2023 GW Epilepsy Board Review & Best Practices

# LESS AGE-SPECIFIC RELATIONSHIP, EPILEPSIES ATTRIBUTED TO AND ORGANIZED BY STRUCTURAL-METABOLIC CAUSES, AND DISTINCTIVE CONSTELLATIONS

**John M. Schreiber, MD**
**Medical Director, EEG**
**Children's National Health System**

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# DISCLOSURES

- **Disclosure of Financial Relationships**
  **Consultant – Neurocrine Biosciences**
  **Speaker Bureau – Zogenix, Inc and Marinus Pharmacueticals**

- **Off-Label Usage**
  **None**

# ILAE Proposed Epilepsy Classification

**Table 3. Electroclinical syndromes and other epilepsies**

- Electroclinical syndromes arranged by age at onset[a]
  - Neonatal period
    - Benign familial neonatal epilepsy (BFNE)
    - Early myoclonic encephalopathy (EME)
    - Ohtahara syndrome
  - Infancy
    - Epilepsy of infancy with migrating focal seizures
    - West syndrome
    - Myoclonic epilepsy in infancy (MEI)
    - Benign infantile epilepsy
    - Benign familial infantile epilepsy
    - Dravet syndrome
    - Myoclonic encephalopathy in nonprogressive disorders
  - Childhood
    - Febrile seizures plus (FS+) (can start in infancy)
    - Panayiotopoulos syndrome
    - Epilepsy with myoclonic atonic (previously astatic) seizures
    - Benign epilepsy with centrotemporal spikes (BECTS)
    - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
    - Late onset childhood occipital epilepsy (Gastaut type)
    - Epilepsy with myoclonic absences
    - Lennox-Gastaut syndrome
    - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
    - Landau-Kleffner syndrome (LKS)
    - Childhood absence epilepsy (CAE)
  - Adolescence – Adult
    - Juvenile absence epilepsy (JAE)
    - Juvenile myoclonic epilepsy (JME)
    - Epilepsy with generalized tonic–clonic seizures alone
    - Progressive myoclonus epilepsies (PME)
    - Autosomal dominant epilepsy with auditory features (ADEAF)
    - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies
- Distinctive constellations
  - Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypothalamic hamartoma
  - Hemiconvulsion–hemiplegia–epilepsy
  - Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor
  - Infection
  - Trauma
  - Angioma
  - Perinatal insults
  - Stroke
  - Etc.
- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

[a]The arrangement of electroclinical syndromes does not reflect etiology.

[b]Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

*Epilepsia*, 51(4):676–685, 2010

# ILAE 2022 Classification and Definitions

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Epilepsia®

SPECIAL REPORT

## Methodology for classification and definition of epilepsy syndromes with list of syndromes: Report of the ILAE Task Force on Nosology and Definitions

Elaine C. Wirrell[1] | Rima Nabbout[2,3] | Ingrid E. Scheffer[4] | Taoufik Alsaadi[5] | Alicia Bogacz[6] | Jacqueline A. French[7] | Edouard Hirsch[8] | Satish Jain[9] | Sunao Kaneko[10] | Kate Riney[11,12] | Pauline Samia[13] | O. Carter Snead[14] | Ernest Somerville[15] | Nicola Specchio[16] | Eugen Trinka[17,18,19] | Sameer M. Zuberi[20,21] | Simona Balestrini[22,23,24] | Samuel Wiebe[25] | J. Helen Cross[26,27] | Emilio Perucca[28,29] | Solomon L. Moshé[30] | Paolo Tinuper[31,32]

# EpilepsyDiagnosis.org

The ILAE welcomes you to EpilepsyDiagnosis.org, a cutting edge online diagnostic manual of the epilepsies.

## Goal

The goal of ***epilepsydiagnosis.org*** is to make available, in an easy to understand form, latest concepts relating to seizures and the epilepsies. The principle goal is to assist clinicians who look after people with epilepsy anywhere in the world to diagnose seizure type(s), epilepsy type, diagnose epilepsy syndromes and define the etiology of the epilepsy. The site is principally designed for clinicians in primary and secondary care settings caring for people with epilepsy and we hope will also serve as a useful teaching aid.

## Structure

The structure of this site reflects the importance of seizure type, epilepsy type, syndrome, and etiology in clinical practice. On this website, you will find current classification concepts for seizures, with their clinical features, video examples, EEG correlate, differential diagnosis and related epilepsy type, epilepsy syndrome and etiology. Epilepsy syndromes are detailed by their clinical features, seizure types, EEG, imaging and genetic correlates and differential diagnoses. The site includes sections on etiologies of epilepsies and epilepsy imitators with cross-referencing between these sections and seizure and syndrome sections.

## Videos

A short and instantaneous registration process is required to view videos on this site, and this is open to anyone, anywhere in the world with an internet connection. Individuals with seizures or epilepsy imitating conditions and their families have kindly given consent for videos to be freely available in this way.

## Further development

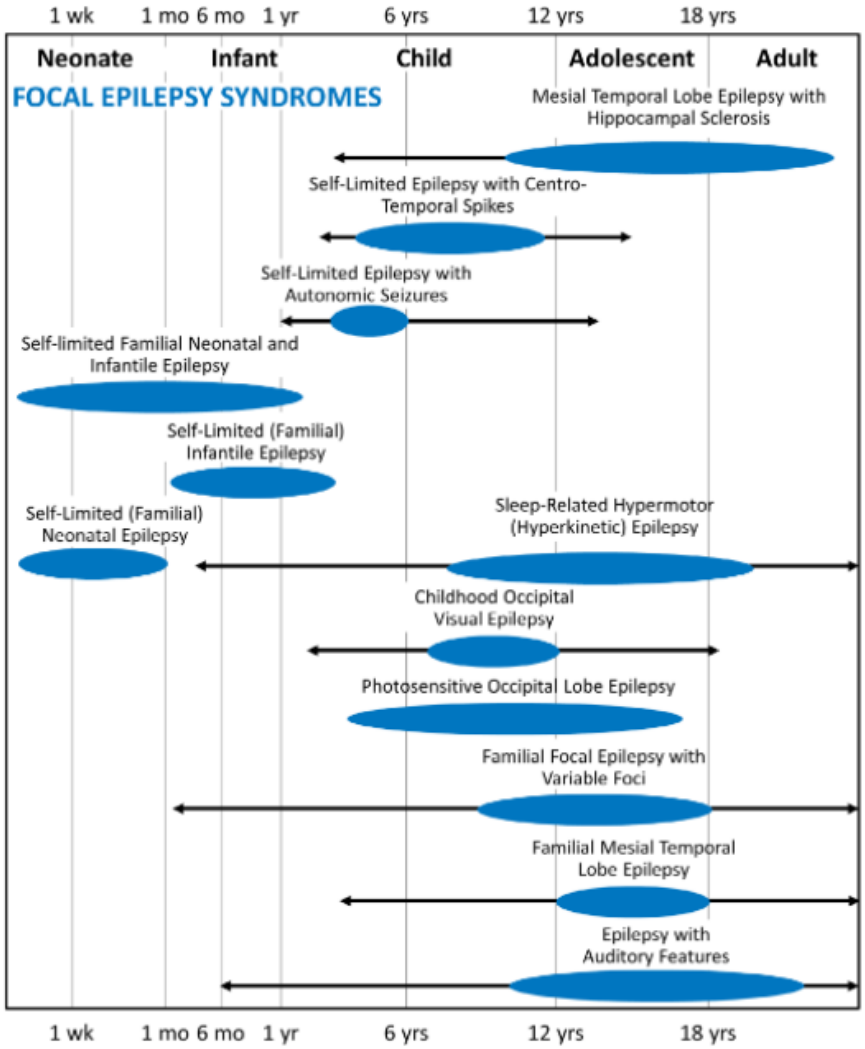
You will notice that there are some sections that do not have video examples as yet, notably *Epilepsy Imitators*, and some text sections that require expansion. The ILAE will continue to develop EpilepsyDiagnosis.org and add further videos and text over time.

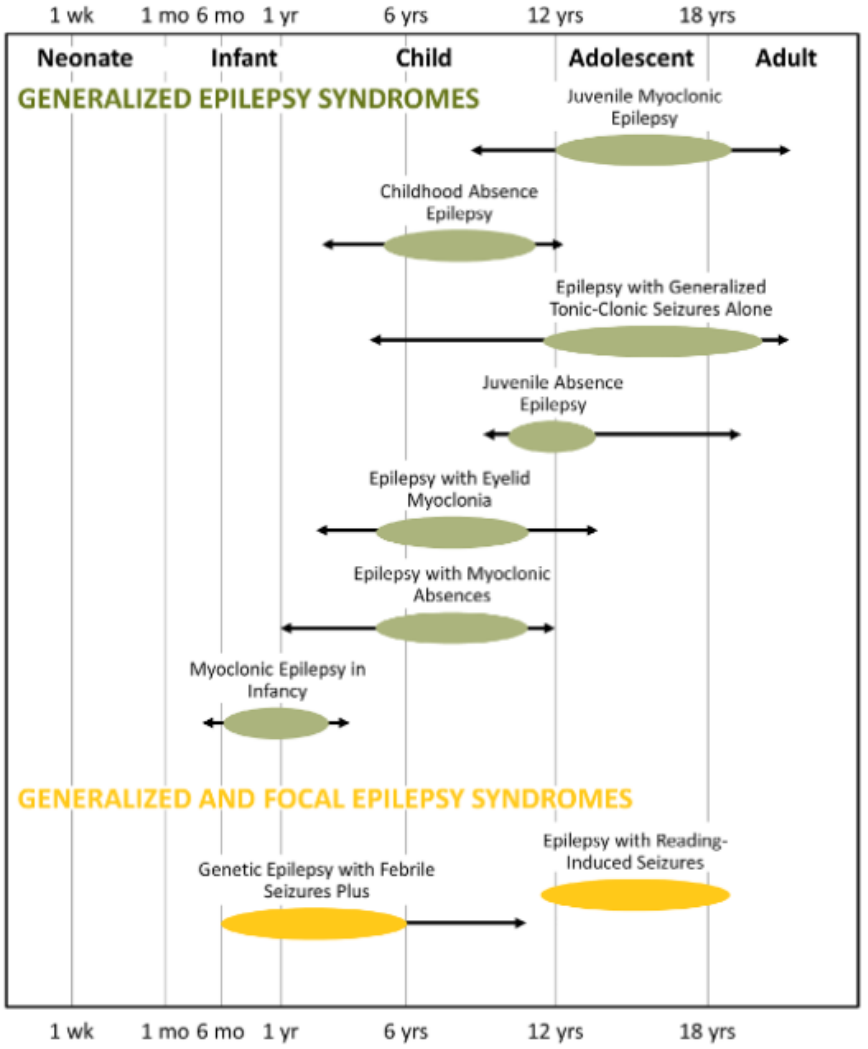
Please have a look EpilepsyDiagnosis.org, use it for your own education, for teaching and let colleagues, patients and families know about the resources on this site. We would be very grateful if you could complete the survey on the Give Feedback page. This will help us in our further development of this continually evolving site. Future plans include developing continuing medical education (CME) packages linked to the site and providing downloadable information for people with epilepsy, their families and carers.

## Acknowledgement

The website has been developed in partnership with eResearch at the University of Melbourne, Australia.

# ILAE 2022 Classification and Definitions



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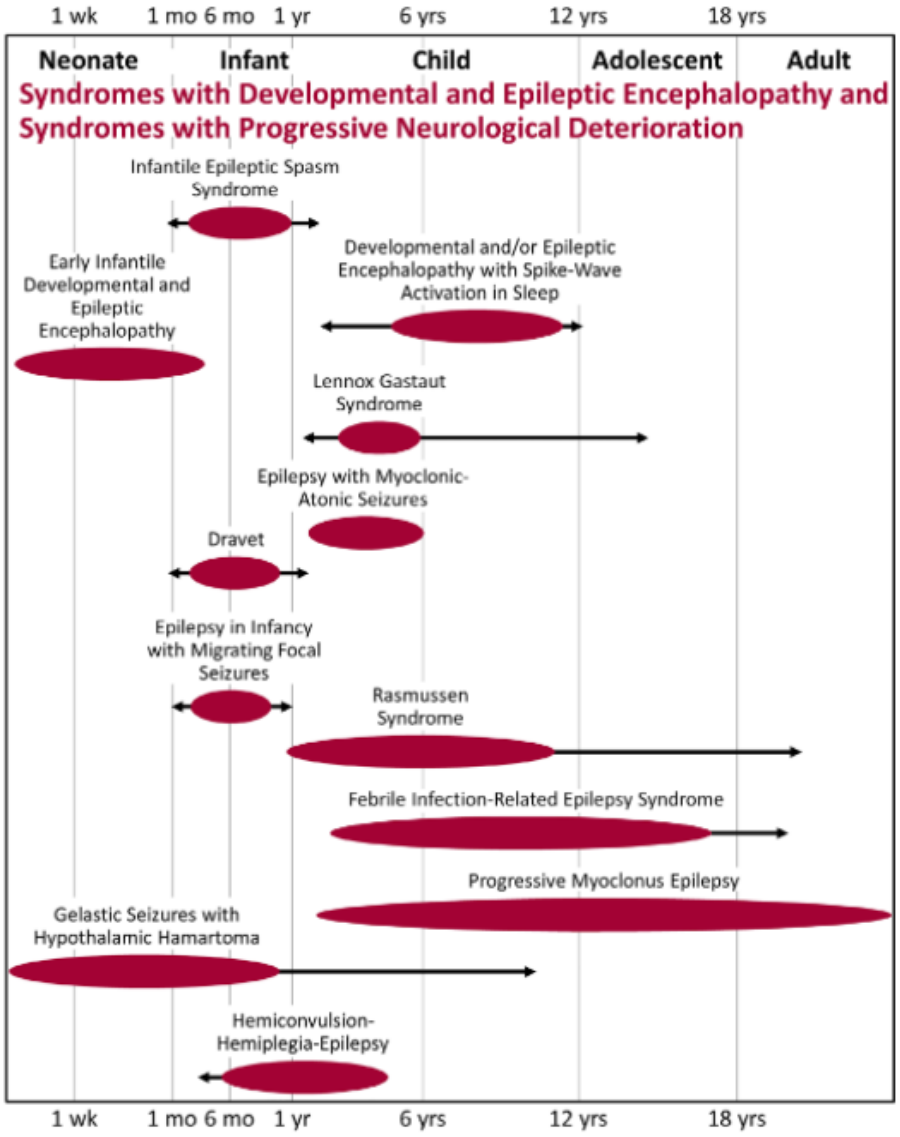
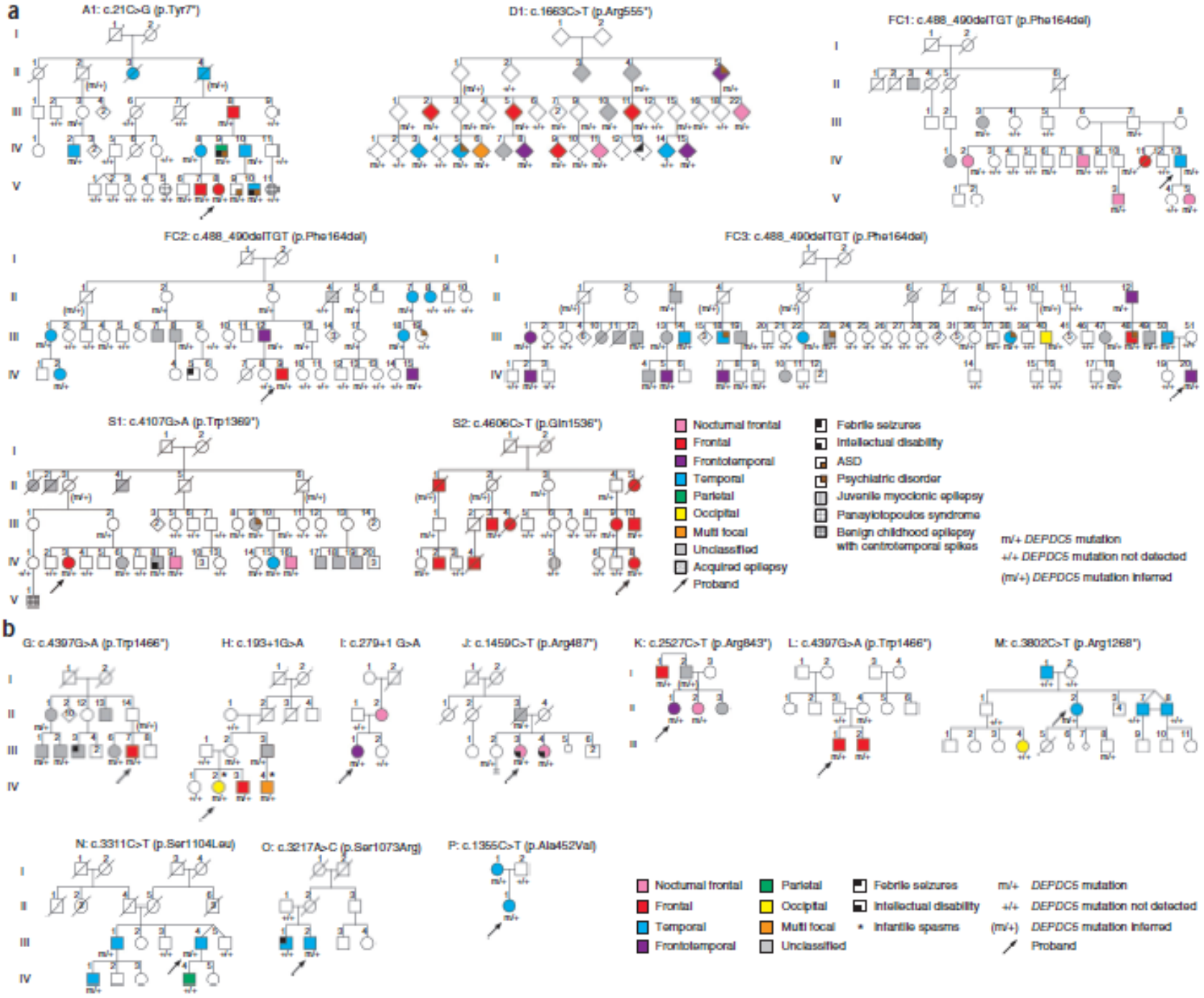


# Less Specific Age Relationship

- Familial focal epilepsy with variable foci – *DEPDC5*
- Reflex epilepsies

# Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

Leanne M Dibbens[1,2,23], Boukje de Vries[3,23], Simona Donatello[4], Sarah E Heron[1,2], Bree L Hodgson[1], Satyan Chintawar[4], Douglas E Crompton[5,6], James N Hughes[7], Susannah T Bellows[6], Karl Martin Klein[6,8], Petra M C Callenbach[9], Mark A Corbett[10], Alison E Gardner[10], Sara Kivity[11], Xenia Iona[1], Brigid M Regan[6], Claudia M Weller[3], Denis Crimmins[12], Terence J O'Brien[13], Rosa Guerrero-López[14], John C Mulley[7,15,16], Francois Dubeau[17], Laura Licchetta[18], Francesca Bisulli[18], Patrick Cossette[19], Paul Q Thomas[7], Jozef Gecz[7,16], Jose Serratosa[14], Oebele F Brouwer[9], Frederick Andermann[17], Eva Andermann[17], Arn M J M van den Maagdenberg[3,20], Massimo Pandolfo[4], Samuel F Berkovic[6] & Ingrid E Scheffer[6,21,22]


a
A1: c.21C>G (p.Tyr7*)
D1: c.1663C>T (p.Arg555*)
FC1: c.488_490delTGT (p.Phe164del)
FC2: c.488_490delTGT (p.Phe164del)
FC3: c.488_490delTGT (p.Phe164del)
S1: c.4107G>A (p.Trp1369*)
S2: c.4606C>T (p.Gln1536*)
Nocturnal frontal
Frontal
Frontotemporal
Temporal
Parietal
Occipital
Multi focal
Unclassified
Acquired epilepsy
Proband
Febrile seizures
Intellectual disability
ASD
Psychiatric disorder
Juvenile myoclonic epilepsy
Panayiotopoulos syndrome
Benign childhood epilepsy with centrotemporal spikes
m/+ DEPDC5 mutation
+/+ DEPDC5 mutation not detected
(m/+) DEPDC5 mutation inferred
b
G: c.4397G>A (p.Trp1466*)
H: c.193+1G>A
I: c.279+1 G>A
J: c.1459C>T (p.Arg487*)
K: c.2527C>T (p.Arg843*)
L: c.4397G>A (p.Trp1466*)
M: c.3802C>T (p.Arg1268*)
N: c.3311C>T (p.Ser1104Leu)
O: c.3217A>C (p.Ser1073Arg)
P: c.1355C>T (p.Ala452Val)
Nocturnal frontal
Frontal
Temporal
Frontotemporal
Parietal
Occipital
Multi focal
Unclassified
Febrile seizures
Intellectual disability
* Infantile spasms
m/+ DEPDC5 mutation
+/+ DEPDC5 mutation not detected
(m/+) DEPDC5 mutation inferred
Proband

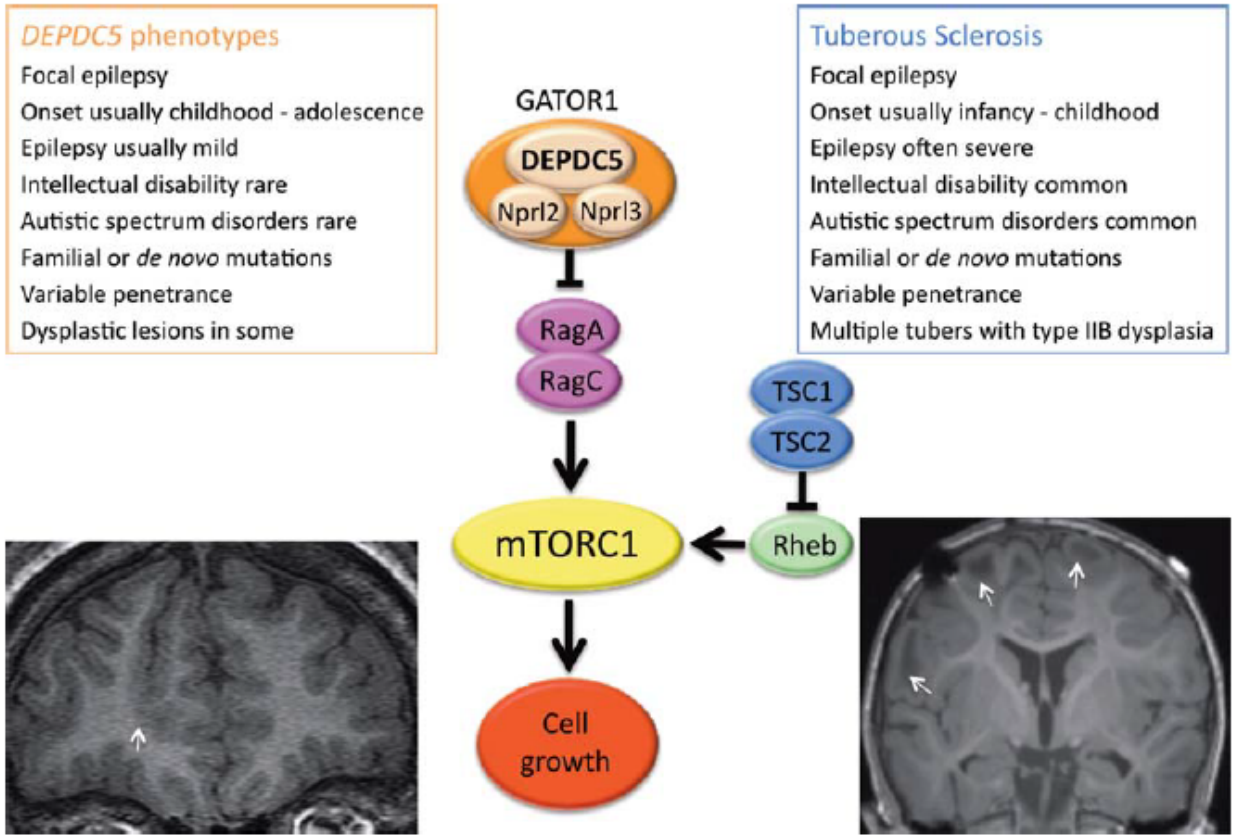



FIGURE 2: *DEPDC5* mutations and tuberous sclerosis show overlapping phenotypes and imaging abnormalities associated with activation of the mammalian target of rapamycin (mTOR) pathway.[11]

# Reflex epilepsies

- Visual/photosensitive
- Eye closure sensitivity – usually repeated eyelid fluttering (ie Jeavons)
- Orofacial reflex myoclonia (brought on by reading, talking, eating)
- Praxis induction – muscle jerks induced by visual motor tasks
- Hot water (India, Japan)
- Musicogenic epilepsy
- Tactile
- Tooth brushing
- Math
- Etc

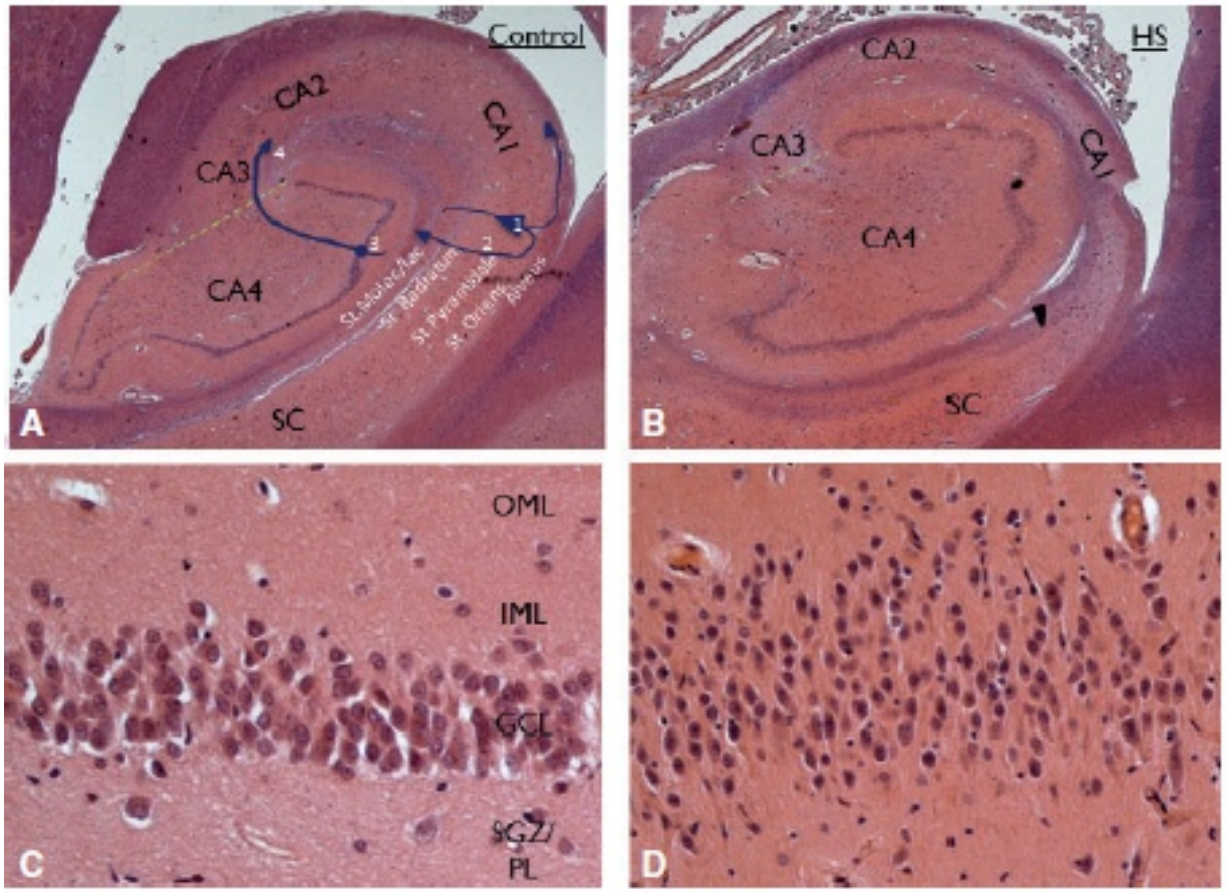
# Distinctive Constellations

- Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
- Rasmussen Syndrome
- Gelastic with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia epilepsy
- [Progressive Myoclonic Epilepsies]
- Other epilepsies that can be classified based on presence of absence of structural or metabolic cause and focal or generalized onset

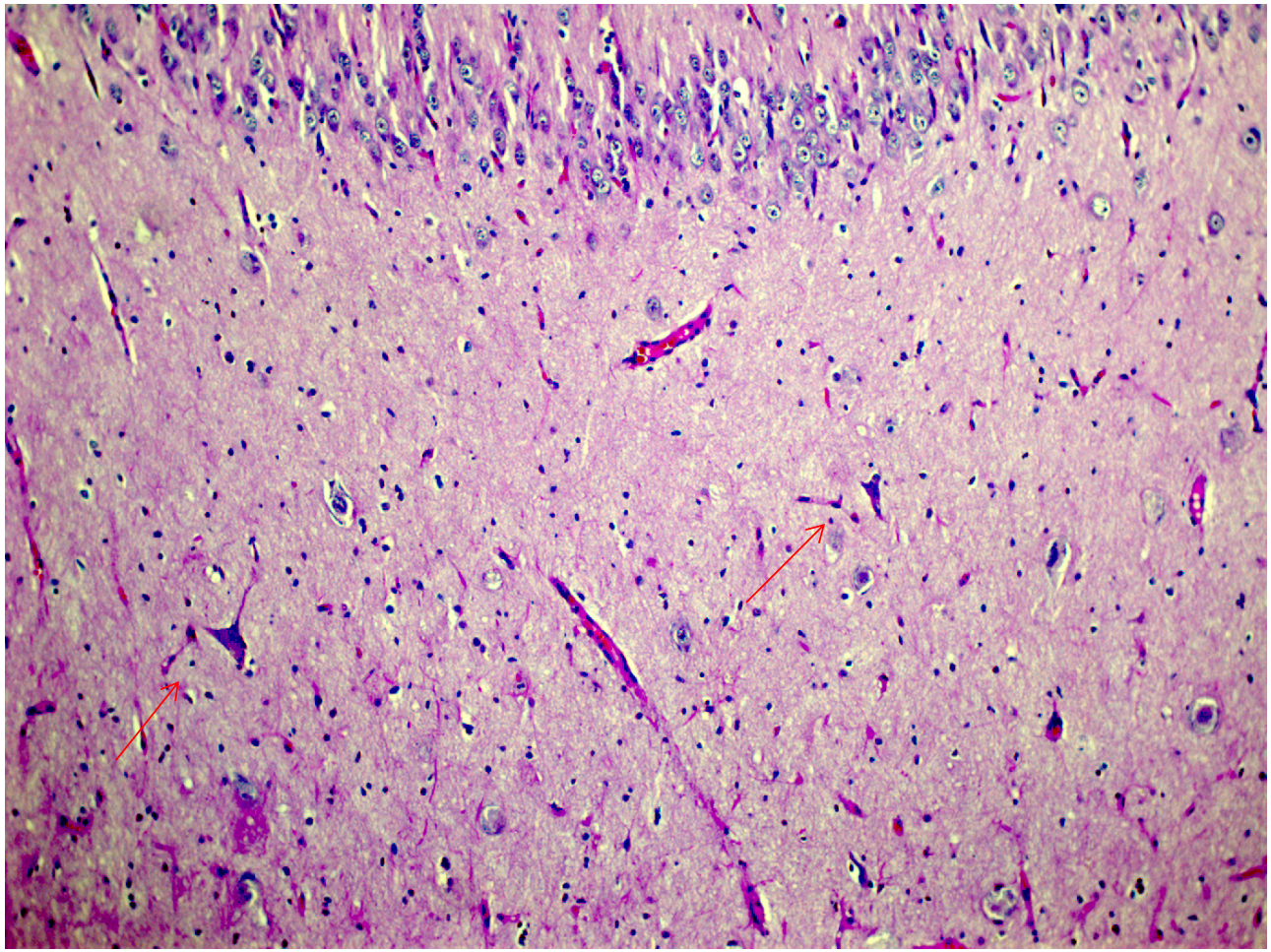
# Hippocampal Sclerosis

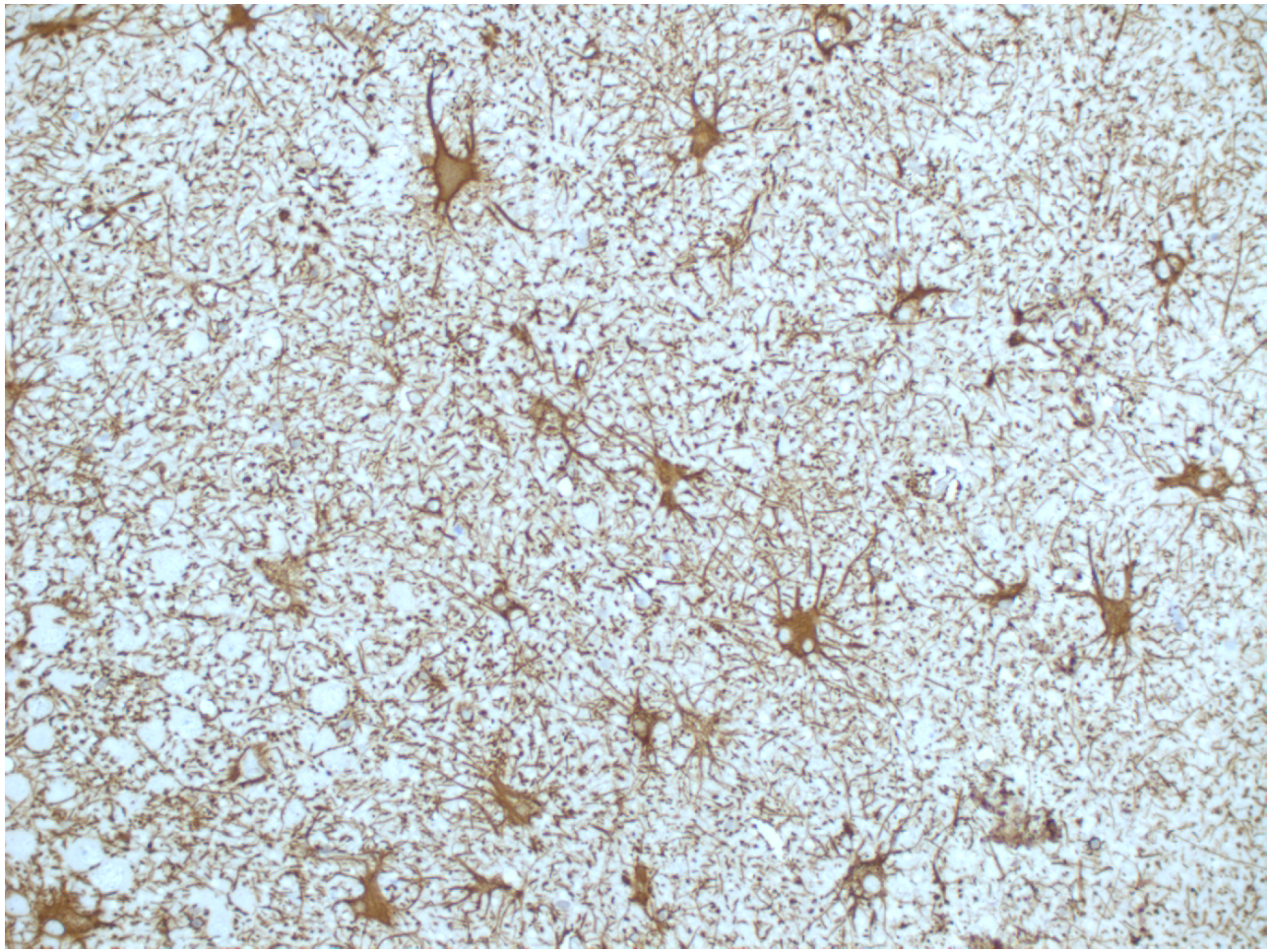
- Neuronal loss in the pyramidal cell layer
  - Classical HS – neuronal loss primarily involving CA1 > CA4 with relatively preserved subiculum and CA2 and variable loss from CA3
- Granule cell dispersion
- Mossy fiber sprouting
- Chronic fibrillary gliosis
- Altered interneurons
- "HS Plus"/ MTS
- "Dual" pathology – FCD IIIa, low-grade tumors (DNETs, gangliogliomas), vascular and cortical malformations

# Histology




Malmgren & Thom, 2012





# History of Hippocampal Sclerosis

- HS is the most common pathologic finding in adult epilepsy surgery
- Ammon's horn sclerosis linked to epilepsy – Sommer (1880) and Bratz (1899)
  - Neuronal loss largely restricted to CA1 (*cornu ammonis*)
- Jackson & Beevor (1889) – associated clinical symptoms of TLE with focal lesions in hippocampus
- Sano and Malamud (1953) – associated HS with EEG evidence of TLE
- Jackson et al., 1990; Berkovic et al., 1991 – recognized that MRI can detect HS

# Hippocampal Sclerosis in Temporal Lobe Epilepsy Demonstrated by Magnetic Resonance Imaging

Samuel F. Berkovic, MD, Frederick Andermann, MD, André Olivier, MD, Roméo Ethier, MD, Denis Melanson, MD, Yvon Robitaille, MD, Ruben Kuzniecky, MD, Terence Peters, PhD, and William Feindel, MD

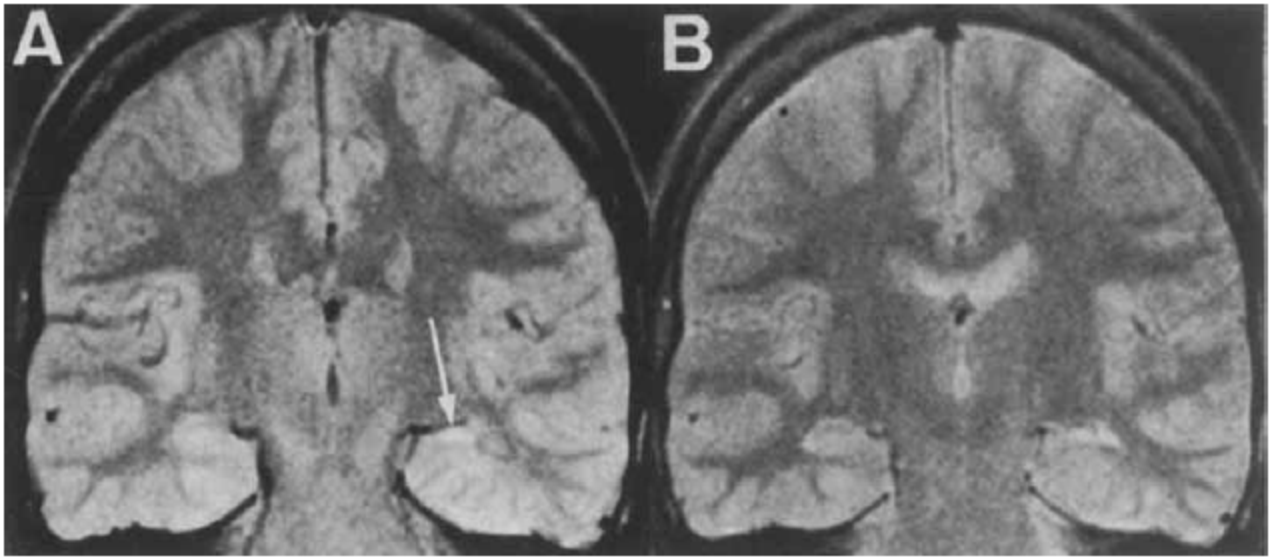



*Fig 3. Magnetic resonance imaging, Patient 10. (A) First echo image. The left hippocampus* (arrow) *is severely shrunken with slightly increased signal compared with the left. (B) Second echo image. The asymmetry in the hippocampal signals is better appreciated; the abnormal left hippocampus can be resolved from the adjacent high signal of the temporal horn.*

# MRI features of HS

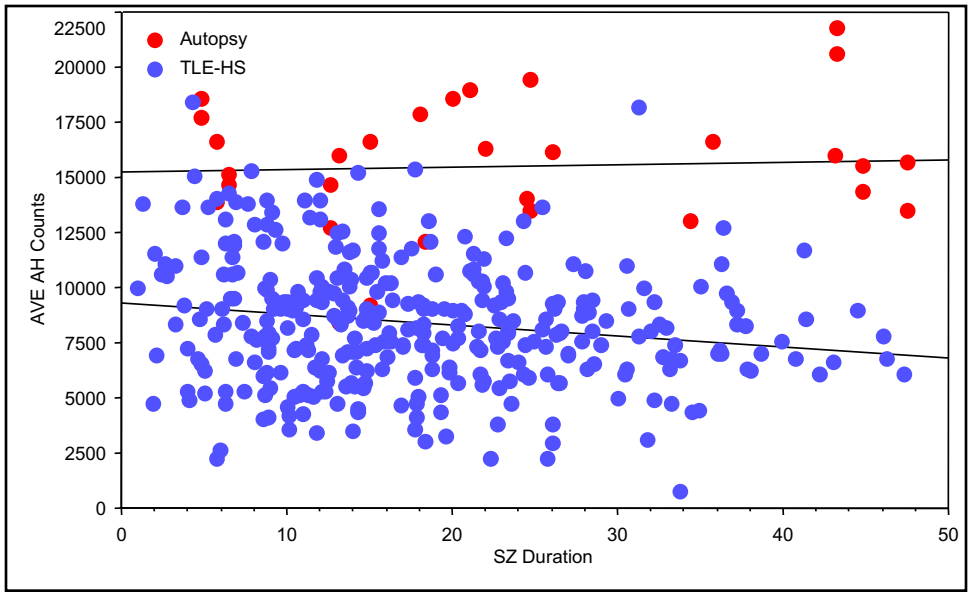
- T2 hyperintensity (hippocampal hyperintense FLAIR signal occurs in about 1/3 of normal controls (Labate et al., 2010) but is not associated with hippocampal atrophy
- Reduced hippocampal volume
- Disturbed internal architecture
- Others
  - Temporal lobe atrophy
  - Dilatation of the temporal horn
  - Blurring of the gray-white junction

Labate A, Gambardella A, Aguglia U, et al. Temporal lobe abnormalities on brain MRI in healthy volunteers: a prospective case-control study. Neurology 2010, 74: 553-557.

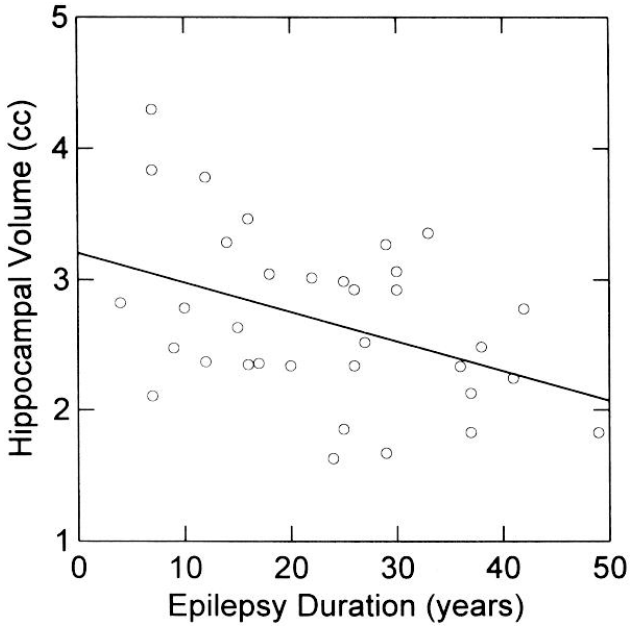
# Temporal Lobe Epilepsy and HS/ MTS

- Kim et al., 1999 – 104 patients with MTS followed for > 2 years
  - 25% completely controlled with adequate therapy
  - 37% had ≥50% reduction in seizures
  - *38% intractable*
- Kobayashi et al., 2001 – 98 patients with epilepsy (68 with MTLE); HS in 48/84 (57%) who had MRI; proportion of HS in MTLE outcome groups
  - 6/13 (46%) remission
  - 16/31 (51%) good seizure control
  - *16/16 (100%) with refractory MTLE*

# HS and Epilepsy Duration




Mathern et al., 2002




Theodore et al., 1999

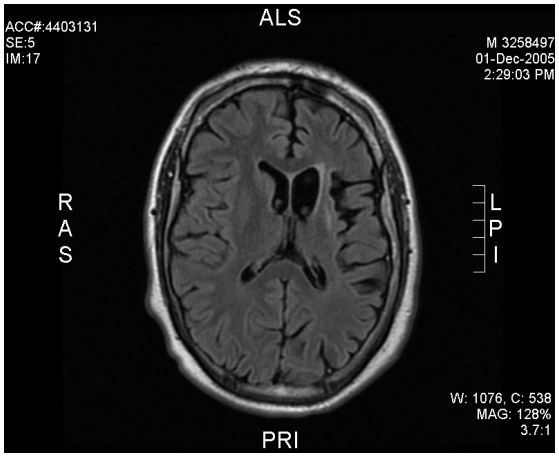
# Rasmussen Syndrome

- Mean age of onset 5 years, most 14 months – 14 years
- Seizures are the initial manifestation – GTC, focal motor, complex partial
- Epilepsia partialis continua in 56%
- Progressive hemiparesis and usually cognitive deterioration
- Prodromal period → acute phase → residual stage
- Neuroimaging – progressive hemispheric atrophy
- CSF – oligoclonal or monoclonal bands
- Pathology – chronic inflammatory changes with intense perivascular cuffing, microglia, astrocytosis, neuronal cell loss
- Treatment:
  - Medical
  - Hemispherectomy – could be considered earlier to limit dysfunction in the contralateral hemisphere

# Rasmussen Syndrome: Diagnosis

Part A (3/3):

1. Clinical: Focal seizures (+/- Epilepsia partialis continua) & Unilateral cortical deficit(s)
2. EEG: Unihemispheric slowing +/- epileptiform activity & Unilateral seizure onset
3. MRI: Unihemispheric focal cortical atrophy and at least one of the following:
   - Grey or white matter T2/FLAIR hyperintense signal
   - Hyperintense signal/atrophy of ipsilateral caudate head




Part B (2/3):

1. Clinical: Epilepsia partialis continua or Progressive unilateral cortical deficit(s)
2. MRI: Progressive unihemispheric focal cortical atrophy
3. Histopathology: T cell dominated encephalitis w/activated microglial cells (typically, but not necessarily forming nodules) & reactive astrogliosis

Bien CG et al., Brain 2005;128:454

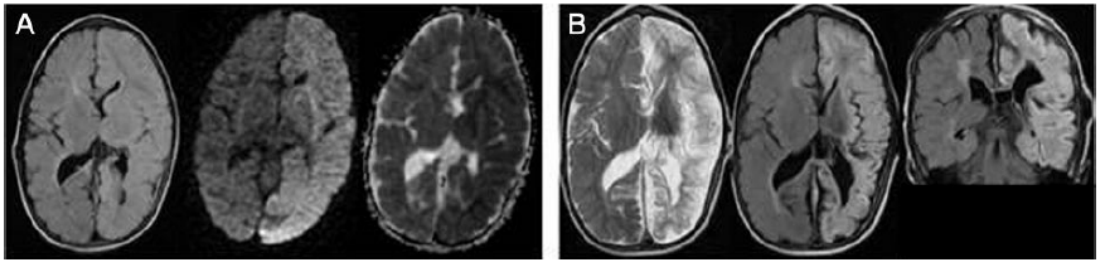
# Gelastic seizures with hypothalamic hamartoma

- Classic description: gelastic seizures ("mirthless laughter"), other seizure types (focal or generalized), crying-like sounds
- Precocious puberty
- Cognitive problems and decline
- Behavior problems: hyperactivity, rage, aggression, oppositional defiant disorder, ADHD, conduct disorder, affective disorders
- EEG findings highly variable (incl normal) and seizures may appear to arise from various locations; some with temporal lobe dysplasia
- HH has intrinsic epileptogenicity
- Drugs ineffective; surgery usually effective

Mittal et al., Neurosurg Focus 2013;34:E6

# Hemiconvulsion-hemiplegia-epilepsy

- Onset: 85% 6 months-4 years old
- Classic description: initial prolonged focal/generalized status epilepticus, then hemiplegia (may resolve in < 12 months in 20%)
- Radiologic: acute cytotoxic edema followed by chronic atrophy
- Decreasing incidence due to better early seizure control? (1967 – 7.5/10,000; 1978 – 1.6/10,000)
- Subtypes
  - "Idiopathic" – fever, extracranial infection
  - "Symptomatic" – associated with other pathology (trauma, infection, stroke)




Tenney & Schapiro, Neurology 2012;79:e1

# Progressive myoclonus epilepsies (PME)

- Myoclonus, Epilepsy (GTC, CTC, C, others), dementia, usually with cerebellar manifestations
- <1% of epilepsies (Genton et al, in Roger) – 2273 total newly referred epilepsy cases
- Unvericht-Lundborg disease (Baltic myoclonus)- 63
- Lafora disease - 41
- Neuronal ceroid lipofuscinosis - 15
- Myoclonic epilepsy with ragged red fibers (MERRF) - 2
- Also: other mitochondrial disorders, sialidosis, dentatorubral-pallidoluysian atrophy, biotinidase deficiency, Gaucher's type III, Huntington disease, pantothenate kinase-associated neurodegeneration, subacute sclerosing panencephalitis, Creutzfeld-Jacob disease

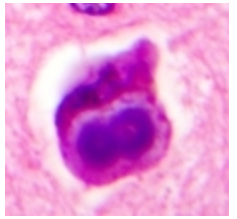
# EPM1 & 2

**Unvericht-Lundborg syndrome**

- Autosomal recessive
- Chromosome 21q22
- Cystatin B
- Present at 6-18 yrs (mostly 9-13 yrs) but survive to adulthood
- Myoclonus before ataxia and dementia
- Cognitive impairment – nil-moderate

**Lafora disease (EPM2)**

- Autosomal recessive
- Chromosome 6
- Laforin (EPM2A) or malin (EPM2B)
- Present at 6-19 yrs and have a rapid decline
- Seizures, **visual** seizures (~50%), then ataxia and dementia
- Very photosensitive
- Death in 2-10 yrs



# Neuronal ceroid lipofuscinosis (NCL)

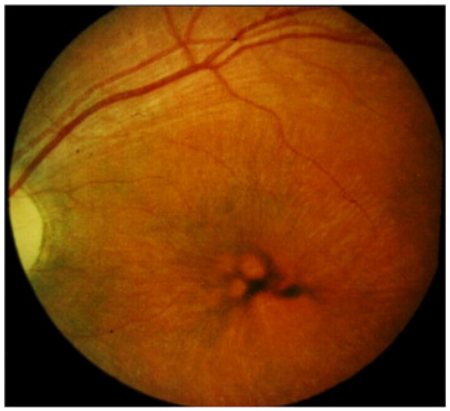
- Variable ages of onset
- Seizures, visual changes, ataxia, cognitive decline
- EEG: typically, background becomes abnormal over time, epileptiform activity, photosensitivity with giant evoked potentials
- Imaging: progressive atrophy
- Genetics (next slide): autosomal recessive but CLN4 is dominant
- Diagnosis: genetics or biopsy of axilla (sweat glands), muscle, conjunctiva, rectum

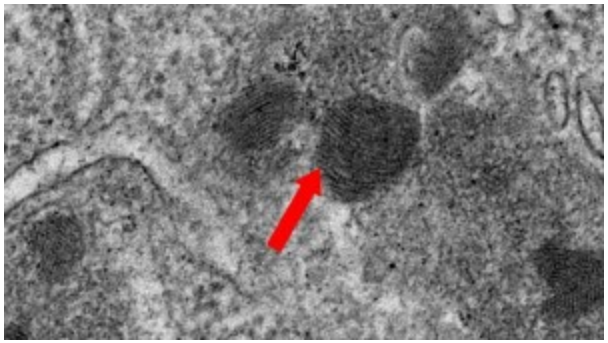
# Neuronal ceroid lipofuscinosis (NCL)

**Table 1.** Classification of NCLs.

| Gene | Age of onset | Chromosome | Protein | Ultrastructure |
|---|---|---|---|---|
| CLN1 | Infantile, but also late-infantile, juvenile, and adult | 1p32 | PPT1 | Granular osmiophilic deposits (GRODS) |
| CLN2 | Late-infantile, but also juvenile | 11p15 | TPP1 | Curvilinear profiles |
| CLN3 | Juvenile | 16p12 | Lysosomal transmembrane protein | Fingerprint profiles |
| CLN4 (DNAJC5) | Adult (Parry) | 20q13.33 | Cysteine string protein | Rectilinear profiles |
| CLN5 | Late-infantile (Finnish variant) | 13q22 | Soluble lysosomal protein | Rectilinear profiles, curvilinear profiles, fingerprint profiles |
| CLN6 | Late-infantile Adult (Kufs Type A) | 15q21 | Transmembrane protein of ER | Rectilinear profiles, curvilinear profiles, fingerprint profiles |
| CLN7 | Late-infantile, Turkish variant | 4q28 | MFSD8, lysosomal membrane protein | Fingerprint profiles |
| CLN8 | Late-infantile, Northern epilepsy | 8q23 | Transmembrane protein of ER | Curvilinear profiles |
| CLN10 | Congenital | 11p15 | Cathepsin D | GRODS? |

Abbreviations: ER, endoplasmic reticulum; GRODS, granular osmiophilic deposits; NCLs, neuronal ceroid lipofuscinoses.





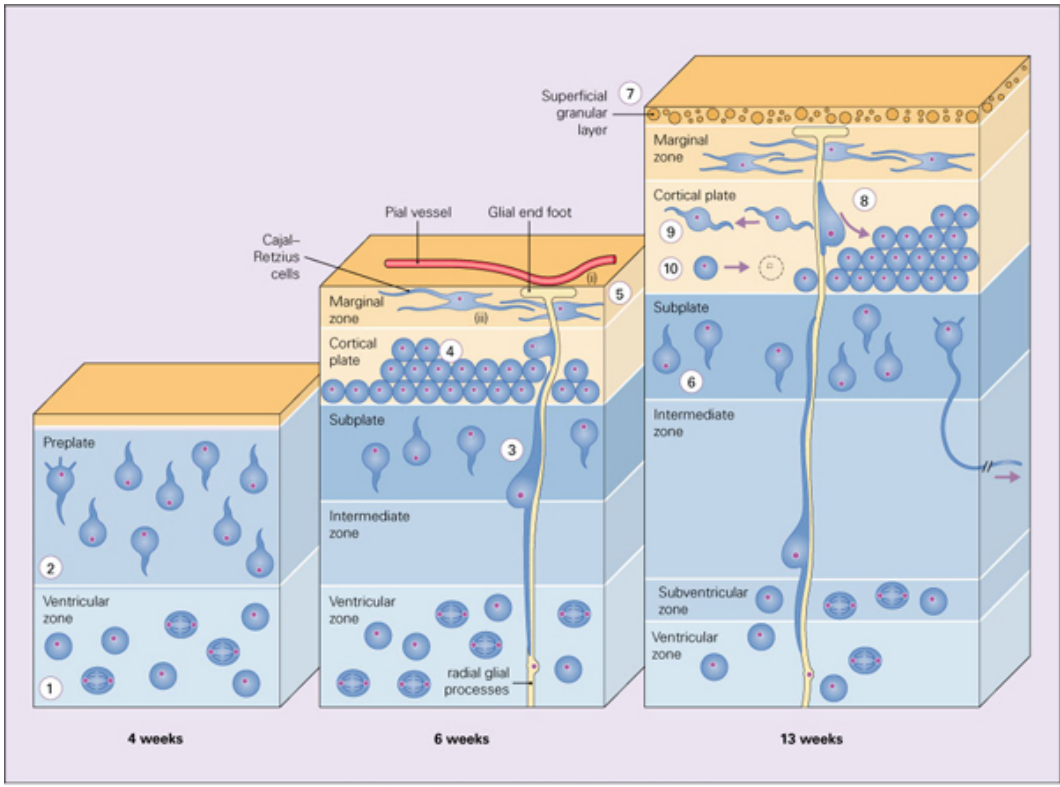
Mink et al., J Child Neurol 2013;28:1101
Schultz et al., Biochim Biophys Acta 2013;1832:1801
beyondbatten.org/understanding-batten/diagnosis-symptoms/

# Epilepsies attributed to and organized by structural-metabolic cause

- Malformations of cortical development
- Neurocutaneous syndromes
- Tumor
- Infection
- Trauma
- Angioma/ vascular (cavernoma, AVM)
- Perinatal insults
- Stroke
- Metabolic/ Mitochondrial

# Cerebral Cortex Embryology

- Week 7: proliferation of neuroblasts in the germinal matrix
- Week 8: radial migration begins
- Migration along radial glial cells (dependent on recognition, attachment, and calcium entry/ NMDA activation)
- Neurons migrate in an inside out sequence (except for layer 1 – molecular layer)



Ellison & Love: Neuropathology 2e © 2004 Elsevier Ltd.

# Etiology of MCD

- Mutations
  - Stem cell production
  - Radial glial fascicle development
  - Neuronal migration
  - Ability to disengage from radial glial fascicle and organize
- Destructive events
  - Infection
  - Ischemia
- Exogenous/ endogenous toxins
  - Drugs/ alcohol
  - Metabolic disorders (PDH deficiency, NKH)

# MCD

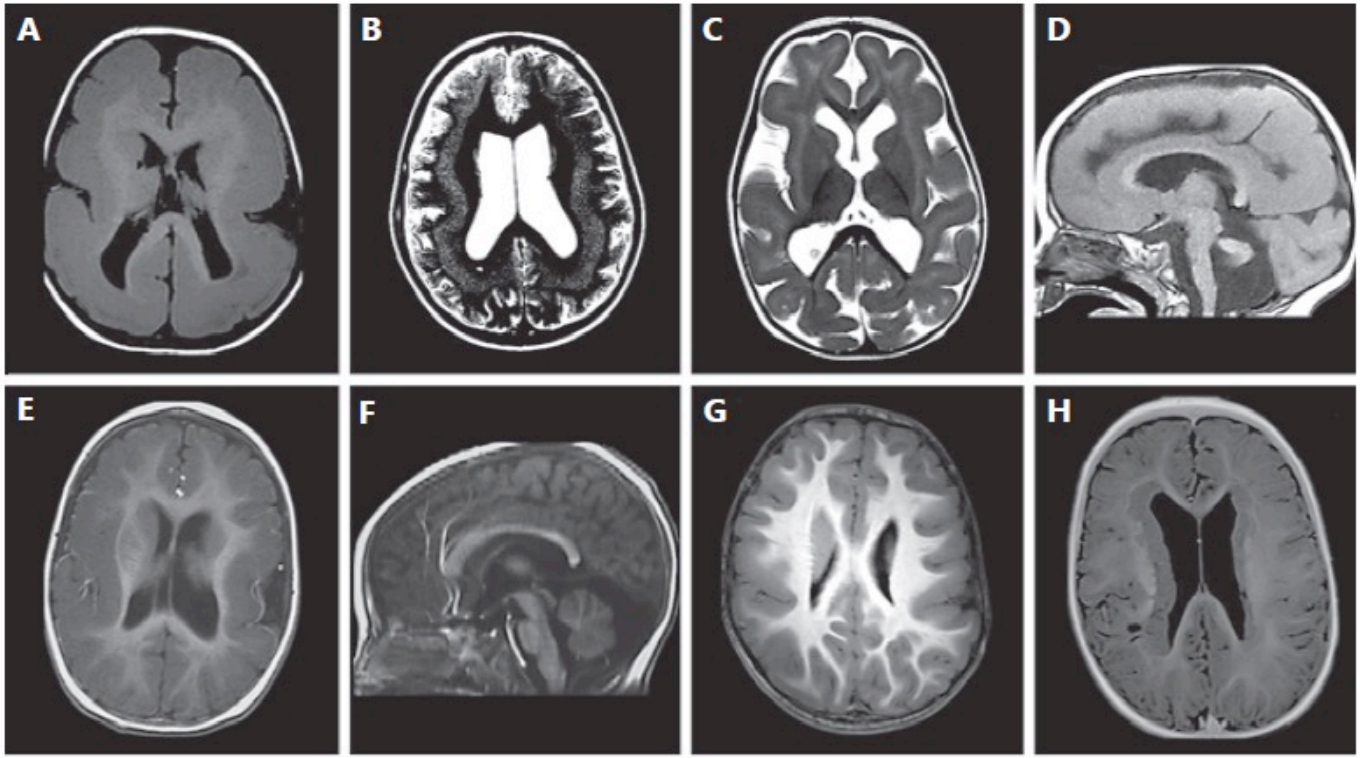
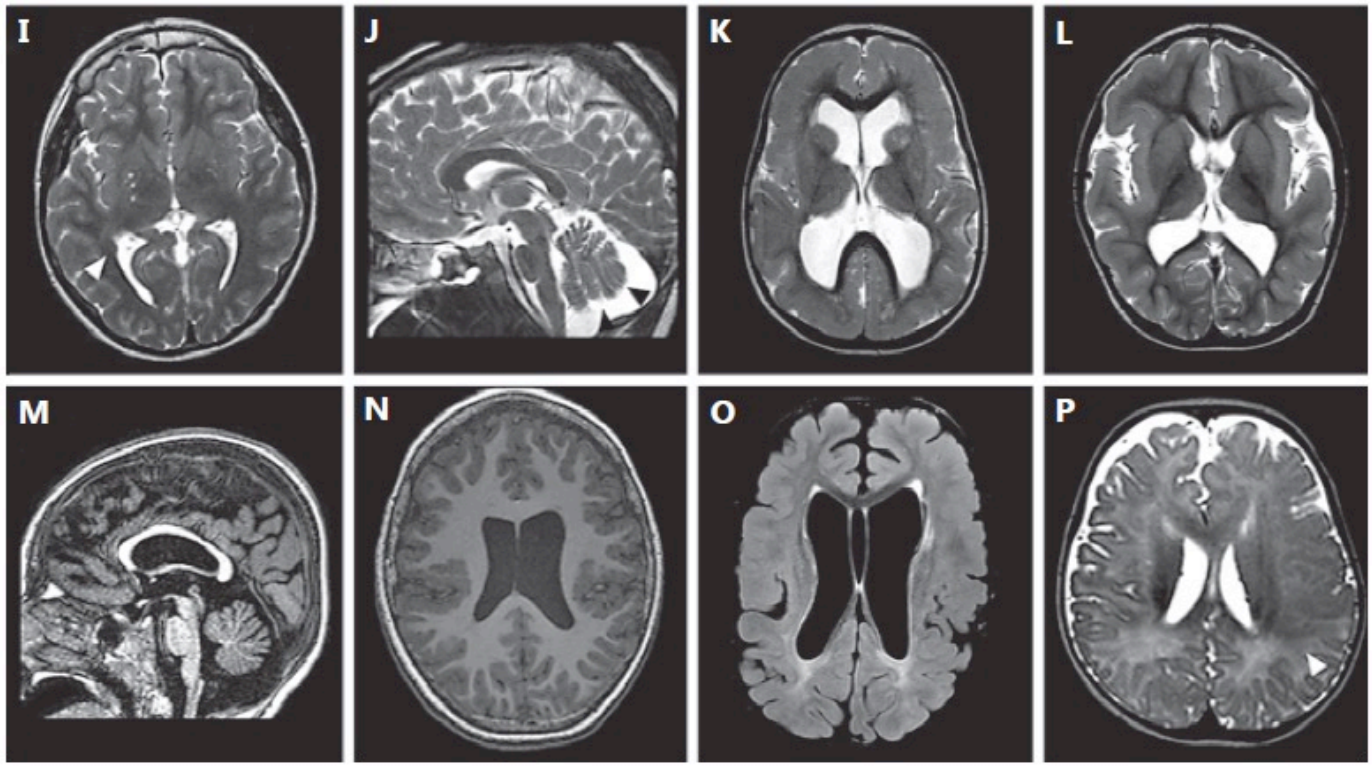



**Fig. 1.** Brain MRI of patients with different malformations of the cerebral cortex. **A** T1-weighted axial section. Posterior to anterior pachygyria in a boy with *LIS1* mutation. **B** T2-weighted axial section. Diffuse SBH in a girl with *DCX* mutation. **C**, **D** T2-weighted axial section and T1-weighted sagittal section. Lissencephaly and cerebellar hypoplasia in a girl with *RELN* mutation. **E**, **F** T1-weighted axial section and T1-weighted sagittal section. Thickened cortex with simplified gyral pattern and cerebellar hypoplasia in a girl with *TUBA1A* mutation. **G** T1-weighted axial section. Diffuse simplified gyral pattern with prominent thickening and infolding of the sylvian fissures in a boy with *TUBB2B* mutation. **H** T1-weighted axial section. Typical, classical bilateral PNH in a girl with an *FLNA* mutation. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls.

Mol Syndromol 2016;7:220–233
DOI: 10.1159/000448639



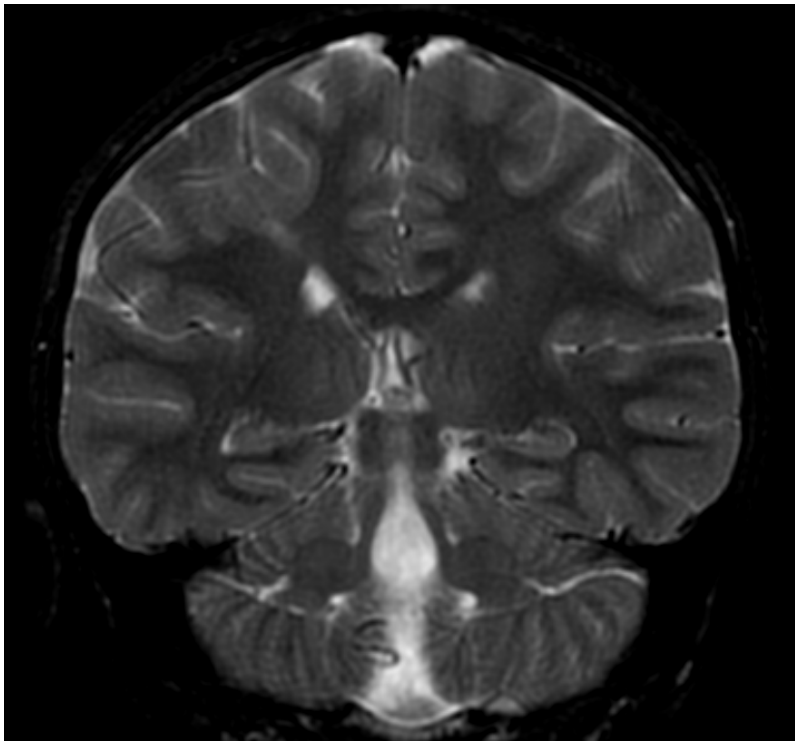

**I**, **J** T2-weighted axial section showing mild colpocephaly with unilateral PNH (white arrowhead) and T2-weighted sagittal section through the midline, showing cerebellar vermis hypoplasia (black arrowhead) with mega cisterna magna in a patient carrying a deletion in the 6q27 chromosomal region. **K** T2-weighted axial section. Bilateral frontoparietal polymicrogyria in a boy with *GPR56* mutation. **L**, **M** T2-weighted axial section and T1-weighted coronal section. Pachygyria and perisylvian polymicrogyria in a girl with *DYNC1H1* mutation. **N** Axial T1-weighted section in a patient with a mosaic *PIK3R2* mutation. **O**, **P** T1-weighted and T2-weighted axial images form patients carrying mosaic mutations in the *MTOR* gene with different percentages of mosaicism [**O**: p.Thr1977Ile, 20% of mosaicism in blood, **P**: p.Ser2215Phe, 5.5% of mosaicism in dysplastic brain tissue) showing bilateral cortical dysgyria (**O**) and focal cortical dysplasia (**P**, white arrowhead)].

Genetic and imaging findings associated with MCDs

| MCD Type | Group | Associated Genes | Associated Pathways and etiology | Imaging Findings |
|---|---|---|---|---|
| **Microcephaly** | Group I | *MCPH1, CENPJ, CDK5RAP2, WDR62, NDE1, NDE1, ASPM, CDK5RAP2, TUBA1A, TUBB2B, TUBB3, TUBG1, LIS1, DCX, DYNC1H, KIF5C, NDE1* | Neurogenesis and cell replication, tubulin and microtubule-associated proteins (MAP) | Small head size, small cerebellum and pons and lissencephaly (with tubulin and MAP-associated genes) |
| **Megalencephaly spectrum** | Group I | *AKT3, PIK3CA,* and *PIK3R2* | mTOR | Focal (localized), hemispheric or diffuse cortical enlargement, cerebellum and deep gray nuclei also enlarged, gray/white boundary blurring |
| **FCD type IIa** | Group I | *MTOR, DEPDC5,*and *PIK3CA* | mTOR | Gray/white matter blurring with apparent cortical thickness |
| **FCD type IIb** | Group I | *MTOR, DEPDC5, NPRL3* | mTOR | Cortical/sulcal T2 hyperintensity may extend to ventricular surface (transmantle sign) |
| **Tubulinopathies** | Group II | *TUBA1A, TUBB2B, TUBB3, TUBG1, LIS1, DCX, DYNC1H, KIF5C, NDE1* | Microtubule structure and function | Microcephaly, lissencephaly, fused basal ganglia (BG), cortical dysgyria, callosal abnormalities, asymmetric brainstem and small cerebellar vermis |
| **Variant lissencephalies** | Group II | *ARX, DCX, RELN* and *VLDR* | Reelin | **ARX** -Lissencephaly, callosal abnormalities, dysmorphic BG, hydrancephaly **Reelin** – lissencephaly in anterior-posterior gradient, cortical thicknening, small cerebellum and vermis |
| **Gray matter heterotopia** | Group II | *FLNA* and *ARFGEF2* | Neuroependyma/neuroepitheliium | Normal gray matter in abnormal locations |
| **Cobblestone malformations** | Group II | *GPR56, LAMB1, LAMB2, LAMC3* and *SRD5A3* | Dystroglycanopathies affecting pial limiting membrane | Lissencephaly/pachygyria or polymicrogyria (PMG), possible cerebellar involvement |
| **Polymicrogyria (PMG)** | Group III | 1p36.3 and 22q11.2 mutations, mTOR genes | Etiology can be from prenatal ischemic, teratogenic or infectious brain injury | Perisylvian bilateral PMG (most common), associated with schizencephaly |

# Focal Cortical Dysplasia

- Altered cell morphology
- Altered synaptic connectivity/ disrupted cytoarchitecture
- Changes in ion channel or neurotransmitter receptor expression



# FCD Classification Schema (ILAE)

**TABLE 1.** The histopathology-based FCD classification update (new categories highlighted in gray)

| | | | | |
|---|---|---|---|---|
| FCDI [a] | FCDIa abundant microcolumns | FCDIb abnormal layering | FCDIc vertical and horizontal abnormalities | |
| FCDII [a] | FCDIIa dysmorphic neurons | | FCDIIb dysmorphic neurons and balloon cells | |
| FCDIII [a] | FCDIIIa cortical dyslamination associated with hippocampal sclerosis | FCDIIIb cortical dyslamination adjacent to brain tumor | FCDIIIc cortical dyslamination adjacent to vascular malformation | FCDIIId cortical dyslamination adjacent to lesion acquired during early life, e.g. stroke |
| White Matter [a] | mMCD [b] with excessive heterotopic neurons [a] | | mMCD with oligodendroglial hyperplasia in epilepsy (MOGHE) [c] | |
| No definite FCD on histopathology [a] | Abnormality of cortical organization remains ambiguous and histopathological findings not compatible with FCDI, II or III [d] | | | |

Najm et al., *Epilepsia* 2022

# FCD Ia

*Epilepsia*, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

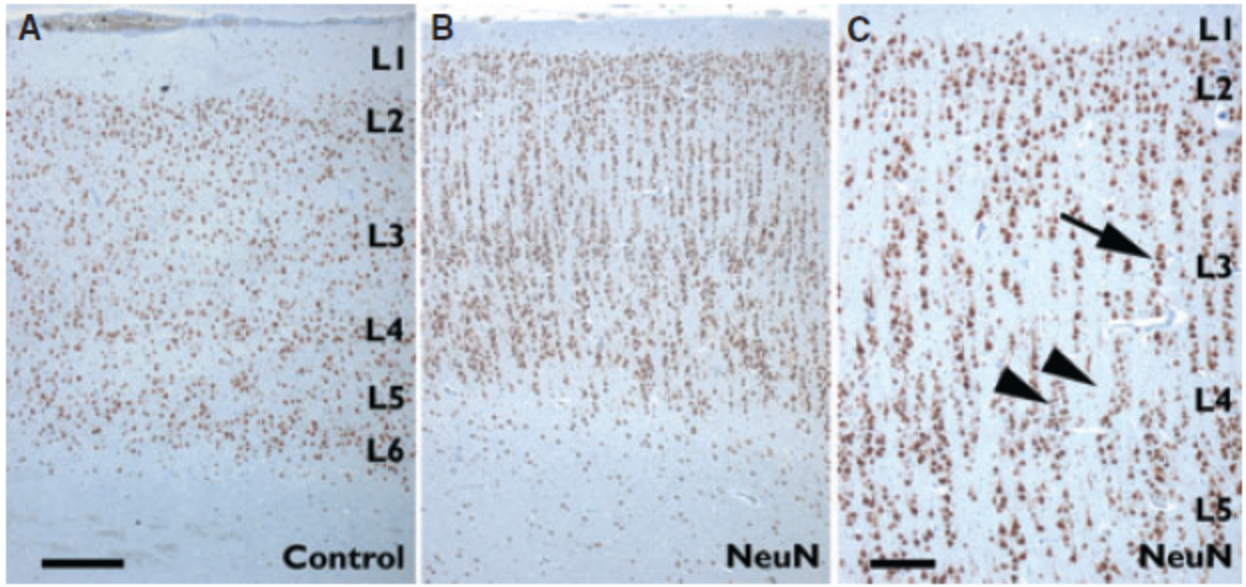



**Figure 1.**
Histopathologic findings in FCD Type Ia (abnormal radial lamination and abundant microcolumns). Eleven-year-old girl with a 10-year history of drug-resistant seizures. (**A**) Normal appearing neocortex adjacent to the lesion shown in **B** and **C**. Selective labeling of neuronal cell bodies using antibodies directed against NeuN reveals a characteristic layering of the human isocortex (L1–L6). Scale bar = 500 $\mu$m, applies also to **B**. (**B**) Distinct microcolumnar arrangements of small diameter neurons can be detected in FCD Type Ia, when surgical specimen is cut perfectly perpendicular to the pial surface and 4-$\mu$m paraffin embedded sections were used. MRI showed smaller cortical (parietooccipitotemporal) lobes in affected versus nonaffected hemispheres (Blumcke et al., 2010). High magnification in **C** reveals abundant microcolumns, which are composed of more than eight neurons (arrow). In addition, layer 4 is less clearly visible (arrowheads). Scale bar = 200 $\mu$m.

# IIa

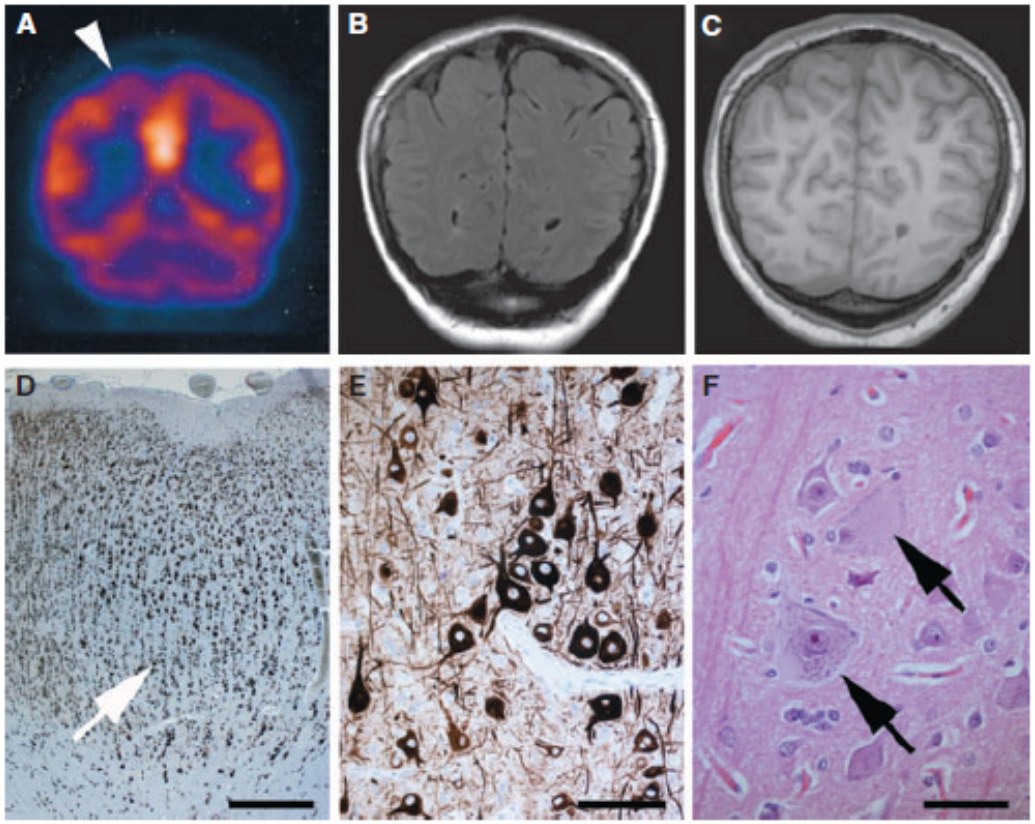



**Figure 3.**

Imaging and histopathologic findings in FCD Type IIa. FCD Type IIa in an 18-year-old female patient with refractory seizures from age 5 years that would start with sensory disturbance in the left foot. (**A**) $^{18}$F-FDG-PET showing an area of slight hypometabolism in the superior, medial right parietal lobe (arrowhead). (**B**) Coronal $T_2$-FLAIR did not reveal definitely abnormal signal intensities. (**C**) Coronal $T_1$-weighted MRIs were also reported normal. Please note the different orientation of the planes of the PET and MR images. The MRI is oblique coronal, so that the inferior part of the image is posterior to that seen on the PET. (**D**) Microscopic inspection of surgical specimen revealed severe cortical dyslamination (arrow) without distinguishable layer formation (except layer I). NeuN immunohistochemistry. Scale bar = 1000 $\mu$m. Section thickness = 15 $\mu$m. (**E**) Abundant dysmorphic neurons with dense accumulation of SMI32-neurofilament proteins can be identified. Scale bar = 100 $\mu$m. Section thickness = 7 $\mu$m. (**F**) High-power magnification of dysmorphic neurons (arrows) depicted from same area shown in E (H&E stain). Note their variable morphologic appearance, which may also result from plane of sectioning. No balloon cells can be recognized. Scale bar = 30 $\mu$m. Section thickness = 4 $\mu$m.



*Epilepsia*, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

# IIb

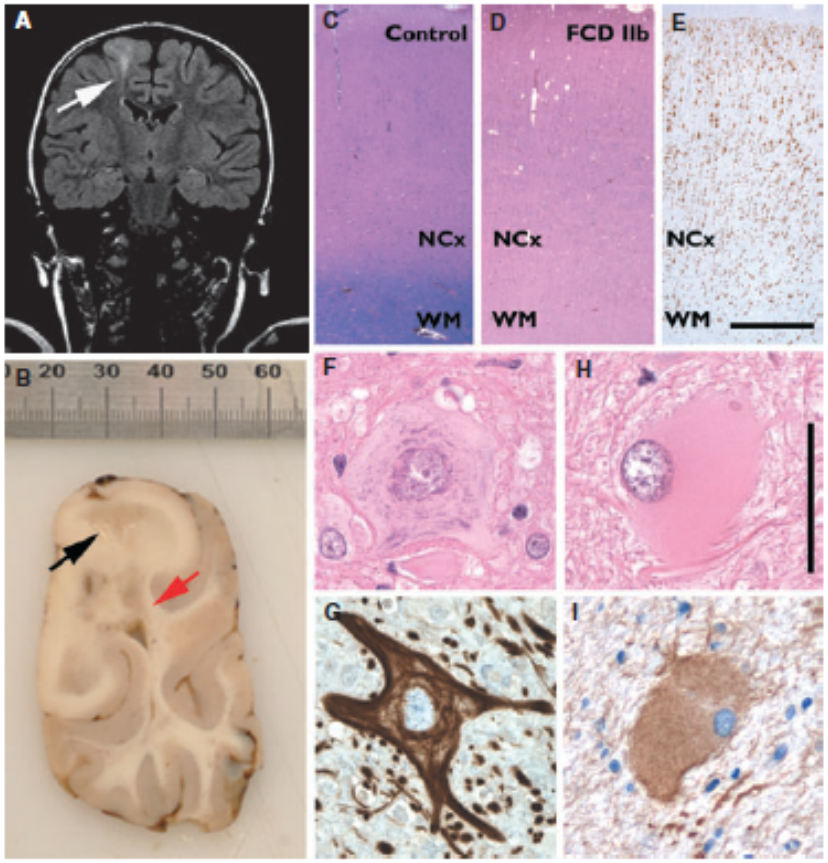
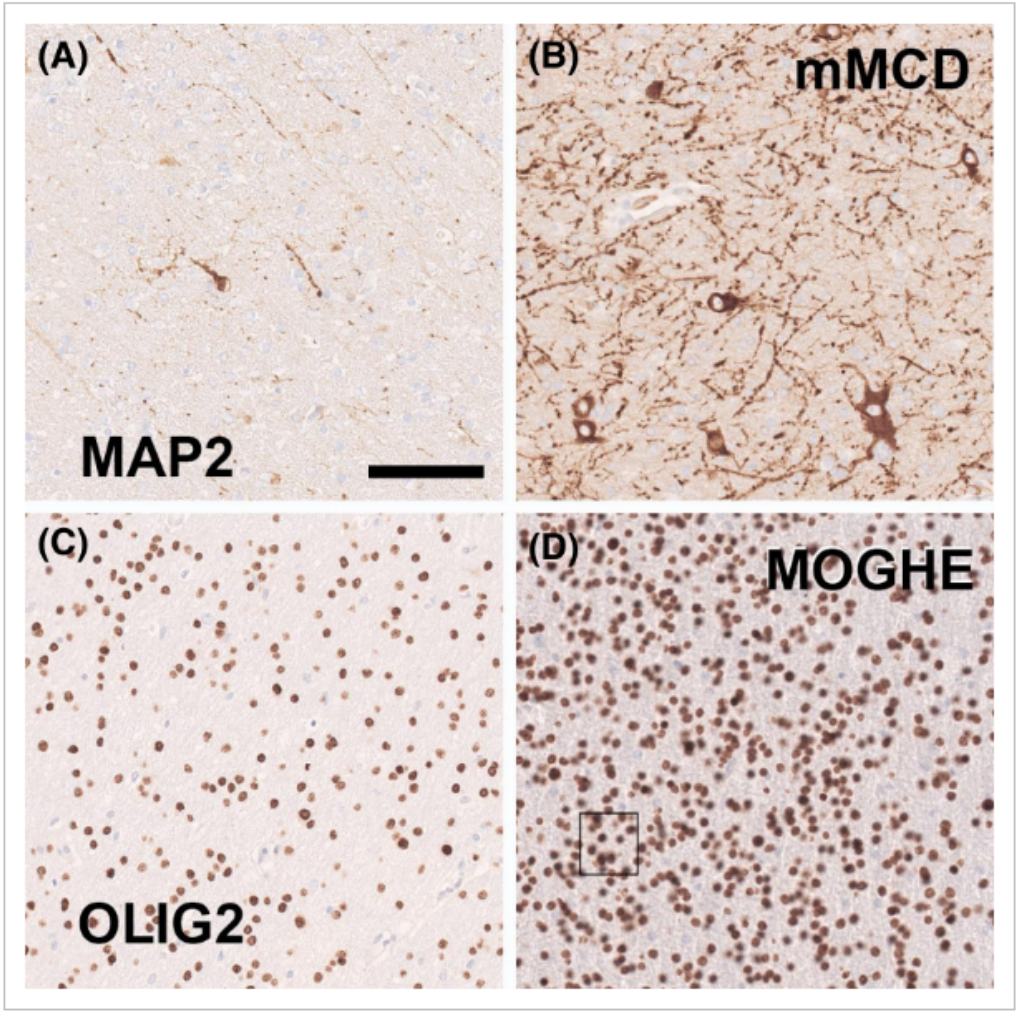



**Figure 4.**
Imaging and histopathologic findings in FCD Type IIb. (**A**) The "transmantle-sign" in $T_2$-FLAIR imaging is characterized by a funnel-like hyperintensity (arrow) tapering from the gyrus to the ventricle. (**B**) Inspection of the surgical specimen reveals a distinct correlation between $T_2$-FLAIR hyperintensity and lack of normal myelin content (black arrow points to grayish subcortical areas), which can be identified from the subcortical white matter to the ventricle (red arrow). (**C**) H&E staining combined with Luxol-Fast-Blue (H&E-LFB) allows visualization of a sharp boundary between neocortex (NCX) and white matter (WM) in a control subject. (**D**) H&E-LFB. In this FCD Type IIb specimen, the myelin content is significantly reduced (see also macroscopic image in B). (**E**) NeuN immunohistochemistry, 4-$\mu$m paraffin embedded serial section to **D**. Severe cortical dyslamination is visible (with the exception of layer I). In addition, cortical thickness is increased and not distinguishable from WM border (same magnification as **C** and **D**). Scale bar = 1 mm. (**F**) In FCD Type IIb, enlarged dysmorphic neurons present with a huge nucleus and abnormal intracytoplasmic Nissl aggregates. (**G**) Antibodies to nonphosphorylated neurofilament proteins (SMI32) reveal aberrant NFP accumulation in a dysmorphic neuron. (**H**) Balloon cells are another hallmark of this FCD variant. Scale bar = 50 $\mu$m, applies also to **F**, **G**, and **I**. (**I**) Balloon cells express the intermediate filament vimentin. **E**, **G**, and **I**: 4-$\mu$m paraffin-embedded sections, counterstained with hematoxylin.


*Epilepsia*, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

# mMCD and MOGHE

- mMCD (mild malformatic of cortical development) – excess heterotopic neurons in WM
- MOGHE (mMCD with oligodendroglial hyperplasia in epilepsy) – increase in heterotopic neurons in WM and high oligodendroglial cell density; 45-100% have *SLC35A2* somatic variant




Najm et al., *Epilepsia* 2022

# mTOR, TSC, and FCD type IIb

- Loss of function mutations in *TSC1* or *TSC2* lead to constitutive activation of mTOR
- Activation of mTOR signaling distinguishes type II from type I FCD

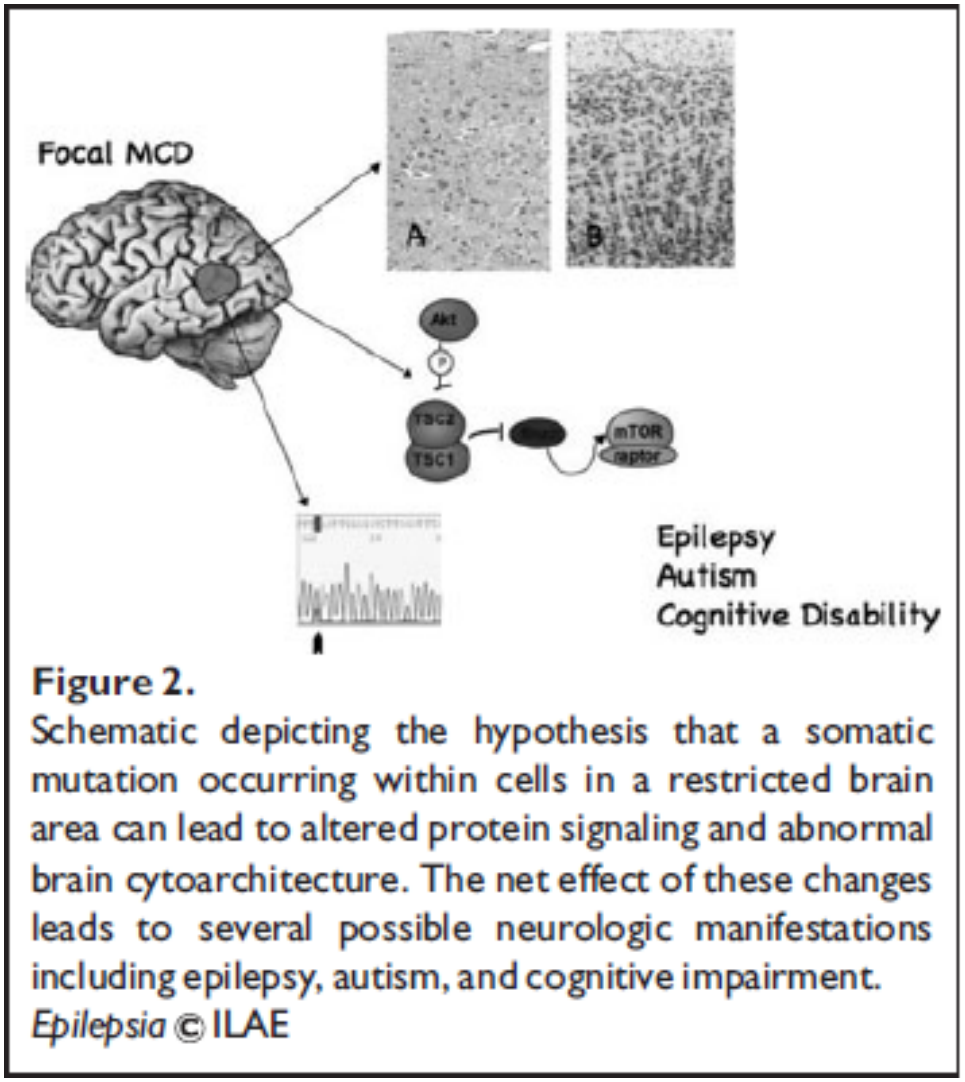
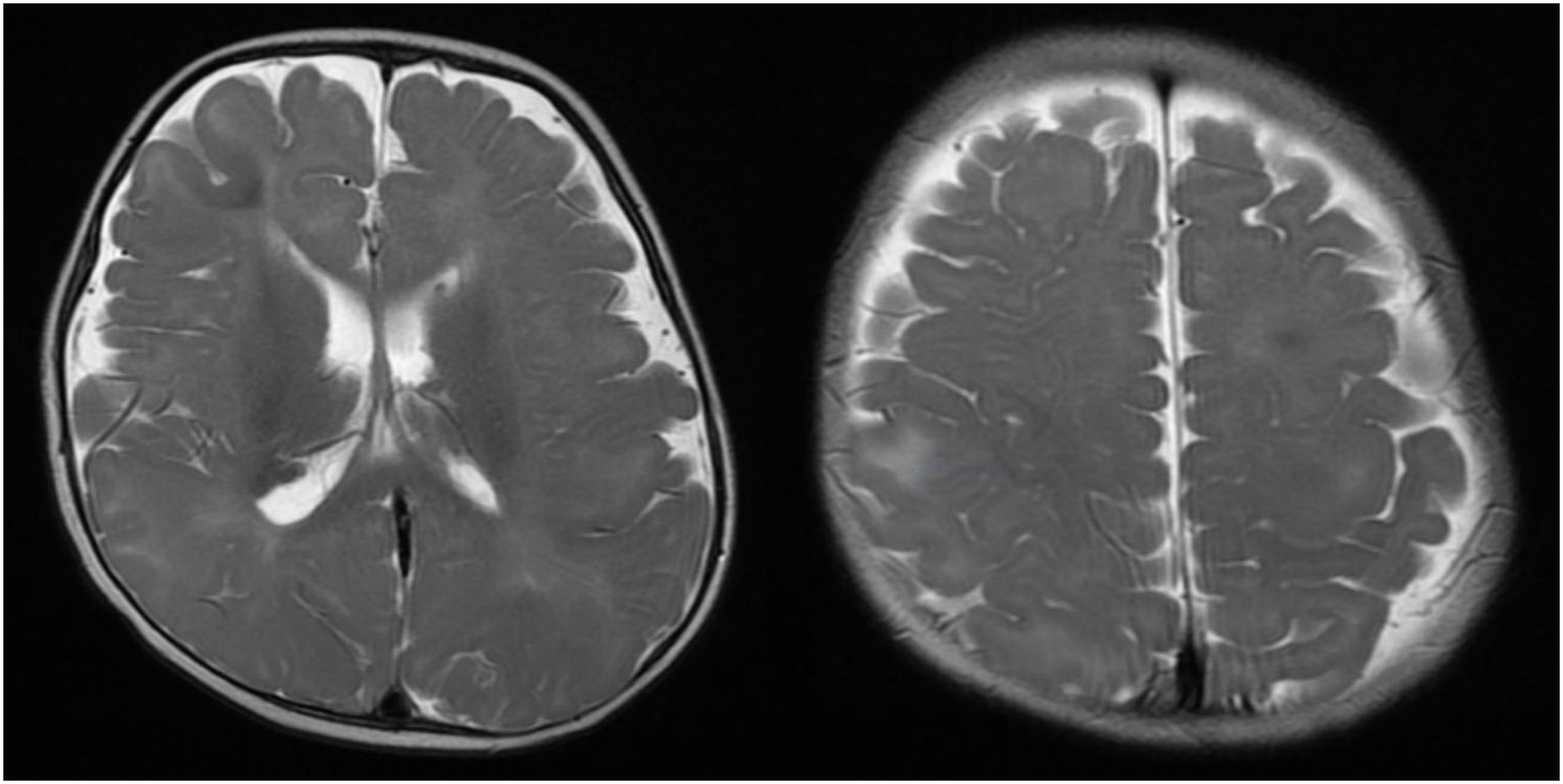



**Figure 2.**
Schematic depicting the hypothesis that a somatic mutation occurring within cells in a restricted brain area can lead to altered protein signaling and abnormal brain cytoarchitecture. The net effect of these changes leads to several possible neurologic manifestations including epilepsy, autism, and cognitive impairment.
*Epilepsia* © ILAE

*Epilepsia*, 50(Suppl. 9):3–8, 2009
doi: 10.1111/j.1528-1167.2009.02289.x

# Tuberous Sclerosis Complex



**Definite TSC:** Two major OR one major + two minor

**Probable TSC:** One major + one minor

**Possible TSC:** One major feature OR two or more minor

**Genetic diagnosis:** A pathogenic variant in *TSC1* or *TSC2* is diagnostic for TSC (most TSC-causing variants are sequence variants that clearly prevent TSC1 or TSC2 protein production. Some variants compatible with protein production [e.g., some missense changes] are well established as disease-causing; other variant types should be considered with caution)

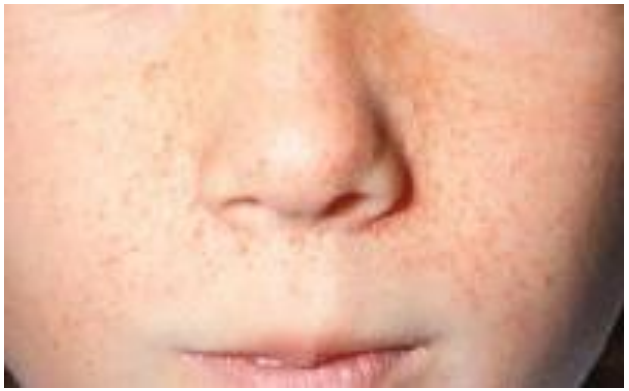
**Major Features**

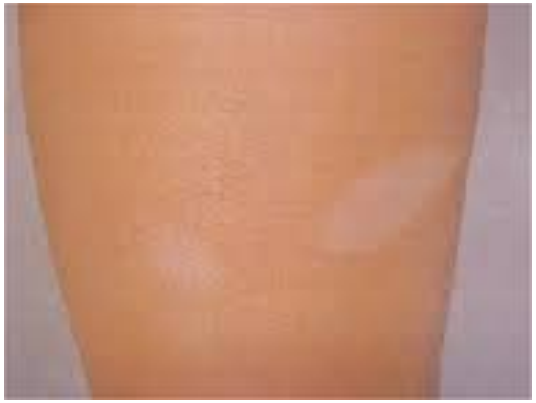
- Facial angiofibromas or forehead plaque
- Ungual or periungual fibromas
- ≥ 3 Hypomelanotic macules
- Shagreen patch
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodule (SEN)
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangiomyomatosis
- Renal angiomyolipoma

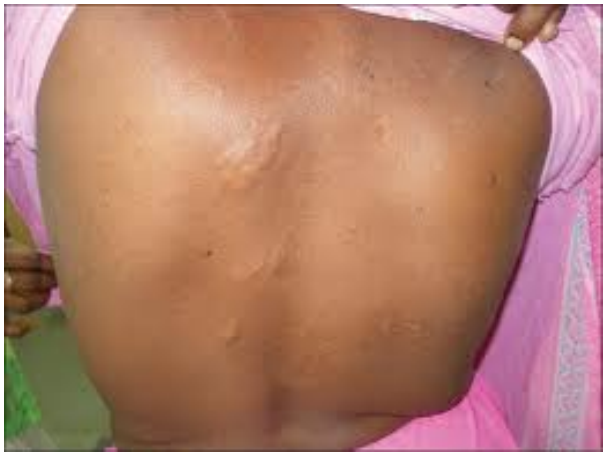
**Minor Features**

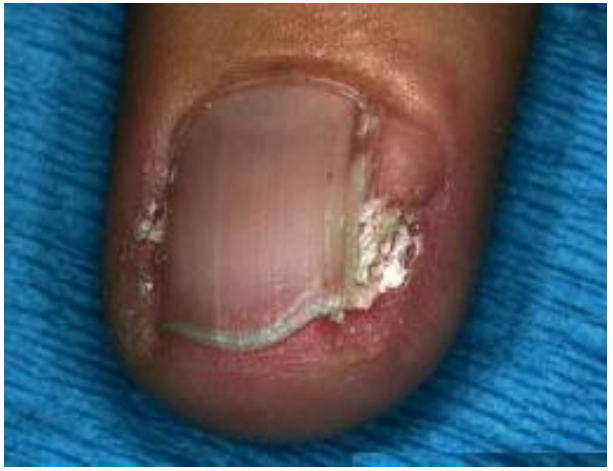
- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

# Skin exam findings in TS









# Tuberous Sclerosis Complex

- PREVeNT Trial
  - Early identification of EEG biomarkers
  - Early treatment versus delayed treatment with vigabatrin
  - Outcomes
    - developmental outcomes at 24 months
    - infantile spasms and refractory seizures
- Everolimus
  - Now approved for focal seizures associated with TSC

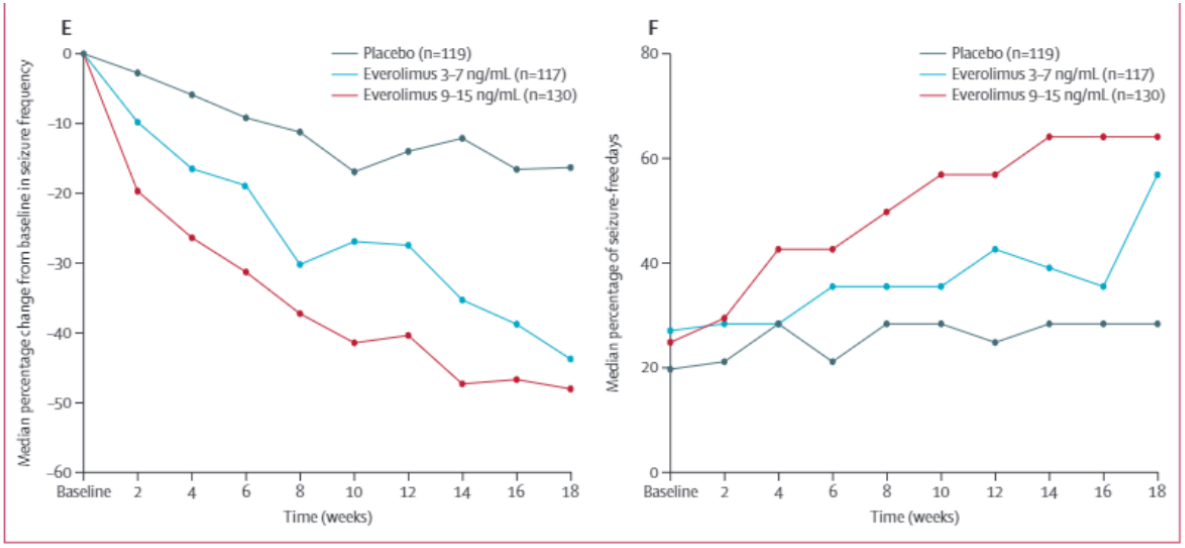
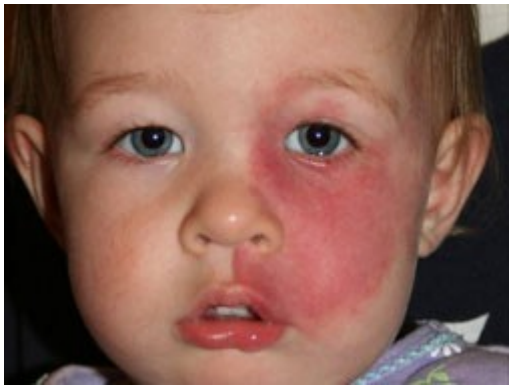



***Figure 2:*** **Seizure outcomes**
(A) Response rate by treatment group. Bars represent 95% CIs. (B) Median percentage reduction in seizure frequency by treatment group. Bars represent 95% CIs. (C) Distribution of reduction from baseline in seizure frequency by treatment group. (D) Response rate among various seizure types. Numbers on the x axis denote the number of patients with at least one occurrence of the seizure type during the baseline phase; bars represent 95% CIs. (E) Median percentage change from baseline in seizure frequency. (F) Median percentage of seizure-free days.

# Sturge-Weber



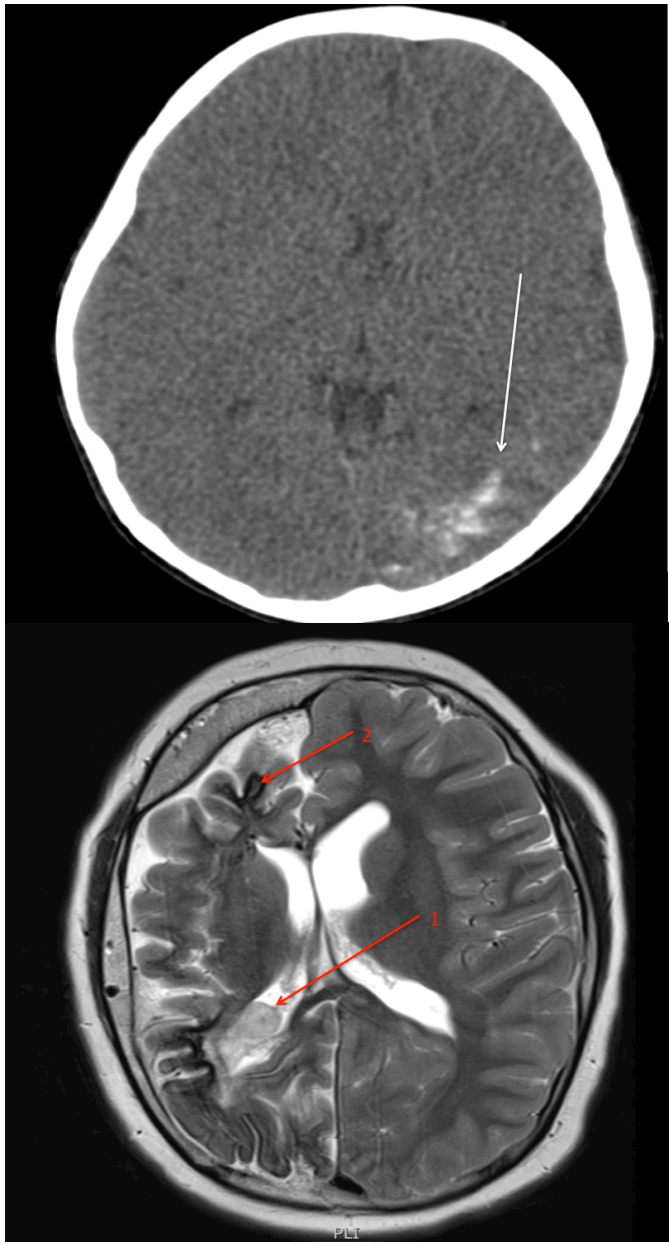
- Facial port-wine stain in the distribution of the ophthalmic branch of the trigeminal nerve (may be absent in 15% of Sturge-Weber syndrome patients); 26% with V1 have SWS (Ch'ng et al., 2008)
- Leptomeningeal angioma ipsilateral to the side of the port-wine stain, over occipital and posterior parietal regions predominantly, causing ischemia, atrophy and calcification in the affected cortex
- Ocular (choroidal, scleral) angioma (in 30% of patients), causing glaucoma, iris heterochromia, or buphthalmos.
- Seizures are seen in 75-90% of patients, usually starting at < 12 months; may also have hemiparesis, hemianopsia

https://www.epilepsydiagnosis.org/aetiology/sturge-weber-overview.html

*Sturge-Weber syndrome can be classified according to the presence/absence of facial and leptomeningeal angiomas:

- **type I**: represents classic syndrome, with both facial and leptomeningeal angiomas; may have glaucoma
- **type II**: facial angioma without evidence of intracranial disease; may have glaucoma
- **type III**: isolated leptomeningeal angioma; usually no glaucoma

*Roach et al (1992)



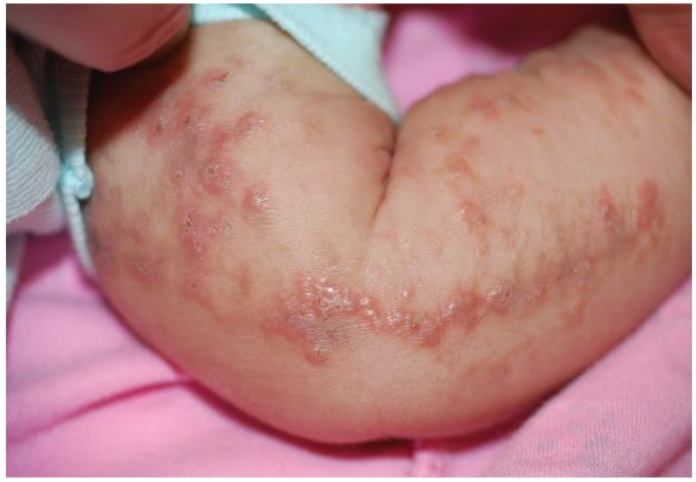

https://www.epilepsydiagnosis.org/aetiology/sturge-weber-imaging.html

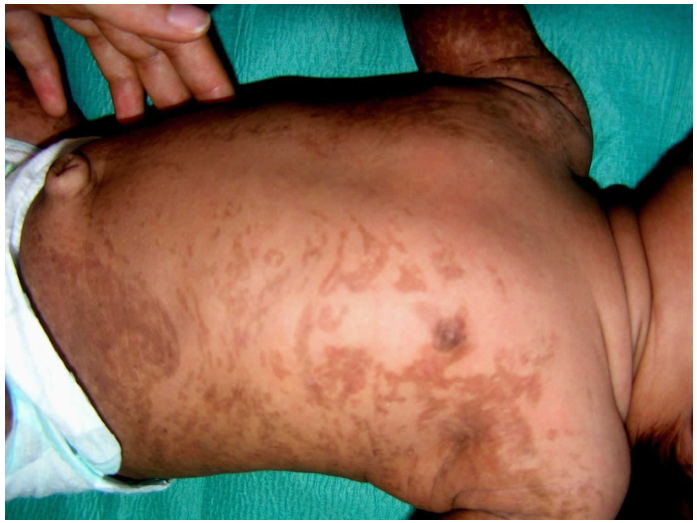
## Treatment:

- Surgical resection indicated in refractory epilepsy
- Ophthalmologic exam

# Incontinentia Pigmenti

- X-linked dominant due to mutations in *IKBKG*
- Skin: erythema, blisters, boils (birth/ infancy) → wart-like verrucous lesions (birth/ infancy) → hyperpigmented lesions (6-12 months) → atrophic stage (pale/ hypopigmented and hairless)
- Dental abnormalities in 50-75%
- Nail abnormalities
- Ocular abnormalities in 1/3
- Neurological abnormalities in 1/3 (stroke, seizures, developmental delay)

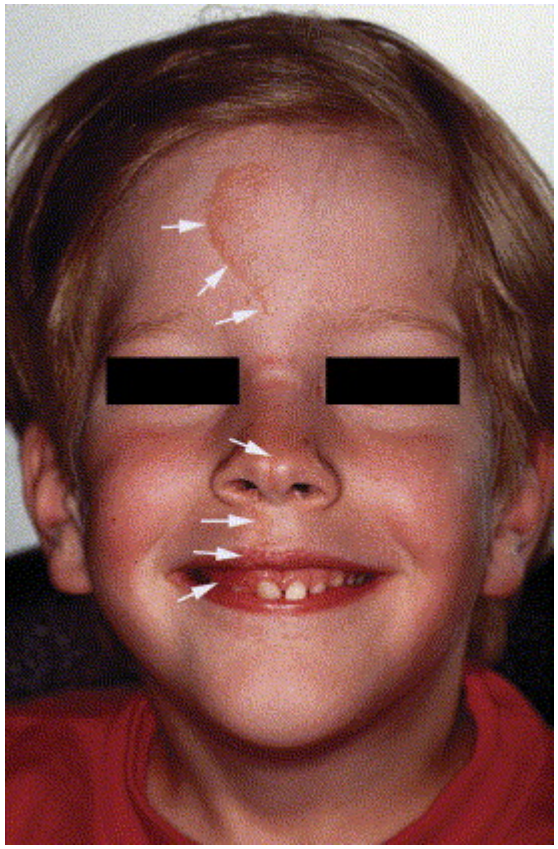




https://rarediseases.org/rare-diseases/incontinentia-pigmenti

# Nevus Sebaceous Syndrome (of Jadassohn)

- Postzygotic mutations in *KRAS* and *HRAS* (mosaic RAS mutations, regulating cell survival, proliferation, and differentiation) (Pan et al., BMC Med Gen. 2020;13:188)
- Hairless, yellow–orange plaques of varying sizes and shapes, and is most frequently located in areas with abundant sebaceous glands; ~7% have extracutaneous manifestations, primarily CNS (Davies et al., Austr J Dermatol. 2002;43(1):20–3; Chiang et al., Pediatr Neurosurg. 2019;54(3):201–6)
- Associated with seizures and various malformations of cortical development and other cerebral malformations (eg ACC)
- Other – ocular, skeletal, craniofacial



# Tumor - Epidemiology

- Proportion of incident epilepsy cases with brain tumors – 4-6%[1, 2]

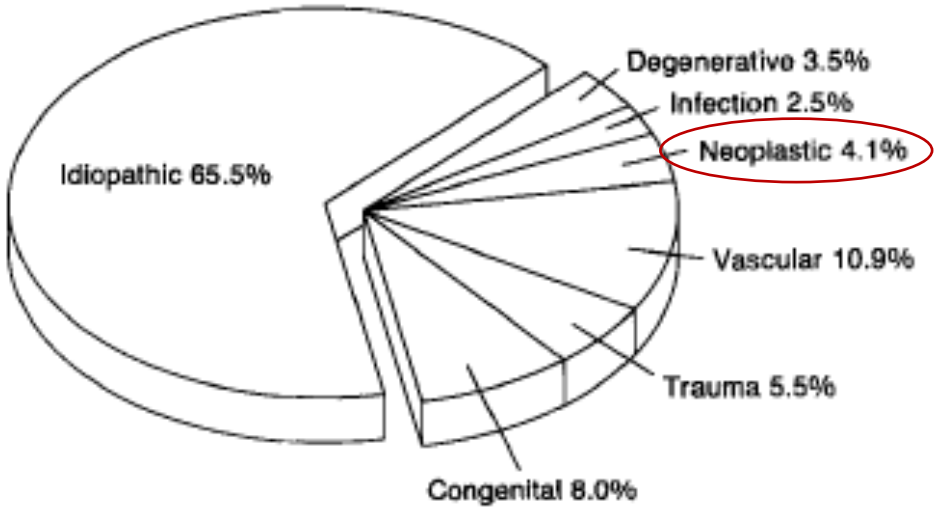



**FIG. 2.** Proportion of incidence cases (1935–1984) by etiology of epilepsy (all ages).

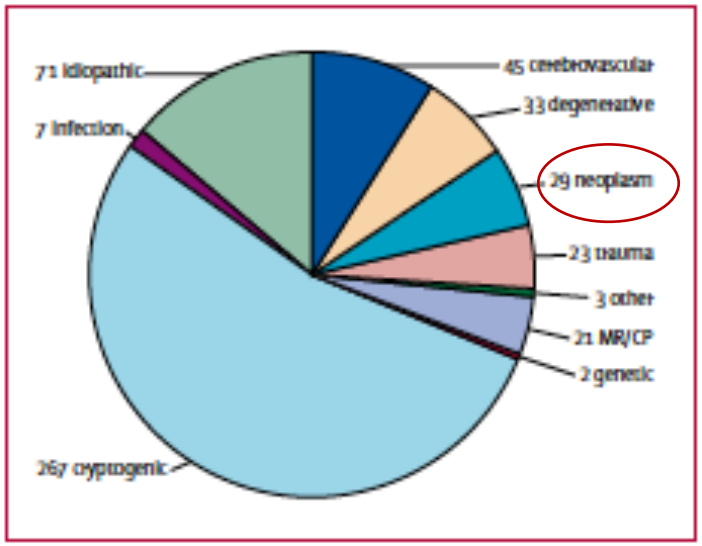



Figure 3: Distribution of causes of and risk factors for all (501) unprovoked seizures in Iceland from 1995 to 1999
MR/CP=mental retardation/cerebral palsy.


1. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993, 34: 453-68.
2. Olafsson E, Ludvigsson P, Gudmundsson G, et al. Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol 2005, 4: 627-34.

# Etiology according to age

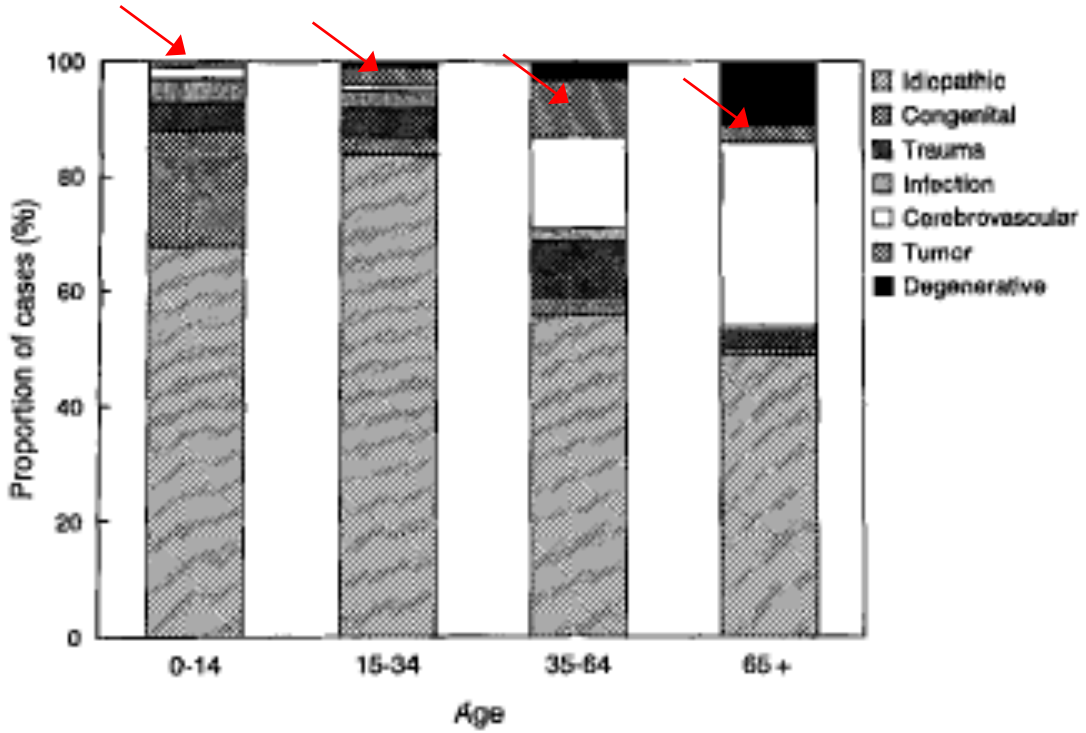



**FIG. 10.** Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups, including idiopathic/cryptogenic category. Area: idiopathic (gray cross-hatched), congenital (dashed), trauma (dotted), trauma (widely dotted), infection (hatched), cerebrovascular (closely dotted), tumor (black), degenerative (light cross-hatch).

# Seizure frequency according to tumor type

| | Seizure frequency |
|---|---|
| Dysembryoblastic neuroepithelial tumour[5,11] | 100% |
| Ganglioglioma[5,12] | 80–90% |
| Low-grade astrocytoma[12,13] | 75% |
| Meningioma[5,12] | 29–60% |
| Glioblastoma multiforme[5,13] | 29–49% |
| Metastasis[5,12] | 20–35% |
| Leptomeningeal tumour[14,15] | 10–15% |
| Primary CNS lymphoma[14] | 10% |

*Table 1:* **Association between tumour type and seizure frequency**

Van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007, 6: 421-30.

# Seizure frequency according to tumor location

- Supratentorial 22-68% vs. infratentorial 6%
- Superficial/ cortical 63% vs. non-cortical/ deep 29%
- Parietal, temporal, frontal > occipital
- Increased seizure incidence with proximity to rolandic fissure


1. Recht LD, Glantz M. Neoplastic diseases. In: Engel J, Pedley TA, eds. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven, 1998: 2579-85 (vol 3).
2. Lynam LM, Lyons MK, Drazkowski JF, et al. Frequency of seizures in patients with newly diagnosed brain tumors: A retrospective review. ClinNeurolNeurosurg 2007, 109: 634-8.

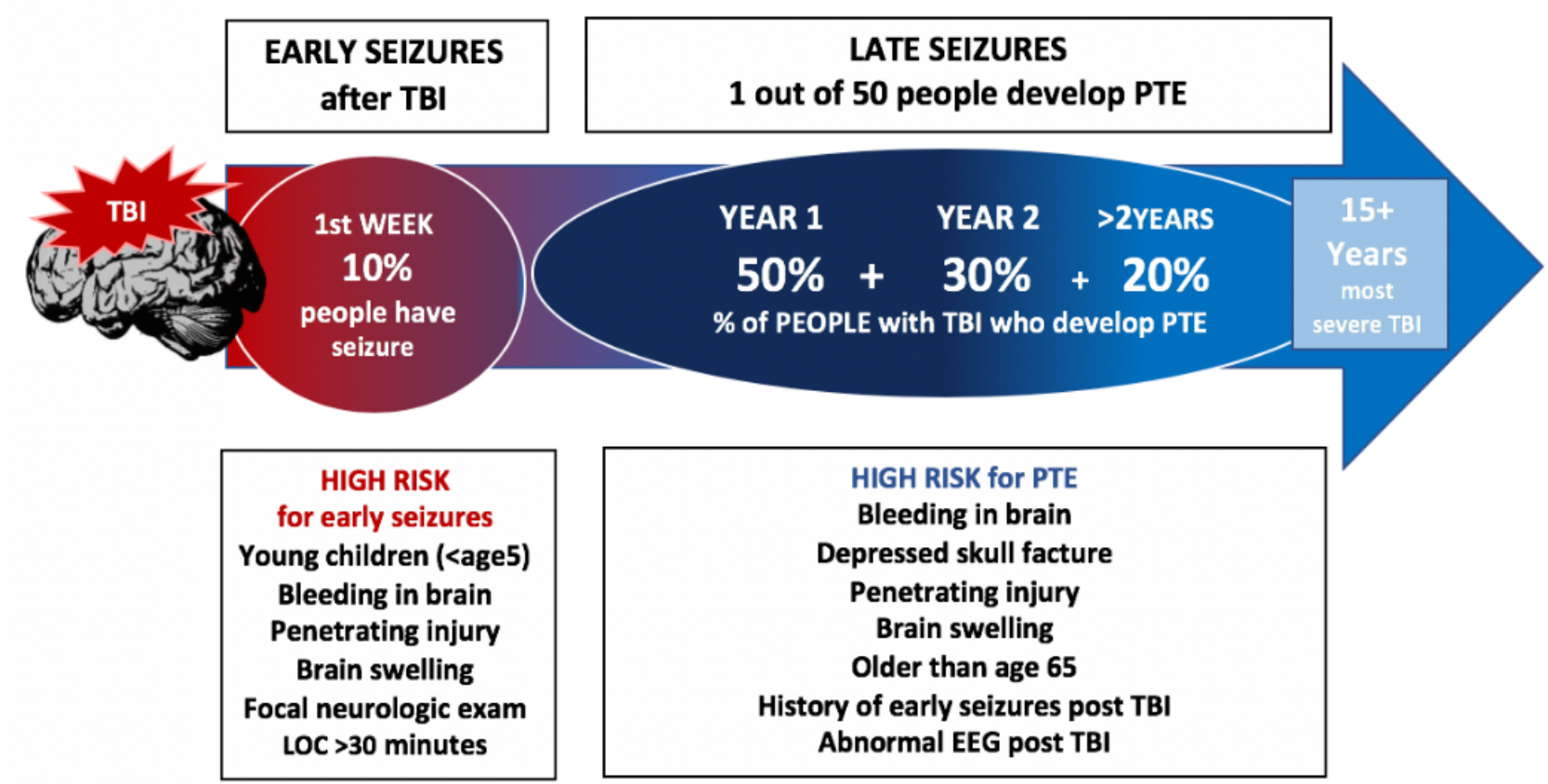
# Epileptogenesis

- Lesions are often electrically inert; epileptogenic activity probably arises from perilesional tissue
- Mirror focus – actively discharging epileptiform region may induce similar activity in a homologous site

1. Wolf HK, Roos D, Blumcke I, et al. Perilesionalneurochemical changes in focal epilepsies. ActaNeuropathol 1996, 91: 376-84.
2. Gilmore R, Morris H 3rd, Van Ness PC, Gilmore-Pollak W, Estes M. Mirror focus: function of seizure frequency and influence on outcome after surgery. Epilepsia 1994, 35: 258-63.

# Seizures after TBI

- Early (< 1 week)
- Late (> 1 week)



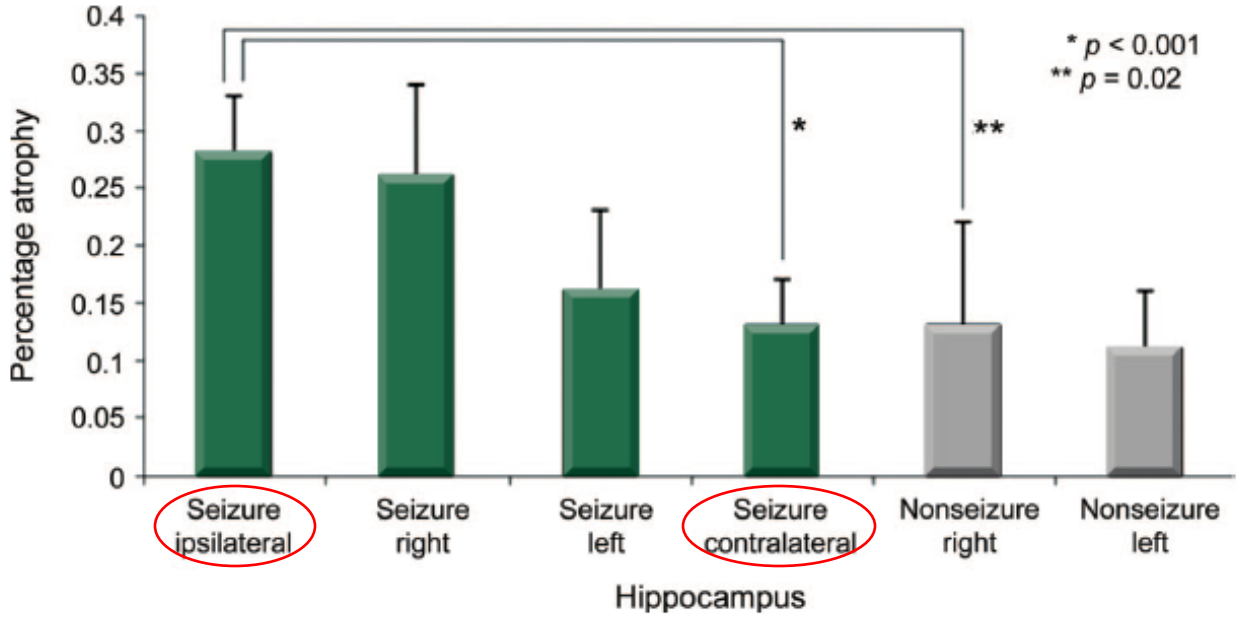
# Nonconvulsive seizures after traumatic brain injury are associated with hippocampal atrophy

*Neurology*® 2010;75:792-798

**Table 2** Global and hippocampal brain atrophy by group

| Atrophy | Seizure | Nonseizure | *p* Value |
|---|---|---|---|
| Hippocampal | 0.21 ± 0.09 | 0.12 ± 0.06 | 0.007 |
| Global | 0.08 ± 0.05 | 0.08 ± 0.03 | 0.907 |

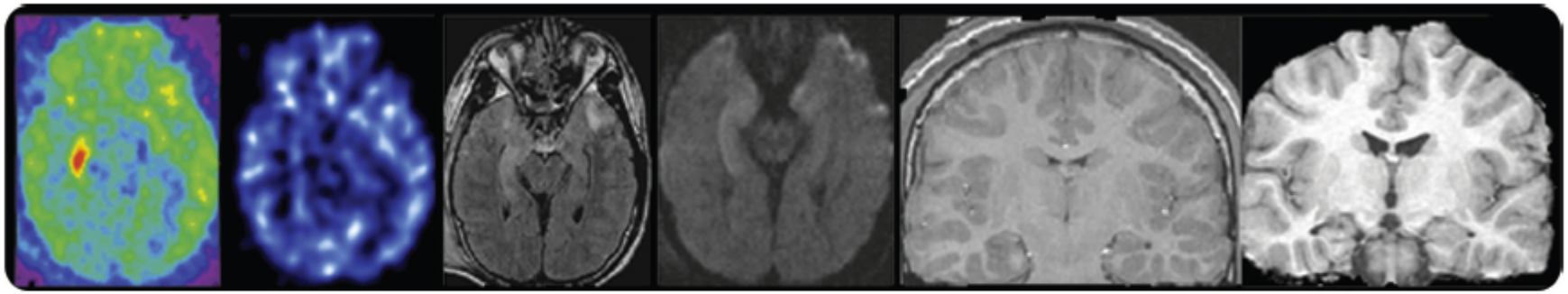
**Figure 2** Long-term brain atrophy in hippocampal regions are shown for the seizure and nonseizure groups




Bars are labeled by group (seizure, black; nonseizure, white) and by hippocampus location (right, left, ipsilateral or contralateral to the EEG seizure focus). There is greatest hippocampal atrophy in the seizure patients' hippocampi ipsilateral to the EEG seizure focus. The right hemisphere was ipsilateral to seizures more commonly than the left. Late hippo atrophy = percentage atrophy at 6 months as compared with the acute image.

P.M. Vespa, MD, FCCM, FAAN
D.L. McArthur, PhD
Y. Xu, MD
M. Eliseo, BS
M. Etchepare, BSN, RN
I. Dinov, PhD
J. Alger, PhD
T.P. Glenn, PhD
D. Hovda, PhD

**Figure 3** **Hippocampal atrophy ipsilateral to the seizure focus**

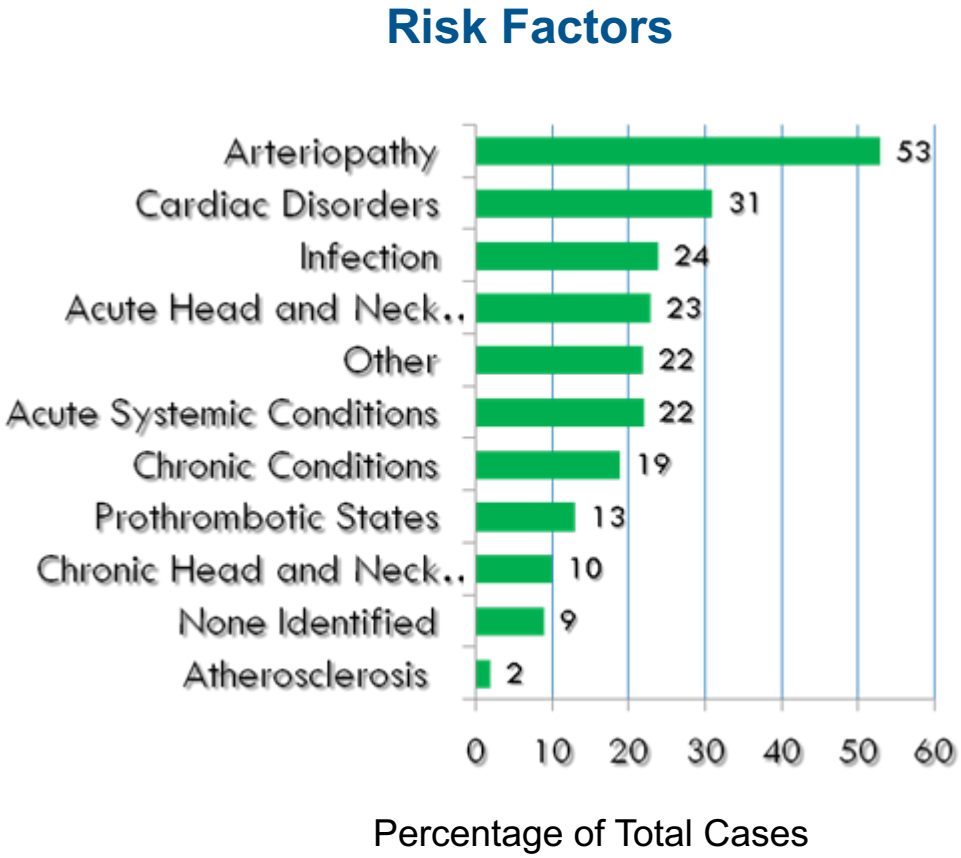



Composite of acute PET scan and acute and chronic MRI volumetric scans on seizure subject 4. The patient has increased glucose metabolism in the right hippocampus without a similar increase in CMRO2. The hyperintensity on the fluid-attenuated inversion recovery (FLAIR) sequence was due to acute seizure activity and not traumatic hemorrhage. MRI at 6 months shows right hippocampal atrophy and also right temporal lobe atrophy. CMRO2 = oxidative metabolism PET; FDG = fluorodeoxyglucose PET; PIH = postinjury hour.

Salmenperä T, Kälviäinen R, Partanen K, Pitkänen A. Quantitative MRI volumetry of the entorhinal cortex in temporal lobe epilepsy. Seizure 2000, 9: 208-215.

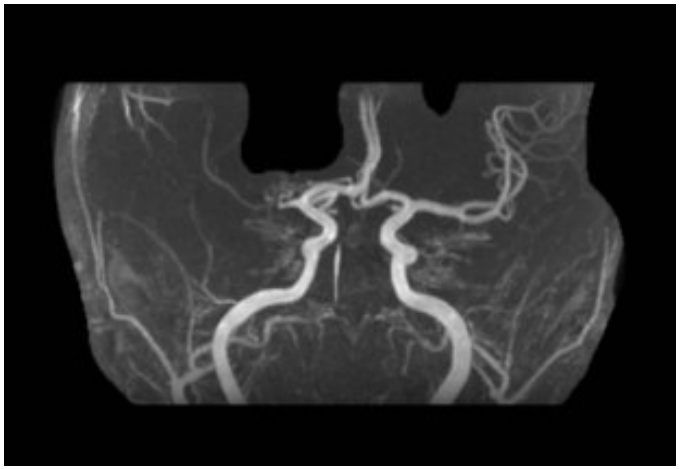
# Risk Factors – Stroke in Children

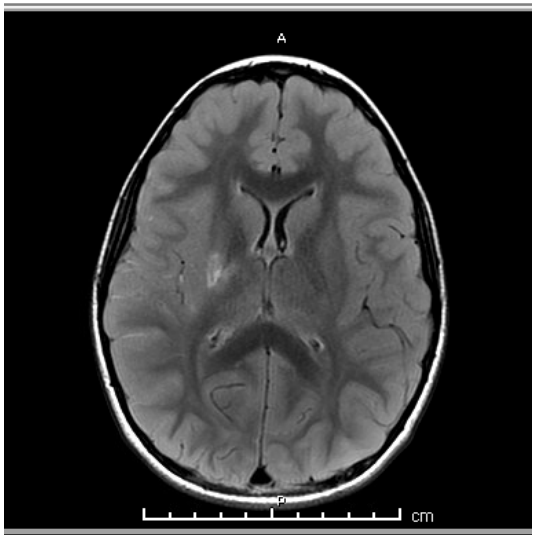
- Childhood AIS (IPSS)
  - N=676
  - 2003-2007
  - 30 centers
  - Median age – 5.9 y
  - 52% with multiple RF



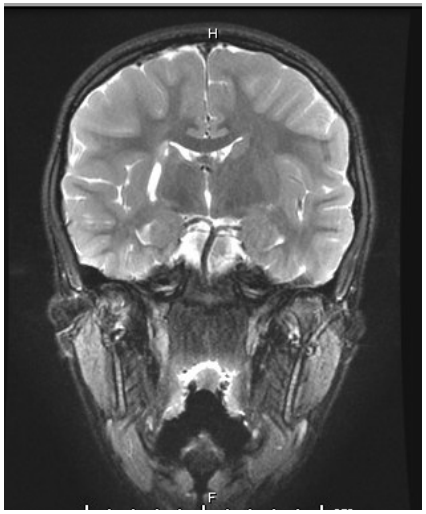

Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V; International Pediatric Stroke Study Group. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann Neurol. 2011

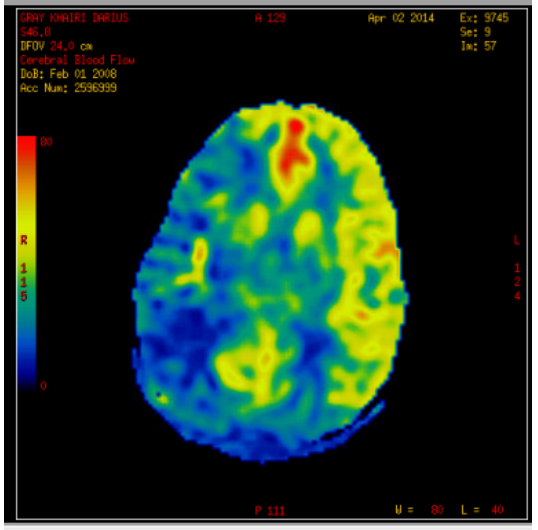
# Focal Cerebral Arteriopathy






Imaging 6 years post stroke



# Infection

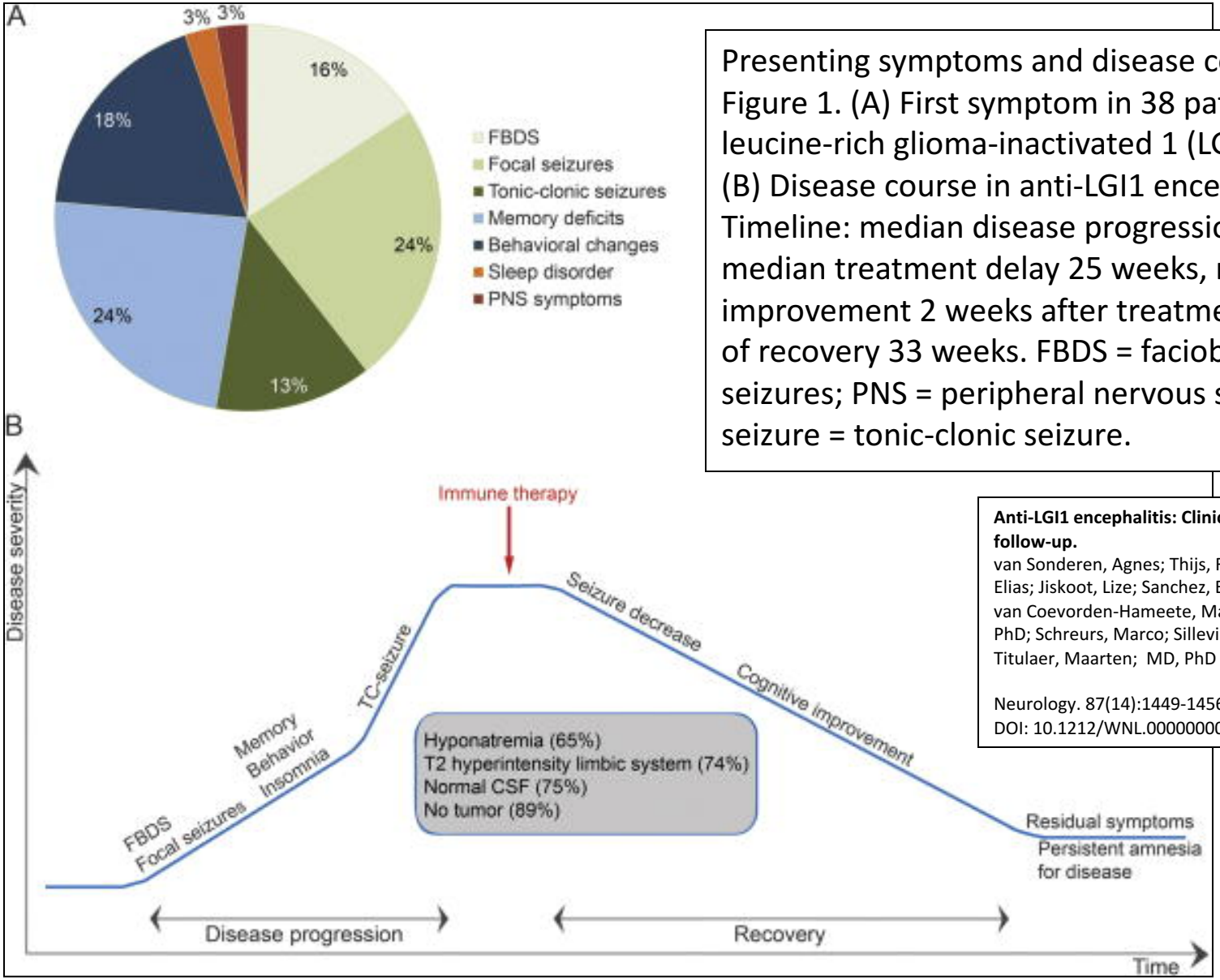
- Viral encephalitis
- Bacterial meningitis
- Abscess
- Neurocysticercosis
- Cerebral malaria
- TORCH infections (toxoplasmosis, rubella, CMV, HSV, Zika, etc)
- Tuberculosis
- HIV
- HSV
- Etc

# Immune Etiology

- ANTI-NMDA RECEPTOR ENCEPHALITIS
- VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODY
- GAD65 ANTIBODY
- GABA-B RECEPTOR ANTIBODY
- AMPA RECEPTOR ANTIBODY
- STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH THYROID DISEASE
- CELIAC DISEASE, EPILEPSY AND CEREBRAL CALCIFICATION SYNDROME

**Table 3**
Clinicoradiological characteristics of VGKC-complex, NMDA, GAD and AMPA antibody associated encephalitis. AED = Antiepileptic drugs; AMPAR = Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CSF = Cerebrospinal fluid; CASPR2 = Contactin-associated protein2; CV2/CRAMP5 = Collapsin response mediator protein; CPS = Complex partial seizure; EEG = Electroencephalogram; FBDS = Faciobrachial dystonic seizures; GTC = Generalized tonic clonic; GABA = Gamma aminobutyric acid; GlyR = Glycine receptor; GluR = Glutamate receptor; GAD = Glutamic acid decarboxylase; LGI1 = Leucine-rich glioma inactivated1; MRI = Magnetic resonance imaging; MTL = Medial temporal lobe; NMDAR = N-methyl-D-aspartate; OCB = Oligoclonal bands; SE = Status epilepticus; SOX1 = Sex determining region Y-box 1; SPS = Stiff Person Syndrome; SCLC = Small cell lung cancer; T1DM = Type 1 diabetes; VGCC = Voltage gated calcium channel.

| Characteristic features | LGI1>CASPR2 (VGKC-complex) | NMDAR | GAD | $GABA_BR$ | AMPAR |
|---|---|---|---|---|---|
| Gender | M>F | F>M | F>M | M>F | F>M |
| Typical age group | >50 years | <40 years | >20 years | > 40 years | > 40 years |
| Neurological features | Memory loss<br>Confusion<br>Temporal lobe seizures<br>FBDS | Multistage encephalopathy with: Psychiatric symptoms<br>Extratemporal seizures<br>Movement disorders<br>Autonomic instability<br>Coma | Memory loss<br>Temporal lobe seizures<br>Coexisting autoimmune disorders including T1DM, SPS | Memory loss<br>Seizures<br>Confusion | Amnesia<br>Seizures<br>Insomnia<br>Confusion |
| Psychiatric Features | Psychosis<br>Personality changes<br>Depression<br>Anxiety | Psychosis<br>Behavioural disturbances<br>Delusions<br>Agitation | Depression<br>Anxiety | Psychosis<br>Hallucination<br>Behavioural changes | Psychosis<br>Confabulation<br>Agitation<br>Personality changes |
| Characteristic seizures | FBDS<br>CPS<br>GTC | GTC<br>SE<br>CPS | GTC<br>CPS | CPS<br>GTC<br>SE<br>Focal motor | GTC<br>CPS |
| Tumour association | Thymoma<br>SCLC | Ovarian teratoma | SCLC | SCLC | Thymoma<br>SCLC |
| Target antigen | LGI1 & CASPR2 | NR1 subunit | GAD-65 | $GABA_BR$ | GluR1/2 |
| MRI | High signal change in MTL, less commonly basal ganglia | Normal although non-specific signal changes in medial temporal structures | Normal, although increased signal in MTL | Increased signal in MTL | Increased signal in MTL |
| EEG | Focal or generalized slowing | Extreme delta brush, focal or diffuse delta/theta activity | Focal or generalized slowing | Focal or generalized epileptic activity | Focal epileptic activity |
| Treatment & outcome | Good response to immunotherapy | Responds slowly to immunotherapy | Poor treatment outcome with immunotherapy and AEDs | Good response to immunotherapy | Relapses are common although there is good response to immunotherapy |

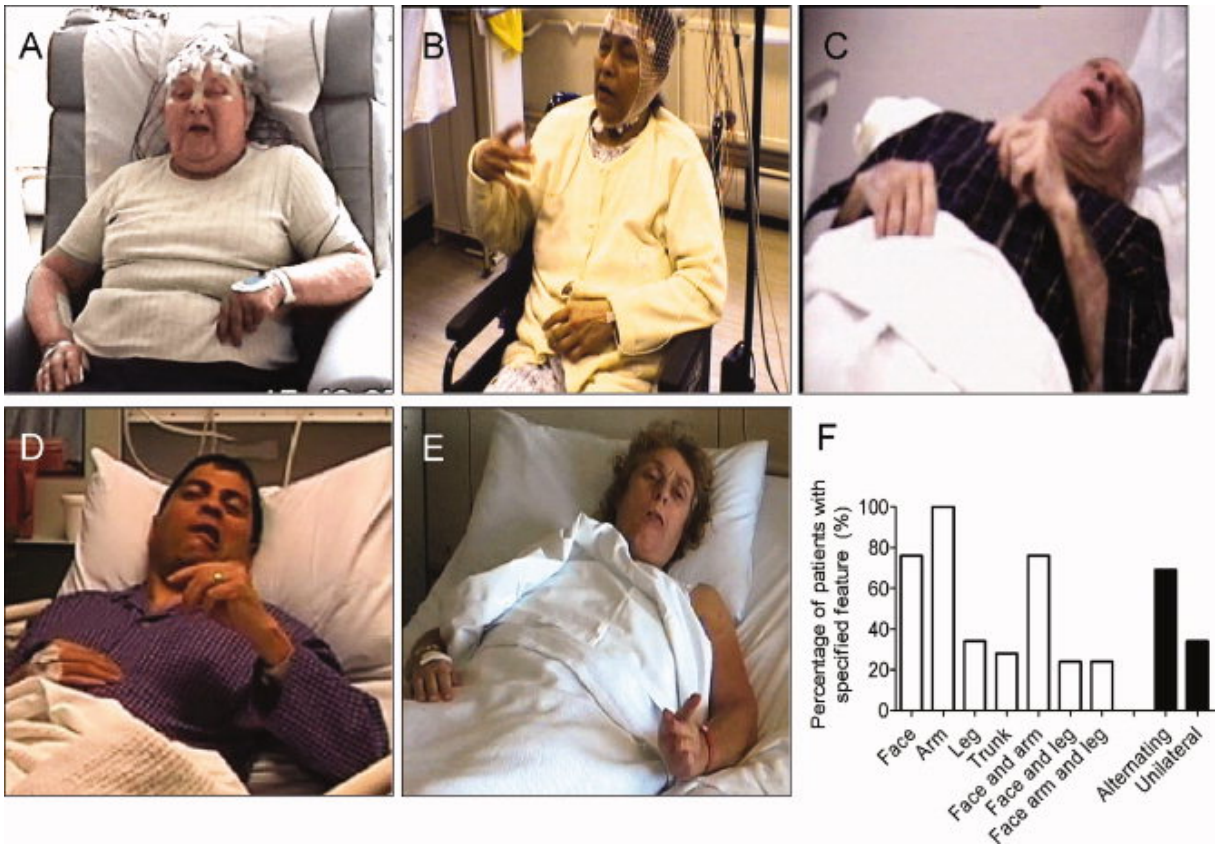



Presenting symptoms and disease course
Figure 1. (A) First symptom in 38 patients with anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis. (B) Disease course in anti-LGI1 encephalitis. Timeline: median disease progression 22 weeks, median treatment delay 25 weeks, median start of improvement 2 weeks after treatment, median time of recovery 33 weeks. FBDS = faciobrachial dystonic seizures; PNS = peripheral nervous system; TC seizure = tonic-clonic seizure.

**Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up.**
van Sonderen, Agnes; Thijs, Roland; MD, PhD; Coenders, Elias; Jiskoot, Lize; Sanchez, Esther; de Bruijn, Marienke; van Coevorden-Hameete, Marleen; Wirtz, Paul; MD, PhD; Schreurs, Marco; Sillevis Smitt, Peter; MD, PhD; Titulaer, Maarten; MD, PhD

Neurology. 87(14):1449-1456, October 04, 2016.
DOI: 10.1212/WNL.0000000000003173

# Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis




**Annals of Neurology**
Volume 69, Issue 5, pages 892-900, 17 MAR 2011 DOI: 10.1002/ana.22307
http://onlinelibrary.wiley.com/doi/10.1002/ana.22307/full#fig1

# Perinatal Insults

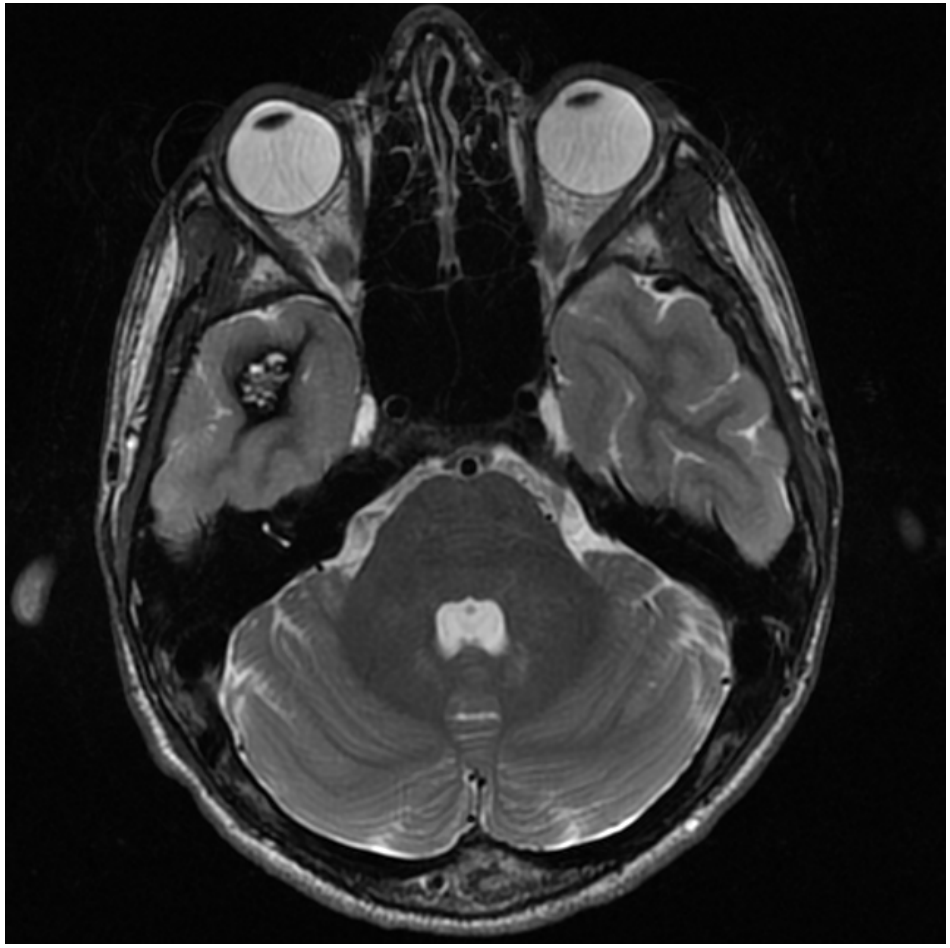
- Periventricular Leukomalacia
- Intraventricular Hemorrhage
- Hydrocephalus
- Hypoxic-Ischemic Encephalopathy
- Stroke

# Cavernoma

- 1% bleeding risk per year
- Familial CCM – 50% asymptomatic

# AVM

- 2-4% ICH risk per year
- Can be limited or catastrophic



# IEM with seizures as a prominent feature

- Amino acid and organic acid disorders
- Glucose transport/ regulation disorders – GLUT1, HI/HA, DEND
- Hyperhomocysteinemia – cobalamin deficiencies, homocysteinuria, MTHFR deficiency
- Urea cycle disorders
- Fatty acid oxidation disorders
- Creatine synthesis/ transport disorders
- Neurotransmission – biopterin deficiencies, SSADH-D
- Sulfite oxidase deficiency
- Vitamins/ co-factors: biotinidase, cerebral folate, holocarboxylase, molybdenum cofactor, pyridoxine, thiamine
- Mitochondria – Co-Q10 deficiency, MELAS, PDH complex deficiency
- Metals - Menkes
- Lysosomal and peroxisomal disorders

2022 EPILEPSY BOARD REVIEW AND BEST PRACTICES

# EPILEPSIES OF UNKNOWN CAUSE AND CONDITIONS WITH EPILEPTIC SEIZURES TRADITIONALLY NOT DIAGNOSED AS A FORM OF EPILEPSY

John M. Schreiber, MD
Medical Director, EEG
Children's National Health System

# Febrile Seizures

- 2-5% of children (Hauser 1975, Nelson 1978, Offringa 1991) between 6 months and 60 months (5 years) of age (AAP guidelines)
- 10-20% risk in 1st degree family members
- Complex:
  - Duration > 15 minutes
  - Focal features
  - ≥ 2 in 24 hours

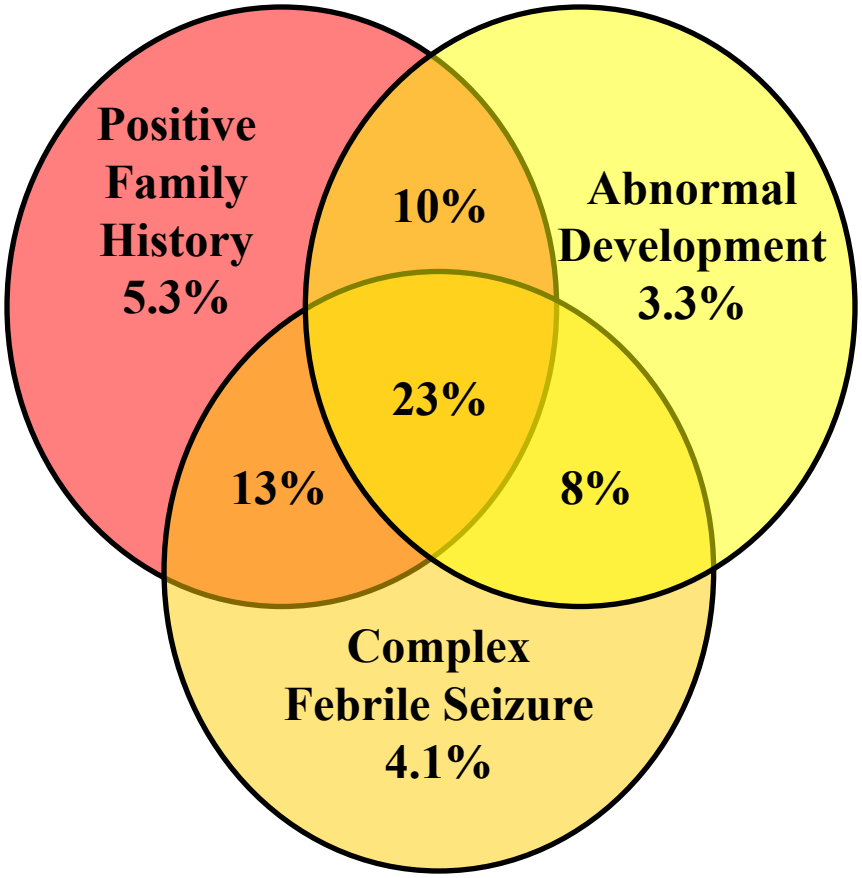
Nelson & Ellenberg. NEJM 1976, 295: 1029-1033.

# Prognosis

- Overall, 1/3 have recurrence of FS
- ~10% have ≥3 FS
- Nelson & Ellenberg (1978):
  - 1% without risk factors will develop epilepsy by age 7
  - Compared to 10% with 2/3 risk factors – complex, preexisting neurological abnormality, family history of afebrile seizures
- Annegers et al. (1987):
  - 2.4% with simple FS will develop epilepsy by age 25
  - 6-8% if complex (17-22% if 2 features, 49% if 3)
  - Generalized epilepsy a/w multiple FS and family history

Nelson & Ellenberg. Pediatrics 1978, 61: 720-727.
Annegers et al. NEJM 1987, 316: 493-498.

# Epilepsy after a Febrile Seizure?




- Other factors
  - Focal seizure
  - Todd's paralysis
  - Number of febrile seizures
  - Age of occurrence
  - Duration of febrile seizure
  - Duration of fever before seizure

# FS+ and GEFS+

- Febrile Seizures Plus – FS beyond 6 years old
- Genetic/ Generalized Epilepsy with Febrile Seizures Plus – FS and afebrile seizures that may include various generalized or focal types
- >10-20% due to *SCN1A, SCN1B, GABRG2, SCN2A, STX1B* variants

# Original pedigree

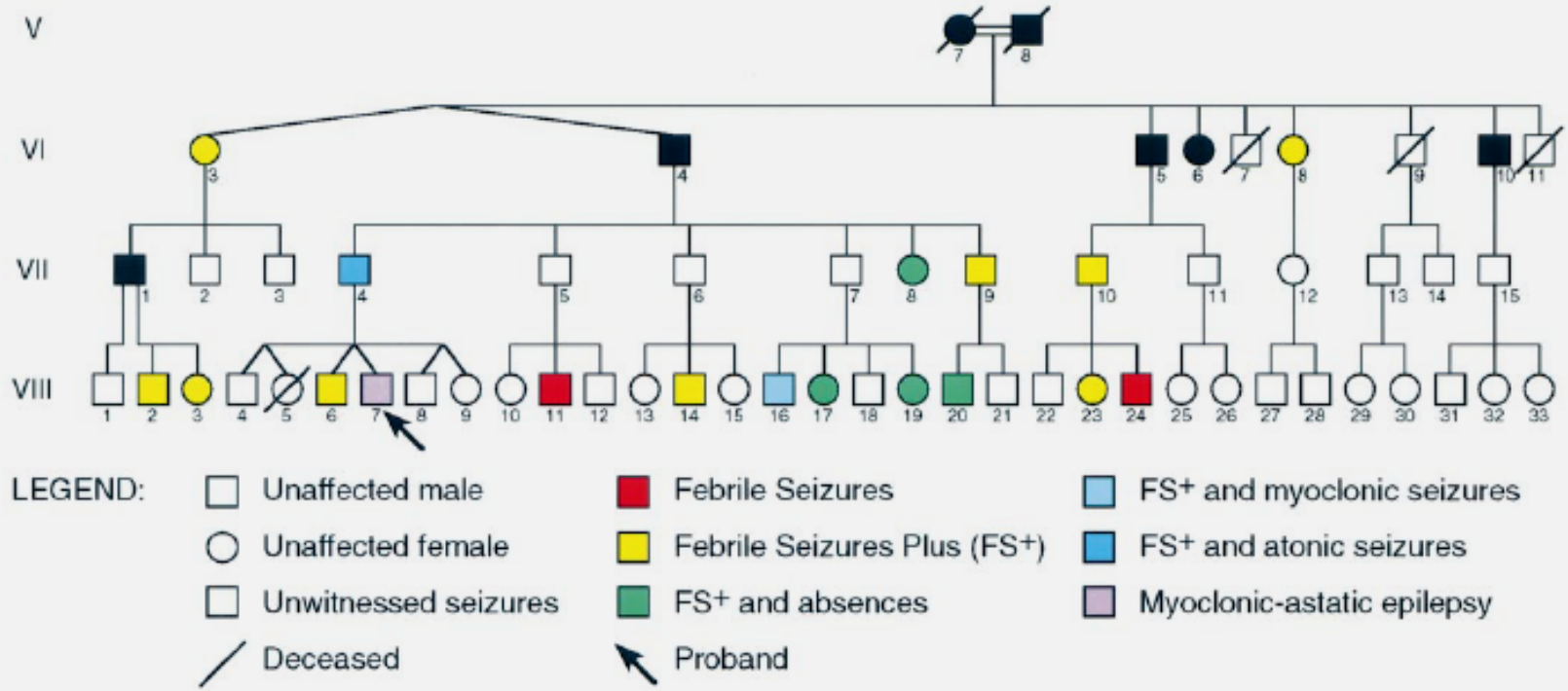


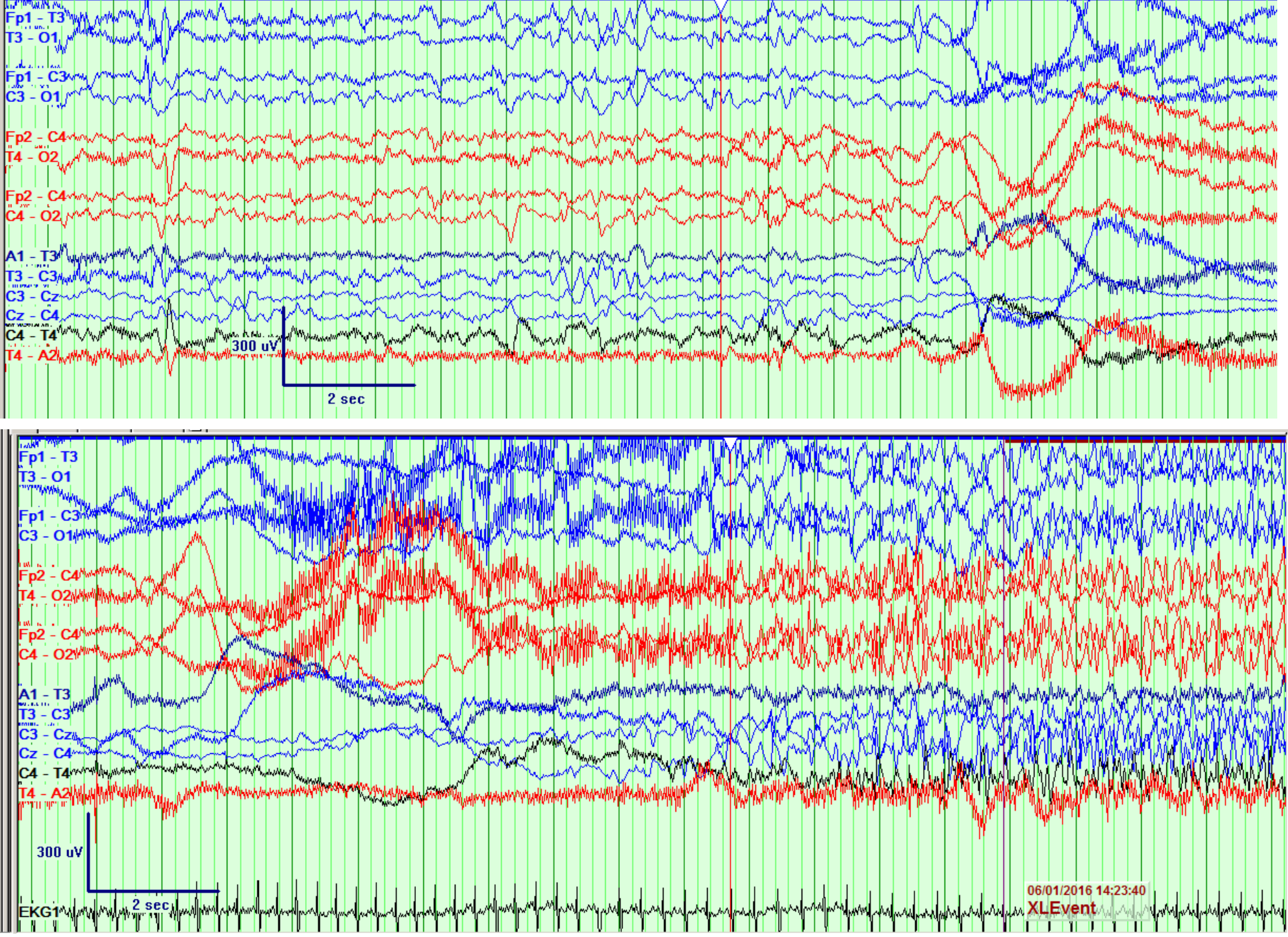

**Fig. 4** Pedigree of the core family showing the heterogeneity of epilepsy phenotypes seen.

Scheffer & Berkovic, 1997

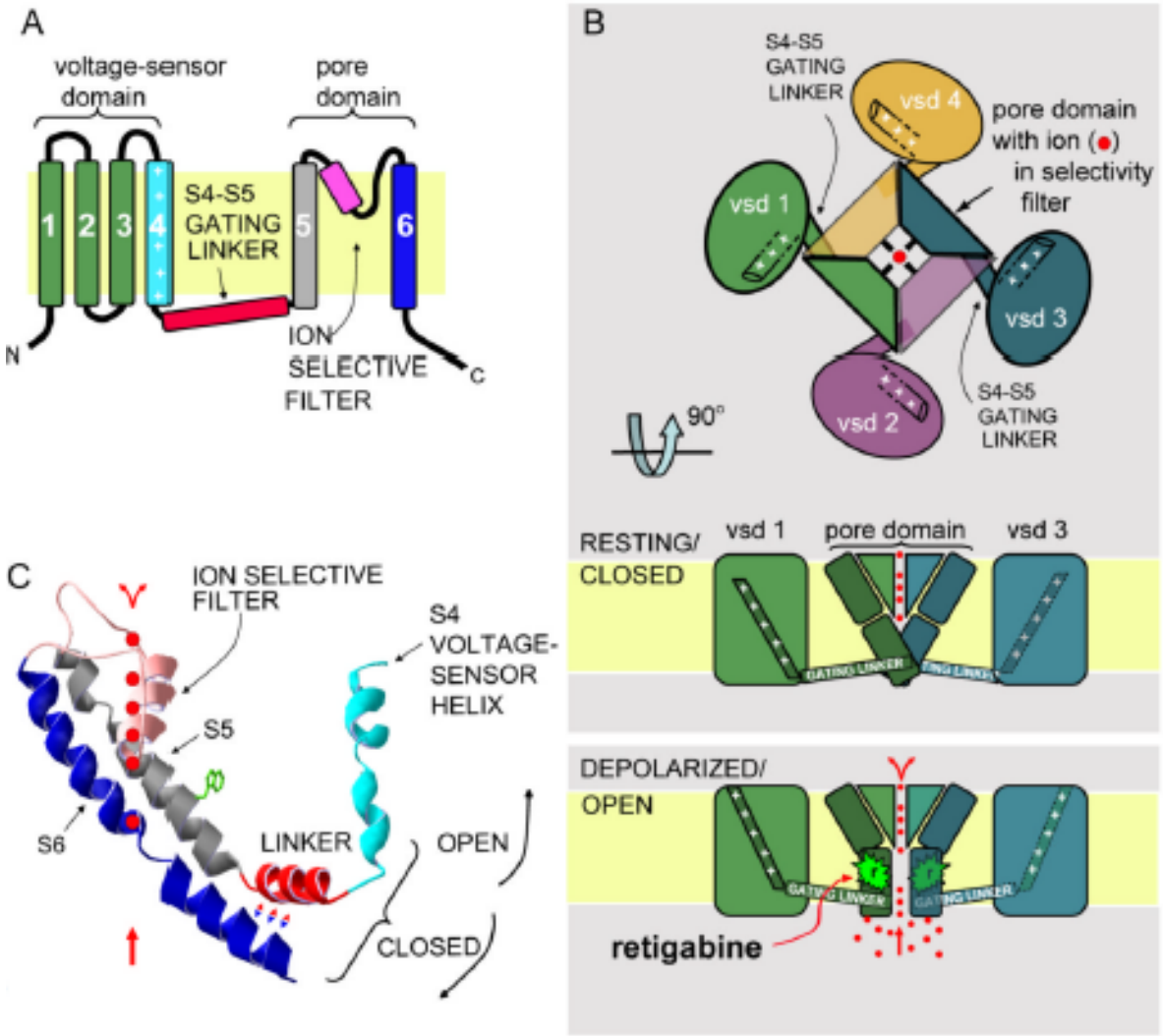
# Benign Familial/ Non-Familial Neonatal Seizures

- "Fifth Day Fits"
- EEG background may be normal or abnormal
- Mutations in KCNQ2, or less commonly, KCNQ3
  - AD mutations, result in small reduction in current and less hyperpolarization
- Seizures - clonic, tonic, apneas, orofacial automatisms
- Benign idiopathic neonatal seizures
  - Almost always clonic seizures, mostly partial ± apnea

J Roger *et al.*, Epileptic Syndromes in Infancy, Childhood, and Adolescence


Fp1 - T3
T3 - O1
Fp1 - C3
C3 - O1
Fp2 - C4
T4 - O2
Fp2 - C4
C4 - O2
A1 - T3
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
T4 - A2
300 uV
2 sec
Fp1 - T3
T3 - O1
Fp1 - C3
C3 - O1
Fp2 - C4
T4 - O2
Fp2 - C4
C4 - O2
A1 - T3
T3 - C3
C3 - Cz
Cz - C4
C4 - T4
T4 - A2
300 uV
2 sec
EKG1
06/01/2016 14:23:40
XLEvent

# Voltage-gated potassium channel




Cooper EC, in *Jasper's Basic Mechanisms of the Epiilepsies, 4th Ed.*

# ILAE Proposed Epilepsy Classification

**Table 3. Electroclinical syndromes and other epilepsies**

- Electroclinical syndromes arranged by age at onset[a]
  - Neonatal period
    - Benign familial neonatal epilepsy (BFNE)
    - Early myoclonic encephalopathy (EME)
    - Ohtahara syndrome
  - Infancy
    - Epilepsy of infancy with migrating focal seizures
    - West syndrome
    - Myoclonic epilepsy in infancy (MEI)
    - Benign infantile epilepsy
    - Benign familial infantile epilepsy
    - Dravet syndrome
    - Myoclonic encephalopathy in nonprogressive disorders
  - Childhood
    - Febrile seizures plus (FS+) (can start in infancy)
    - Panayiotopoulos syndrome
    - Epilepsy with myoclonic atonic (previously astatic) seizures
    - Benign epilepsy with centrotemporal spikes (BECTS)
    - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
    - Late onset childhood occipital epilepsy (Gastaut type)
    - Epilepsy with myoclonic absences
    - Lennox-Gastaut syndrome
    - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
    - Landau-Kleffner syndrome (LKS)
    - Childhood absence epilepsy (CAE)
  - Adolescence – Adult
    - Juvenile absence epilepsy (JAE)
    - Juvenile myoclonic epilepsy (JME)
    - Epilepsy with generalized tonic–clonic seizures alone
    - Progressive myoclonus epilepsies (PME)
    - Autosomal dominant epilepsy with auditory features (ADEAF)
    - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies
- Distinctive constellations
  - Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypothalamic hamartoma
  - Hemiconvulsion–hemiplegia–epilepsy
  - Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)
- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor
  - Infection
  - Trauma
  - Angioma
  - Perinatal insults
  - Stroke
  - Etc.
- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

[a]The arrangement of electroclinical syndromes does not reflect etiology.

[b]Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

*Epilepsia*, 51(4):676–685, 2010

# THANK YOU

# EXTRA SLIDES

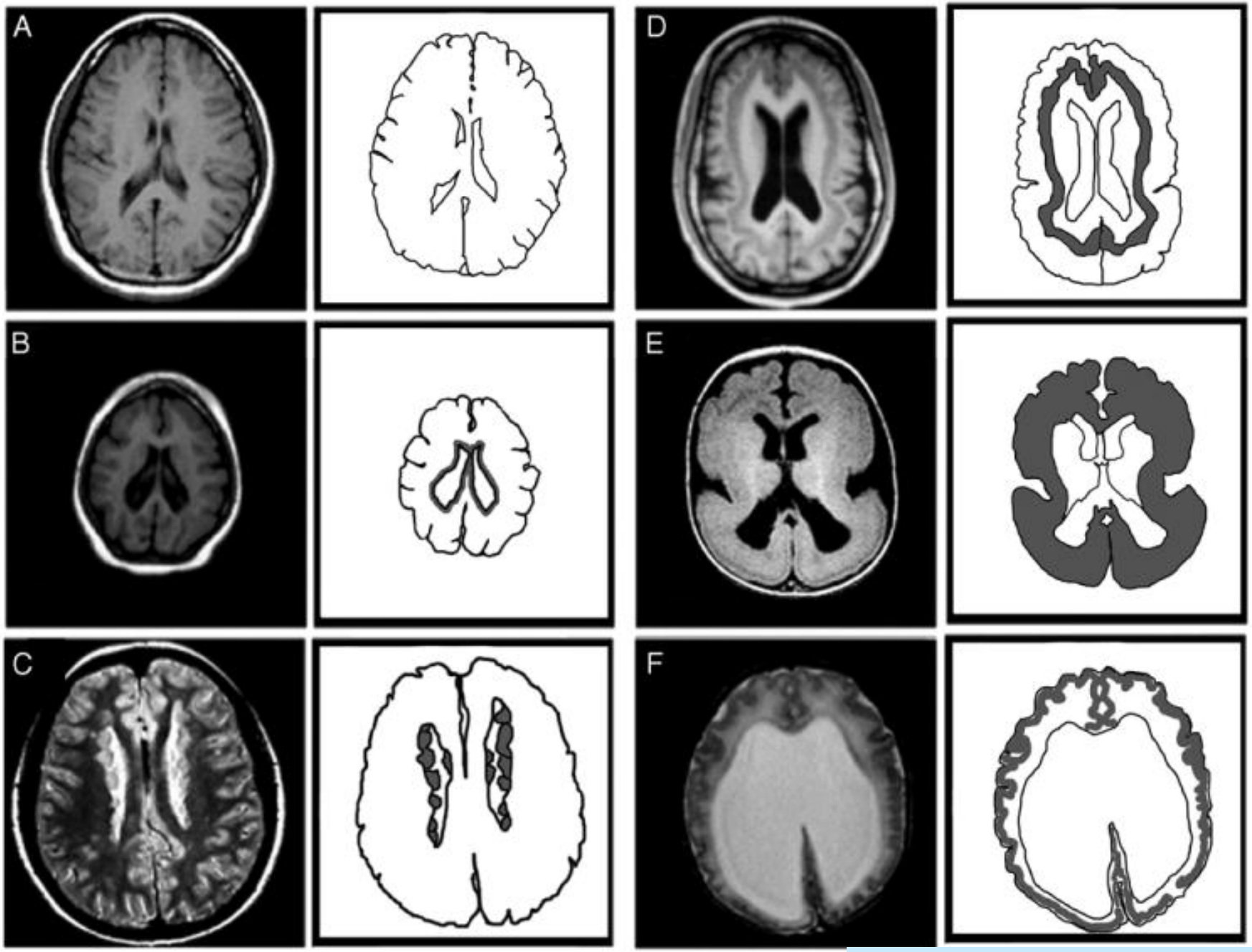
doi:10.1093/brain/aws019 Brain 2012: 135; 1348–1369 | 1348

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

# A developmental and genetic classification for malformations of cortical development: update 2012

A. James Barkovich,[1] Renzo Guerrini,[2,3] Ruben I. Kuzniecky,[4] Graeme D. Jackson[5,6] and William B. Dobyns[7,8]




Brain 2012: 135; 1348–1369

# Malformations due to abnormal neuronal and glial proliferation or apoptosis

- Severe congenital microcephaly (pre-migrational reduced proliferation or excess apoptosis)
  - ± IUGR, short stature, ID, ACC, other syndromic features, cortical malformations (genetic, other)
- Megalencephaly
  - ± PNH, PMG, other cortical dysgenesis (PTEN, Sotos)
- Cortical dysgenesis with abnormal cell proliferation but without neoplasia
  - Diffuse or focal/ multifocal (putative postzygotic mosaicism) – FCD, HMEG
- Cortical dysplasias with abnormal cell proliferation and neoplasia
  - DNET, ganglioglioma, gangliocytoma

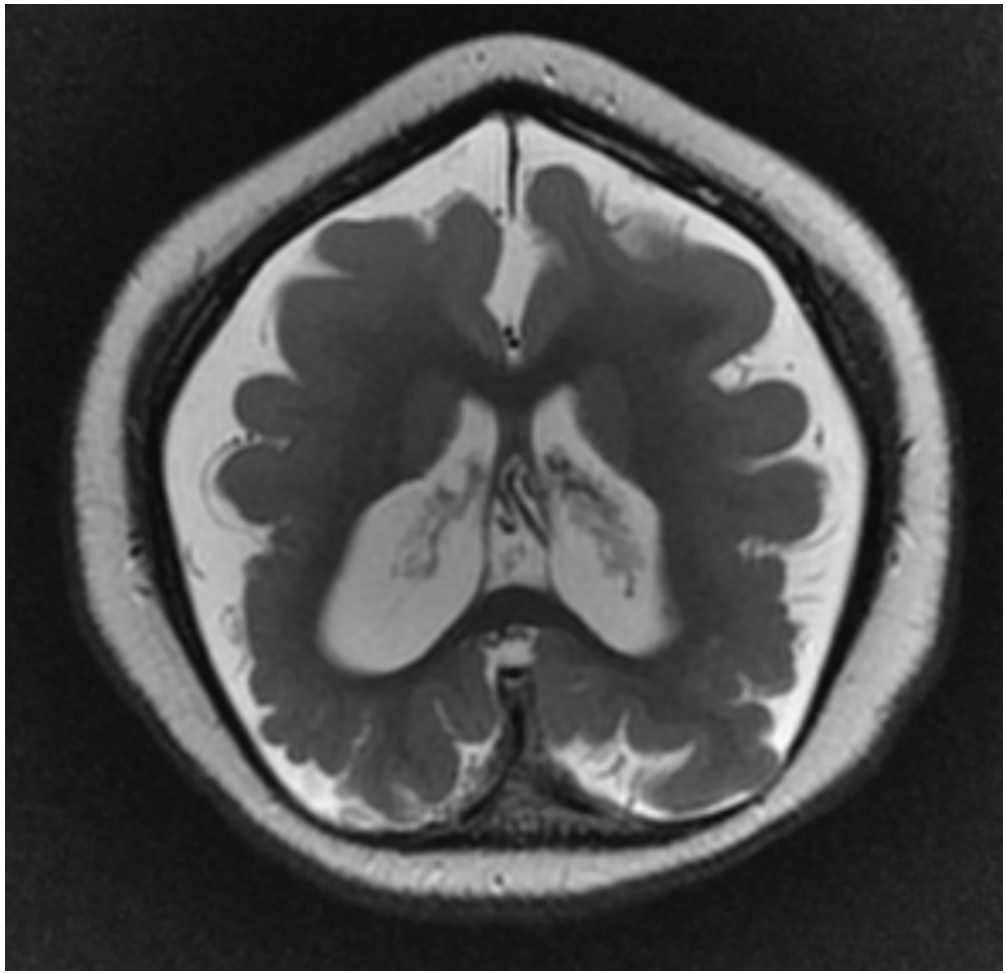
Brain 2012: 135; 1348–1369

# Malformations due to abnormal neuronal migration

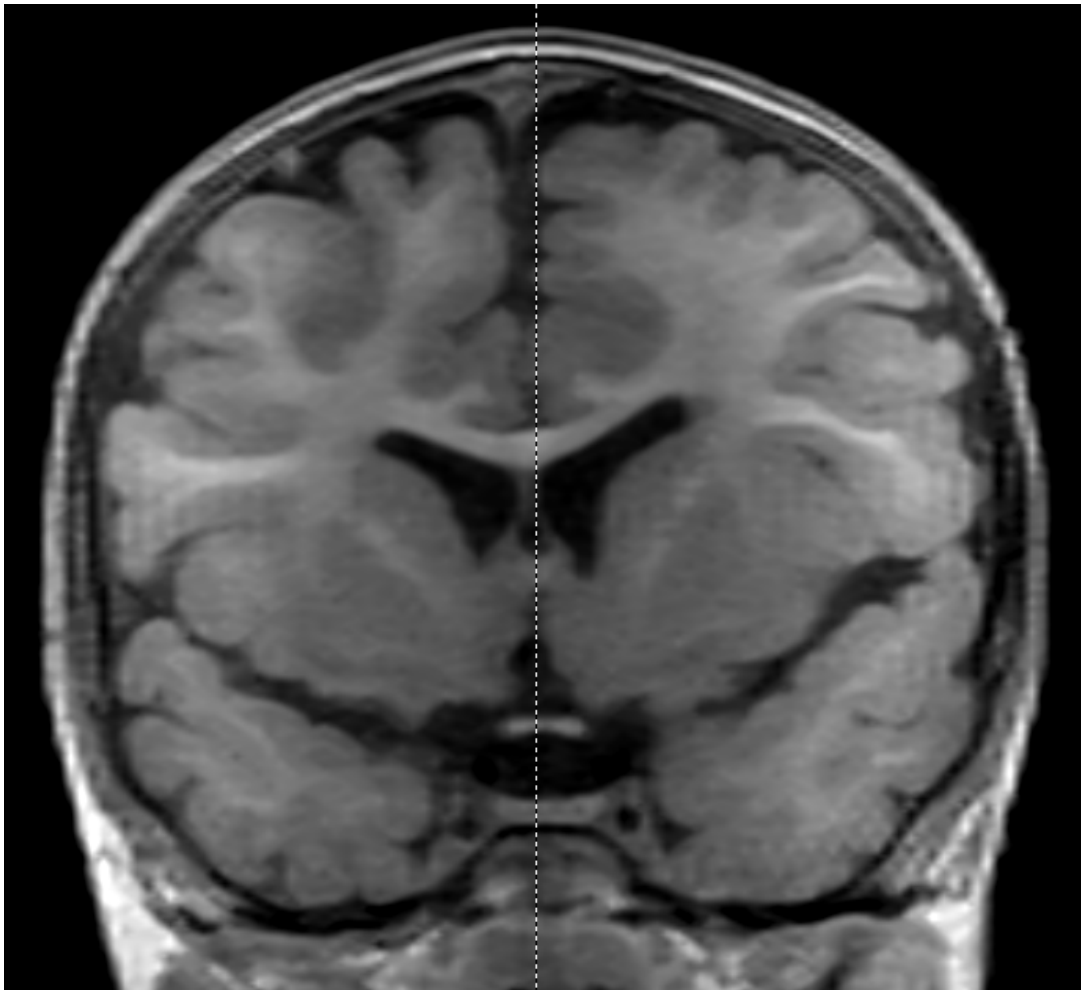
- Nuroependymal abnormalities – periventricular heterotopia
  - chromosomal deletions (Williams), *FLNA* (with ACC)
- Generalized abnormal transmantle migration (LIS/SBH)
  - *DCX* (Xq22.3-q23), *LIS1* (classic 4 layer)
  - *RELN* (7q22), *VLDLR* (9q24)
- Localized abnormal late radial or tangential transmantle migration
  - Subcortical heterotopias, sublobar dysplasia
- Abnormal terminal migration and defects in pial limiting membrane
  - dystroglycan-laminin complex abnormalities, CDG, other cobblestone malformations, fetal alcohol syndrome

Brain 2012: 135; 1348–1369

# Lissencephaly



# SEH – 20 mo with GDD



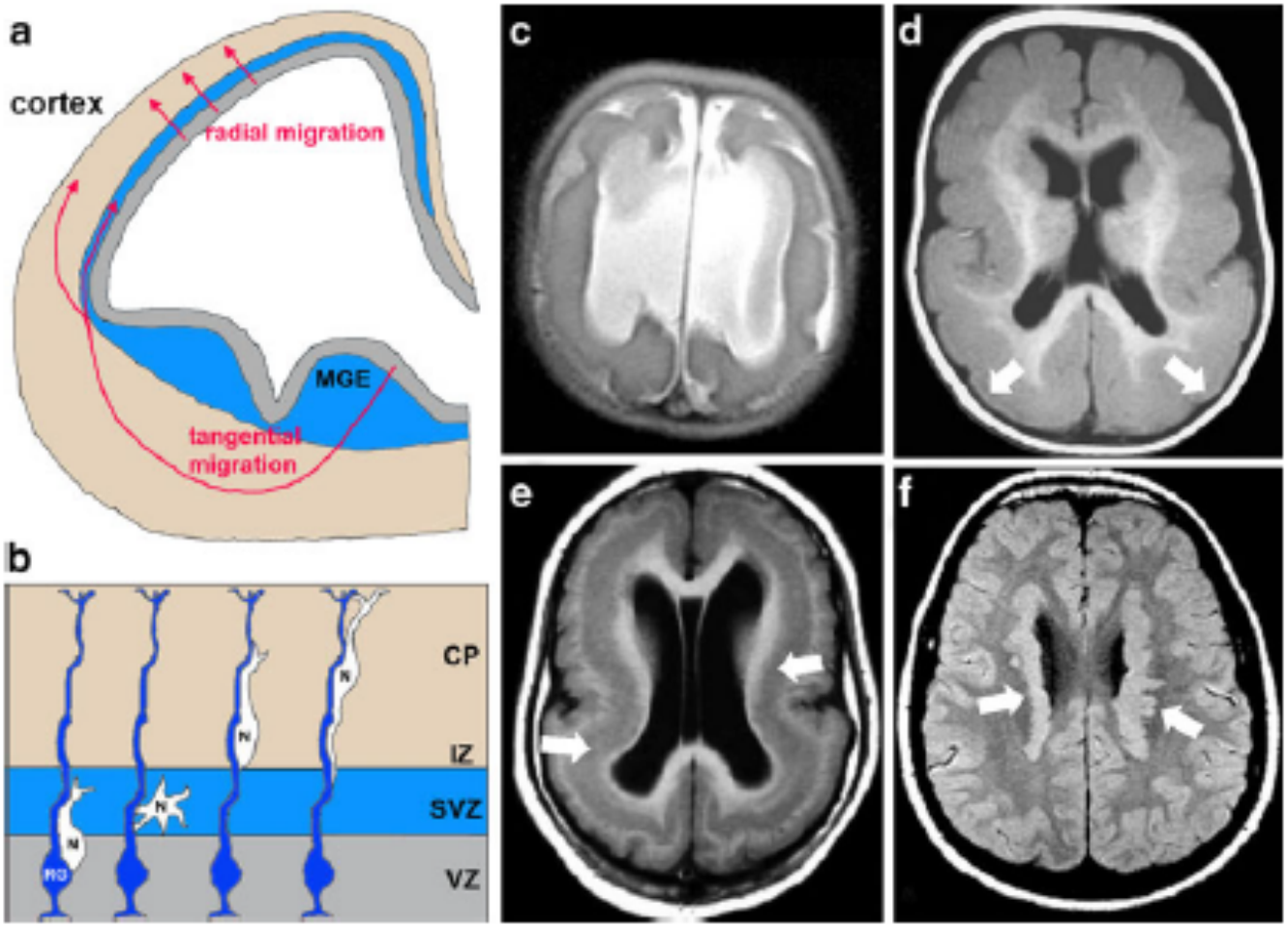



**Fig. 1** Defects in neuronal migration result in cortical malformations. **a** The diagram of the coronal section of the developing cerebral cortex illustrates the migratory pathways of both excitatory neurons (radial) and inhibitory interneurons (tangential). Excitatory neurons and inhibitory neurons arise from the dorsal and ventral regions adjacent to the lateral ventricles, respectively. **b** In the cerebral cortex, newly born excitatory neurons (N) undergo a series of morphologic changes during migration along radial glial progenitors (RG). These alterations in neuronal morphology occur through changes of the cytoskeleton including microtubules and actin. **c** A T2-weighted image of an infant with lissencephaly and agenesis of the corpus callosum is shown. The patient has a mutation in the *ARX* gene. **d** A patient with posteriorly predominant pachygyria (*arrows*) from a *LIS1* mutation. **e** An MRI of a female patient with subcortical band heterotopia (*arrows*) due to a *DCX* mutation. **f** An MRI of a patient with bilateral periventricular nodular heterotopia (*arrows*) due to a *FilaminA* mutation. *CP* cortical plate; *IZ* intermediate zone; *MGE* medial ganglionic eminence; *SVZ* subventricular zone; *VZ* ventricular zone. (MRI panels *adapted from* Guerrini and Filippi [50]; with permission)

# Malformations due to abnormal postmigrational development

- Polymicrogyria
  - Classified by location
  - Syndromes (Adams-Oliver, Joubert, Aicardi)
  - ± schizencephaly/ calcification (vascular, CMV, familial)
- IEM
  - Mitochondrial and pyruvate, NKH
  - Peroxisomal
- FCDs without dysmorphic neurons
- Postmigrational microcephaly
  - Pitt-Hopkins, *FOXG1*, Angelman, Rett

Brain 2012: 135; 1348–1369