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Genetic Characterization of a Syndromic Cortical Dysplasia and the Development of a Small Animal Model

Gregory G. Heuer, MD/PhD
Ksenia Orlova, Whitney Parker, Kevin A. Strauss, Erik G. Puffenberger, Gordon H. Baltuch, D. Holmes Morton, and Peter B. Crino

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Studying the Molecular Biology of Cortical Dysplasia

Crino lab focus- the genetics and the molecular mechanisms and that lead to Focal Cortical Dysplasia (FCD)

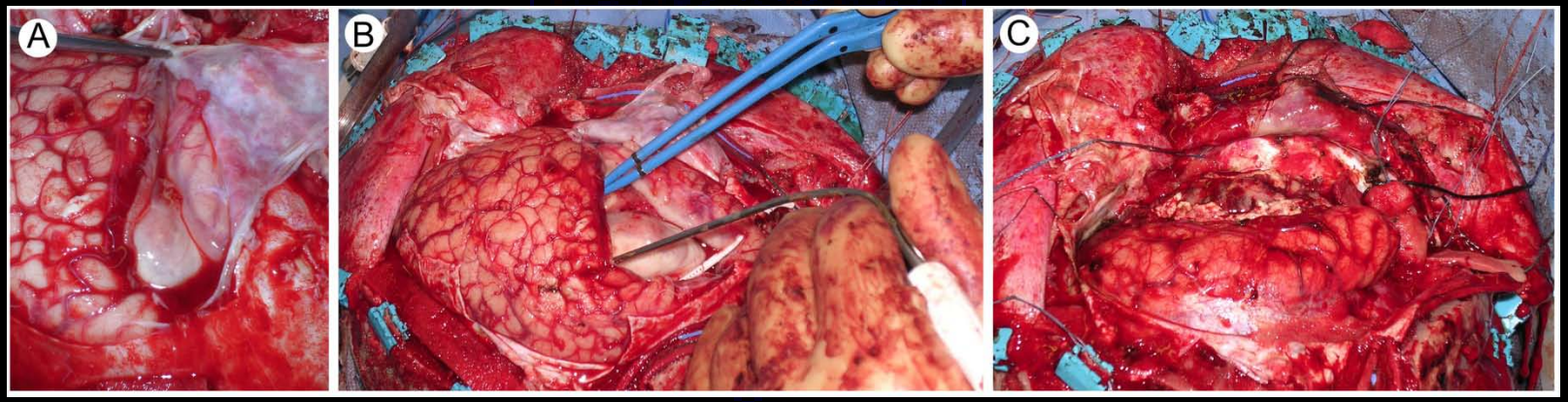
Roadblocks in studying FCD:

Most cases of FCD occur sporadically and are not associated with a known inherited genetic cause

Limited animal models to study cortical dysplasia

Goals

Short-term: identify gene(s) altered within the lesion that are involved at the cellular level with the development of FCD



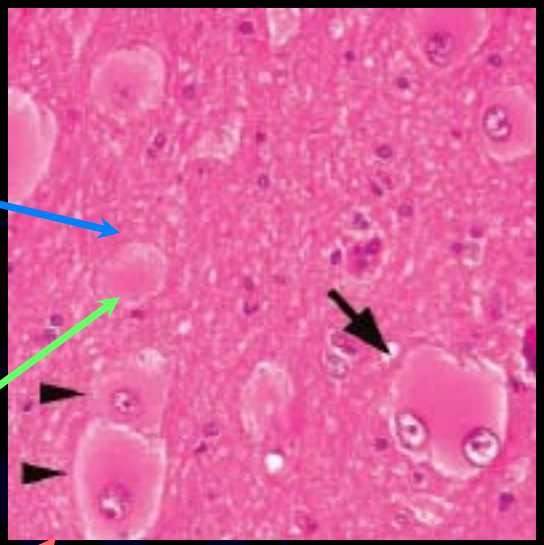
Long-term: develop molecular based treatment strategies to treat these conditions

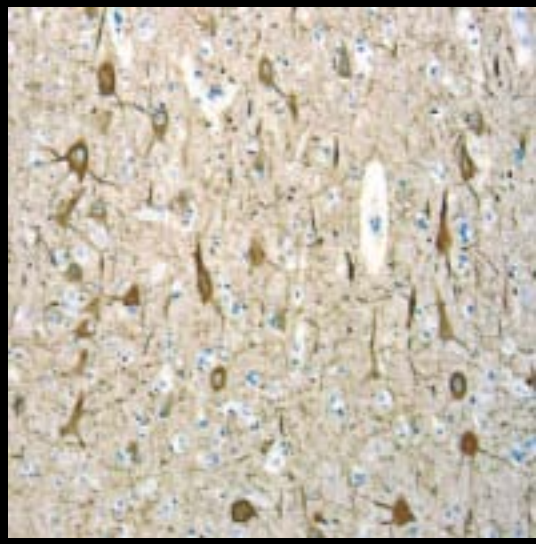
Malformations of Cortical Development- Disorders of Abnormal Proliferation

Tuberous Sclerosis

Focal Cortical Dysplasia w/ balloon cells

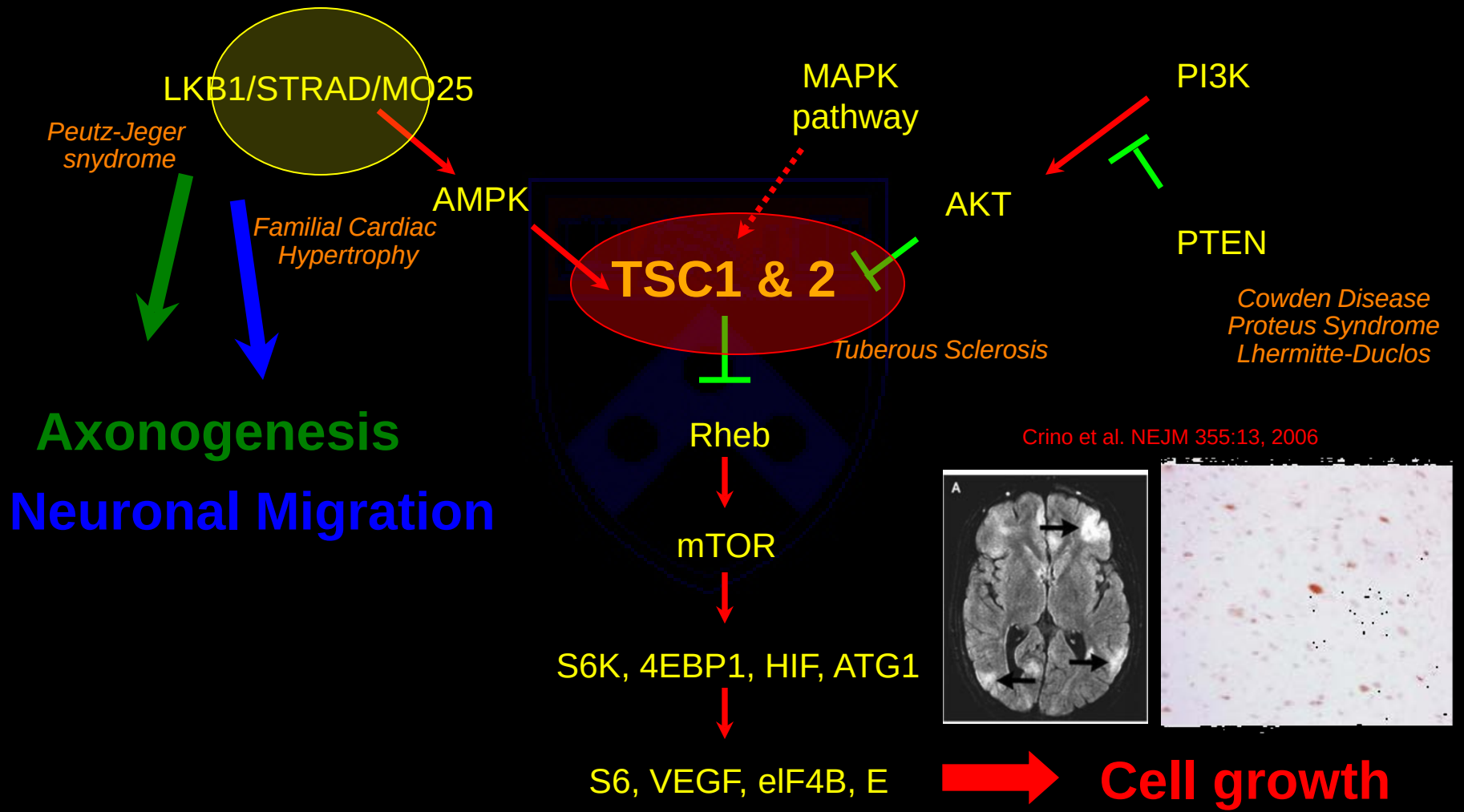
Hemimegalencephaly





All lesions have:
1.disorganized lamination
2. neuronal dysmorphism,
3. enlarged cells known as balloon cells or giant cells

mTOR Pathway and Associated Disorders



Crino et al. NEJM 355:13, 2006

Clinic for Special Children
Pretzel Syndrome: Clinical Features

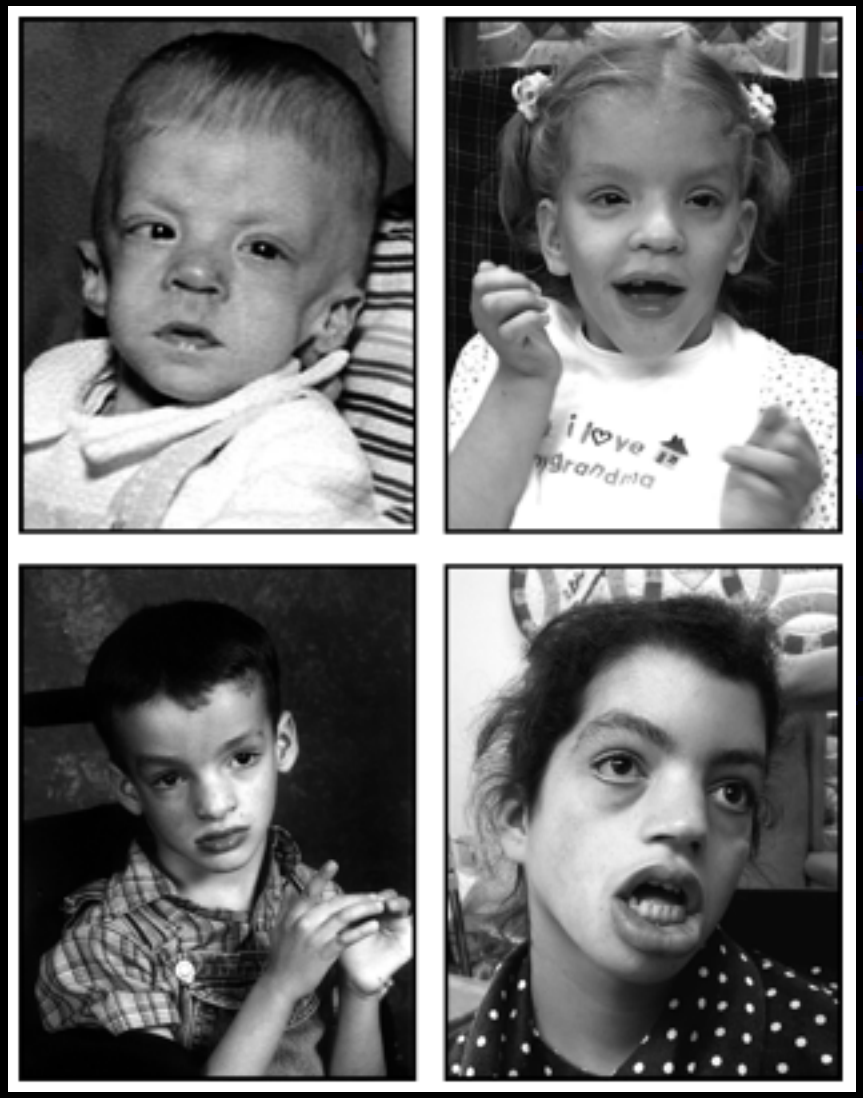


Table 1: Clinical features of 16 patients with Pretzel Syndrome

Clinical Variable	Percent of patients affected (n=16)
Prenatal	
Polyhydramnios	100
Preterm labor [a]	75
Postnatal	
Macrocephaly [b]	100
Infantile-onset partial epilepsy	100
Hypotonia	100
Craniofacial dysmorphism	100
Skeletal muscle hypoplasia	100
Joint laxity	100
Strabismus	56
Atrial septal defect	25
Nephrocalcinosis [c]	13
Diabetes insipidus [d]	13
Supraventricular tachycardia	6
Leukemia	6

Developmental Domain [e]	Maximum developmental age (range in months)
Gross motor	6-14
Fine motor-adaptive	4-10
Language-communication	2-6
Personal-social	2-6

NOTES

a Mean onset of labor at 31 weeks gestation, range 25-37 weeks

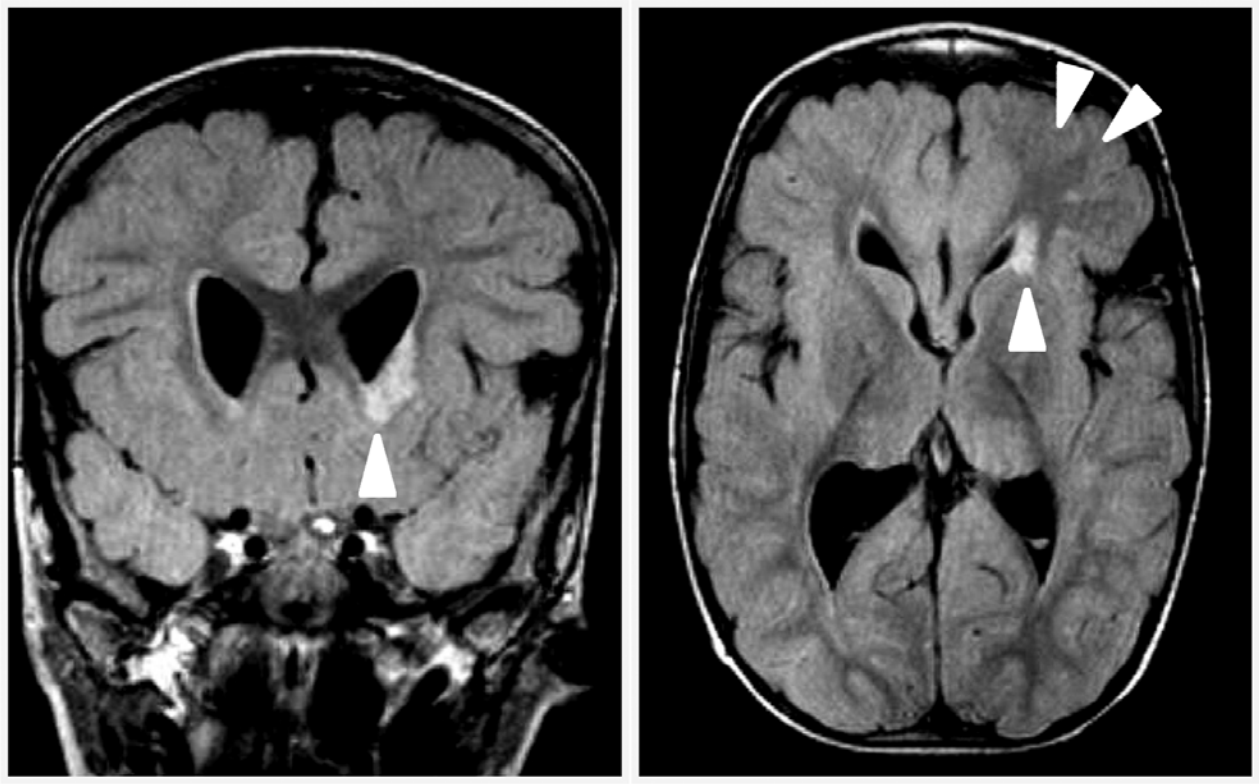
b Due to a combination of megalencephaly and hydrocephalus.

c Renal ultrasounds were only performed in four patients, two of whom (imaged at ages 6 and 28 years) had nephrocalcinosis.

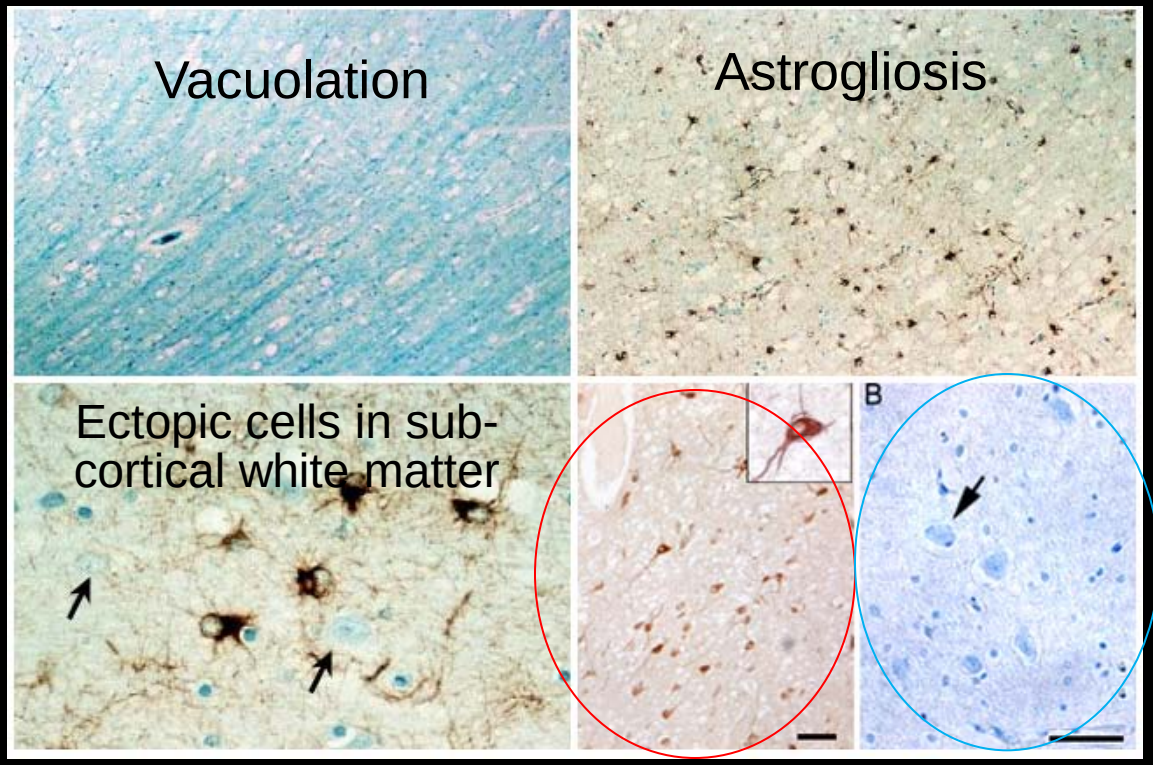
d One patient with DI had bilateral nephrocalcinosis on CT scan. The cause of DI was mixed, with both central and nephrogenic components.

e Developmental outcomes based on Denver Developmental Screening Test II

Pretzel Syndrome:
Syndromic Cortical Dysplasia



Pretzel Syndrome: Syndromic Cortical Dysplasia: HISTOPATHOLOGY



S6 Positive

CYTOMEGALY

Hypercellularity

ectopic neurons in the subcortical white matter

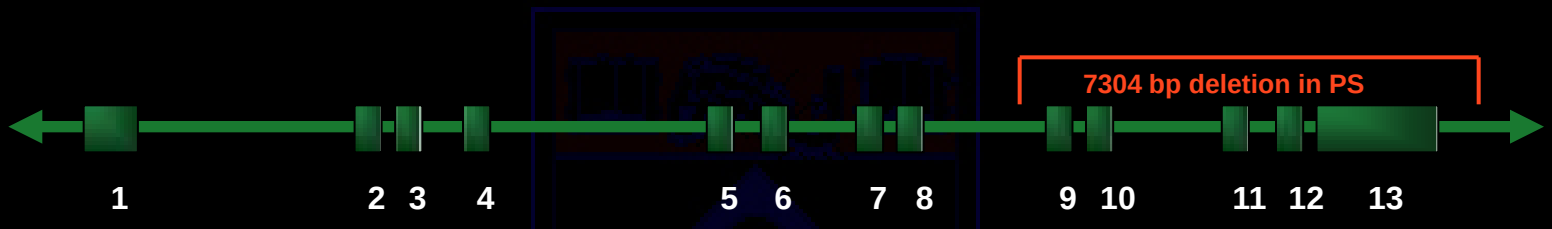
gray/white matter blurring

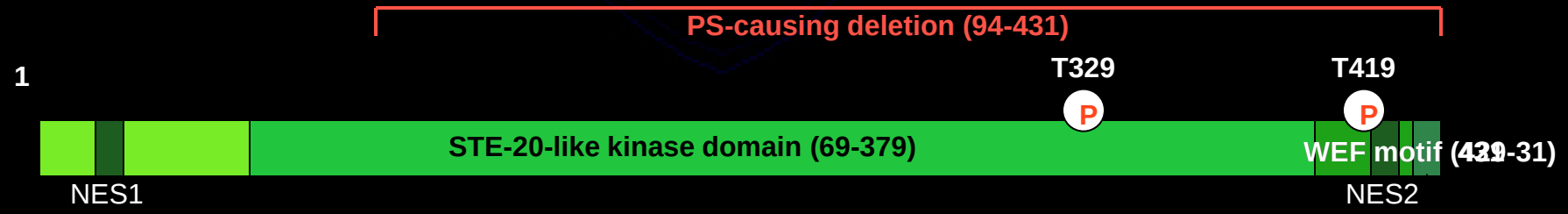
cytomegalic cells

Activation of mTOR pathway

Pretzel Syndrome Mapping Analyses- using single nucleotide polymorphism (SNP) arrays

large homozygous deletion in *STRADα*





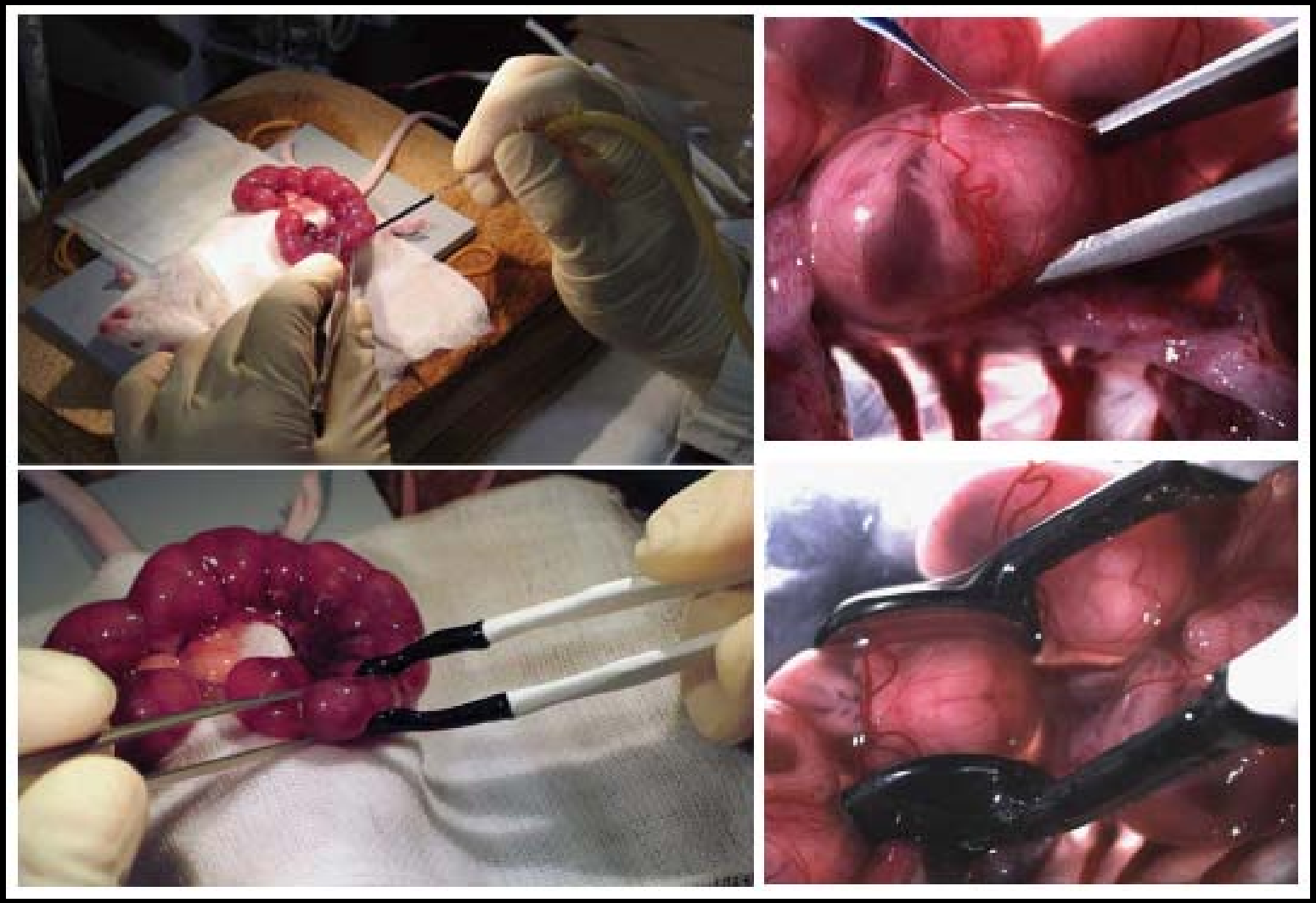
STRADα (17q23.3) gene and protein with

PS-causing deletion

Puffenberger et al., 2007

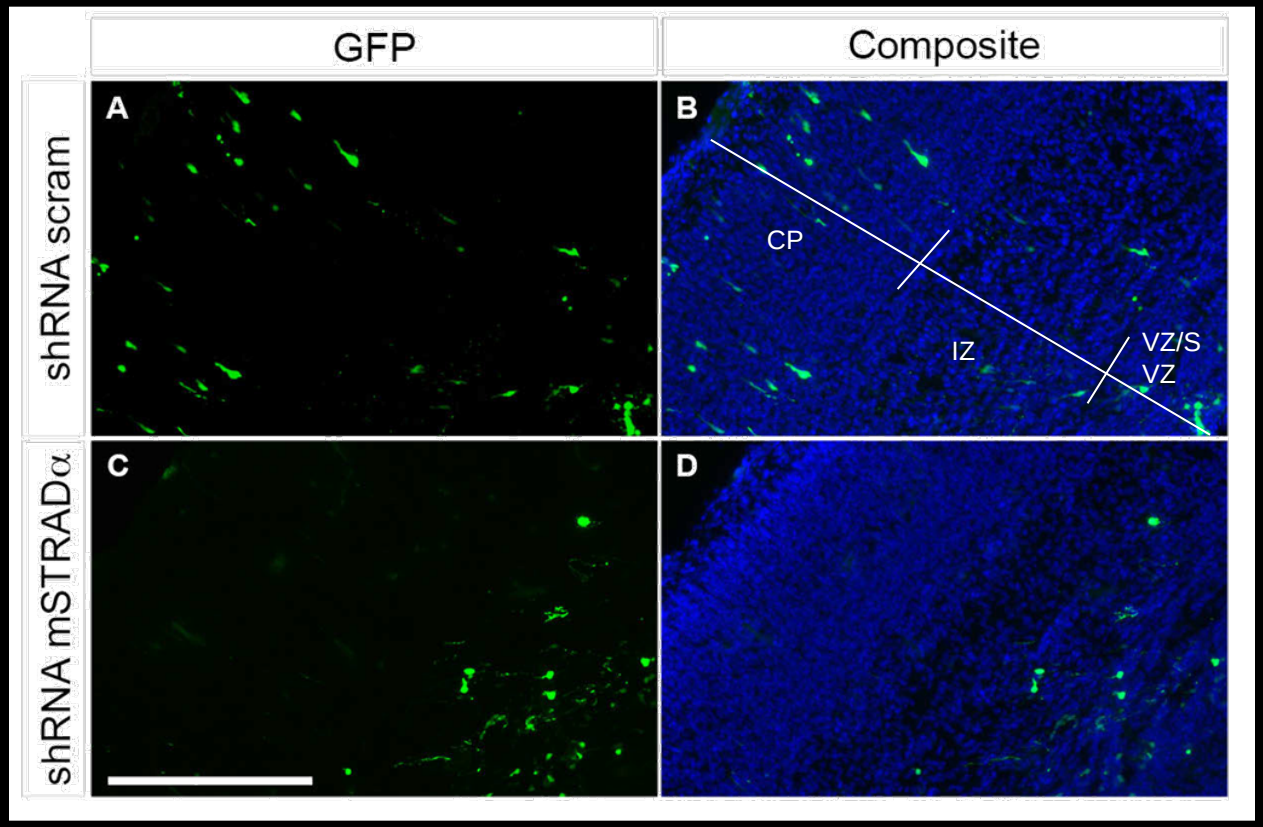
Development of Animal Models of FCD

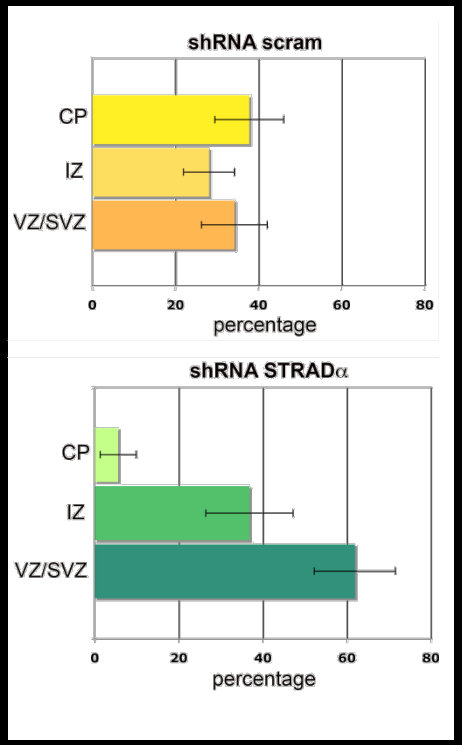
Methods: *In utero* electroporation (IUE) of embryonic mouse brains



Saito et al., 2006

Knockdown of STRADα *in vivo* results in failure of STRADα–deficient cells to migrate into the cortical plate





Conclusions

Discovered a new genetic form of cortical dysplasia, Pretzel syndrome

This condition shares histopathologic features with type IIb focal cortical dysplasia, tuberous sclerosis, hemimegalencephaly

Developed an animal model of focal cortical dysplasia using the newly discovered condition that results in cortical migration disorders

Future Directions

Genetic characterization of other forms of cortical dysplasia

Further characterization of animal model of pretzel syndrome and the molecular interactions leading to the migration abnormality

Analysis of sporadic samples of FCD for genetic alterations in genes known to cause or found to cause syndromic cortical dysplasia, with special emphasis on genes in the mTOR signaling pathway.

Contributors

Crino Lab:

Peter Crino
Marianna Baybis
Ksenia Orlova
Whitney Parker

Neurosurgery:
Phillip Storm CHOP
M.Sean Grady
Gordon Baltuch

Clinic for Special Children:
Erik Puffenberger
Kevin Strauss
D. Holmes Morton
http://www.clinicforspecialchildren.org

Eleonora Aronica, Amsterdam
Howard Weiner, NYU
Guy McKann, Columbia