Impact of Genetic Testing in Epilepsy and its Treatment

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Objectives

• Describe typical presentations of pediatric epilepsy syndromes and indications for genetic testing.

• Discuss impact of genetic diagnosis on the management of pediatric epilepsy.
Epilepsy Genetics

- ~approximately 150,000 new cases of epilepsy in the USA each year, and onset highest in children and older adults.1
- ~1800 members of the Child Neurology Society
- ~1600 certified clinical geneticists in USA

Epilepsy Genetics in the Clinic

- Prognosis and Diagnosis
  - Counselling parents
  - Limit invasive or unnecessary testing

- Treatment
  - Choosing anticonvulsants

- Precision medicine
  - Understanding pathogenesis and development of novel treatments

- Paradigm shift
  - de novo, not inherited, mutations most important for epileptic encephalopathy
Causes of Epilepsy in Infancy

- **Genetic/Metabolic**
  - Single-gene mutations (e.g. SCN1A, SLC2A1, KCNQ2)
  - Chromosome abnormalities (e.g. Trisomy 21)
  - Mitochondrial diseases (e.g. POLG1)

- **Structural**
  - Malformations of cortical development
  - Infection (e.g. meningitis, encephalitis)
  - Perinatal insults (hypoxic ischemic encephalopathy, intraventricular hemorrhage, stroke)
  - Neurocutaneous syndromes (e.g. Tuberous Sclerosis Complex)
  - Neoplasm
  - Trauma

- **Unknown**

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**Figure 1** Advances in understanding the causes of epilepsy

- Thomas, R. H. & Berkovic, S. F. (2014) The hidden genetics of epilepsy—a clinically important new paradigm
Types of Genetic Testing

- **Karyotype**
  - Down syndrome
  - Ring chromosome 20
- **CGH Microarray**
  - First step in epilepsy with intellectual disability
- **Next-generation sequencing panel**
  - Focused (70-400 genes)
- **HLA typing**
  - Hypersensitivity reaction to carbamazepine
- **Whole exome sequencing**
  - Trios (parents and child)
Classification of the Epilepsies: 2010
Electroclinical Epilepsy Syndromes

- Age of onset
- Development
  - (examination)
- Seizure type
- EEG pattern
- Prognosis
- Management
Distribution of epilepsy diagnoses overall and by age
Groups of causes: “genetic,” “structural-metabolic,” and “unknown”

<table>
<thead>
<tr>
<th>Old Term and Definition</th>
<th>New Term and Concept/Definition</th>
<th>Rationale for New Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>idiopathic: No underlying cause other than a possible hereditary predisposition exists. Idiopathic epilepsies are defined by age-related onset, clinical and electroencephalographic characteristics, and a presumed genetic etiology.</td>
<td>Genetic: Epilepsy is the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests or the evidence for a central role of a genetic component may come from appropriately designed family studies.</td>
<td>The notion that epilepsy has no cause and that a genetic predisposition can only be presumed is antiquated. Further, the term idiopathic was used for disorders that did not have clear evidence of a genetic basis but were self-limited and had an excellent prognosis and no major associated disability. Thus, idiopathic was used to connote benign.</td>
</tr>
<tr>
<td>Symptomatic: Symptomatic epilepsies and syndromes are considered the consequence of a known or suspected disorder of the CNS.</td>
<td>Structural/metabolic: A distinct structural or metabolic condition or disease has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies.</td>
<td>All epilepsies and seizures are caused by something, thus the definition of symptomatic is circular. In practice it was used to infer an underlying brain lesion and also connote bad outcome. As various genetic encephalopathies have been reported recently, this definition is at odds with the current scientific literature.</td>
</tr>
<tr>
<td>Cryptogenic: Refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic, but the etiology is not known.</td>
<td>Unknown: Meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate or unrecognized disorder.</td>
<td>Many of the formerly cryptogenic epilepsies have been shown to have a genetic basis (eg, Dravet syndrome, autosomal dominant nocturnal frontal lobe epilepsy). Rather than feign knowledge about a symptomatic cause, the preference is to say that the cause is unknown.</td>
</tr>
</tbody>
</table>

The 2010 Revised Classification of Seizures and Epilepsy.
Berg, Anne; Millichap, John

DOI: 10.1212/01.CON.0000431377.44312.9e
Genes with treatment implications

- **Established**
  - *SCN1A*
    - avoid carbamazepine
  - *ALDH7A1*
    - pyridoxine
  - *PNPO*
    - pyridoxal-5-phosphate
  - *SLC2A1*
    - ketogenic diet
  - *TSC1/2*
    - vigabatrin
  - *CHRNA2*
    - carbamazepine
  - *POLG1*
    - avoid valproate

- **What’s new?**
  - *KCNQ2*
    - ezogabine
  - *KCNT1*
    - quinidine
  - *GRIN2A*
    - memantine
  - *SCN2A*
    - carbamazepine
  - *SCN8A*
    - carbamazepine
  - *PCDH19*
    - levetiracetam
3 Very Valuable Components Found in the Routine EEG

• What is the EEG Background?
  – Normal
  – Slowed
    • Focal
    • Diffuse

• What is the Morphology of interictal epileptiform activity?
  – Stereotyped-> familial
  – Pleomorphic-> structural

• What is the Topography of the Interictal epileptiform activity?
  – Focal
  – Multifocal
  – Generalized

Courtesy Doug Nordli
## Epilepsy EEG Patterns

<table>
<thead>
<tr>
<th>Spikes</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. None or Infrequent</td>
<td>Normal</td>
</tr>
<tr>
<td>2. Stereotyped <em>generalized</em></td>
<td>Normal</td>
</tr>
<tr>
<td>3. Stereotyped <em>focal or multifocal</em></td>
<td>Normal</td>
</tr>
<tr>
<td>4. Pleomorphic <em>multifocal &amp; diffuse</em></td>
<td>Diffusely Slowed</td>
</tr>
<tr>
<td>5. Pleomorphic <em>focal</em></td>
<td>Focal slowing</td>
</tr>
</tbody>
</table>
### Electroclinical Syndromes

<table>
<thead>
<tr>
<th>EEG FEATURES</th>
<th>NEONATAL</th>
<th>INFANCY</th>
<th>CHILDHOOD</th>
<th>ADOLESCENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal</td>
<td>- Benign familial neonatal epilepsy</td>
<td>- Benign familial infantile epilepsies</td>
<td>- Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>- AD with auditory features</td>
</tr>
<tr>
<td>2. Generalized stereotyped spikes; normal background</td>
<td>- No recognized syndromes</td>
<td>- Myoclonic epiphenomena</td>
<td>- Myoclonic atonic epilepsy</td>
<td>- AD temporal lobe</td>
</tr>
<tr>
<td>3. Focal/Multifocal Stereotyped Spikes; Normal Background</td>
<td>- No recognized syndromes</td>
<td>- <strong>Febrile Seizures</strong></td>
<td>- Myoclonic atonic epilepsy</td>
<td>- Juvenile absence</td>
</tr>
<tr>
<td>4a. Multifocal Spikes; Background Slowing</td>
<td>- No recognized syndromes</td>
<td>- <strong>Febrile Seizures</strong></td>
<td>- Panayiotopoulos syndrome</td>
<td>- Juvenile myoclonic</td>
</tr>
<tr>
<td>4b. Multifocal spikes, discontinuity, background slowing</td>
<td>- EME (Aicardi) - EIEE (Ohtahara)</td>
<td>- Dravet; EFMR - Migrating focal seizures - Non-Progressive Myoclonic Status</td>
<td>- Landau Kleffner Syndrome - Continuous Spike Wave Sleep</td>
<td>- With frontal foci</td>
</tr>
<tr>
<td>5. Focal pleomorphic spikes; focal slowing/attenuation</td>
<td>- West syndrome - Late Infantile Epileptic Encephalopathy</td>
<td>- Lennox-Gastaut Syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Nonsyndromic Epilepsies

- Epilepsies due to focal structural lesions
- Can have homotopic EEG foci
# Role of Genetics Based Upon EEG Findings

<table>
<thead>
<tr>
<th>NAME</th>
<th>EEG BACKGROUND</th>
<th>SPIKES</th>
<th>GENETICS</th>
<th>GENETIC TESTING CLINICALLY USEFUL</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAMILIAL EPILEPSIES</strong></td>
<td>Normal</td>
<td>NONE</td>
<td>Autosomal Dominant</td>
<td>+/-</td>
<td>Mostly Favorable</td>
</tr>
<tr>
<td><strong>BCSSS</strong></td>
<td>Normal</td>
<td>FOCAL/MULTIFOCAL AND STEREOTYPED</td>
<td>SPIKES ARE STRONGLY GENETIC; EPILEPSY TENDENCY IS NOT</td>
<td>NO</td>
<td>VERY FAVORABLE</td>
</tr>
<tr>
<td><strong>GENETIC GENERALIZED EPILEPSIES</strong></td>
<td>Normal</td>
<td>GENERALIZED AND STEREOTYPED</td>
<td>SPIKES ARE OFTEN AD; EPILEPSY TENDENCY IS COMPLEX</td>
<td>NO</td>
<td>FAVORABLE, THOUGH SOME REQUIRE LONG TREATMENT</td>
</tr>
<tr>
<td><strong>EPILEPTOGENIC ENCEPHALOPATHIES</strong></td>
<td>SLOWED</td>
<td>MULTIFOCAL AND PLEOMORPHIC</td>
<td>MIXED</td>
<td>YES</td>
<td>UNFAVORABLE</td>
</tr>
<tr>
<td><strong>SEVERE EPILEPTIC ENCEPHALOPATHIES</strong></td>
<td>SLOWED, DISORGANIZED, AND DISCONTINUOUS</td>
<td>MULTIFOCAL AND PLEOMORPHIC</td>
<td>USUALLY DE NOVO, RARELY RECESSIVE</td>
<td>YES</td>
<td>SEVERE</td>
</tr>
<tr>
<td><strong>FOCAL STRUCTURAL</strong></td>
<td>FOCAL SLOWING/ATTENUATION</td>
<td>FOCAL PLEOMORPHIC</td>
<td>NONE</td>
<td>NO</td>
<td>MIXED</td>
</tr>
<tr>
<td>NAME</td>
<td>EXAMPLES</td>
<td>BACKGROUND</td>
<td>SPIKES</td>
<td>GENETICS</td>
<td>CLINICAL TESTING USEFUL IF NO OTHER CAUSE IDENTIFIED?</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>------------</td>
<td>---------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>FAMILIAL EPILEPSIES</td>
<td>BFNC BFIC ADNFLE</td>
<td>NORMAL</td>
<td>NONE</td>
<td>AUTOSOMAL DOMINANT</td>
<td>IN SELECTED CASES- SPECIFIC GENES</td>
</tr>
<tr>
<td>BCSSS</td>
<td>PS BREC</td>
<td>NORMAL</td>
<td>FOCAL/MULTIFOCAL AND STEREOTYPED</td>
<td>SPIKES- AD EPILEPSY- &lt;5%</td>
<td>NO</td>
</tr>
<tr>
<td>GENETIC GENERALIZED</td>
<td>BMEI CAE MAE JEAVONS JAE JME</td>
<td>NORMAL</td>
<td>GENERALIZED AND STEREOTYPED</td>
<td>SPIKES- AD; EPILEPSY ~30%</td>
<td>NO</td>
</tr>
<tr>
<td>EPILEPTOGENIC ENEPHALOPATHIES</td>
<td>MIGRATING FOCAL DRAVET EFMR MYOCCLONIC STATUS</td>
<td>SLOWED</td>
<td>MULTIFOCAL AND PLEOMORPHIC</td>
<td>MIXED; MANY DE NOVO</td>
<td>YES- CMA OR SPECIFIC GENES, EPILEPSY PANEL, THEN EXOME</td>
</tr>
<tr>
<td>SEVERE EPILEPTIC ENCEPHALOPATHIES</td>
<td>EME EEEE WS LIEE LGS</td>
<td>SLOWED, DISORGANIZED AND DISCONTINUOUS</td>
<td>MULTIFOCAL AND PLEOMORPHIC</td>
<td>MOSTLY DE NOVO</td>
<td>YES- CMA, OR SPECIFIC GENES, EPILEPSY PANEL THEN EXOME</td>
</tr>
<tr>
<td>NON-SYNDROMIC DUE TO STRUCTURAL LESIONS</td>
<td>MTS RASMUSSEN GELASTIC</td>
<td>FOCAL SLOWING/ATTENUATION</td>
<td>FOCAL AND PLEOMORPHIC</td>
<td>LITTLE ROLE</td>
<td>NO</td>
</tr>
</tbody>
</table>
Neonatal-onset Epilepsy Syndromes

• Benign familial neonatal epilepsy (BFNE)

• Early Myoclonic Epilepsy (EME)

• Ohtahara syndrome (Early infantile epileptic encephalopathy, EIEE)
Benign Familial Neonatal Epilepsy (BFNE)
Rett and Teubel, 1964

- Description of four generation family with 9 individuals with BFNC
- Seizure onset in the first week of life and occurred multiple times daily
- Seizures consisted of stiffening and cyanosis
- Seizures stopped within several weeks
- 3/9 developed seizures later in childhood
Benign Familial Neonatal Epilepsy

• Onset of brief, multifocal, tonic or clonic seizures, +/- apnea during the first week of life.

• Seizures may be treated briefly, but usually self-resolve within several months.

• Normal neurologic examination, normal EEG, and negative evaluation for another etiology of the seizures.

• Prognosis is good (10% seizure recurrence) with usually normal developmental outcome.
Neonatal Encephalopathy:
EME & Ohtahara syndrome
# EME vs Ohtahara syndromes

<table>
<thead>
<tr>
<th></th>
<th>Ohtahara (EIEE)</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures</strong></td>
<td>Tonic spasms</td>
<td>Myoclonus</td>
</tr>
<tr>
<td></td>
<td>Focal seizures</td>
<td>focal seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonic spasms</td>
</tr>
<tr>
<td><strong>Major Etiology</strong></td>
<td>Lesional</td>
<td>Genetic or Metabolic</td>
</tr>
<tr>
<td><strong>Burst-suppression</strong></td>
<td>continuous in sleep and wake</td>
<td>Accentuated in sleep</td>
</tr>
<tr>
<td><strong>Bursts</strong></td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td><strong>Suppression</strong></td>
<td>Shorter</td>
<td>Longer</td>
</tr>
<tr>
<td><strong>→ West syndrome</strong></td>
<td>~75%</td>
<td>Commonly atypical form</td>
</tr>
</tbody>
</table>

Ohtahara, Epilepsy Res, 2006
Neonatal Encephalopathy: Case

- Seizure onset at 1 day of age with rhythmic twitching of face and jerking of his extremities.
- Seizures initially responded to phenobarbital.
- Neonatal EEG showed burst suppression
Initial tonic seizures
4b. Epileptic Encephalopathy

Diagram showing:
- Underlying Cause
- Epilepsy
- Encephalopathy

Courtesy Doug Nordli
Evaluation of Early Onset Epileptic Encephalopathy in 2010

Table 2. Etiologic differential diagnosis for infantile spasms

<table>
<thead>
<tr>
<th>History</th>
<th>Neuroimaging/MRI</th>
<th>Metabolic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxic-Ischemic Encephalopathy</td>
<td>Tuberous Sclerosis</td>
<td>Pyridoxine Dependent Seizures</td>
</tr>
<tr>
<td>Perinatal HIE</td>
<td>Aicardi Syndrome</td>
<td>Phenylketonuria</td>
</tr>
<tr>
<td>Near Miss SIDS</td>
<td>Cortical Dysplasias</td>
<td>Maple Syrup Urine Disease</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>Lissencephaly</td>
<td>Biotinidase Deficiency</td>
</tr>
<tr>
<td>Near Drowning</td>
<td>Pachygyria</td>
<td>Menkes Disease</td>
</tr>
<tr>
<td>Maternal Toxemia</td>
<td>Hemimegalencephaly</td>
<td>Hyperammonemia disorders</td>
</tr>
<tr>
<td>Trauma</td>
<td>Band Heterotopia</td>
<td>Non-ketotic Hyperglycinuria</td>
</tr>
<tr>
<td>Encephalitis (usually Herpes)</td>
<td>Focal Cortical Dysplasia</td>
<td>Leigh Disease</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Porencephaly</td>
<td>Krabbe Disease</td>
</tr>
<tr>
<td>Cerebral Abscess</td>
<td>Hypoxic-Ischemic Encephalopathy</td>
<td>ARX and other emerging genes</td>
</tr>
<tr>
<td>Transplacental Infections</td>
<td>Tumor</td>
<td>Others as indicated by patient course</td>
</tr>
<tr>
<td>Post Cardiac Surgery</td>
<td>AVM</td>
<td></td>
</tr>
<tr>
<td>Neonatal Hypoglycemia</td>
<td>Stroke</td>
<td></td>
</tr>
</tbody>
</table>

Physical/Neurological Exam

- Neurocutaneous Disorders
- Tuberous Sclerosis
- Neurofibromatosis
- Sebaceous Nevus Syndrome
- Incontinentia Pigmenti
- Sturge-Weber Syndrome
- Epidermal Nevus Syndrome
- Hydrocephalus (+Imaging)
- Miller-Dieker Syndrome (+ Imaging)
- Down Syndrome
- Menkes Disease

*Hypoxic-ischemic encephalopathy; ^Sudden infant death syndrome; ①Arteriovenous malformation; ②ARX ariless-related homeobox.

Table courtesy of W.D. Shields, MD.
Case Summary of Clinical Course

- Extensive initial evaluation including MR neuroimaging was negative.

- Evolved to infantile spasms and hypsarhythmia by 2 months old.

- Epileptic spasms and brief tonic seizures remain refractory to multiple treatment trials at 3 years old.

- Developmental outcome: Profound intellectual disability, quadriplegia, and diffuse hypotonia.
Prior Anticonvulsants and Treatments

| 1. Phenobarbital          | 9. Clobazam            |
| 2. Fosphenytoin          | 10. Levetiracetam      |
| 3. ACTH                  | 11. Divalproex         |
| 4. Pyridoxine            | 12. Ketogenic diet     |
| 5. Topiramate            | 13. L-serine           |
| 7. P-5-P                 | 15. Gabapentin         |
| 8. Vigabatrin            |                        |
KCNQ2 DNA Sequencing

Interpretation
This test detected a DNA sequence variant whose clinical significance is unknown (see details in Comments section).

Technical Results
DNA Variant 1: Transition C > T
Nucleotide Position: 821
Codon: 274
Amino Acid Change: Threonine > Methionine
Variant Type: Variant of unknown significance

No other abnormal DNA sequence variants were identified in the remainder of the coding sequence or intron/exon junction.

Comments
Most Significant Result: This test detected a DNA sequence variant of unknown clinical significance (KCNQ2 c.821 C>T), but the following data indicate that this variant may be more likely pathogenic than benign:

Variant: KCNQ2 c.821 C>T (p.Thr274Met)
KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

Sarah Weckhuysen, MD,1,2,3 Simone Mandelstam, MB ChB,4,5 Arvid Suls, PhD,1,2 Dominique Audenaert, PhD,1,2,6 Tine Deconinck, MSc,1,2 Lieve R.F. Claes, PhD,1,2 Liesbet Deprez, PhD,1,2 Katrien Smets, MD,1,2,7 Dimitrina Hristova, MD,8 Iglika Yordanova, MSc,9 Albena Jordanova, PhD,1,2 Berten Ceulemans, MD, PhD,2,10 An Jansen, MD, PhD,11,12 Danièle Hasaerts, MD,11 Filip Roelens, MD,13 Lieven Lagae, MD, PhD,14 Simone Yendle, BSc (Hons),15 Thorsten Stanley, MD,16 Sarah E. Heron, PhD,17 John C. Mulley, PhD,18,19 Samuel F. Berkovic, MD, FRS,15 Ingrid E. Scheffer, MBBS, PhD,4,15,20 and Peter de Jonghe, MD, PhD1,2,7

Objective: KCNQ2 and KCNQ3 mutations are known to be responsible for benign familial neonatal seizures (BFNS). A few reports on patients with a KCNQ2 mutation with a more severe outcome exist, but a definite relationship has not been established. In this study we investigated whether KCNQ2/3 mutations are a frequent cause of epileptic encephalopathies with an early onset and whether a recognizable phenotype exists.

Methods: We analyzed 80 patients with unexplained neonatal or early-infantile seizures and associated psychomotor retardation for KCNQ2 and KCNQ3 mutations. Clinical and imaging data were reviewed in detail.

Results: We found 7 different heterozygous KCNQ2 mutations in 8 patients (8/80; 10%); 6 mutations arose de novo. One parent with a milder phenotype was mosaic for the mutation. No KCNQ3 mutations were found. The 8 patients had onset of intractable seizures in the first week of life with a prominent tonic component. Seizures generally resolved by age 3 years but the children had profound, or less frequently severe, intellectual disability with motor impairment. Electroencephalography (EEG) at onset showed a burst-suppression pattern or multifocal epileptiform activity. Early magnetic resonance imaging (MRI) of the brain showed characteristic hyperintensities in the basal ganglia and thalamus that later resolved.

Interpretation: KCNQ2 mutations are found in a substantial proportion of patients with a neonatal epileptic encephalopathy with a potentially recognizable electroclinical and radiological phenotype. This suggests that KCNQ2 screening should be included in the diagnostic workup of refractory neonatal seizures of unknown origin.
WHAT IS RIKEE?

Rational Intervention for KcnQ2 Epileptic Episodic Lengthy

MY EPILEPSY STORY

The Jack Pribaz Foundation
Elizabeth Pribaz

Epilepsy doi:

Pribaz Foundation in December of 2011. Our mission is to raise awareness and fund research of the KcnQ2 gene. Liz and I didn’t want any other parents to have to feel alone with this diagnosis. We wanted them to have a place...
Neonatal-onset epileptic encephalopathy due to KCNQ2-deficiency

- Initial epilepsy syndrome diagnosis: usually Ohtahara syndrome or EME.

- Onset of tonic seizures in the 1st week of life.

- Seizure frequency diminished over the first few years of life.

- EEG showed burst suppression in the first week of life that gradually evolved to multifocal epileptiform activity.

- In early childhood, most patients have profound cognitive/motor disability with few seizures and little epileptiform activity on EEG.

Extending the KCNQ2 encephalopathy spectrum

• 3 clinical groups

<table>
<thead>
<tr>
<th>Group</th>
<th>A (largest)</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure onset</td>
<td>Severe in newborn</td>
<td>Severe in newborn</td>
<td>Mild and/or later in life</td>
</tr>
<tr>
<td>Seizure control</td>
<td>Poor</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>MRI atrophy</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ID</td>
<td>Severe-profound</td>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
</tr>
</tbody>
</table>
Ezogabine for KCNQ2 Encephalopathy
Mutations in KCNQ2 encephalopathy are clustered in critical gating and pore forming domains.

Tetrameric arrangement of subunits around the ion pore.

Coupling allows voltage-gated opening and closing; EZG binds pore domain.

Millichap and Cooper, Epilepsy Curr. 2012.
Model of dominant negative suppression by KCNQ2 subunits

KCNQ2 homotetramers: 15/16 or 92.5%

KCNQ2-3 heterotetramers 75%
Testing 2 Q2 EE mutations and a known “dominant negative” mutant

- **T274M**
- **G279S**
- **A294V**

Mutations seen in multiple published case series and unpublished US series

**G279S**

Based on homologous KCNQ1 mutation causing LQT. Known dominant negative
2 Q2 EE pore mutations strongly but incompletely suppress currents when co-expressed in 1:1 ratio with wt KCNQ2
2 Q2 EE pore mutations strongly but incompletely suppress currents when co-expressed with wt KCNQ2 and wt KCNQ3

Li Li et al. AES 2013 Poster 3.022 (Monday)
Ezogabine/Retigabine

• 2011: approved by FDA as adjunctive treatment of partial-onset seizures in patients aged 18 years and older.

• 2013: FDA warning regarding eye and skin abnormalities

• Safety screening:
  - ophthalmology exams
  - skin exams
  - urinary frequency monitoring
  - bladder scan
  - EKG
  - routine serum tests
Ezogabine for KCNQ2 Encephalopathy

- 11 patients treated with ezogabine
  - Of 4 treated under 6 mos old, 3 reported improvement in seizures and development
  - 1 treated at 3 yrs old reported improvement in seizures and development
  - 1 had improved alertness and EEG background activity
  - 1 had improvement in development only
  - Side effects were temporary: urinary retention, chromaturia, and somnolence
  - Monitoring did not detect skin or retinal discoloration

Abstract presented AES 2014, publication in preparation
ILAE 2010 Classification

- Neonatal period
  - Benign neonatal convulsions (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome

- Infancy
  - Epilepsy of infancy with migrating partial seizures
  - West syndrome
  - Myoclonic epilepsy in infancy
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in non-progressive disorders

Berg, 2010
Epilepsy of infancy with migrating partial seizures

- **Onset:**
  - birth-7 months old (mean 1 month).

- **Seizures:**
  - Focal motor (eye deviation, eyelid/face jerking, tonic/clonic).
  - Autonomic (apnea, cyanosis, flushing, hiccups).

- **Psychomotor development:**
  - Normal prior to onset of seizures with gradual deterioration.

- **EEG:**
  - Seizures from multiple bilateral foci.

- **Etiology:**
  - $\text{KCN}T1$ more common than $\text{PLCB1, TBC1D24, SCN1A, SCN2A, SLC25A22}$

- **Prognosis:**
  - Highly refractory to anticonvulsants and ketogenic diet.
  - Usually very poor outcome; death within 1-2 years.

Panayiotopoulos, 2010
MPSI due to gain of function in \textit{KCNT1} Treated with quinidine

\textit{KCNT1} encodes alpha subunit of \textit{Na}\textsuperscript+-activated \textit{K} channel

Quinidine acts as a pore blocker

In vitro studies suggested that quinidine normalized \textit{K} conductance

Case: 2 year old treated with quinidine
– Onset of seizures at 10 weeks old and developed clinical epilepsy syndrome diagnosis of MPSI
– Standard metabolic serum and CSF tests unrevealing
– WES revealed heterozygous missense mutation (previously reported with this phenotype)

\textbf{TABLE 2.} Timeline of Treatment and Response

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Patient having 5–20 seizures per day, minimal psychomotor development</td>
</tr>
<tr>
<td>Day 1</td>
<td>Test dose of quinidine initiated</td>
</tr>
<tr>
<td>Day 4</td>
<td>Quinidine increased to 33mg/kg/day</td>
</tr>
<tr>
<td>Day 11</td>
<td>Seizures resolve</td>
</tr>
<tr>
<td>Days 11–53</td>
<td>Patient remains seizure-free, some improvement in psychomotor development</td>
</tr>
<tr>
<td>Day 54</td>
<td>Seizures recur, patient begins having 0–2 seizures/day</td>
</tr>
<tr>
<td>Day 56</td>
<td>Quinidine increased to 42mg/kg/day</td>
</tr>
<tr>
<td>Day 61</td>
<td>Seizures again resolve</td>
</tr>
<tr>
<td>Days 61–180</td>
<td>Patient seizure-free except in the setting of acute infection; patient says first words; quinidine dose weight-adjusted to maintain level of 2–5(\mu)g/ml</td>
</tr>
<tr>
<td>Days 180–210</td>
<td>Patient completely seizure-free; patient says first complete sentence</td>
</tr>
</tbody>
</table>

GRIN2A Epileptic Encephalopathy

- **GRIN2A** encodes the GluN2A subunit of NMDAR
- Initially associated with spectrum of childhood focal epilepsies
- Case: gain-of-function EE
  - Seizure onset at ~2 months old
  - In vitro testing showed the specific mutant-GluN2A was inhibited by memantine, and other NMDA blockers
  - Treatment trial started at 6.5 years old
  - Seizures and interictal epileptiform activity ceased, but there was no cognitive change

Genetic Diagnostic Approach to Early Onset Epilepsy

- EEG shows slowed background with multifocal interictal epileptiform discharges
- History/exam findings: specific testing for suspected diagnosis (e.g. trisomy 21, TSC)

- If no etiology, then MR neuroimaging (with spectroscopy)
- If no etiology, then consider metabolic tests and vitamin trials
- If no etiology, but recognized Epilepsy Syndrome diagnosis
  - Epilepsy specific NGS panels (70-400 genes) or single gene tests
- If no etiology, no recognized Epilepsy Syndrome diagnosis, and/or Epilepsy NGS panel negative
  - Whole exome sequencing
Epilepsy Genetics in the Clinic

• Prognosis and Diagnosis
  – Counselling parents: development, parent support groups
  – Limit invasive or unnecessary testing: LP, muscle biopsy, repeated MRI

• Treatment
  – Choosing anticonvulsants: effective and potentially detrimental

• Precision medicine
  – Understanding pathogenesis: e.g. ezogabine, quinidine, memantine
  – development of novel treatments

• Paradigm shift
  – de novo, not inherited, mutations most important for epileptic encephalopathy: genetic counselling
What is EGI?

- The EGI will create a data repository of clinical exome and genome sequences.
- Data will be reanalyzed every 6 months for novel genetic changes.
- New results will be communicated back to patients via their doctor.
- Data will also be made available to advance epilepsy research.