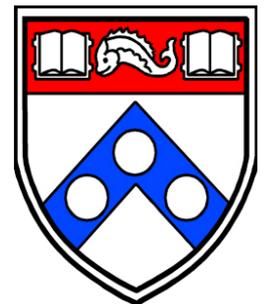


# Epilepsy Genetics: State of the Science and Translation to Clinical Practice

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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**

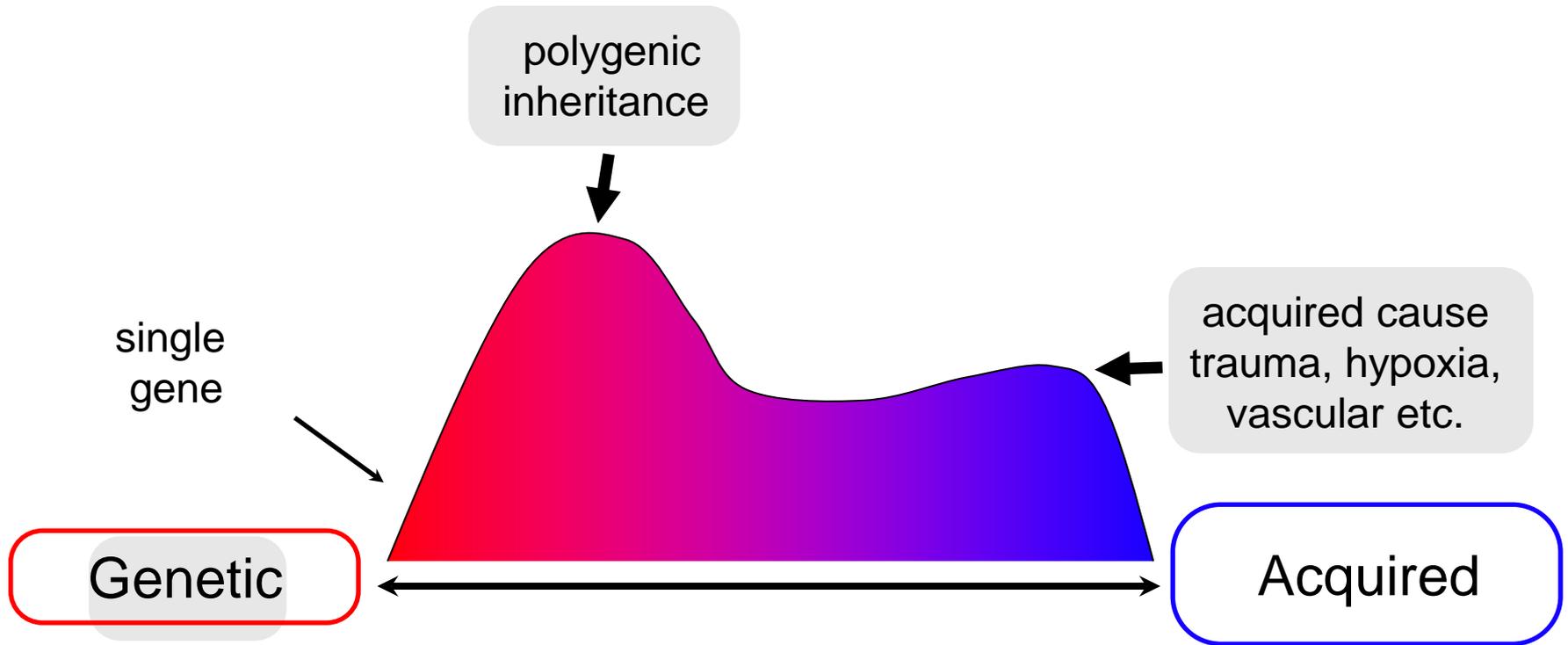
# Road Map

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- ◆ **Precision diagnostics**
- ◆ **Precision therapeutics**
- ◆ **Epilepsy precision medicine clinical trials**



# 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%**

# Road Map

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- ◆ 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

# Precision therapeutics – emerging

- ◆ **KCNT1 – Quinidine**
- ◆ **KCNQ2 – Ezogabine**
- ◆ **GRIN2A – Memantine**
- ◆ **SCN1A – Clemizole**
- ◆ **DEPDC5 – mTOR inhibitors**

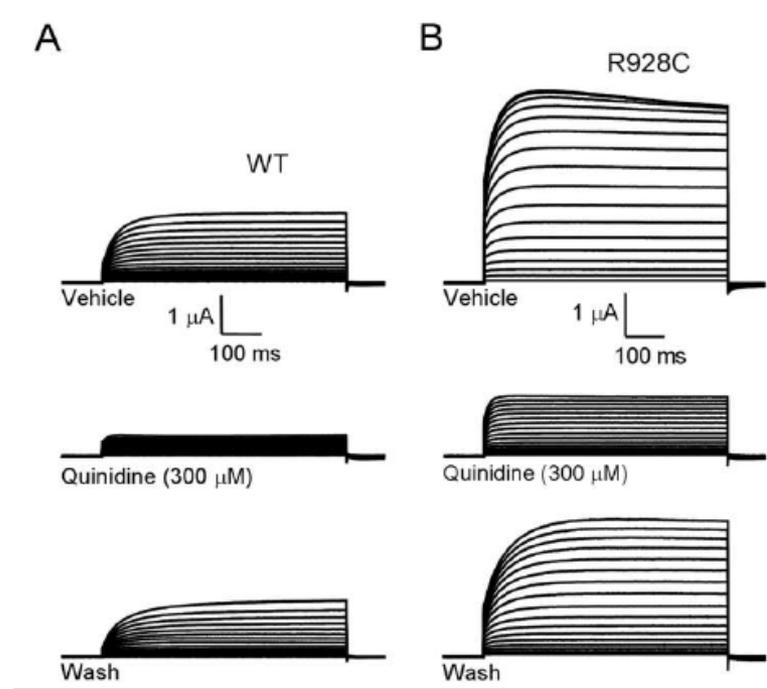
# The MPSI-KCNT1 story

- ◆ 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<sup>+</sup>-activated K<sup>+</sup> channel
  - ◆ Expressed in neurons and cardiac muscle
  - ◆ Gain of function mutations
  - ◆ Pharmacologic inhibition with Quinidine possible

◆ Coppola G et al, Epilepsia 1995; Marsh E et al, Epilepsia 2005; Barcia G et al, Nat Genet 2012; Poduri A et al, Ann Neurol 2013; Yuan A et al, Neuron 2003; Yang B et al, Neuropharm 2006

# KCNT1 and Quinidine – in-vitro

- ◆ Quinidine normalizes K<sup>+</sup> conductance in mutant KCNT1 channels
- ◆ 30 KCNT1 mutations studied



# KCNT1 and Quinidine – patient

- ◆ Case report: 2014
  - ◆ 3-year old female
  - ◆ Epilepsy onset at 10 weeks
  - ◆ MPSI
  - ◆ KCNT1 mutation
    - c.1283G>A; R428Q
    - 4<sup>th</sup> report in humans
    - Quinidine responsive in-vitro



# Response to Quinidine

TABLE 2. Timeline of Treatment and Response

| Day of Treatment | Event   |
|------------------|---|
| Day 0            | Patient having 5–20 seizures per day, minimal psychomotor development   |
| Day 1            | Test dose of quinidine initiated  |
| Day 4            | Quinidine increased to 33mg/kg/day  |
| Day 11           | Seizures resolve  |
| Days 11–53       | Patient remains seizure-free, some improvement in psychomotor development   |
| Day 54           | Seizures recur, patient begins having 0–2 seizures/day  |
| Day 56           | Quinidine increased to 42mg/kg/day  |
| Day 61           | Seizures again resolve  |
| Days 61–180      | 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 |
| Days 180–210     | Patient completely seizure-free; patient says first complete sentence   |

# 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

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- ◆ **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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