Translational Research Symposium: Epilepsy Benchmarks: Major Advances
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Epilepsy Benchmarks: Major Advances

December 1, 2012

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University of California San Francisco

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University of Utah
Disclosure

• Daniel Lowenstein, MD discloses receiving support as Consulting/Advisory Board Activity from UCB Pharma.

• Karen Wilcox, PhD has nothing to disclose.
Learning Objectives

• Recognize genetic epilepsies and understand the presumptive mechanisms that underlie conditions such as astatic myoclonic epilepsy and that may contribute to comorbidities such as autism. When managing such patients, address both the mechanism of the epilepsy and the expected comorbidities.

• Review data concerning cell based therapies in models of intractable epilepsy that may provide new insights into novel approaches for correcting network dysfunction in epilepsy.

• Use state-of-the-art EEG technologies to improve seizure classification and localization.
Agenda

- Role of CNTNAP2 in Epilepsy, Neuronal Migration Abnormalities, and Core Autism-related Deficits
  Brett Abrahams, PhD
- Using Multi-electrode Array Recordings to Detect Unrecognized Electrical Events in Epilepsy
  Catherine Schevon, MD, PhD
- Embryonic MGE Cells as a Treatment for Epilepsy
  Scott C. Baraban, PhD
- Glucose Transporter 1 Deficiency as a Treatable Cause of Myoclonic Astatic Epilepsy
  Saul Mullen, MD
The Epilepsy Research Benchmarks

• Benchmarks Area I: Prevent epilepsy and its progression.
• Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy
• Benchmarks Area III: Prevent, limit and reverse the comorbidities associated with epilepsy and its treatment.
Role of *CNTNAP2* in Epilepsy, Neuronal Migration Abnormalities, and Core Autism-related Deficits

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Disclosure

There is no conflict of interest with any commercial organization regarding the material discussed in this presentation.
Learning Objectives

• Autism as a common neurobehavioral comorbidity in epilepsy

• Characterization of their potential common underlying pathophysiology

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NINDS Epilepsy Research Benchmarks

Benchmarks Area I: Prevent epilepsy and its progression

   A. Identify as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious)

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

Benchmarks Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment

   B2. Develop and validate at least one animal model of a co-morbidity of epilepsy
The ASDs: an Overview

Core Impairments:
- Language Use
- Social Behavior
- Restricted / Repetitive Behaviors

ASDs are common ~ 1/88

ASD frequency is more common in males than in females (1 in 54 boys)
Autism and Epilepsy

• Common cause or causal relationship?
Risk factors of epilepsy in ASD

IQ

Age (bimodal)

Genetics

Sex?

Regression?

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Disease-related genetic variation fails to respect clinical boundaries

Epilepsies
- Strauss et al., 2006, *NEJM*
- Lai et al., 2010, *Lancet Neurology*
- Lesca et al., 2012, *Epilepsia*

Intellectual Disability
- Strauss et al., 2006, *NEJM*

Schizophrenia / Bipolar Disorder
- Wang et al., 2010, *Schizophr Res.*

Autism Spectrum Disorders
- Alarcon et al., 2008, *AJHG*
- Arking et al., 2008, *AJHG*
- Bakkaloglu et al., 2008, *AJHG*

Language Impairment
- Vernes et al., 2008, *NEJM*
- Alarcon et al., 2008, *AJHG*

Tourette Syndrome
- Verkerk et al., 2003, *Genomics*
The CNTNAP2 gene and ASD

Peñagarikano and Geschwind
Cortical Dysplasia and Focal Epilepsy Syndrome (CDFE)

- Epileptic seizures
- Language regression
- Hyperactivity (80%)
- Autism (70%)

Strauss et al., NEJM, 2006
The CNTNAP2 protein (CASPR2)

Poliak and Peles
Nat Rev, 2003
<table>
<thead>
<tr>
<th>Behavioral domain</th>
<th>Mouse behavioral test</th>
<th>Cntnap2 mutants</th>
</tr>
</thead>
<tbody>
<tr>
<td>General activity</td>
<td>Open field</td>
<td>Increased activity</td>
</tr>
<tr>
<td>Home cage</td>
<td>Nesting</td>
<td>Deficit</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>Rotarod</td>
<td>Improved</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Light-dark box</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensory reactivity</td>
<td>Hot plate</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Startle response</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensorimotor integration</td>
<td>Prepulse inhibition</td>
<td>Normal</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>Morris water maze (MWM)</td>
<td>Normal</td>
</tr>
<tr>
<td>Repetitive behavior, stereotypies, resistance to change</td>
<td>Grooming</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>T maze</td>
<td>Deficit</td>
</tr>
<tr>
<td></td>
<td>MWM reverse learning</td>
<td>Deficit</td>
</tr>
<tr>
<td>Communication</td>
<td>Ultrasonic vocalization</td>
<td>Decreased</td>
</tr>
<tr>
<td>Social interaction</td>
<td>Juvenile playing</td>
<td>Deficit</td>
</tr>
<tr>
<td></td>
<td>3 chamber social interaction</td>
<td>Deficit</td>
</tr>
</tbody>
</table>
Social behavior

WT vs WT

KO vs KO

Peñagarikano et al.
*Cell, 2011*

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Communication
Repetitive behavior/perseverance

Ultrasonic vocalizations

Grooming

Spontaneous alternation

Peñagarikano et al.
*Cell, 2011*
The *Cntnap2* knockout mouse as a mouse model of ASD and epilepsy

<table>
<thead>
<tr>
<th>Number of animals exhibiting seizures</th>
<th>9 (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals exhibiting seizure-related behaviors</td>
<td></td>
</tr>
<tr>
<td>Scratching</td>
<td>10</td>
</tr>
<tr>
<td>Wet dog syndrome</td>
<td>10</td>
</tr>
<tr>
<td>Number of seizures per mouse</td>
<td>1 - 4</td>
</tr>
<tr>
<td>Total number of seizures observed</td>
<td>19</td>
</tr>
<tr>
<td>Stage 1 (orofacial automatisms)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Stage 2 (clonic head movements)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Stage 3 (clonic forelimb movement)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Stage 4 (rearing)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Stage 5 (clonic/tonic loss of balance)</td>
<td>8 (42%)</td>
</tr>
</tbody>
</table>

Per Racine, 1972
Seizures associated with astrocytosis

Peñagarikano et al. *Cell*, 2011
Reduced neuronal synchrony in *Cntnap2* mutants

Peñagarikano et al.  
*Cell*, 2011
Presence of ectopic neurons in lower cortical layers

Peñagarikano et al.  
Cell, 2011
Neuron birth-dating analysis indicates migration abnormalities

Ang et al.  
PNAS, 2006

Migration deficit

Peñagarikano et al.  
Cell, 2011
Reduced number of GABAergic interneurons

Peñagarikano et al.  
*Cell, 2011*
### Risperidone rescues behavioral anomalies

<table>
<thead>
<tr>
<th>Behavioral Domain</th>
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<th>Cntnap2 mutants</th>
<th>Risperidone treatment</th>
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<tbody>
<tr>
<td>General activity</td>
<td>Open field</td>
<td>Increased</td>
<td>Rescued</td>
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<tr>
<td>Sensory reactivity</td>
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<td>Unchanged</td>
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<td>Increased Deficit</td>
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Risperidone rescues behavioral anomalies
NINDS Epilepsy Research Benchmarks

Benchmarks Area I: Prevent epilepsy and its progression

A. *Mutations in CNTNAP2 can cause epilepsy in patients*

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

Benchmarks Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment

B2. *Mice harboring mutations in CNTNAP2 may be useful in modeling disease*
15q11-13 genomic disease locus prone to rearrangement

BP1-BP2 deletions and duplications implicated in epilepsy, autism, schizophrenia, intellectual disability
Overexpression of CYFIP1 *in vitro* and *in vivo* alters cell size and neurite morphology

CYFIP1 interacts functionally with Fragile X Syndrome protein

Oguro-Ando A *et al.*, Submitted

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Towards function, biomarkers and therapeutics via nationwide recruitment

with Herb Lachman and John Foxe, Albert Einstein

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Conclusions

• ASD and epilepsy are often comorbid

• investigation of pathophysiology will lead towards improved treatment

• Abnormalities in *Cntnap2* KO mice show striking parallels to CDFE & the Autism Spectrum Disorders

• Exploration of functional overlap with separate disease loci (e.g. CYFIP1 at 15q11.2) will prove informative
Acknowledgments

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Asami Oguro

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CART/Autism Center of Excellence Project II
Autism Speaks Translational Fellowship

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... it’s reasonable to expect substantial biological heterogeneity