Dissecting the Neural Circuitry of ASD with Tuberous Sclerosis as a Model

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[PII redacted] Story

- At 20 week *in utero* ultrasound showed “growths” in his heart
- Fetal MRI showed tubers in the brain
- Born at full term
- Started having seizures at 3 months
Today, [Pll redacted] seizures are under good control.

He has significant sleep problems.

[Pll redacted] was diagnosed with autism spectrum disorder.
Why is TSC a good model to study autism?

• ~ 50% of TSC patients are affected with Autism Spectrum Disorder.
• Many of the TSC patients may be diagnosed before birth or at the time of birth.
• Cellular mechanisms aberrant in TSC are beginning to be understood.
• FDA-approved specific inhibitors are available.
What is Tuberous Sclerosis Complex?

• Causes benign tumors in brain, eye, skin, kidneys, and heart

• Usually presents with seizures, intellectual disability, autism

• Incidence: 1:6,000-10,000

• Genes: $TSC1$ and $TSC2$
TSC is a disease of cell size...

Tapon et al., 2001
TSC is a disease of cell size

Growth Factors

Energy Level

\[ \uparrow \text{AMP} \]

AMPK

\[ \uparrow \text{Protein synthesis} \]

\[ \downarrow \text{Cell growth} \]

 Akt

 TSC2

 TSC1

 TSC is a disease of cell size

rheb

mTOR

S6K

S6

Growth Factors

Akt

TSC2

TSC1

rheb

mTOR

S6K

S6
Cortical Tubers and Autism

- Cortical tubers in temporal lobes necessary, but not sufficient (Bolton et al., *Brain* 2002).
- Several studies have failed to show a similar correlation, and others have implicated tubers in the cerebellum as a correlate of autism.
  - Walz et al., *J Child Neurol* 2002
  - Wang et al., *J Child Neurol* 2006
  - Eluvathingal et al., *J Child Neurol* 2006
Hypothesis: Miswiring of neuronal connections may contribute to the pathogenesis of TSC
Cerebellum in Autism and TSC

• Most consistent finding on brain pathology in ASD: reduced Purkinje cell numbers

• 37% of newborns with isolated cerebellar hemorrhage are diagnosed with subsequent ASD (Limperopoulos et al., 2007)

• Hypermetabolism in deep cerebellar nuclei (PET imaging) in TSC patients with ASD vs No ASD (Asano et al., 2001)
Autistic-like Behaviors in TSC Mice

Treatment with rapamycin prevents autistic-like features

Tsai et al., *Nature*, 2012
Autism spectrum disorders: developmental disconnection syndromes
Daniel H Geschwind\(^1\) and Pat Levitt\(^2\)

Current Opinion in Neurobiology
Many of the TSC patients are diagnosed pre- or neo-natally.

Among fetuses or newborns with multiple cardiac tumors, the chances of having TSC is 95%.

Early Detection of Autism in TSC

Can we detect which infants with TSC will develop autism?

1. Neurocognitive assessment of infants
2. Diffusion tensor imaging (MRI)
3. Neurophysiological assessment of face processing and other visual paradigms

In collaboration with Simon Warfield, Shafali Jeste and Chuck Nelson
Diffusion Tensor Imaging
(Peters et al. 2012)

TSC ASD+ 4.9 yo AFA 0.34  TSC ASD- 4.7 yo AFA 0.54  Control 5.3 yo AFA 0.53
TACERN
(TSC Autism Center of Excellence Research Network)

Boston Children’s Hospital

U01 NS082320 PIs: Sahin and Krueger
P20 NS080199 PI: Bebin
mTOR inhibitors in TSC mouse models

1. Improves myelination and seizures (Meikle et al., 2008)
2. Prevents or stops seizures (Zeng et al., 2008)
3. Improves learning (Ehninger et al., 2008)
4. Prevents autistic-features (Tsai et al., 2012)
Randomized Phase II Trial of an mTOR inhibitor in TSC: 

**Neurocognition**

- 6-21 year olds with TSC, IQ>60
- Randomized placebo controlled, double blind
- 50 patients from 2 sites (Cincinnati & Boston)
- Neurocognitive testing at baseline, 3 months, 6 months
- Secondary endpoints: autism, seizures, sleep
Summary

• TSC is a model for understanding the early biomarkers associated with ASD.

• Mutations in TSC genes affect neuronal connectivity.

• Mouse models of TSC provide insight into autistic-like behaviors and enable pre-clinical trials.

• Treatment trials in TSC may shed light on related neurodevelopmental disorders.