Epilepsy Genetics: State of the Science and Translation to Clinical Practice

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Conclusions

- Epilepsy precision diagnostics and therapeutics already impact clinical care
- More precision therapies are on the horizon
- Epilepsy precision medicine clinical trials will look very different from traditional epilepsy clinical trials
- Epilepsy genetic testing is clinically indicated (medically necessary) for many patients
Road Map

- Precision diagnostics
- Precision therapeutics
- Epilepsy precision medicine clinical trials
FIG. 1. Schematic diagram of the International Classification of Epilepsies and Epileptic Syndromes.
Etiologic spectrum of the epilepsies
Single gene epilepsies

- Usually present before 3 years of age
  - Early onset epileptic encephalopathies (EOEE)
  - Early life epilepsies (ELE)
- Phenotypic variability and genetic heterogeneity
- Treatment-resistant
- Growing list of genes with confirmed pathogenicity
Epilepsy etiology evaluation

- History, physical exam, EEG, MRI
- Family history
- Karyotype
- Microarray
- Targeted epilepsy gene panel

- Specific genetic diagnosis made in 10-22% of children with EOEE/ELE

- Whole exome sequencing
  - Best ordered in specialized centers
  - Raises diagnostic yield to 40%

◆ Poduri A, Sheidley B et al, Nat Rev Neurol 2014
Road Map

- Precision diagnostics
- Precision therapeutics
- Epilepsy precision medicine clinical trials
Precision therapeutics – now

◆ Begin targeted, effective therapy
  ◆ Glucose transporter deficiency (SLC2A1)
    • Ketogenic diet
  ◆ Pyridoxine dependent epilepsy (ALDH7A1)
    • Pyridoxine (vitamin B6)

◆ Avoid harmful therapy
  ◆ POLG mutations
    • Fatal liver toxicity with Valproate
  ◆ SCN1A mutations
    • Seizures increase with Carbamazepine, Phenytoin

◆ Poduri A, Sheidley B et al, Nat Rev Neurol 2014
Precision therapeutics – emerging

- KCNTI – Quinidine
- KCNQ2 – Ezogabine
- GRIN2A – Memantine
- SCN1A – Clemizole
- DEPDC5 – mTOR inhibitors
The MPSI-KCNT1 story

- Malignant migrating partial seizures of infancy (MPSI): 1995
- Gene Discovery: 2011-present
  - KCNT1 mutations most common cause
- KCNT1 Gene Function: 2003-present
  - Encodes pore-forming alpha subunit of Na+-activated K+ channel
  - Expressed in neurons and cardiac muscle
  - Gain of function mutations
  - Pharmacologic inhibition with Quinidine possible

Quinidine normalizes K+ conductance in mutant KCNT1 channels

30 KCNT1 mutations studied

Milligan CJ et al, Ann Neurol 2014
Case report: 2014
- 3-year old female
- Epilepsy onset at 10 weeks
- MPSI
- KCNT1 mutation
  - c.1283G>A; R428Q
  - 4th report in humans
  - Quinididine responsive in-vitro

### TABLE 2. Timeline of Treatment and Response

<table>
<thead>
<tr>
<th>Day of Treatment</th>
<th>Event</th>
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<tbody>
<tr>
<td>Day 0</td>
<td>Patient having 5–20 seizures per day, minimal psychomotor development</td>
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<tr>
<td>Day 1</td>
<td>Test dose of quinidine initiated</td>
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<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 2–5µg/ml</td>
</tr>
<tr>
<td>Days 180–210</td>
<td>Patient completely seizure-free; patient says first complete sentence</td>
</tr>
</tbody>
</table>
Limitations

- Single case report
- No control group
  - Unplanned “crossover” when family ran out of Quinidine
- Onset of treatment delayed
- Dosing based on Quinidine approval for malaria in children

- Hypothesis-generating example of precision diagnostics and therapeutics
Road Map

- Precision diagnostics
- Precision therapeutics
- Epilepsy precision medicine clinical trials
Precision medicine clinical trial

- Clinical history c/w MPSI
- Documented gain-of-function KCTN1 mutation in in-vitro model
  - (Quinidine responsive in-vitro)
- Cross-over trial of Quinidine vs placebo lasting 2-6 weeks
- Sample size: 10-20 patients
- Primary outcome: % seizure reduction
- Careful cardiac monitoring
Precision therapeutics – emerging

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