Epilepsy Neurogenetics

American Epilepsy Society
Outline

A. Epilepsy etiology

B. Genetic causes of epilepsy

C. Genetic epidemiology of epilepsy

D. Genetic counseling in epilepsy
A. Epilepsy etiology
Etiology of Epilepsy

- Idiopathic (Genetic)
- Stroke
- MR/CP
- Head trauma
- Brain tumor
- Infection
B. Genetic causes of epilepsy
Genetic causes of epilepsy

- **Microscopic: strong polygenic dysfunction**
  - Chromosomal aberations
  - Angelman/ Prader-Willi syndrome – 15q11-13 region (UBE3A gene defect and likely many other genes)

- **Submicroscopic: monogenic-plus defects**
  - small deletions, insertions, point mutations,
Genetic causes of epilepsy:
Submicroscopic genetic defects

1. Defects of neuronal metabolism
2. Defects of network development
3. Defects of membrane and synaptic signaling
Defects of neuronal metabolism

a. Energy deficiency

b. Storage of the metabolic product

c. Toxic effect

d. Dysfunction of neurotransmitter systems

e. Vitamin/Co-factor dependency
Inborn metabolic errors: Energy deficiency

1. Mitochondrial disorders:
   - 20–60% of children w/ mt disorders develop epilepsy (Darin et al. 2001)
   - Myoclonic seizures +/- partial, tonic, clonic, TC: most common
   - MK common
     • ▼ ATP production → unstable membrane potential

MERRF: mt gene for tRNA-Lys
   • Onset ~20yos, progressive MC epilepsy, photosensitivity, and giant SSEP

MELAS: mt gene for tRNA-Leu

Leigh syndrome: mutations in mt or nuclear-encoded subunits of complex I of the mitochondrial respiratory chain

Alpers: nuclear polymerase gamma (POLLG-A) gene
   • hepato-cerebral disorder
   • childhood onset due to
Inborn metabolic errors: Energy deficiency

2. Creatine metabolism disorders:
   • Impaired creatine transport into the brain
   • Impaired creatine synthesis

GAMT deficiency
- Epilepsy: seizures (West sx)
- Dx: ↑ excretion of the guanidino compounds in the urine
- MR spectroscopy shows absent Cr and CrP04 peak
- Tx: Cr suplementation
  - ↓ dietary arginine, supplement ornithine
Inborn metabolic errors:
Storage of the metabolic product

- **Tay-Sachs:**
  - MC, atypical absence and other sz

- **Sialidosis I**

- **NCL (Batten's disease):**
  - sas non specific, associated with dev delay
  - lysosomal enzymes: palmityl protein thioesterase 1 (PPT1/gene (CLN1)), tripeptidylpeptidase I (TPPP/CLN2)
  - CLN3, CLN5, CLN6 and CLN8: mutations in genes encoding proteins of unknown functions.
  - congenital form of NCL (CLN10: deficiency of cathepsin D.

Inborn metabolic errors:
Storage of the metabolic product

Progressive myoclonic epilepsies
Lafora progressive MC epilepsy
Onset late childhood or teenage years
Progressive neurological deterioration
Stimulus sensitive GTC, Absence, and MC seizures
Death in 10 years
Path: intracellular polyglucosan inclusions (brain, liver, skin)

Genetics: 3 loci
EPM2A (laforin): 6q24
NHLRC1 (EPM2B) malin: 6p22
E3 ubiquitin ligase that ubiquitinates and promotes degradation of laforin
EPM2C?
Disorder of glycogen metabolism??
Defects in neuronal metabolisms
Inborn metabolic errors: Toxic effects

1. Urea cycle defects

2. AA disorder
   - PKU
   • MSUD

3. OA disorders
   Methylmalonic, propionic acidemia, glutaric aciduria: if treated → development of szs is preventable

4. Purine and pyrimidine metabolic disorders
Defects in neuronal metabolisms
Inborn metabolic errors: Toxic effects

5. Progressive Myoclonic Epilepsies

EPM1 Unverricht-Lundborg disease

Age of onset 6-16 yrs
Stimulus sensitive MC
TC SZS

Genetics:
AR inheritance
CSTB gene (cystatin B)
Protease Inhibitor (i.e. cathepsins, exact function unknown)
Defects in neuronal metabolisms
Inborn metabolic errors:

- Dysfunction of neurotransmitter systems
- Monoamine metabolism
- Glycine metabolism
- GABA Metabolism
Defects in neuronal metabolisms
Inborn metabolic errors:

Vitamin or Co-factor Dependency

Pyridoxine-dependent epilepsy

- **Typical: early onset**
  - Multiple sz types
  - Prompt response to B6 i.v. 100mg
  - Resistant to treatment with antiepileptic medications
  - Congenital structural brain abnormalities may be present

- **Atypical: late onset <3yoa**
  - No brain abnormalities
  - Sz onset with febrile illness
  - Initial response to AED
  - B6 at 100mg PO QD - response within 1-2 days
## Defects in neuronal metabolisms
### Inborn metabolic errors:

<table>
<thead>
<tr>
<th>Vitamin or Co-factor Dependency</th>
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<tbody>
<tr>
<td><strong>PNPO epilepsy</strong></td>
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<tr>
<td><em>(pyridox(amine phosphate oxidase)</em></td>
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<tr>
<td><strong>PNPO</strong></td>
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<tr>
<td><strong>Pyridoxine phosphate</strong></td>
<td><strong>→</strong></td>
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<tr>
<td>B6 unresponsive epilepsy</td>
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<tr>
<td>Tx: pyridoxal phosphate</td>
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<td><strong>Folinic Acid responsive Szs</strong></td>
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<td>AED resistant ss in newborn</td>
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<td>Trial of folic acid if B6 and pyridoxal phosphate ineffective</td>
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<td><strong>Biotinidase Holocarboxylase deficiency</strong></td>
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<td>Alopecia and dermatitis</td>
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<tr>
<td>Epilepsy onset 3 – 4 mths (infantile spasms)</td>
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<tr>
<td>TX: Biotin 5-20mg/d</td>
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Defects of network development

- Cell proliferation and specification
  - FCD (focal cortical dysplasia)
  - Tubercous sclerosis
- Neuronal migration
  - Lissencephaly
  - Heterotopia
- Late cortical organization
  - Polymicrogyria
### Defects of network development: Tuberous sclerosis

- Multisystem AD
- **Variable penetrance** of clinical findings
- Neurologic symptoms:
  - Epilepsy 20-30% infantile spasms, MR, autism
- Dermatologic
  - Facial angiofibroma
  - Shagreen patch
  - Hypopigmented macules
- Renal
  - Renal angiomyomas
- Cardiac
  - Rhabdomyomas
- Pulmonary
  - Lymphangiomatosis
Defects of network development
Focal Cortical Dysplasia

- Cytoarchitectural similarities to TS

- Higher incidence of mild potentially pathogenic sequence changes in TSC1 gene in cases vs. controls

- Other genes in the downstream cascade involved
  - mTOR kinase and its target
Defects of network development
Lisencephaly

- Defective neuronal migration
- 6 genes: LIS1, DCX, TUBA1A, RELN, VL1DLR, ARX

- Lisencephaly: DCX (males), LIS1, TUBA1A
- Subcortical band heterotopia DCX in females, rarely in males; LIS1
- Miller-Dieker Syndrome (co-deletion LIS1-YWHAE)
- Lissencephaly with cerebellar hypoplasia (REMN, VL1DLR)
- X-linked lisencephaly with abnormal genitalia (ARX)
Defects of membrane and synaptic signaling

- Ion channels
  - Voltage gated: Na, Ca, K, Cl
  - Ligand gated: GABA$_A$R, nicotinic acetylcholine receptor α, β subunits (CHRNA, CHRNAβ)

- Signaling molecules
  - Associated with ion channels
  - Interact with ion channels
# Defects of membrane and synaptic signaling

## Familial Epilepsy Syndromes

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Gene(s)</th>
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<tbody>
<tr>
<td>Benign familial neonatal seizures</td>
<td>KCNQ2, KCNQ3</td>
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<tr>
<td>Benign familial neonatal-infantile seizures</td>
<td>SCN2A</td>
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<tr>
<td>GEFS+, febrile seizures</td>
<td>SCN1A, SCN1B, GABRG2, GABRD</td>
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<tr>
<td>Dravet syndrome</td>
<td>SCN1A, GABRG2</td>
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<tr>
<td>Defects of membrane and synaptic signaling</td>
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<tr>
<td>Familial Epilepsy Syndromes</td>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Genes</th>
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<tbody>
<tr>
<td>Childhood absence epilepsy</td>
<td>GABRG2, CACNA1H</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>GABRA1, FFHC1</td>
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<tr>
<td>Idiopathic generalized epilepsy (variable phenotype)</td>
<td>CLCN2</td>
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<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>CHRNA4, CHRN B2, CHRNA2</td>
</tr>
</tbody>
</table>
## Defects of membrane and synaptic signaling

### Familial Epilepsy Syndromes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>Autosomal dominant partial epilepsy with auditory features</td>
<td>LG11</td>
</tr>
<tr>
<td>Familial mesial temporal lobe epilepsies</td>
<td>4q, 18q, 1q</td>
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<tr>
<td>Familial occipito temporal lobe epilepsy</td>
<td>9q</td>
</tr>
<tr>
<td>Familial partial epilepsy with variable foci</td>
<td>22q12</td>
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<tr>
<td>Partial epilepsy with pericentral spikes</td>
<td>4p15</td>
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</tbody>
</table>
C. Genetic epidemiology of epilepsy
Genetic epidemiology of epilepsy

> 2/3 of all epilepsies genetic

1%: familial: single gene with major effect + genetic and environmental modifiers

99%: sporadic: polygenic (many genes with variable degree of effect + other modifiers)
## Genetic epidemiology of epilepsy

### Febrile seizures

- 3% baseline population prevalence in children 6 months – 6 years old

- Risk factors for familial recurrence of FS
  - Affected sib: 8 12% risk (RR = 3.5)
  - Multiple affected family members: ≤ 50%

- FS and risk of epilepsy later in life
  - 4% at 7 years
  - 7% at 25 years
Risk of an epileptic patient bearing a child with epilepsy.

- Either Parent With Epilepsy: 6%
- Mother With Epilepsy: 8.7%
- Father With Epilepsy: 2.4%
- Either Parent With Generalized Seizures: 2.3-5.1%
- Either Parent With Absence Seizures: 9%
- Either Parent With Partial Seizures: 2.7%

1% Baseline Risk in General Population by 20 years of age.

Adapted from Hauser WA, Hesdorffer DC. Facts about Epilepsy. Landover, Epilepsy Foundation of America, 1990.
D. Genetic counseling in epilepsy
Genetic counseling in epilepsy

• Straightforward:
  • chromosomal disorders
  • 100% penetrant epilepsy syndromes with AD, AR, XL inheritance

• Almost straightforward:
  • de novo mutations in familial epilepsy syndromes with incomplete penetrance (i.e. Dravet syndrome)
  • Consider germline mosaicism

• Complicated:
  • Familial epilepsy syndromes with incomplete penetrance
  • Sporadic epilepsies
<table>
<thead>
<tr>
<th>Genetic counseling in Epilepsy</th>
<th>Important questions to ask</th>
</tr>
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<tbody>
<tr>
<td>• Seizure type(s)</td>
<td></td>
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<tr>
<td>• Seizure triggers</td>
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<tr>
<td>• Epilepsy risk factors (CNS insult, CNS infections, etc)</td>
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<tr>
<td>• Age of onset</td>
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<tr>
<td>• Family history of epilepsy in the immediate AND extended family</td>
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<tr>
<td>• Presence of neurological dysfunction other than seizures</td>
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# Recommended reading


4. Winawer MR and Shinnar S. *Genetic Epidemiology of Epilepsy or What Do We Tell Families*.

