Somatic Mutation and Mosaic Variants in Epilepsy

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Epilepsy—early in infancy, refractory, focal
Cause?
Specific cause?
Outline

• Framework for precision medicine in epilepsy
• Somatic mutation in human epilepsy
  – Large to small lesions $\rightarrow$ non-lesional epilepsy
  – Rare $\rightarrow$ common
  – mTOR and beyond
Precision Medicine in Epilepsy
Outline

• Framework for precision medicine in epilepsy
• Somatic mutation in human epilepsy
  – Large to small lesions → non-lesional epilepsy
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  – mTOR and beyond
Epilepsy Genetics Explosion

Next Generation Sequencing Era

Microdeletions
- 15q13.3
- 16p13.11
- 15q11.2

Channelopathy Era

1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015

ILAE, Epilepsia, 2016
What explains the unsolved?
Post-zygotic mutation

Epilepsy—early in infancy, refractory, focal
Cause?
Specific cause?
Copy number variants in HMG

Two HMG cases: copy >2 at 1q

HMG-1 had a karyotype that was normal → somatic mosaicism

Candidate gene: AKT3
Sequencing AKT3 identified a mutation in HMG-3: c.49G→A, Glu17Lys
HMG-3 AKT3 c.49G→A mutation
HMG-3 AKT3 c.49G→A mutation
HMG-3 AKT3 c.49G→A mutation

- HMG-3 brain
- HMG-3 leukocytes
- HMG-3 brain (17% of clones)
- HMG-3 brain (83% of clones)
HMG-3 AKT3 c.49G→A mutation

Davies et al., Br J Cancer, 2008
Poduri et al., Neuron, 2012
Somatic Activation of AKT3 Causes Hemispheric Developmental Brain Malformations

Annapurna Poduri,1,4 Gilad D. Evrony,2,5 Xuyu Cai,2,5 Princess Christina Elhosary,1 Rameen Beroukhim,6,9,10,12,15 Maria K. Lehtinen,2,5,7 L. Benjamin Hills,2 Erin L. Heiznen,16 Anthony Hill,2 R. Sean Hill,2,15 Brenda J. Barry,2 Blaise F.D. Bourgeois,1,4 James J. Riviello,1,4,19 A. James Barkovich,17 Peter M. Black,13,16 Keith L. Ligon,5,7,10,11,14 and Christopher A. Walsh5,4,8,15,*

Nat Genet. 44(8): 934–940. doi:10.1038/ng.2331.

De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes


Nat Genet. 44(8): 941–945. doi:10.1038/ng.2329.

De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly

Jeong Ho Lee1,2,9, My Huynh3,4, Jennifer L Silhavy1,2, Sangwoo Kim5, Tracy Dixon-Salazar1,2, Andrew Heiberg1,2, Eric Scott1,2, Vineet Bafna5, Kiley J Hill1,2, Adrienne Collazo1,2, Vincent Funari6,7, Carsten Russ8, Stacey B Gabriel8, Gary W Mathern3,4,10, and Joseph G Gleesons1,2,10
Single cell sequencing from HMG-3 brain tissue

Cell Lineage

Self renewing stem cells

Early progenitor cells

Neuron
~1/3 NeuN+ cells
AKT3 Glu17Lys

Oligodendrocyte
~1/3 NeuN- cells
AKT3 Glu17Lys

Astrocyte

Evrony & Cai et al., Cell, 2012
Extending our early findings:
What else can be attributed to mosaicism?

Hemimegalencephaly
Immature neurons, large pyramidal neurons, dysmorphic neurons, balloon cells

(Hemimegalencephaly: Tassi et al., Brain 2002)

Large neurons
Balloon cells with eccentric nuclei

(Focal cortical dysplasia)

Immature neurons, large pyramidal neurons, dysmorphic neurons, balloon cells

(Tassi et al., Brain 2002)

Large neurons
Balloon cells with eccentric nuclei

(Tuberous sclerosis complex: Arai et al., Acta Neuropath 1999)
Extending our early findings:
What else can be attributed to mosaicism?
– Smaller focal malformations?

Hemimegalencephaly  Focal cortical dysplasia
Somatic Mutations and FCD

MRI courtesy Jim Barkovich, UCSF
FCD due to somatic mosaic duplication of 1q21.1-q44 (containing AKT3), ~70% of the cells

Conti et al., *Clinical Genetics*, 2014
‘Diagnostic yield’ 41%
HME 61%
FCD 26%

D’Gama et al., Cell Rep, 2017
Earlier to later
Bigger to smaller
Mutation burden (VAF)

D’Gama et al., Cell Rep, 2017
Extending our early findings:
What else can be attributed to mosaicism?
  – Smaller focal malformations?
  – Broader category of focal epilepsy without visible lesions?

Hemimegalencephaly  Focal cortical dysplasia  Normal cortex
Shared gene for FCD and non-lesional focal epilepsy: *SLC35A2*

collaboration with Melodie Winawer, Pete Crino, Erin Heinzen, *Annals of Neurology*, 2018
Shared gene for FCD and non-lesional focal epilepsy: *SLC35A2*

Pediatric onset
- Infantile/epileptic spasms
- Glycosylation pathway implicated
- No evidence of mTOR activation

collaboration with Melodie Winawer, Pete Crino, Erin Heinzen, *Annals of Neurology*, 2018
Spectrum of SLC35A2 (X-linked)

Girls with germline variants
Naturally mosaic
Epileptic encephalopathy
All cells with variant, including brain
50% with abnormal protein

Boys or girls with focal lesions and epilepsy (spasms)
~20-50% of brain cells affected

Next steps:
Define phenotypic spectrum
Correlate with mutation burden
Investigate treatment options

Boys or girls with focal non-lesional epilepsy
~2-14% of brain cells affected
The future for mosaic epilepsies

• Precision diagnosis
  – Need to bring **genomic science** to practice
  – Requires **basic neuroscience** studies of new genes

• Precision treatment
  – Pre-clinical data re: specific mechanisms, drugs
  – Science, practice, and ethics of clinical trials
    • N of 1 vs. RCT vs. other design
    • What are meaningful outcomes?
    • Inclusion/exclusion/stopping criteria
    • Cautionary tales (‘do no harm’)

Thank you

• Patients and families
• Colleagues and mentors
• International epilepsy genetics community of collaborators

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NINDS R01 PCDH19, R01 Genetics of MCD/Heinzen
NICHID U24, R21, R01/Haynes