

Targeting Common Signaling Pathways in Cortical Dysplasia

Gabriella D'Arcangelo, Ph.D.

Department of Pediatrics, Baylor College of Medicine

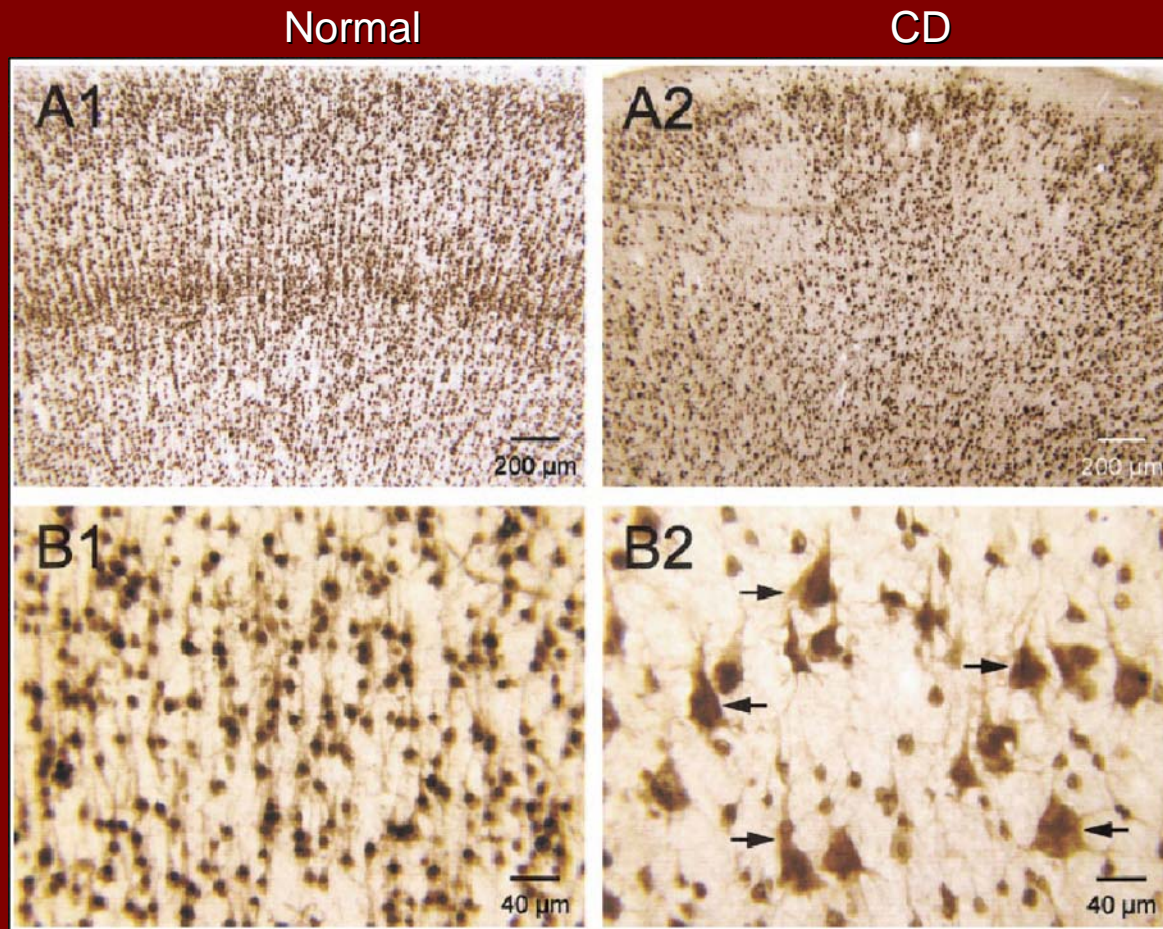
**The Cain Foundation Laboratories, Texas Children's Hospital
Houston, TX**

**Supported by: Citizens United for Research in Epilepsy (CURE) and
NIH/NINDS**

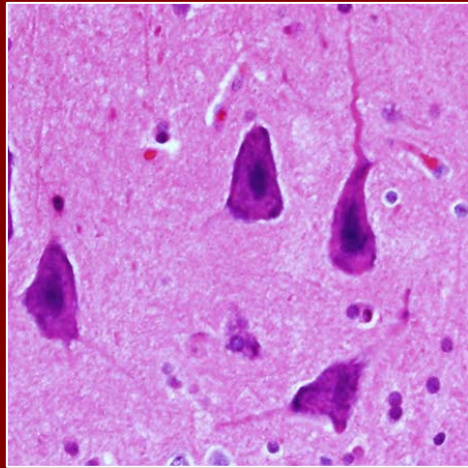
"I do not have significant financial interests related to this conference"

An alternative and accessible version of this presentation is available at 11:10 am in the [Videocast of Day One](#)

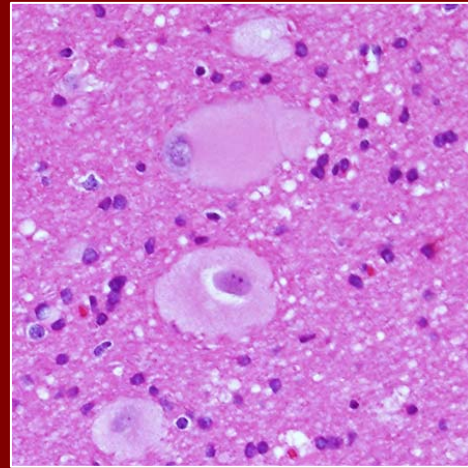
Histological Features of CD



Common Dysplastic Cells found in FCD, HMEG and TSC

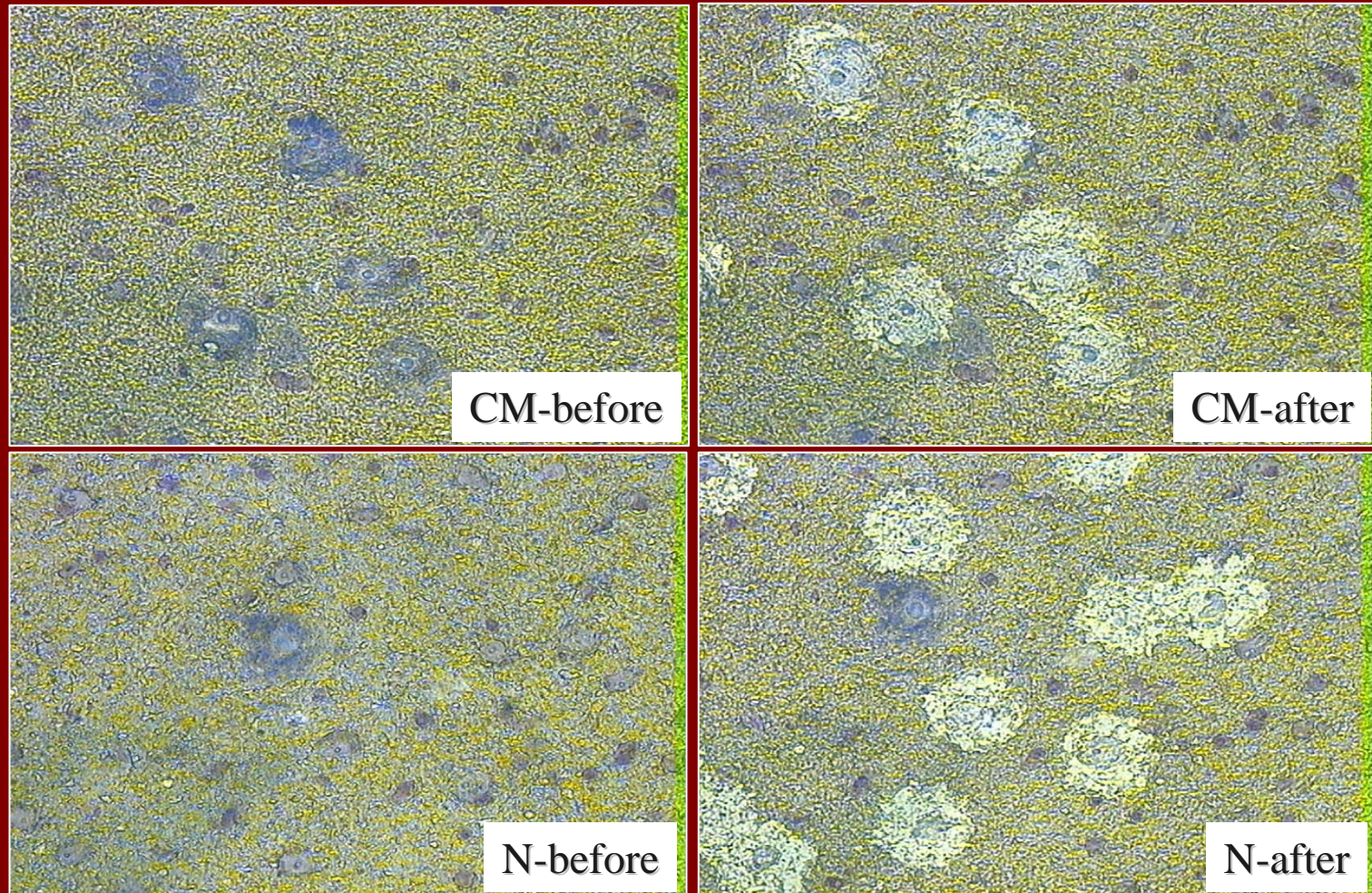


Cytomegalic
neurons (CM)

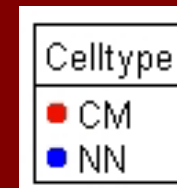
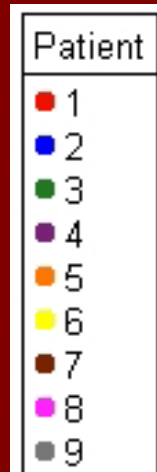
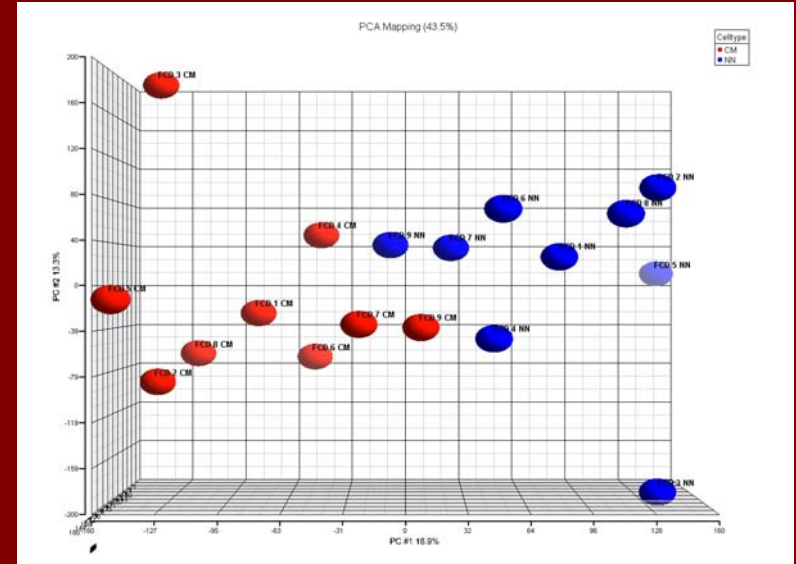
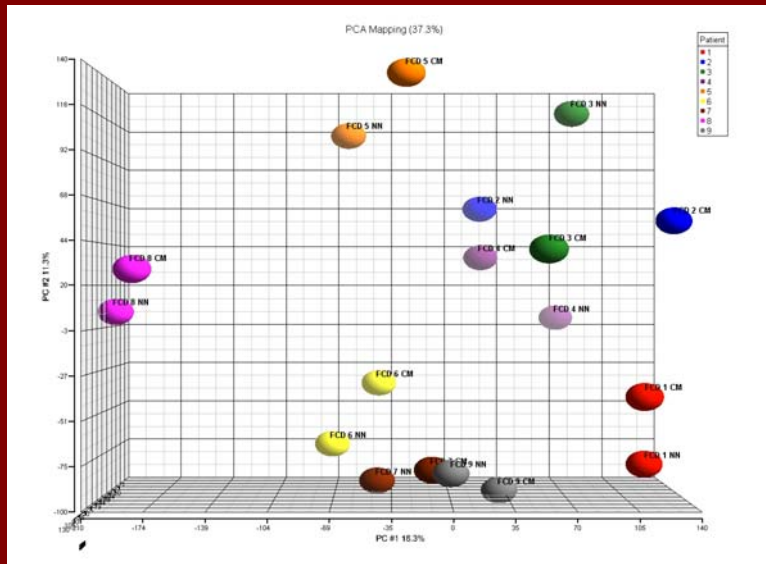


Balloon cells
(BC)

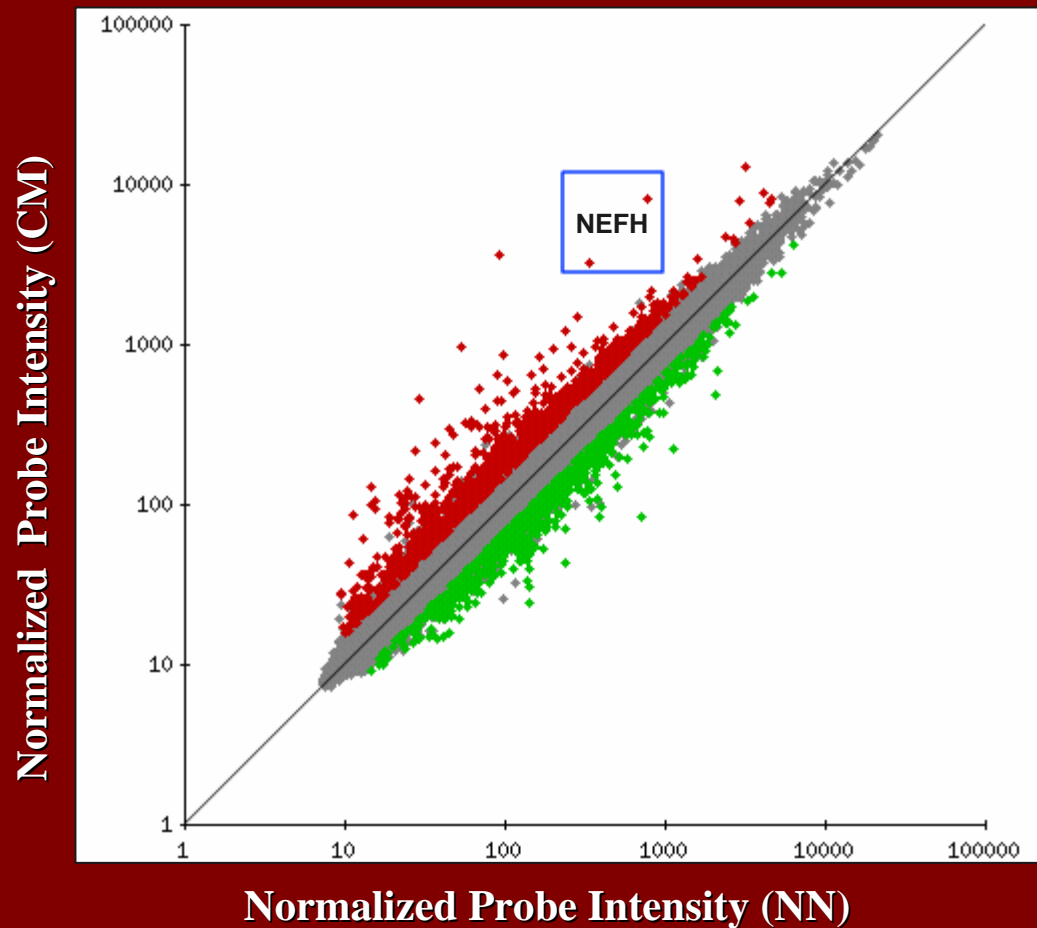
Laser Capture Microdissection of CM Neurons From Frozen CD Specimens



Analysis of the Source of Variability in 9 FCD Samples



Comparison of Gene Expression Profiles in CM Versus Normal Cells in FCD



Upregulation of Neurofilament Genes in CM Neurons of FCD

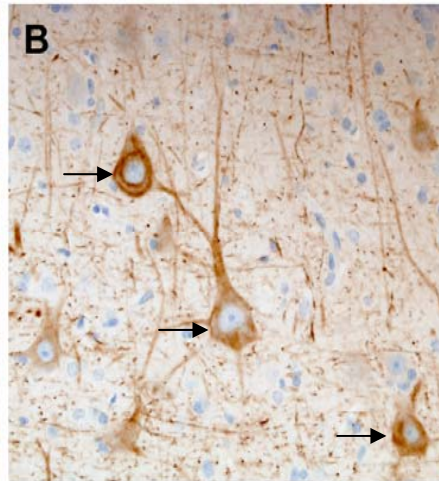
Axonal Components:

neurofilament, heavy polypeptide 200kDa
neurofilament, heavy polypeptide 200kDa
neurofilament 3 (150kDa medium)
neurofilament, light polypeptide 68kDa
Neurofilament, light polypeptide 68kDa
neurofilament, light polypeptide 68kDa

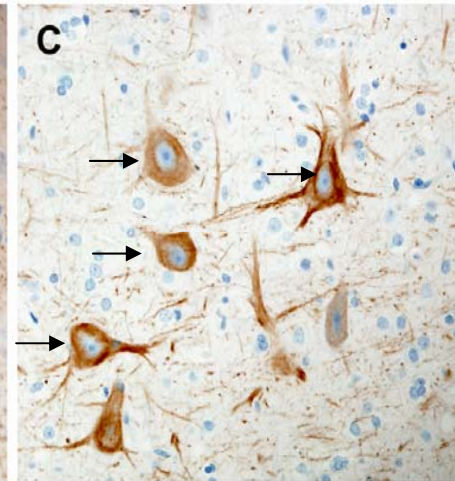
NEFH	4.94E-05	9.46761
NEFH	0.000419893	7.53556
NEF3	0.000330089	3.58968
NEFL	0.00826802	2.35871
NEFL	0.0168554	1.63872
NEFL	0.0182654	1.60166



NFH

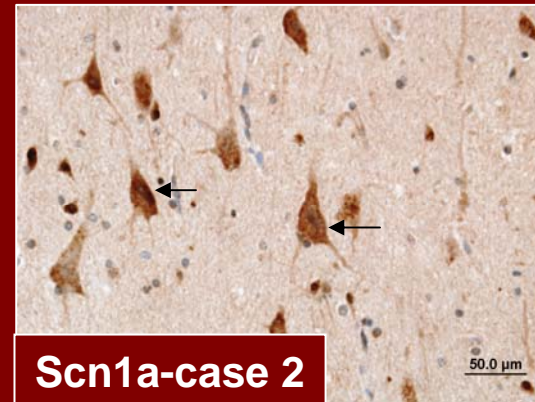


NF3



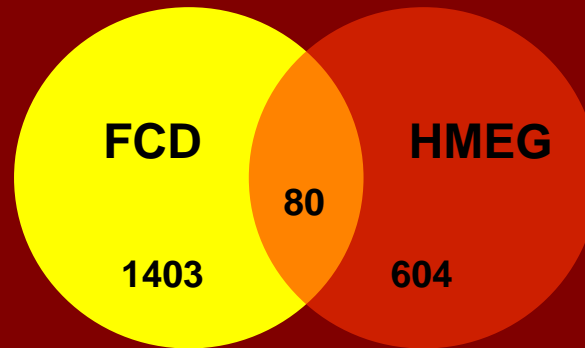
NFL

Dysregulation of Genes Involved in Ion Transport



Scn1a-case 2

Common Genes Dysregulated in CM Neurons of FCD and HMEG



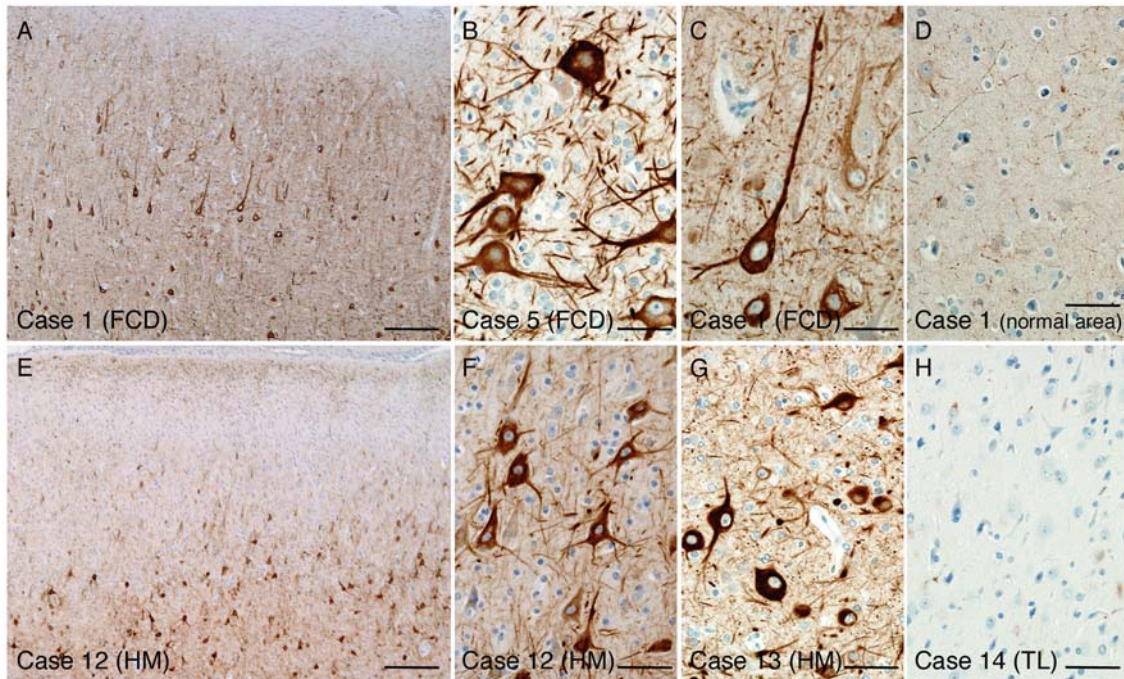
p value < 0.05
CM/NN > 1.5 (+/-)



Probeset ID	Gene Title	Gene Symbol	FCD p-value	FCD (CM/NN)	HM (CM/NN)	HM p-value
33767_at	neurofilament, heavy polypeptide 200kDa	NEFH	0.001898	8.83458	2.71748	0.002001
204412_s_at	neurofilament, heavy polypeptide 200kDa	NEFH	0.006407	5.11328	2.99275	0.008674
208626_s_at	vesicle amine transport protein 1 homolog (T californica)	VAT1	0.000443	3.1343	2.10001	0.045886
1559870_at	L-threonine dehydrogenase	TDH	0.023146	3.10271	1.80257	0.022908
202912_at	adrenomedullin	ADM	0.019242	2.93377	1.61053	0.022121
205943_at	tryptophan 2,3-dioxygenase	TDO2	0.004248	2.91148	1.83269	0.0299
202237_at	nicotinamide N-methyltransferase	NNMT	0.023162	2.88438	2.04592	0.034686
221676_s_at	coronin, actin binding protein, 1C	CORO1C	0.000114	2.7538	1.68473	0.014485
209283_at	crystallin, alpha B	CRYAB	0.010306	2.62556	2.65764	0.044397
201105_at	lectin, galactoside-binding, soluble, 1 (galectin 1)	LGALS1	0.047143	2.54391	1.97137	0.005193
	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2,					
201761_at	methenyltetrahydrof	MTHFD2	0.01578	2.32916	1.94824	0.038143
244069_at	Tachykinin receptor 2	TACR2	0.007354	2.27578	1.7656	0.047748

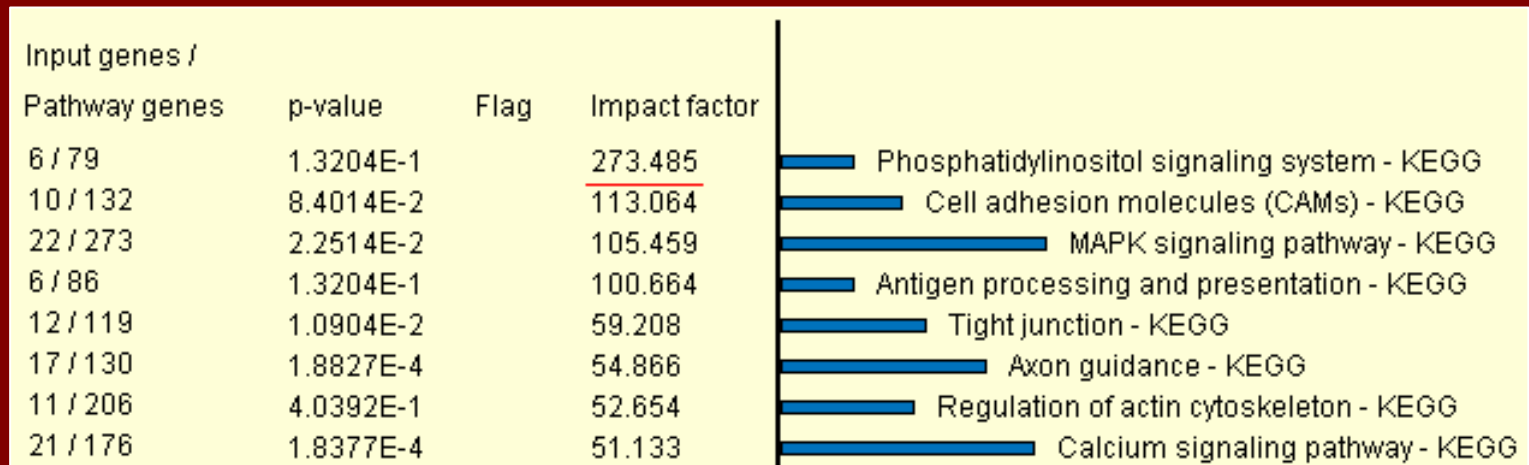
NF-H Is a Marker for CM Neurons in FCD and HMEG

FCD

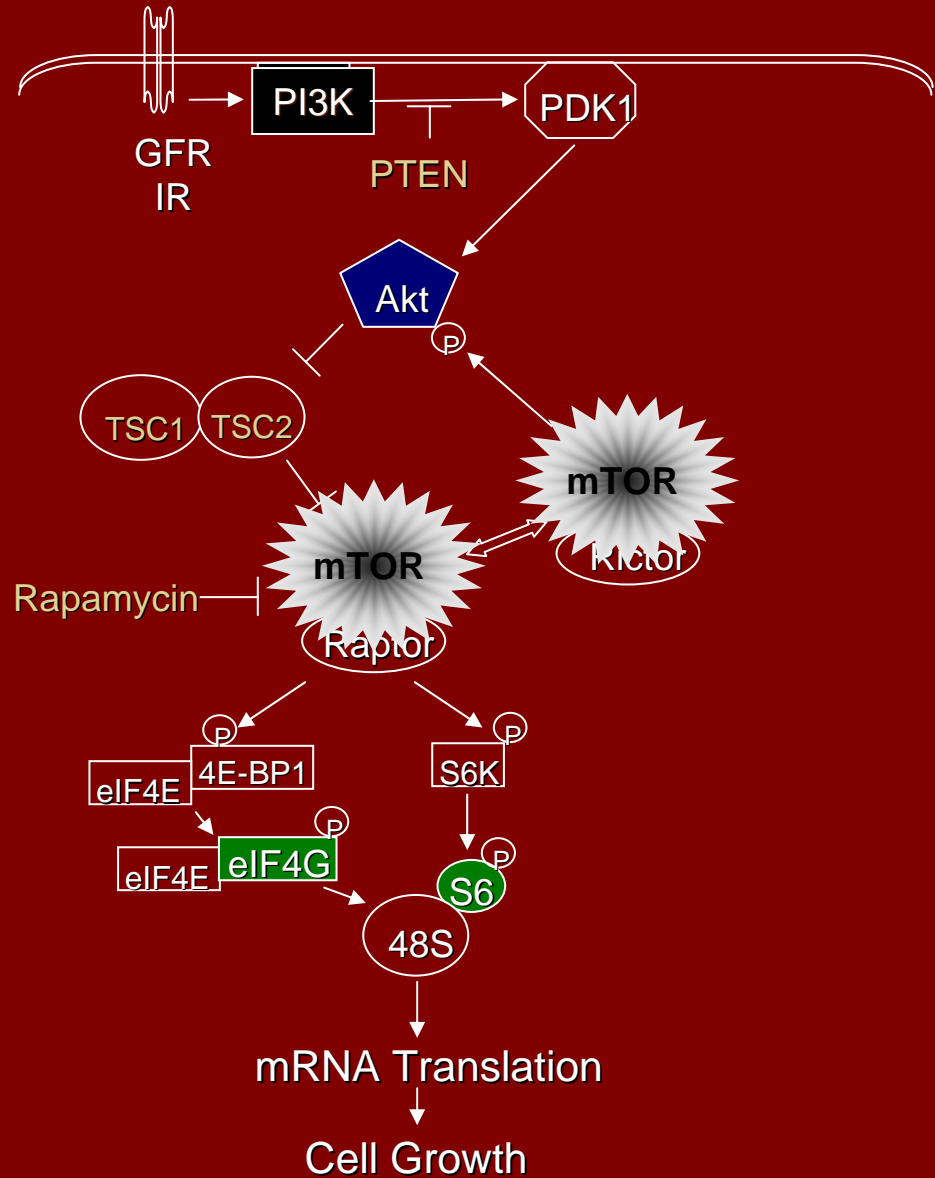


HMEG

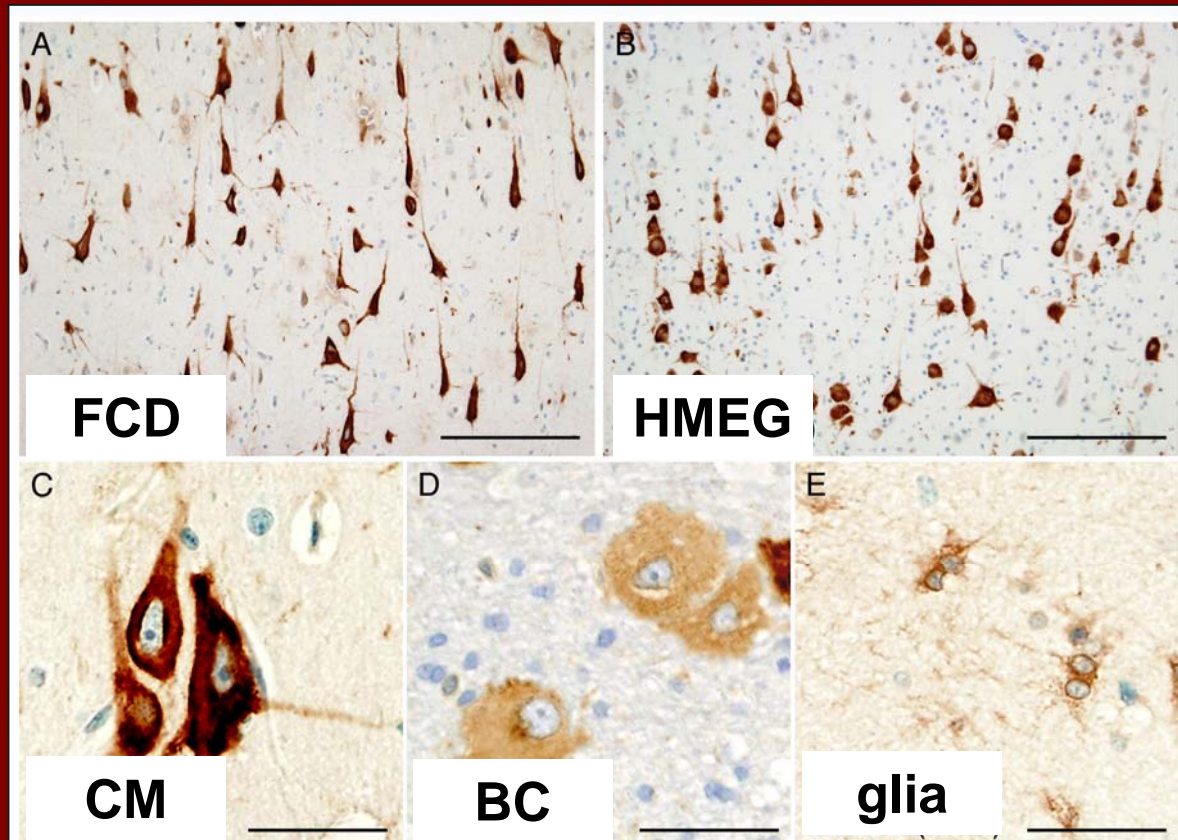
The PI Pathway is Significantly Dysregulated in CM Neurons of FCD



PI3K/Akt/mTOR Signaling

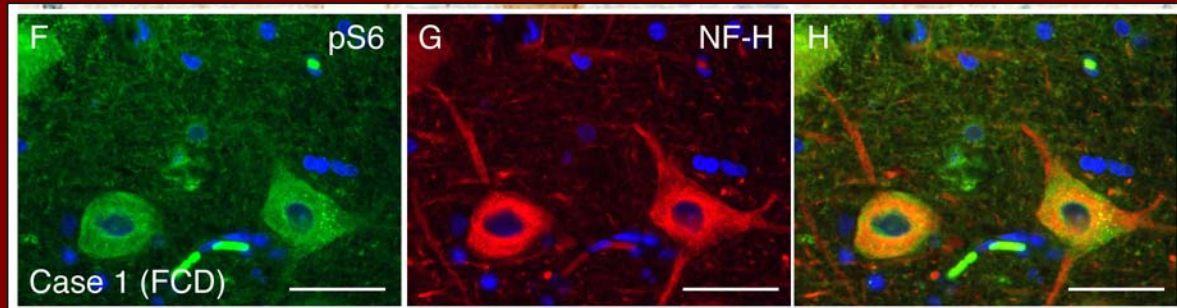


Increased pS6 Immunoreactivity in CM Neurons of FCD and HMEG

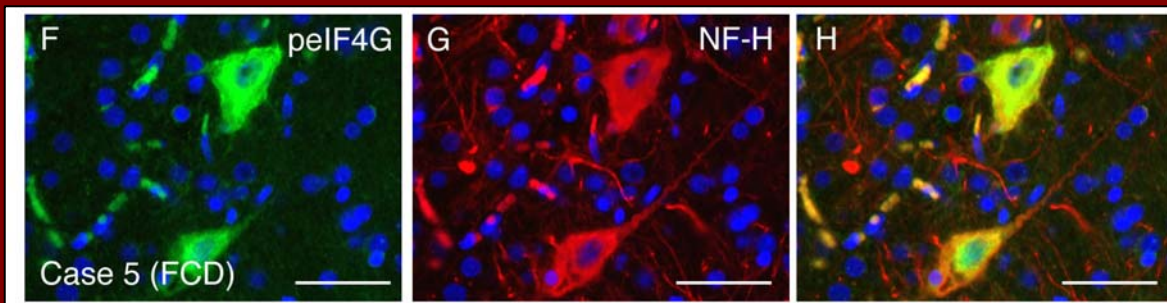


Co-localization of pS6 and peIF4G with NF-H in Cytomegalic Neurons

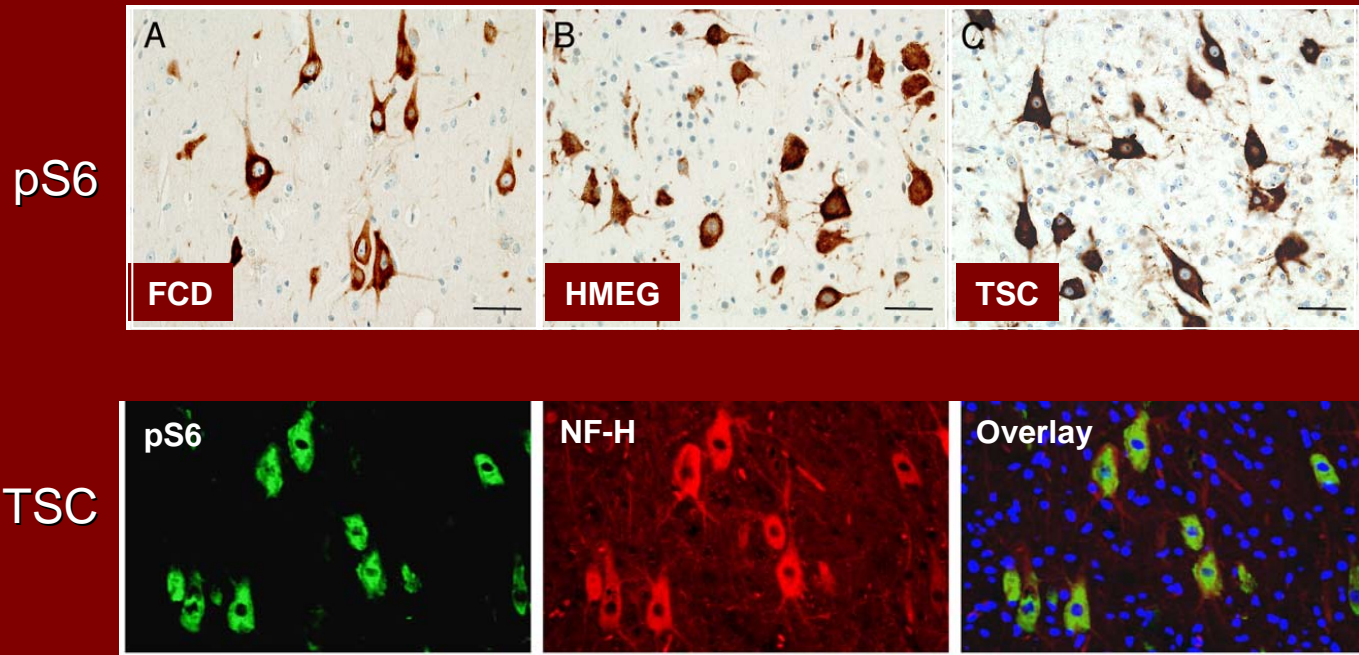
phospho
S6



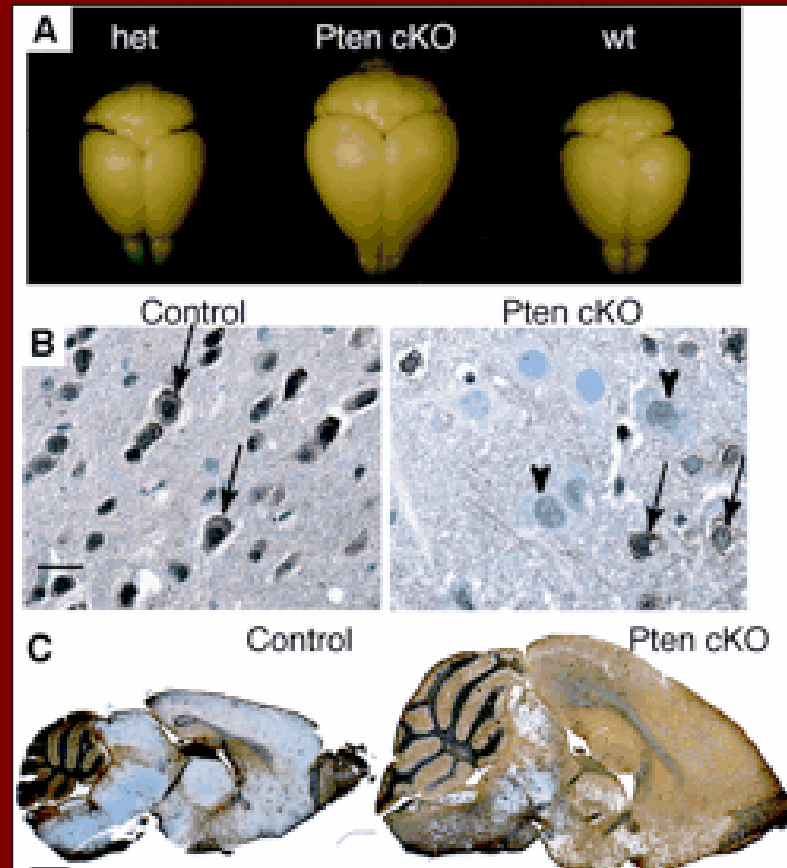
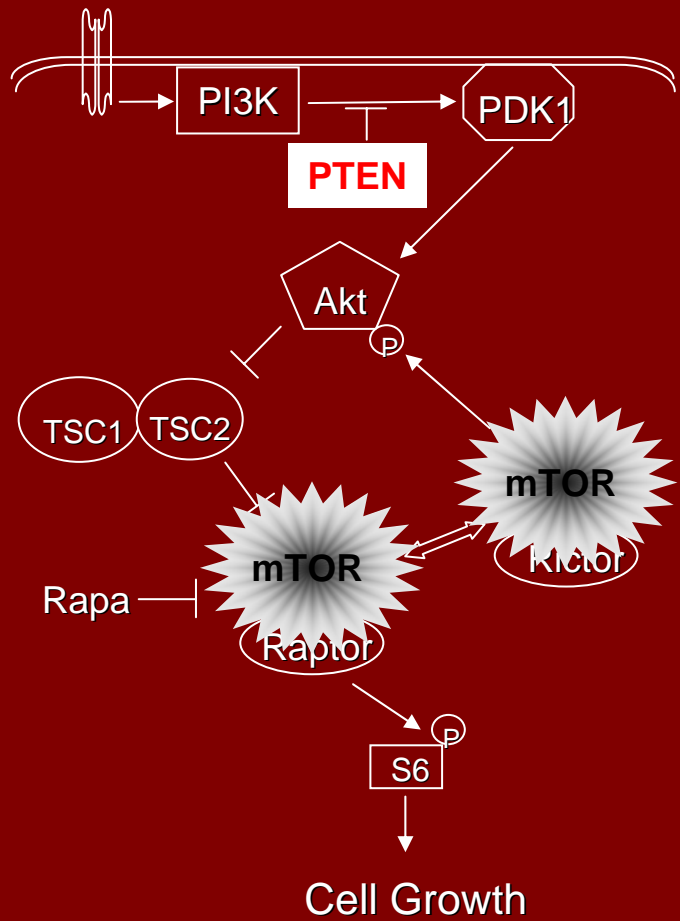
phospho
eIF4G



Co-localization of pS6 and NF-H in Cytomegalic Neurons of TSC

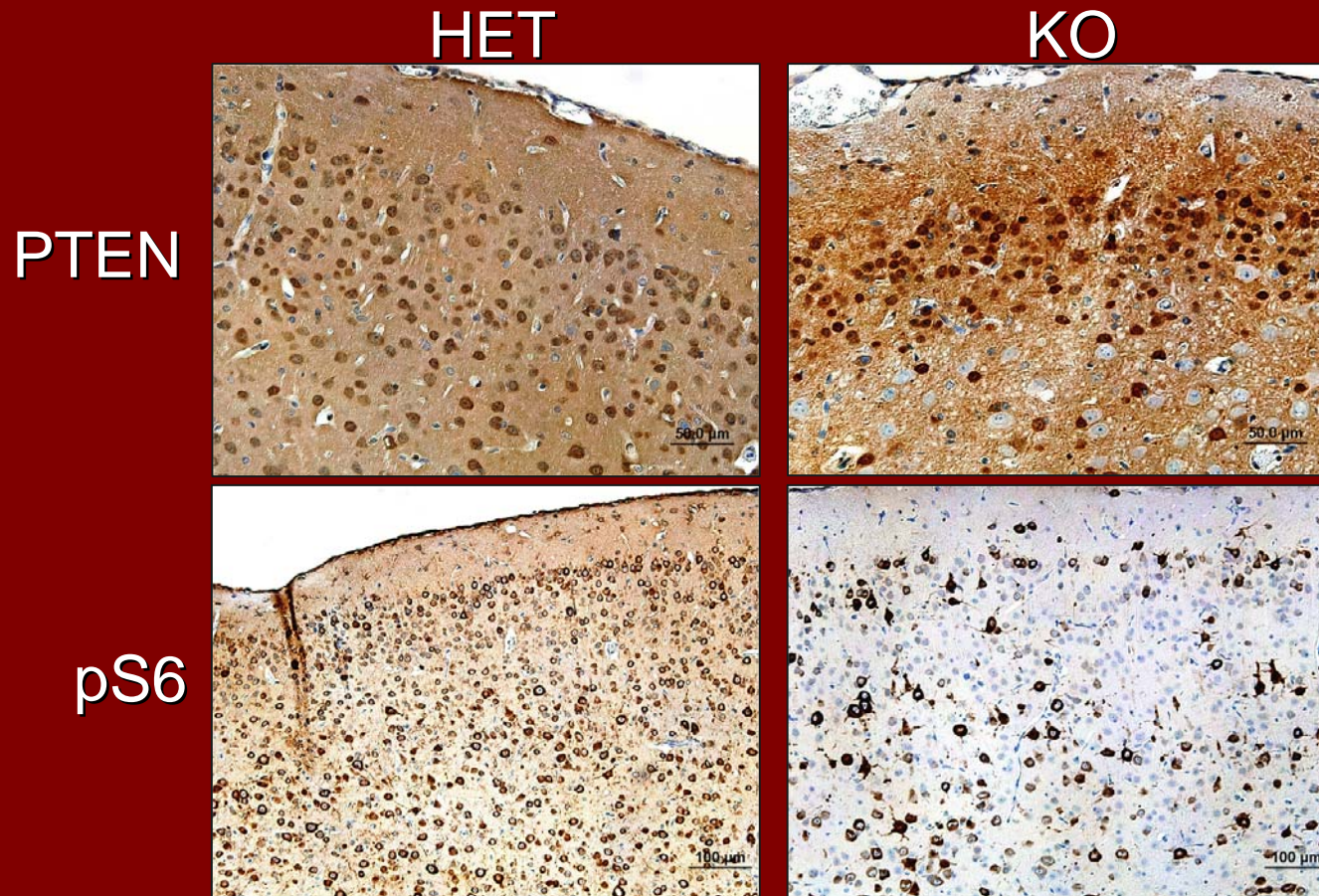


Hypertrophy of hGFAP-Cre/PTEN-fl Mutant Brain

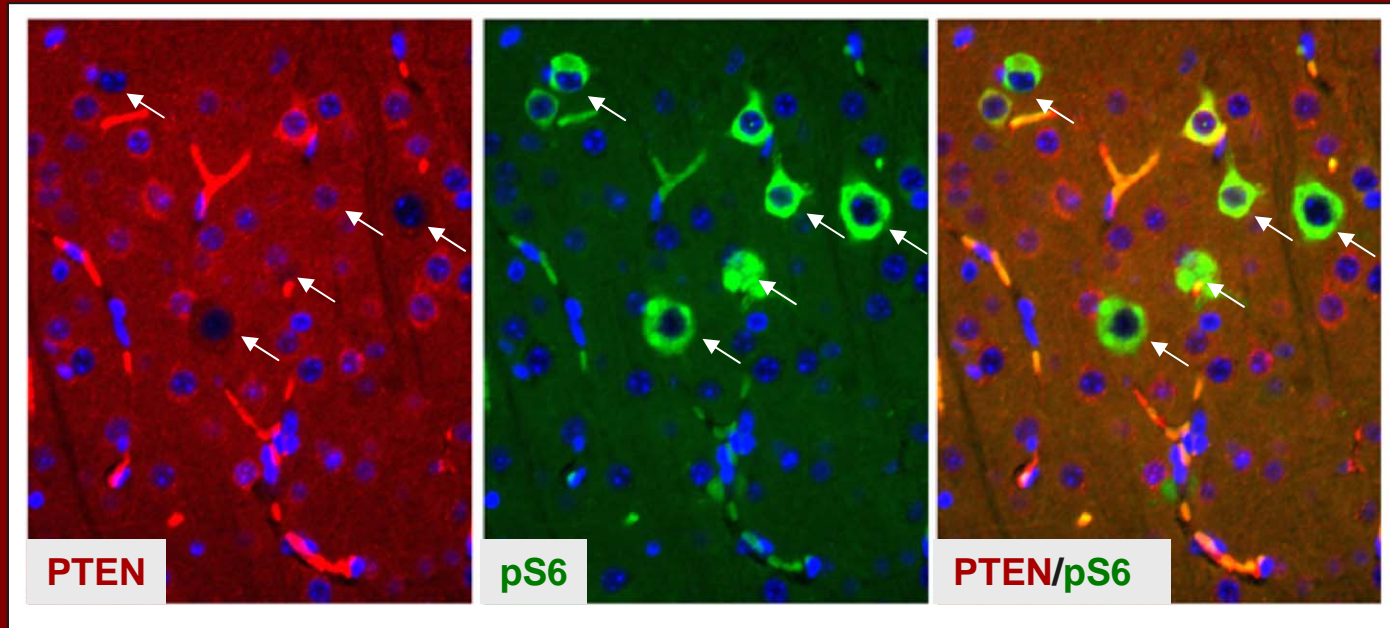


Fraser et al., Cancer Res. 2004

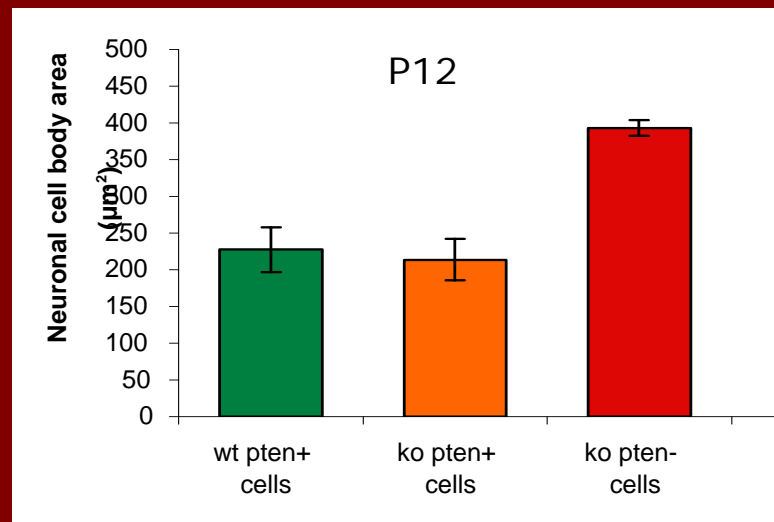
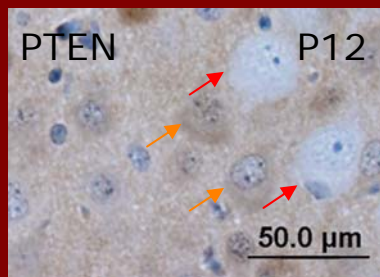
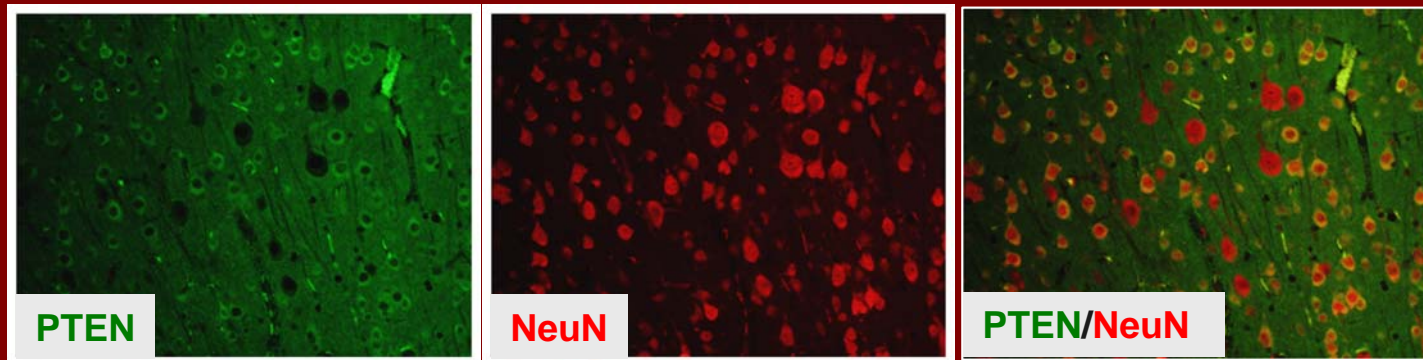
Loss of PTEN and pS6 Overexpression in a Subset of Cortical Neurons



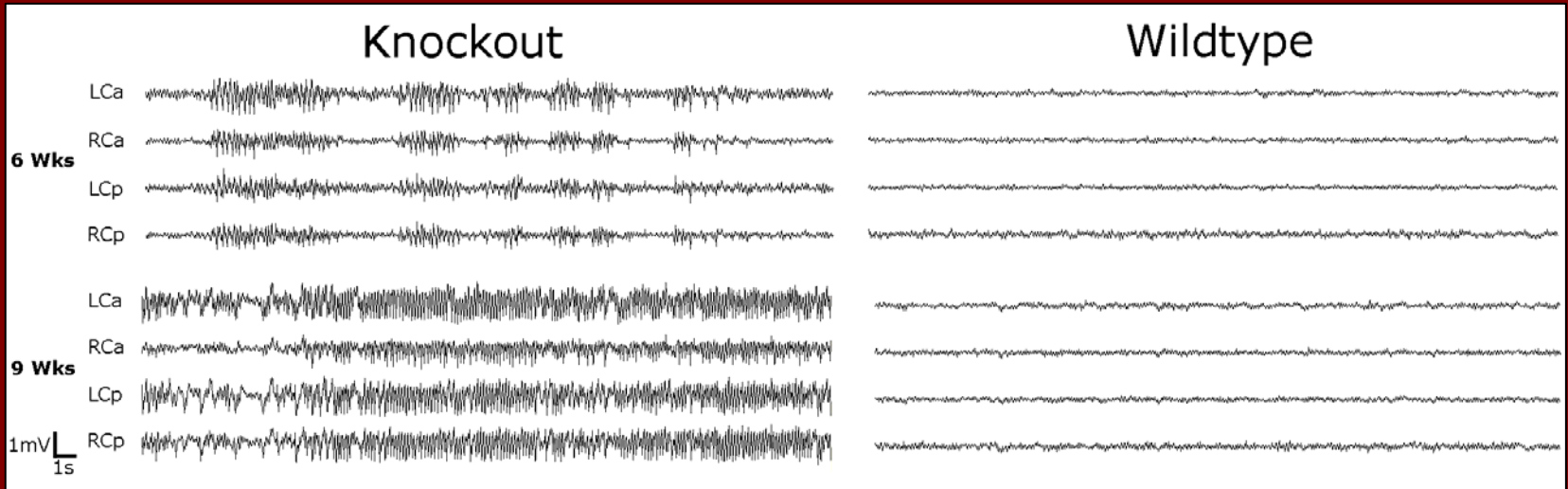
Increased Phosphorylation of S6 in PTEN-Deficient Cells



Increased Size in PTEN-Deficient Cortical Neurons

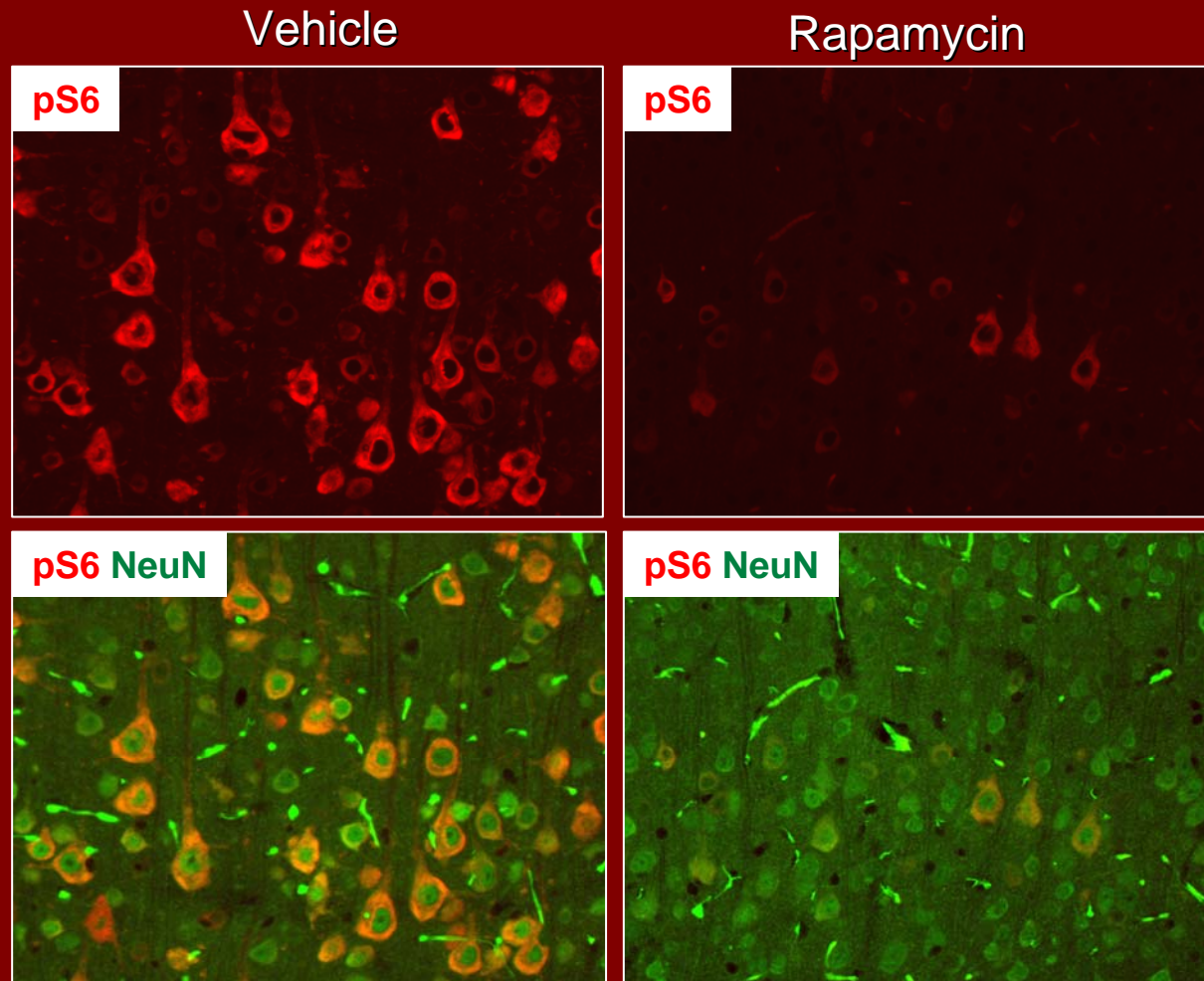


PTEN Mutant Mice Exhibit Electrographic Seizures

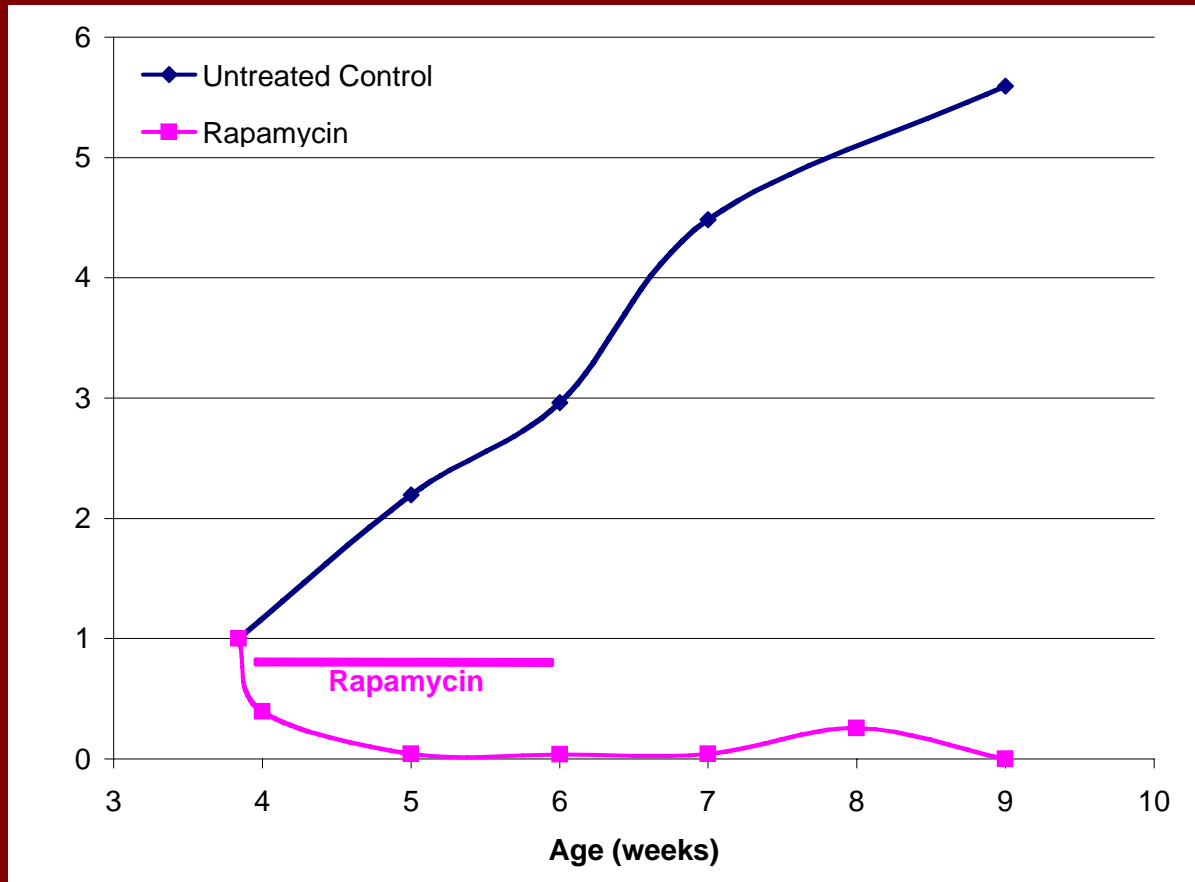


	Knockout	Heterozygous	Wildtype
Electrographic Seizure	4/5 mice (80%)	0/5 mice (0%)	0/6 mice (0%)
Behavioral Seizure	1/5 mice (20%)	0/5 mice (0%)	0/6 mice (0%)

Rapamycin Suppresses mTOR Activity in the Cortex of PTEN Mutants



Rapamycin Treatment Suppresses Seizures in PTEN Mutant Mice



CONCLUSIONS

1. PI3K/Akt/mTOR signaling is a common pathway activated in cytomegalic neurons in FCD, HMEG and TSC.
2. hGFAP-PTEN conditional knockout mice recapitulate at least 3 aspects of CD: mTOR activation, cortical neuron enlargement and electrographic seizures
3. Rapamycin treatment suppresses mTOR activation in cortical neurons and electrographic seizures

Cecilia Ljungberg, Ph.D.

Nikki Sunnen

Gabriella D'Arcangelo, Ph.D. - Pediatrics/BCM

Yaojuan Lu

Michael Sheldon, Ph.D. - Pediatrics/BCM

Joaquin Lugo, Ph.D.

Anne Anderson, M.D. - Pediatrics/BCM

John Swann, Ph.D. - Pediatrics/BCM

Meena Bhattacharjee, M.D. - Pathology/BCM

Dawna Armstrong, M.D. - Pathology/BCM

Daniel Yoshor, M.D. - Neurosurgery/BCM

Gary Mathern, M.D. - UCLA

Suzy Baker, Ph.D. - St Jude Children's Res Hosp