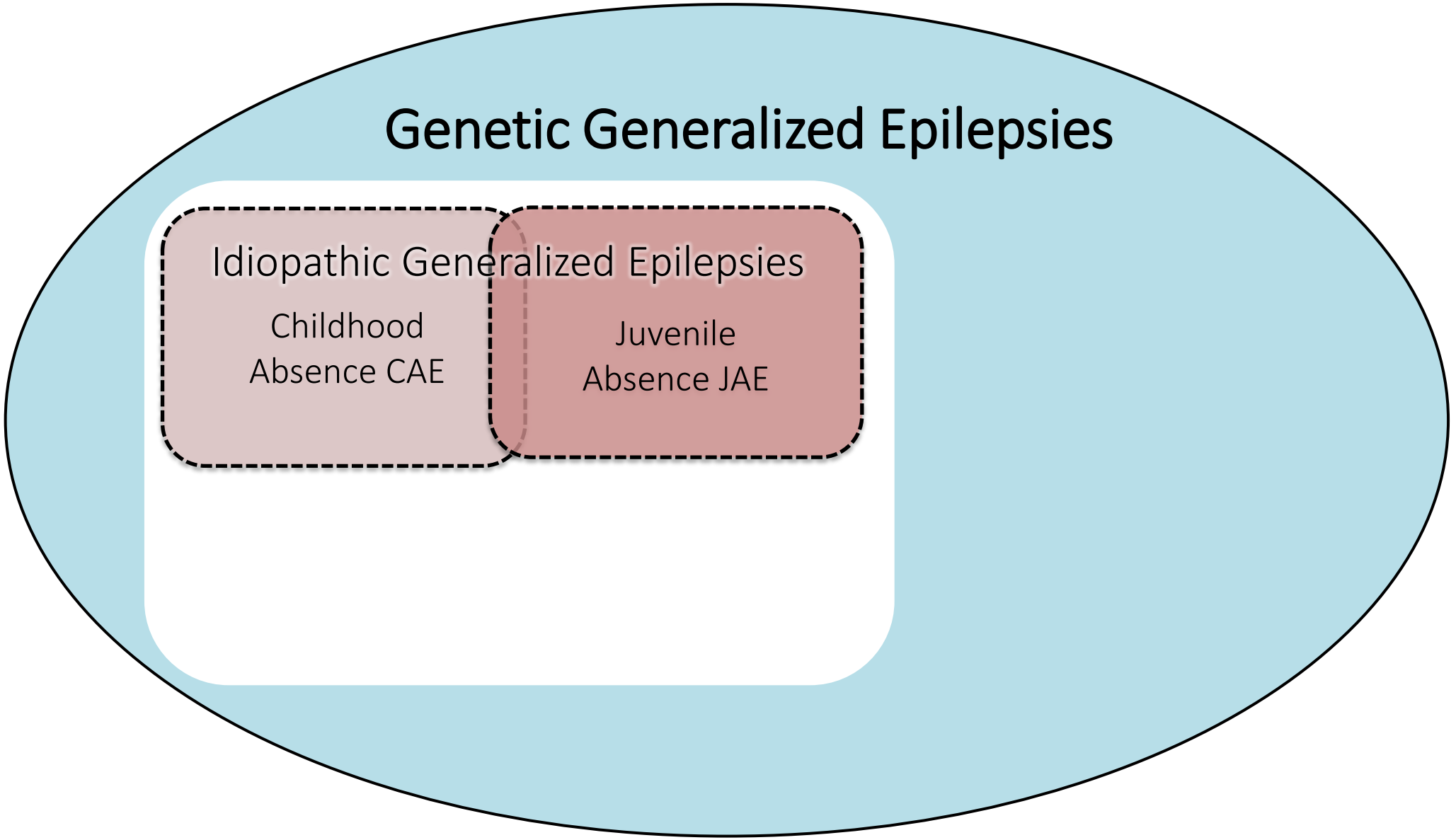
[1,2,3]Ingrid E. Scheffer, [1]Samuel Berkovic, [4]Giuseppe Capovilla, [5]Mary B. Connolly, [6]Jacqueline French, [7]Laura Guilhoto, [8,9]Edouard Hirsch, [10]Satish Jain, [11]Gary W. Mathern, [12]Solomon L. Moshé, [13]Douglas R. Nordli, [14]Emilio Perucca, [15]Torbjörn Tomson, [16]Samuel Wiebe, [17]Yue-Hua Zhang, and [18,19]Sameer M. Zuberi

Epilepsia, 58(4):512–521, 2017
doi: 10.1111/epi.13709




Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
Childhood
Absence CAE


Genetic Generalized Epilepsies
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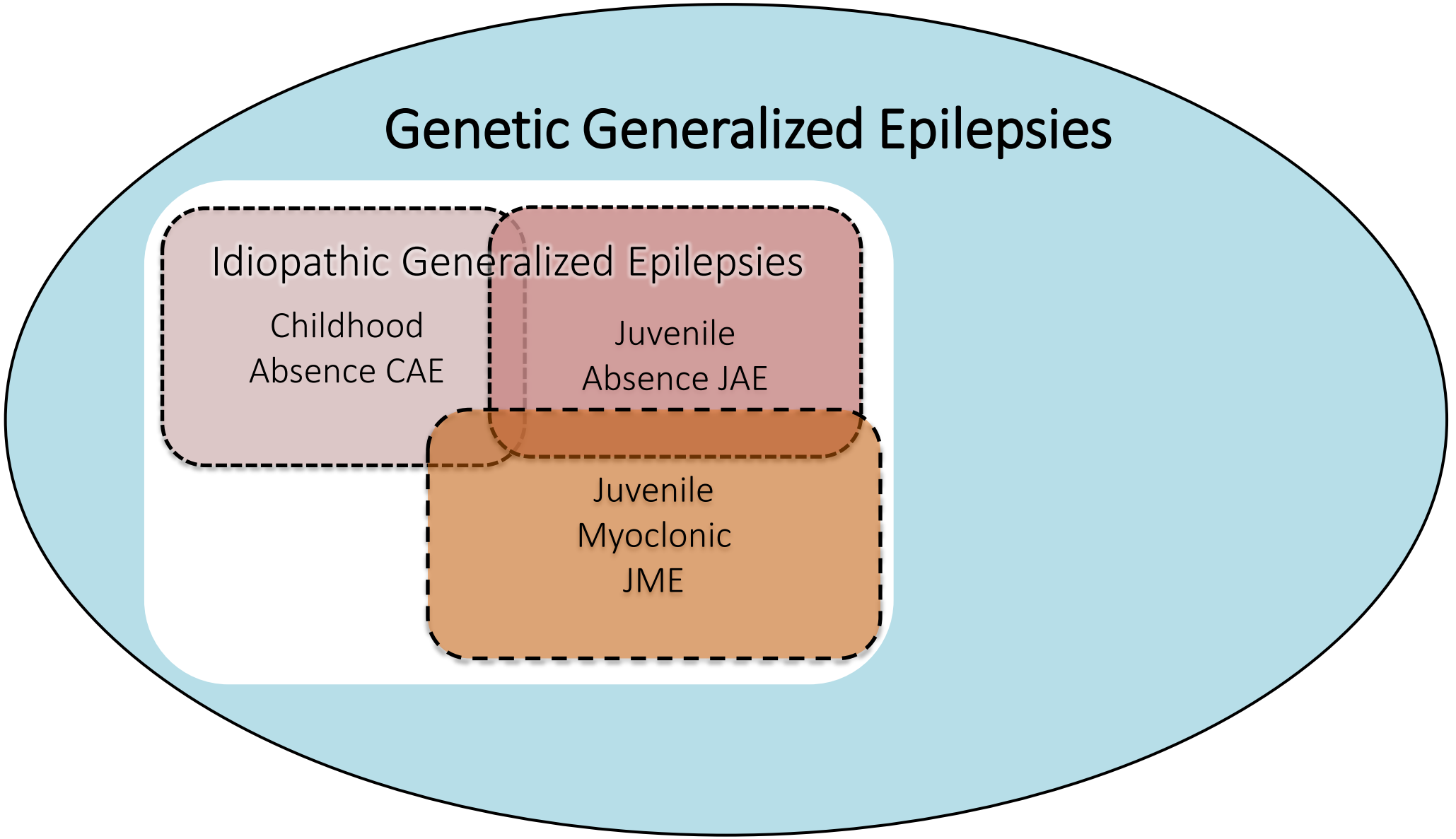
Childhood
Absence CAE
Juvenile
Absence JAE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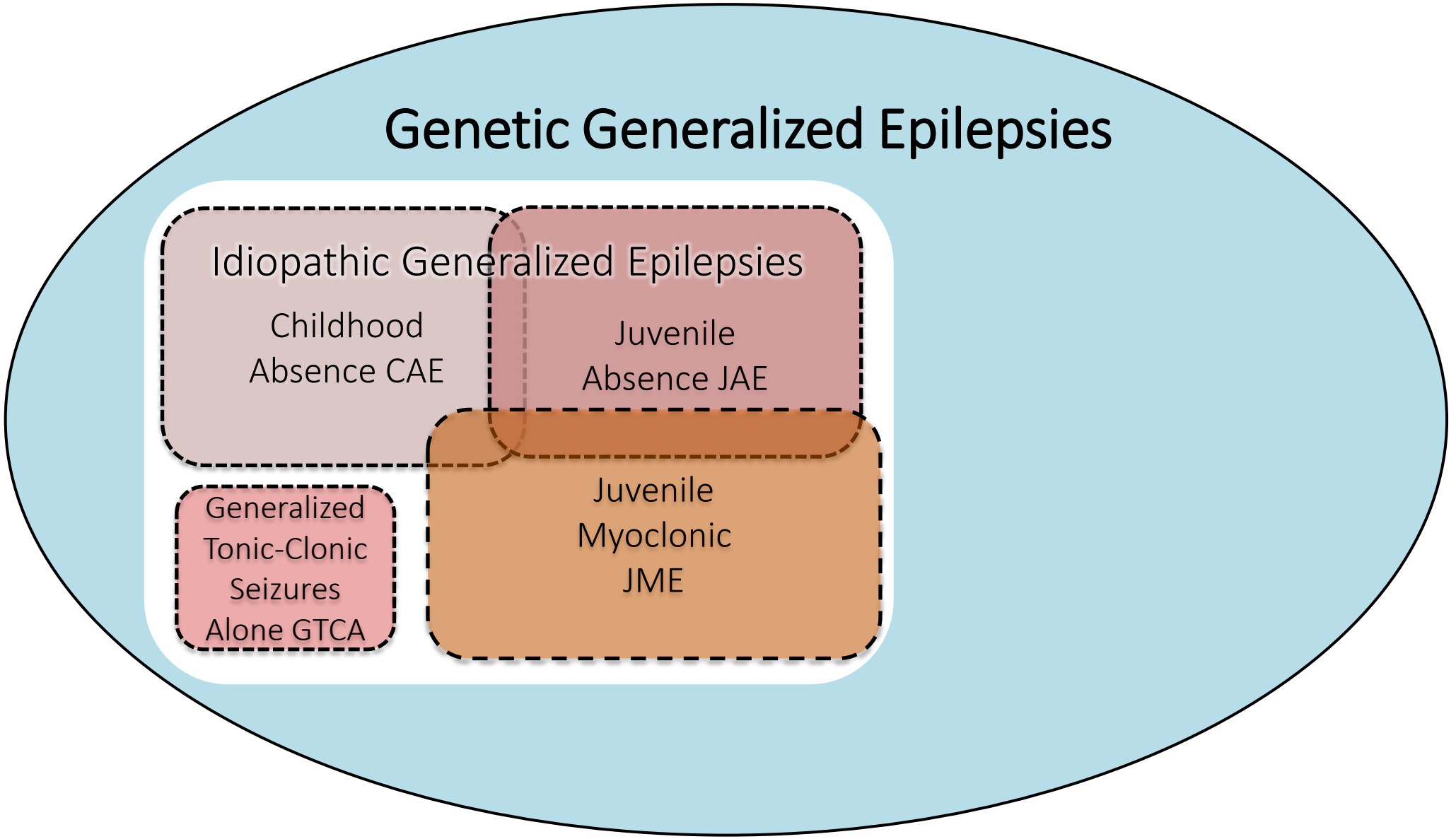
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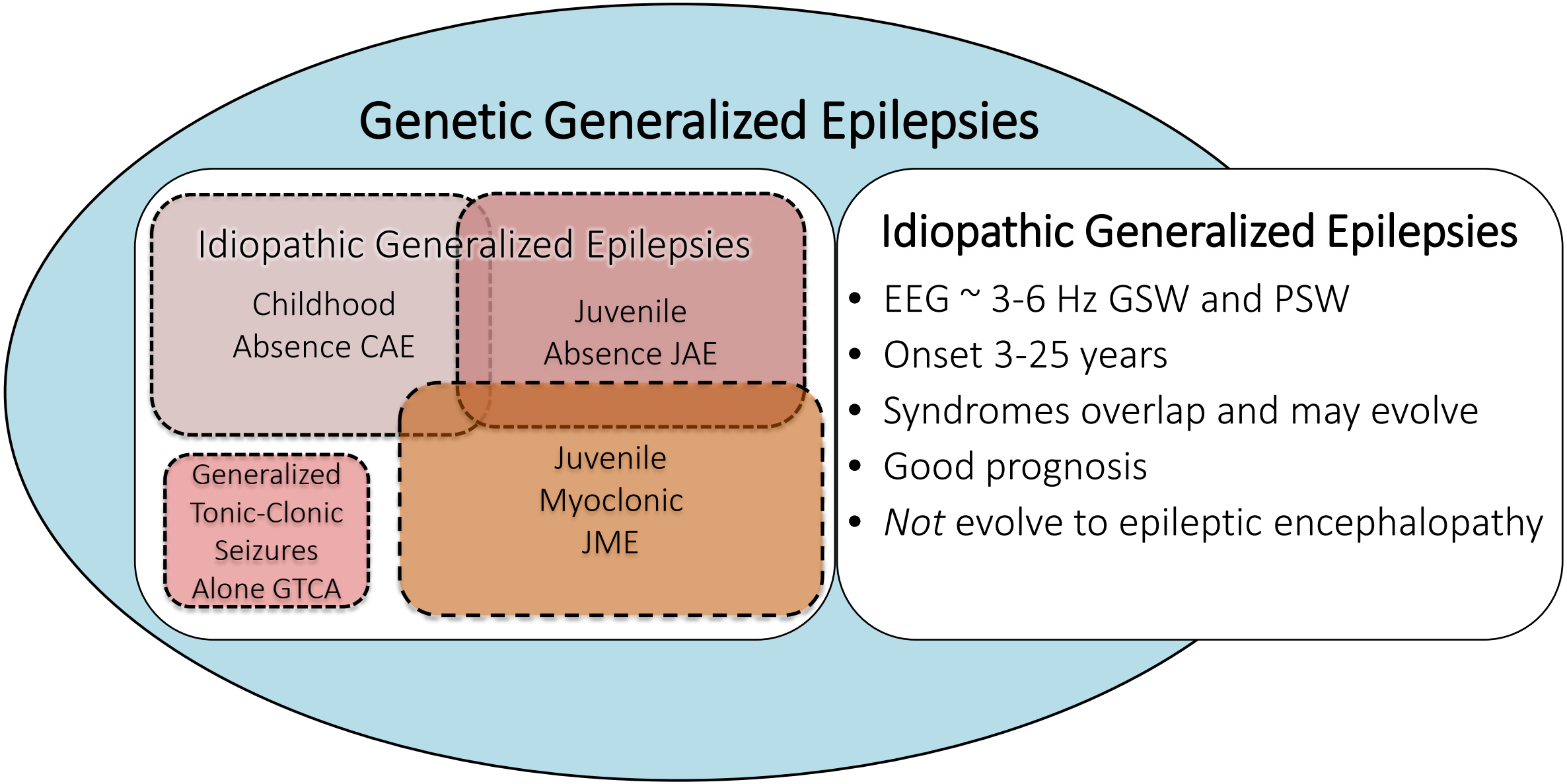
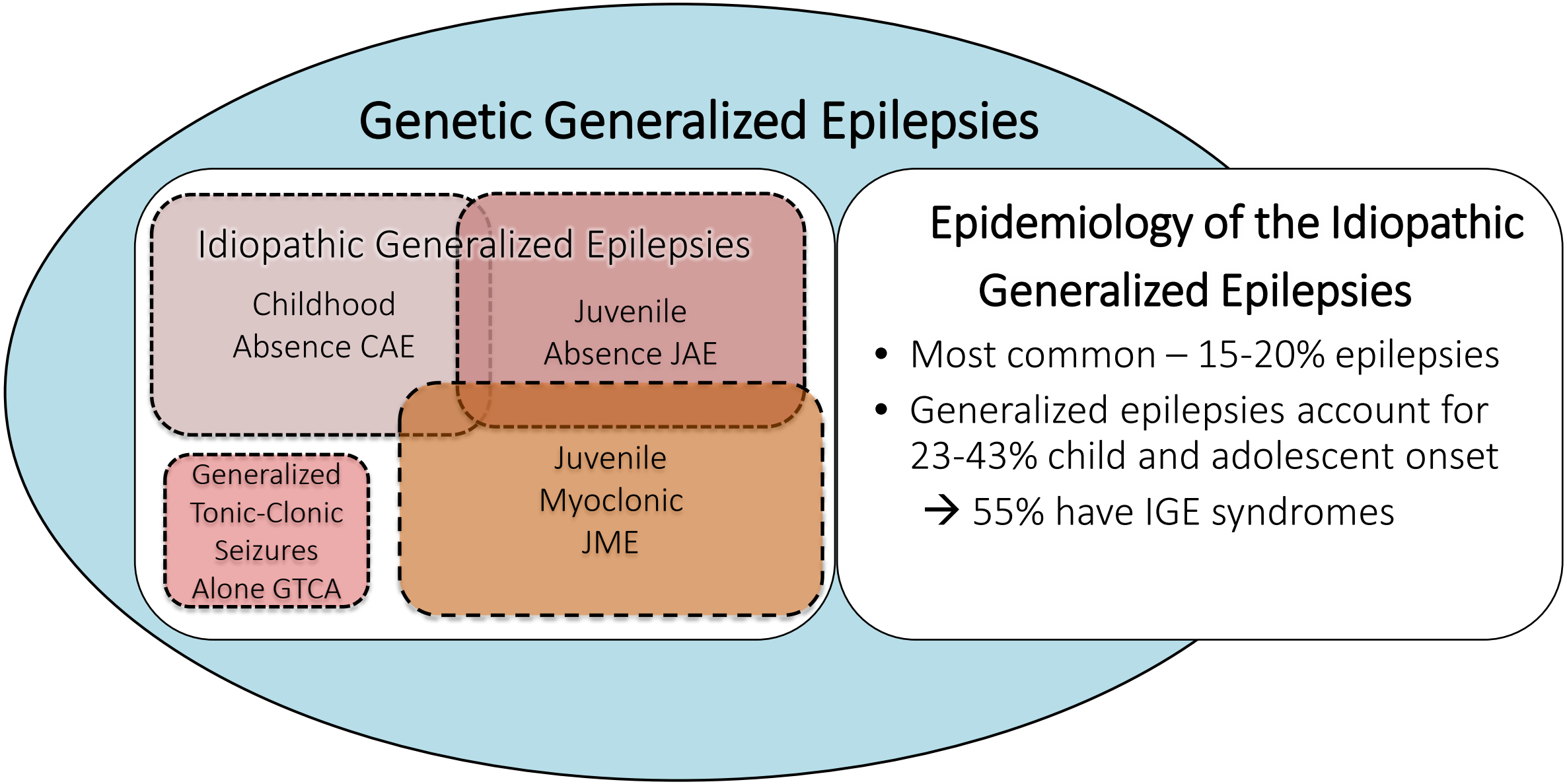
Generalized
Tonic-Clonic
Seizures
Alone GTCA



Jallon et al 2005; Berg et al 1999, Wirrell et al 2011

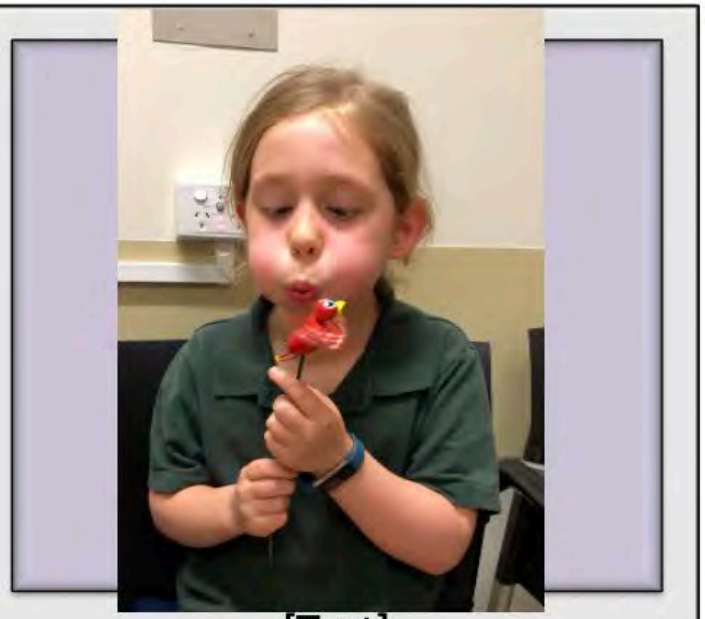


Epidemiology of the Idiopathic Generalized Epilepsies

- Most common – 15-20% epilepsies
- Generalized epilepsies account for 23-43% child and adolescent onset
  → 55% have IGE syndromes

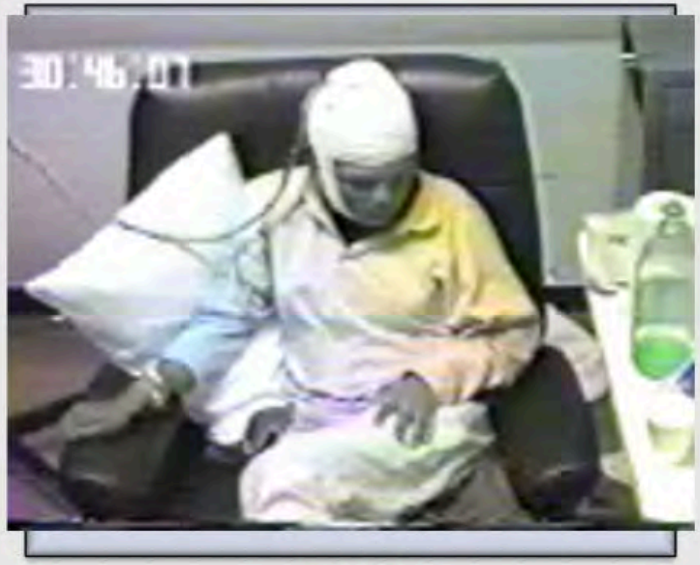
Jallon et al 2005; Berg et al 1999, Wirrell et al 2011

IGE Seizure types



[Text]

Absence



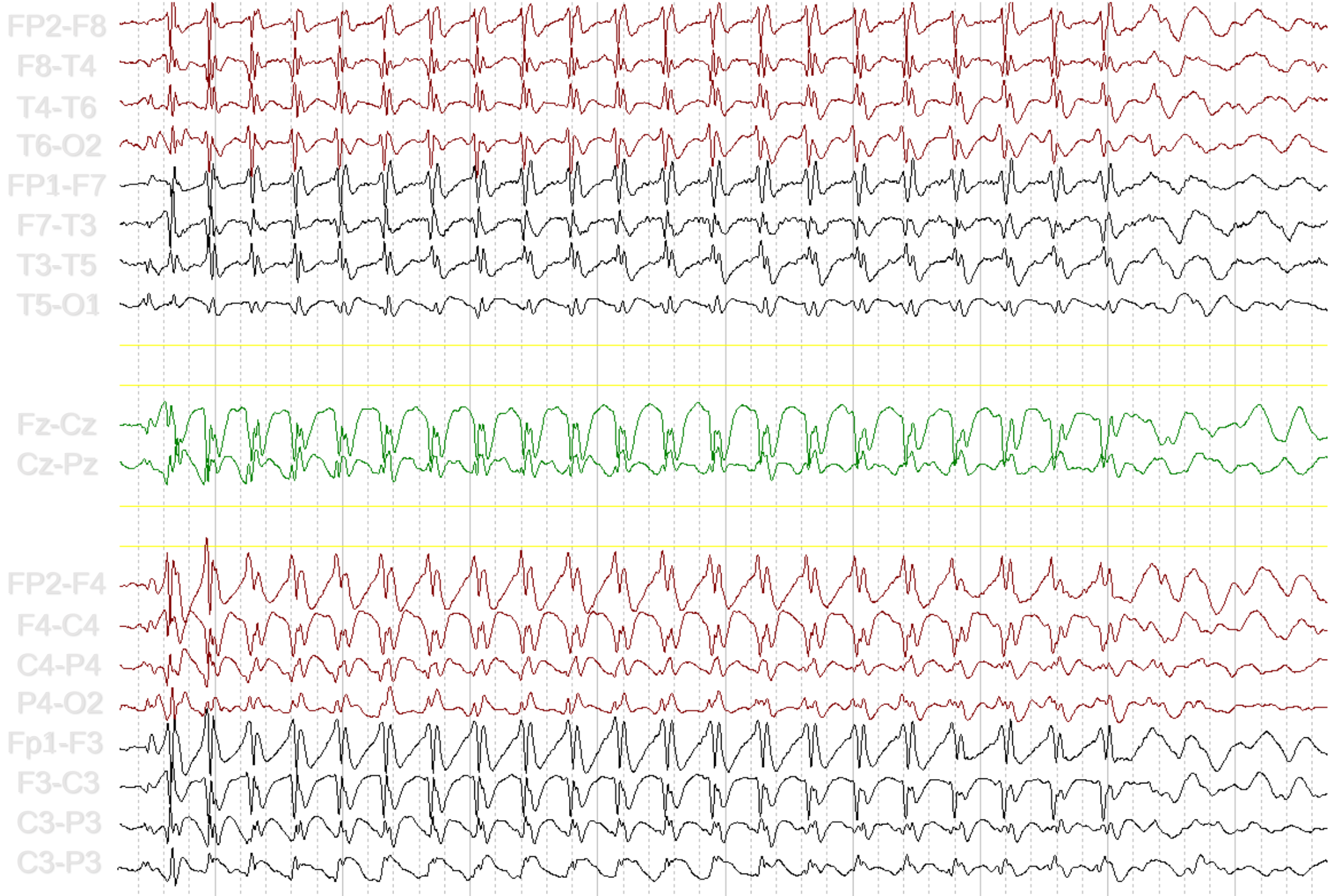
[Text]

Myoclonus

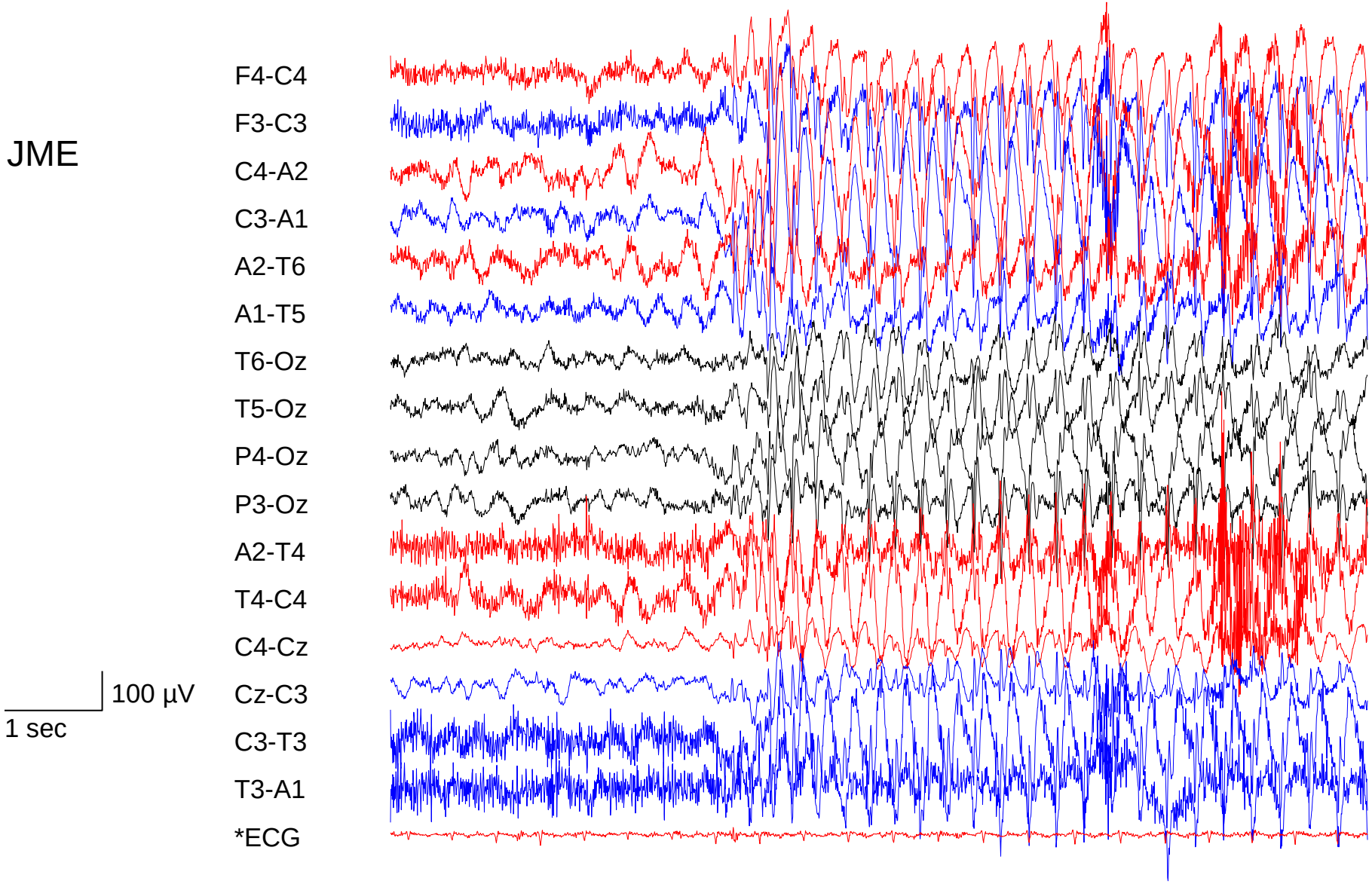
[Text]

Generalized tonic-clonic
Myoclonic-tonic-clonic

Seizure types NOT present in IGE:
tonic, atonic, myoclonic-atonic, focal, epileptic spasms

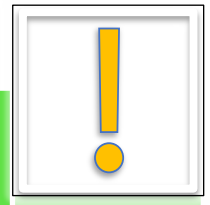

FP2-F8
F8-T4
T4-T6
T6-O2
FP1-F7
F7-T3
T3-T5
T5-O1
Fz-Cz
Cz-Pz
FP2-F4
F4-C4
C4-P4
P4-O2
Fp1-F3
F3-C3
C3-P3
C3-P3

JME


F4-C4
F3-C3
C4-A2
C3-A1
A2-T6
A1-T5
T6-Oz
T5-Oz
P4-Oz
P3-Oz
A2-T4
T4-C4
C4-Cz
Cz-C3
C3-T3
T3-A1
*ECG
100 µV
1 sec

Childhood Absence Epilepsy

- Typical absence seizures
- Paroxysms of 3 Hz (2.5-4 Hz) generalized spike-wave at the start of the absence (may have been obtained historically)



- Seizures
  - GTCS prior to or during the period of frequent absence seizures
  - Staring spells with typical duration >30 seconds or with postictal change
  - Absences occurring <daily in untreated patient
- EEG
  - Consistent unilateral EEG
  - Lack of HV activat^{n} 2.5-4Hz
  - no EEG correlate to staring
  - Persistent slowing EEG
- 2-3 or 11-13 years
- Potentially relevant neuro abn
- Potentially relevant abnormal MRI

- < 2 or >13 yrs
- Any seizure types except GTC
- Diffuse background slowing on EEG
- Moderate to profound intellectual disability
- Cognitive stagnation or decline
- Low csf glucose and/or *SLC2A1* pathogenic variant

Juvenile Absence Epilepsy

- Typical absence seizures
- Paroxysms of 3-5.5 Hz generalized spike-wave (may have been obtained historically)

- Staring spells with duration >30 secs or postictal change
- Absence seizures > 10/day
- Lack of HV activated 3-5.5 Hz spike-wave
- EEG persistent slowing
- Mild ID
- Potentially relevant abn neuro
- Potentially relevant abn MRI
- *Lack of GTC over course in absence relevant ASMs*

- Other seizure types except GTC
- Consistent unilateral EEG
- Diffuse slowing
- No EEG correlate to typical spell
- <8 or >20
- Mod to profound ID
- Cognitive stagnation or decline
- Low csf glc and/or *SLC2A1* variant

Juvenile Myoclonic Epilepsy

- Myoclonic seizures
- 3-5.5 Hz generalized spike-wave or generalized polyspike-wave on EEG (may be obtained historically)

- GTC status epilepticus
- Consistent unifocal semiology
- Consistent unifocal myoclonus
- Onset 8-9 years or 25-40 years
- Mild ID
- Potentially relevant neuro abn
- Potentially relevant MRI abn

- Other Seizure types except GTC, typical absence
- Absent polyspike and spike wave with habitual myoclonic event
- Focal EEG slowing
- Unilateral EEG
- SW freq <2.5Hz
- Diffuse background EEG slowing
- Age at onset <8 yrs or >40 yrs
- Mod to profound ID

- *Progressive cognitive decline*
- *Progressive myoclonus with impaired fine motor function*

Epilepsy with Generalised Tonic Clonic Seizures Alone

- Generalised tonic clonic seizures
- 3-5.5 Hz generalized spike-wave or polyspike-wave on EEG (may be obtained historically)

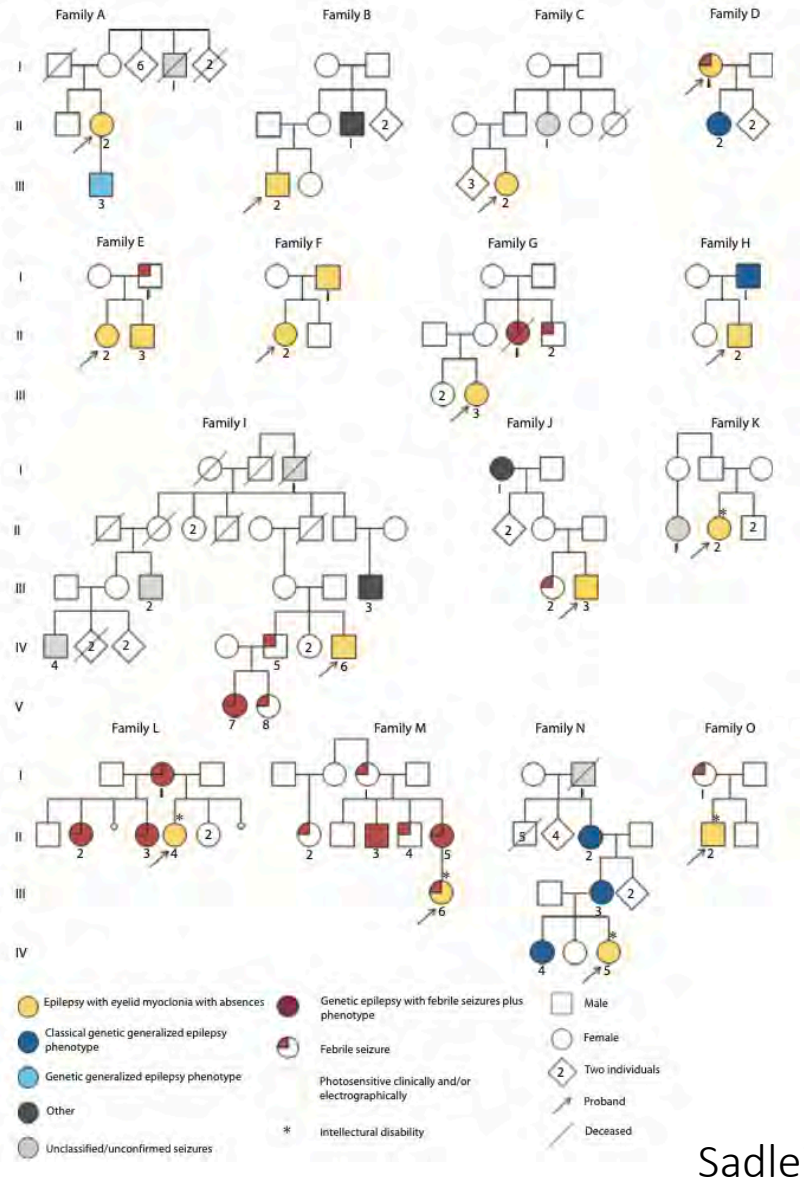
- Consistent unifocal semiology at seizure onset
- Age onset 5-9 or 26-40yr
- Mild ID
- Potentially relevant neuro abn
- Potentially relevant abn MRI

- Generalised MTC seizure, or any other seizure type
- EEG
- Focal slowing
- Consistent unilat abn
- Generalised SSW <2.5Hz
- Diffuse slowing
- Age onset <5 or >40
- Mod to profound ID
- Causative lesion on MRI
- *Progressive cognitive decline*

In resource limited regions, GTCA cannot be diagnosed without interictal EEG showing generalized spike wave, as one cannot exclude focal onset without EEG.

Family history in IGEs

- Most frequently negative
- Family history of mixed IGEs in relatives
- IGEs also in relatives of patients with
  - Epilepsy with Eyelid Myoclonia
  - Epilepsy with Myoclonic Absences
  - Myoclonic Epilepsy in Infancy
  - Genetic Epilepsy with Febrile Seizures Plus

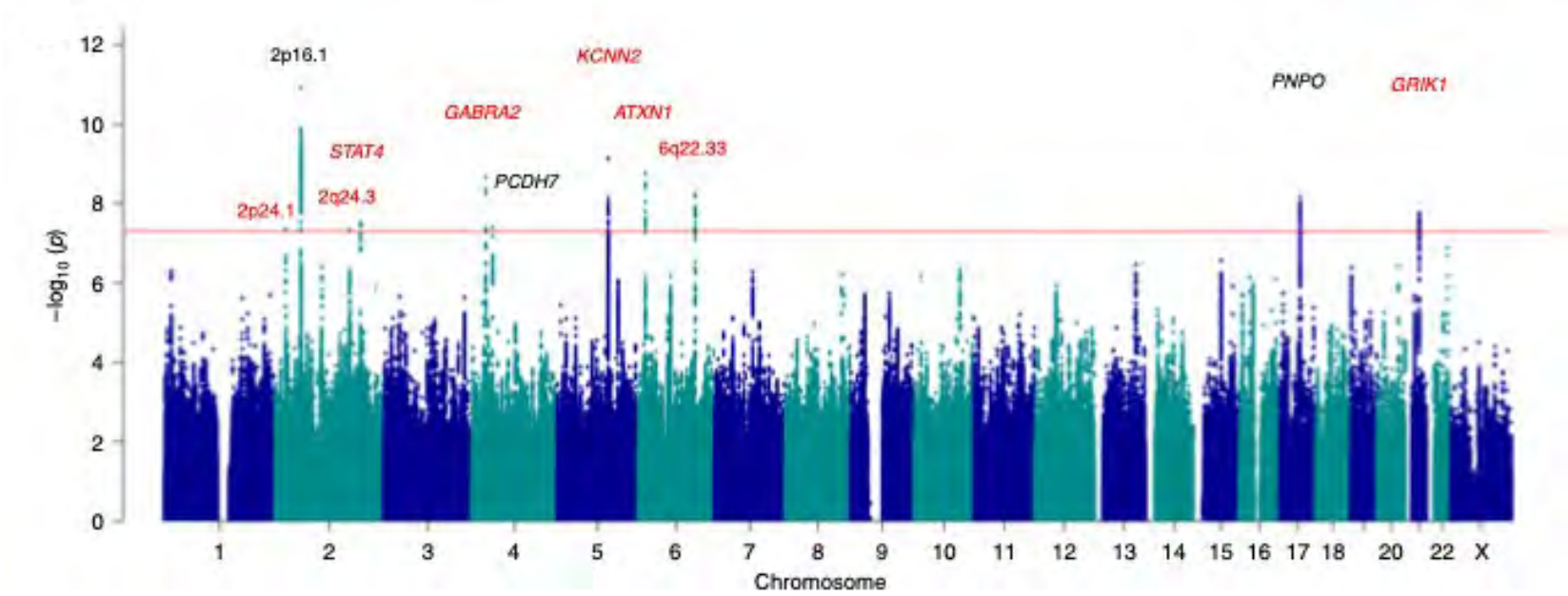


Sadleir et al 2012

Marini et al 2004; Bureau et al 2005;Auvin et al 2006; Zhang et al 2017

IGEs and GGEs have a genetic basis

- Complex inheritance – polygenic ± environmental factors



- De novo pathogenic variants eg. *SLC2A1, GABRG2, GABRA1*
- Copy number variants 3% – recurrent eg. 15q13.3 deletion

ILAE Consortium 2018, Arsov et al 2012, Wallace et al 2001, Helbig et al 2009

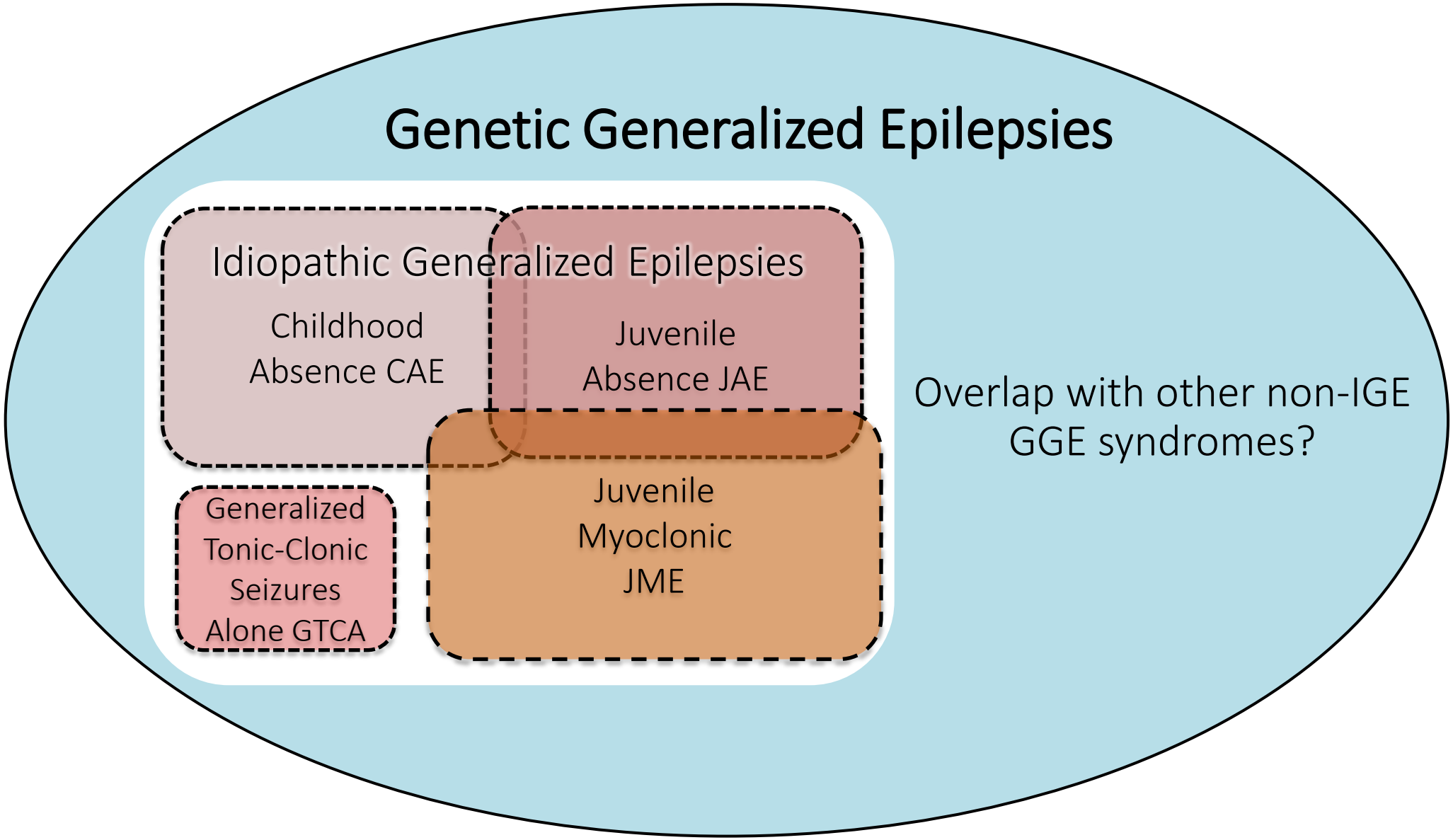
Anti-Seizure Medications

Valproate **most** effective –

- *not* in women of child-bearing age

Contraindicated

- Sodium channel blockers
  - X Carbamazepine, Oxcarbazepine, eslicarbazepine
  - X Phenytoin
  - Lamotrigine – use cautiously
- GABAergic drugs exacerbate absence and myoclonus
  - X Tiagabine, Vigabatrin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Generalized
Tonic-Clonic
Seizures
Alone GTCA
Overlap with other non-IGE
GGE syndromes?

Genetic Generalized Epilepsies

Idiopathic Generalized Epilepsies

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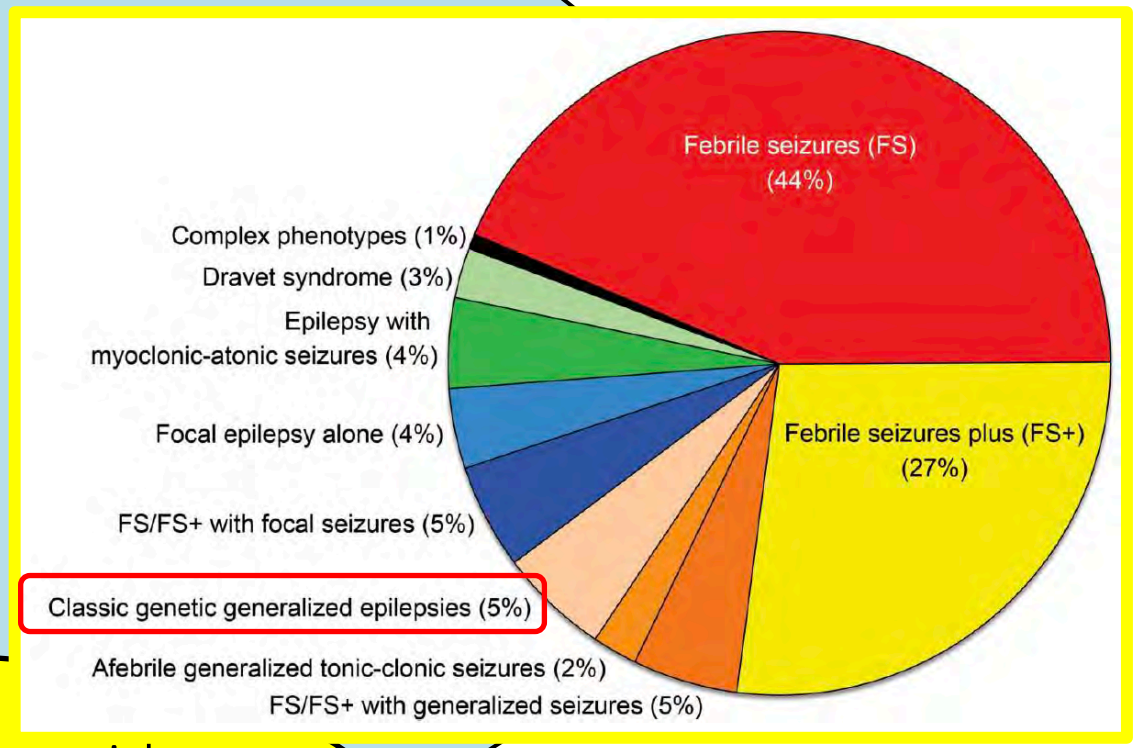
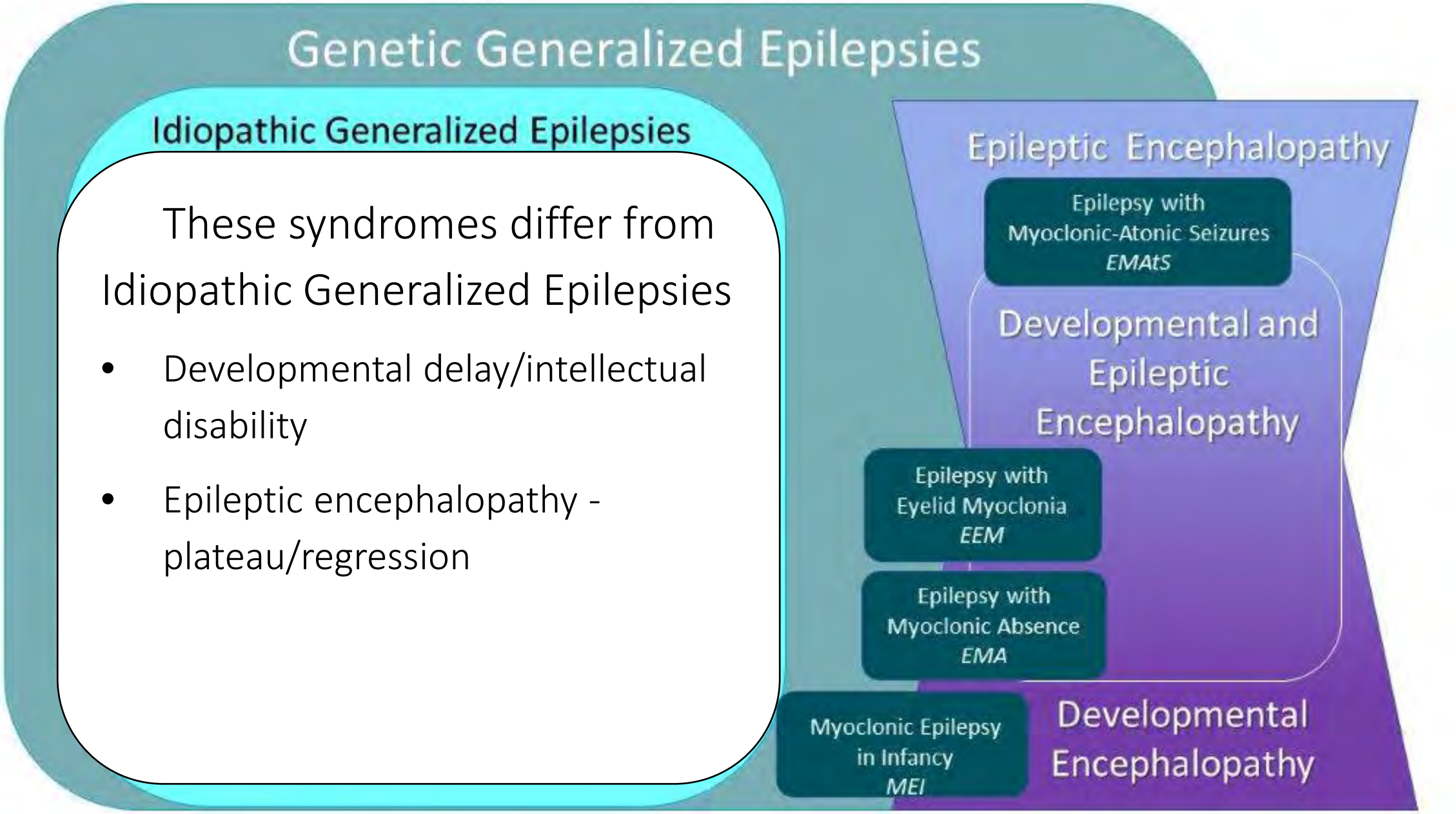
Genetic Epilepsy with
Febrile Seizures Plus
GEFS +



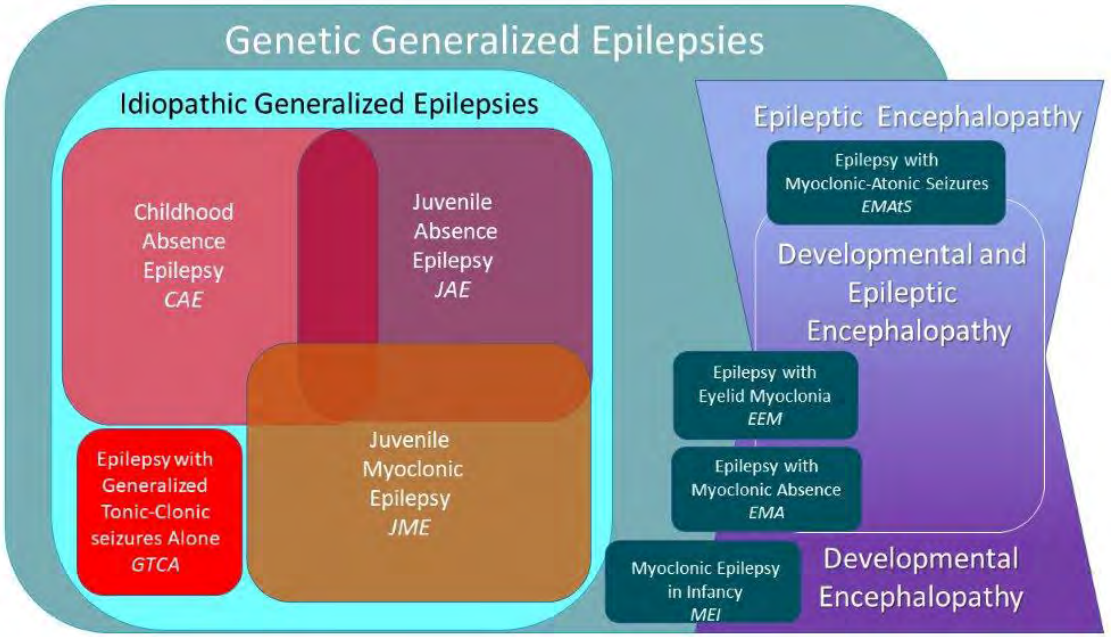
Zhang et al 2017

Scheffer and Berkovic 1997


Genetic Generalized Epilepsies
Idiopathic Generalized Epilepsies
These syndromes differ from Idiopathic Generalized Epilepsies
• Developmental delay/intellectual disability
• Epileptic encephalopathy - plateau/regression
Epileptic Encephalopathy
Epilepsy with Myoclonic-Atonic Seizures
EMAtS
Developmental and Epileptic Encephalopathy
Epilepsy with Eyelid Myoclonia
EEM
Epilepsy with Myoclonic Absence
EMA
Myoclonic Epilepsy in Infancy
MEI
Developmental Encephalopathy

The IGEs

- 4 syndromes, a subset of genetic generalised epilepsies
  - Childhood Absence Epilepsy,
  - Juvenile Absence Epilepsy,
  - Juvenile Myoclonic Epilepsy
  - Epilepsy with Generalized Tonic Clonic Seizures Alone,
- Polygenic inheritance, with or without environmental factors.
- Development is typically normal
  - mood disorders, ADHD and learning disabilities are common comorbidities.
- Seizure types include one, or a combination, of the following: absence, myoclonic, tonic-clonic and myoclonic-tonic-clonic seizures.
- The EEG shows generalized 2.5-5.5 Hz spike-wave which may be activated by hyperventilation or photic stimulation.



ILAE Definition of the Idiopathic Generalized Epilepsy Syndromes: Position Statement by the ILAE Task Force on Nosology and Definitions

Edouard Hirsch[1], Jacqueline French[2], Ingrid E Scheffer[3], Sameer M Zuberi[4], Eugen Trinka[5,6], Nicola Specchio[7], Ernest Somerville[8], Paulinea Samia[9], Kate Riney[10], Rima Nabbout[11], Satish Jain[12], Alicia Bogacz[13], Taoufik Alsaadi[14], Jo M Wilmshurst[15], Stephane Auvin[16], Samuel Wiebe[17], Paolo Tinuper[18,19]*, Elaine C Wirrell[20]*

Are IGEs and GGEs synonymous?

- IGEs are a subgroup of the GGEs
- Specific syndrome details – see ILAE website
- Overlap intriguing from a biological perspective