Epilepsy Specialist Symposium
Malformations of Cortical Development and Epilepsy

Symposium Co-Chairs:

Ruben Kuzniecky, M.D.

and

R. Edward Hogan, M.D.

Friday, December 4, 2015
Convention Center – Grand Ballroom AB

8:30 – 11:30 a.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
This symposium will present an update on MRI functions of cortical development and epilepsy. The classification scheme, imaging findings, clinical phenotypes will be presented. Medical and surgical paradigms will be addressed. As a result of attending this symposium, the attendee will recognize clinical and imaging features and classify MCD patients, ordering genetic testing, treatment and counseling.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Recognize MRI and phenotype patterns of MCD, understand the genetics of MCD, initiate genetic studies and provide appropriate counseling
- Participate in the care and counseling of patients with MCDs
- Recognize the clinical presentation of MCD and the impact of MCD on psychological and neuropsychological function

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background in the specialty is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
C0-Chairs: Ruben Kuzniecky, M.D. and R. Edward Hogan, M.D.

Introduction
Ruben Kuzniecky, M.D.

Case Presentation
R. Edward Hogan, M.D.

Pathophysiology and Genetics of Cortical Malformations
Christopher Walsh, M.D.

Neuroimaging of Cortical Malformations
Ruben Kuzniecky, M.D.

Neurological Syndromes Associated with Cortical Malformations
Elliott Sherr, M.D., Ph.D.

Medical Management of Syndromes Associated with Cortical Malformations
Renee A. Shellhaas, M.D., M.S.

Surgical management of Brain Developmental Anomalies
Dennis Spencer, M.D.

Case Summary and Conclusions
R. Edward Hogan, M.D.

Education Credit
3.0 CME Credits

Nurses may claim up to 3.0 contact hours for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 3.0 contact hours (0.25 CEUs). UAN 0077-9999-15-030-L01-P. Initial Release Date: 12/4/2015.

The American Board of Psychiatry and Neurology has reviewed the Malformations of Cortical Development and Epilepsy Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Robert Hogan, M.D. (Co-Chair)
Dr. Hogan is Professor in the Department of Neurology at Washington University in St. Louis, and the Director of the Comprehensive Epilepsy Center at Barnes Jewish Hospital. Dr. Hogan has research interests in multiple different areas of clinical neurology and epilepsy, including the pharmacology and clinical use of antiepileptic medications, semiology of epileptic seizures, and neuro-imaging changes in patients with epileptic seizures. Research interests in neuro-imaging involve single photon emission computed tomography (SPECT), as well as functional and structural MRI, including correlation of neuroimaging with clinical semiology of seizures and EEG findings.

Dr. Hogan discloses receiving support for Consulting for Upsher-Smith Pharmaceuticals, as Contract Research for Upsher-Smith and Sage Pharmaceuticals (clinical trial support).

Ruben Kuzniecky, M.D. (Co-Chair)
Dr. Ruben Kuzniecky is Professor of Neurology at New York University (NYU) Medical School. He is also Co-Director of the NYU Epilepsy Center and Director of the Epilepsy Research Program. Dr. Kuzniecky has authored three books, 38 book chapters, over 270 articles in peer-reviewed journals, and more than 300 meeting abstracts. He has been awarded over 50 research grants from government, industry, and foundation funding sources. Dr. Kuzniecky had served on the editorial boards of Epilepsia and Epilepsy & Behavior and is an ad-hoc reviewer for many epilepsy- and neurology-focused journals. Dr. Kuzniecky served as Treasurer of the American Epilepsy Society and was Chairman of Oldendorf Award Committee for the American Society of Neuroimaging.

Dr. Kuzniecky has indicated he has no financial relationships with commercial interests to disclose.

Renee Shellhaas, M.D., M.S.
Dr. Shellhaas graduated from the University of Michigan Medical School and then completed her residency in Pediatrics and Pediatric Neurology at the Children's Hospital of Philadelphia (CHOP). She stayed at CHOP for her epilepsy fellowship. Dr. Shellhaas returned to Ann Arbor in 2007 to join the faculty at the University of Michigan, Department of Pediatrics (Division of Pediatric Neurology) where she is now a Clinical Associate Professor. Her research is focused on neonatal brain monitoring and neonatal seizures. She is a steering committee member of the Pediatric Epilepsy Research Consortium. Her clinical practice is centered on difficult-to-control childhood epilepsy.

Dr. Shellhass discloses receiving support from Royalties for UpToDate; Other Services from Epilepsy Consortium; Other Services from the Child Neurology Society, Concillor from the Midwest.

Elliott Sherr, M.D., Ph.D.
Elliott Sherr is a Professor of Neurology, Pediatrics and Genetics at UCSF. He directs the Brain Development Research Program, a group that studies the genetics and biology autism and epilepsy (brain.ucsf.edu). Dr. Sherr is member of an epilepsy genetics consortium (http://www.epgp.org/epi4k/) in which he leads a team trying to understand the genetic causes of severe childhood epilepsies, such as infantile spasms. For his research, Dr. Sherr was the 2006 recipient of the Philip R. Dodge Young Investigator Award from the Child Neurology Society. Dr. Sherr completed his bachelors at Stanford University, his M.D. and Ph.D. at Columbia University and his clinical training at UCSF. He lives in San Francisco with his wife and three children.

Dr. Sherr discloses receiving support for Salary generating W2 from Retrotope, Armagen, neither are directly epilepsy related, but are general CNS companies.; for Receipt Of Intellectual Property Rights/Patent Holder through UCSF; for Consulting from Personalis; as Ownership (i.e. stocks, stock options or other ownership) from InVitae, Retrotope, Chemocentryx, Jacaranda Biosciences.

Dennis Spencer, M.D.
Dr Spencer is the Harvey and Kate Cushing professor and immediate past chairman of the department of Neurosurgery at Yale University School of Medicine. He has directed the Epilepsy Surgery Program and co-directed the comprehensive epilepsy center for the past 37 years. He has developed numerous surgical techniques for epilepsy notably the neocortical sparing anteromedial temporal resection, has been the recipient of the clinical research award from the AES, the research award from the Society of Neurological Surgeons (SNS), held the Presidency of both the AES and SNS, chaired the American Board of Neurological Surgery,vice chaired the Residency Review Committee and acted as interim Dean for the Yale School of Medicine.

Dr. Spencer has indicated he has no financial relationships with commercial interests to disclose.

Christopher Walsh, M.D., Ph.D.
Christopher Walsh is Chief of the Division of Genetics and Genomics at Boston Children's Hospital, and an Investigator of the Howard Hughes Medical Institute. His lab focuses on the development, evolution, and function of the human cerebral cortex, and has identified genetic causes for more than twenty brain diseases of children, associated with autism, intellectual disability, seizures, and cerebral palsy. The work has been recognized by awards from the NINDS, American Academy of Neurology, American Neurological Association, American Epilepsy Society and others. He is an elected member of the Institute of Medicine and the American Association for the Advancement of Sciences.

Dr. Walsh has indicated he has no financial relationships with commercial interests to disclose.

CME Reviewer
Leonardo Bonilha, M.D., Ph.D.
I am a neurologist, epileptologist and clinical neurophysiologist. I am an Associate Professor of Neurology at the Medical University of South Carolina, where I work as a clinician scientist. My research involves the mechanistic aspects of brain structure and function (through neuroimaging and EEG) in relationship with language recovery after brain injury, as well as seizures and epilepsy.

Dr. Bonilha discloses receiving support as Consulting from Health Advances, LLC I have provided paid advice regarding best uses of PACS imaging software.

Kevin Chapman, M.D.
Dr. Chapman is a Pediatric Epileptologist at the University of Colorado at Denver and Children's Hospital Colorado.

Kevin Chapman, M.D. discloses receiving support as Contracted Research local PI for the Insys CBD trials on Dravet and LGS at UC Denver. All funds go to my department.

Peter Widdess-Walsh, M.D.
Dr. Peter Widdess-Walsh is a consultant neurologist and epileptologist at the National Neuroscience Centre at Beaumont Hospital Dublin, Ireland, and Director of Neurosciences at the Beacon Hospital, Dublin.

Dr. Widdess-Walsh has indicated he has no financial relationships with commercial interests to disclose.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS
Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

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PHYSICIANS

Physicians can claim CME credit online at **https://cme.experientevent.com/AES151/**

This Link is NOT Mobile-friendly! You must access it from a laptop, desktop or tablet.

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Questions?
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NURSING & PHARMACY

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The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER

Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

Malformations of Cortical Development and epilepsy: Case presentation

R. Edward Hogan, M.D.
Professor, Department of Neurology
Washington University in St. Louis
Medical Director, The Comprehensive Epilepsy Center at Barnes-Jewish Hospital

December 4, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

- Institutional sponsorship clinical trials
  - Upsher-Smith Pharmaceuticals
  - Eisai Pharmaceuticals
- Consultant
  - Upsher-Smith Pharmaceuticals

Learning Objective

- Identify focal epileptic seizure associated with malformations of cortical development

Impact on Clinical Care and Practice

- Improve care for subjects with epilepsy and malformations of cortical development
  - Understand neuroimaging correlates of malformations of cortical development
  - Identify possible epilepsy surgical options for subjects with epilepsy and malformations of cortical development

Clinical history

- **Onset of seizures at age 17**
- **She described floating blinking lights, always starting in the upper portion of the visual field, moving towards the center and obscuring the vision in the field, typically evolving over 30 seconds.**
- **Some events progressed to LOC, with associated jaw clenching, and bilateral UE stiffening**

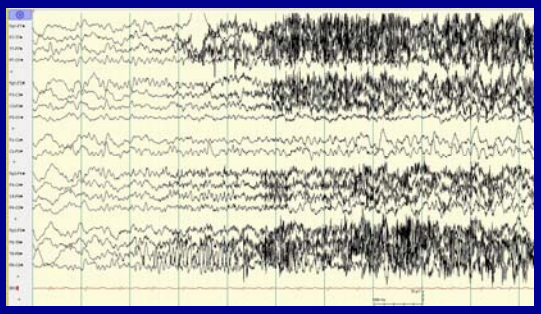
Clinical history

- **At age 20 she had her first secondarily generalized tonic clonic seizure**
- **Diagnosis of epilepsy lead to treatment with lamotrigine**
- **Seizures were well controlled until age 22, when seizures recurred.**

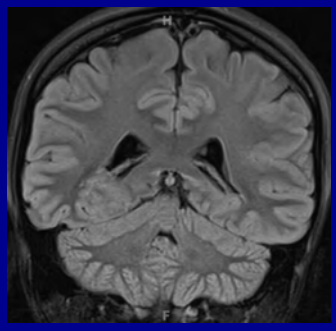
Clinical history

- She subsequently tried trials of carbamazepine, levetiracetam, and topiramate.
- At age 24, she was having partial seizures on a weekly basis.
- During trials of AED treatment, she underwent further work-up for her drug-resistant epileptic seizures.

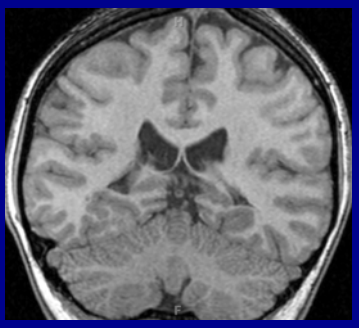
Ictal EEG



FLAIR MRI



T1 MRI



Malformations of cortical development

Group II.A: heterotopia

Peri-ventricular nodular heterotopia

Classification group includes "large subcortical heterotopia that consist of curvilinear swirls of grey matter originating from deep sulci, which wind their way through the cerebral mantle to the ependyma."

Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain 2012 May;135:1348-1369.

Malformations of cortical development and epilepsy

- Genetics
- Neuroimaging
- Neurological Syndromes
- Medical Management
- Surgical Management of Brain Developmental Anomalies

Genetics of Malformations of Cortical Development (MCD)

Christopher A. Walsh, MD, PHD
Division of Genetics and Genomics,
Boston Children's Hospital
Departments of Pediatrics and Neurology
Harvard Medical School

hhmi Howard Hughes Medical Institute | Boston Children's Hospital

December 4, 2015

Disclosure

Consultant, Third Rock Ventures

Consultant, Hoffman LaRoche

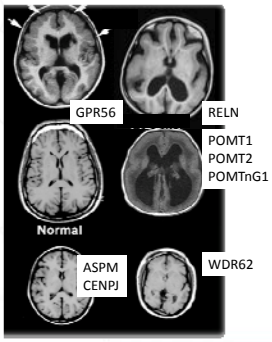
Learning Objectives

- Genetic mechanisms of MCD
  - Genetic and inherited
    - Recessive
    - Dominant
    - X-linked
  - Genetic and not inherited but inheritable
  - Genetic mechanism but uninheritable
  - Important role of *de novo* mutation in epilepsy
- Counseling considerations

Mendelian modes of inheritance of MCD

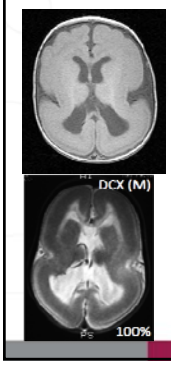
- Genetic mechanisms of MCD
  - Genetic and Inherited
    - Dominant—*TSC1*, *TSC2*, *DEPDC5*, *NPRL2*, *NPRL3*
      - High *de novo* mutation rate
    - X-linked—*DCX*, *FLNA*
      - Usually de novo as well
    - Recessive
      - Virtually always inherited
- Counseling considerations

There are innumerable recessively inherited MCD's



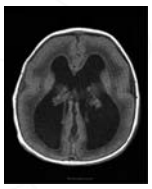
- Mostly rare
- Much more likely if parents are related or of same ethnicity
- Often present early
- Less likely to come to the general epileptologist
- Some are epileptic, some not
- Too numerous to cover in 30 minutes

"Classical" lissencephaly is genetic but rarely inherited due to its severe and lethal nature



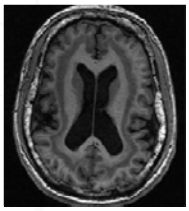
- *De novo LIS1* mutations ("Dominant")
- *De novo DCX* mutations
  - male *DCX* mutations cause lissencephaly
  - female *DCX* mutations cause subcortical band heterotopia-double cortex
- *TUBA1A*, *TUBB2*, other tubulin genes
  - Somewhat more variable picture with lissencephaly or polymicrogyria
- *DYNC1H1* (Dynein Heavy Chain)
- X-linked *ARX* mutations (asymptomatic carrier mothers)
- Mutations once present are theoretically inheritable
  - These lethal disorders are essentially never transmitted from affected probands
  - Can be recurrent in a family due to asymptomatic carrier parent (e.g., *ARX* or *DCX*)

Type II/"Cobblestone" Lissencephaly



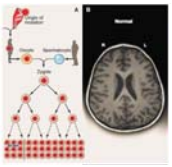
- Usually easy to distinguish from "classical" lissencephaly
- Hydrocephalus, white matter changes
- Associated muscle disease, retinal dysplasia
- Recessive mutations in a large number of genes
  - *POMT1*, *POMT2*, *FKTN*, *POMGnT1*, *GTDC2*, etc.

Subcortical band heterotopia



- Typical patient is female
- X-linked *DCX* mutation in females
- Males with *DCX* mutations show lissencephaly
- About 50% of mutations are *de novo* (absent in parents)
- Mutations can be inherited from affected probands
- *De novo*, but inheritable

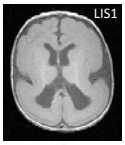
Inherited, *de novo*, somatic mutations are surprisingly important in epileptic MCD's



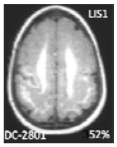
Somatic Mutations in Cerebral Cortical Malformations

Poduri et al., 2013 Science

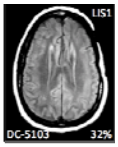
Subcortical band heterotopia can reflect somatic mutations in LIS1



100% of cells with mutation

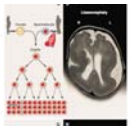


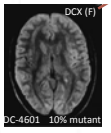
50% of cells with mutation



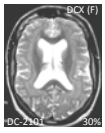
32% of cells with mutation

Subcortical band heterotopia can reflect somatic mutations in DCX

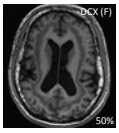




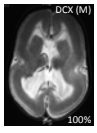
10% of cells with mutation (F)



30% of cells with mutation (F)

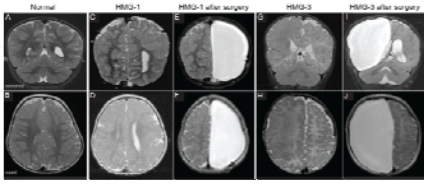


100% of cells with mutation (F)



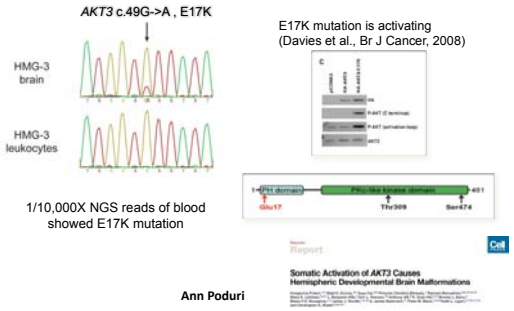
100% of cells with mutation (M)

Hemimegalencephaly represents gain of function mutations in the MTOR pathway



- Essentially the entire hemisphere diffusely enlarged and malformed
- No clear border between affected and unaffected areas
- 8%-35% of cells carry mutation
- Caused by several different genetic lesions
- No obvious differences between different genes

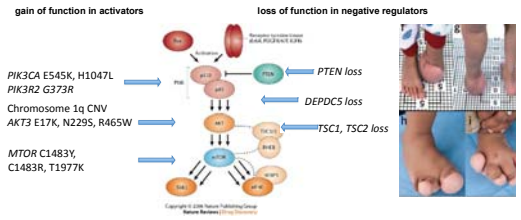
An activating *AKT3* E17K point mutation in brain, but not in blood, causes hemimegalencephaly (HME)



1/10,000X NGS reads of blood showed E17K mutation

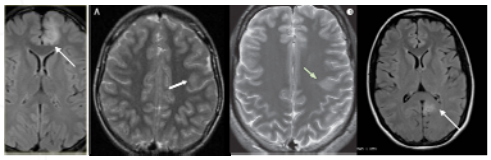
Ann Poduri

Hemimegalencephaly is one of several overgrowth syndromes associated with mutations that activate mTOR:
normally controls protein synthesis, cell size, cell proliferation, and cell identity



Baulac, Biesecker, Dobyns, Gleeson, Lee, Scheffer, Walsh, Warman labs

Focal cortical dysplasias also reflect somatic mutations

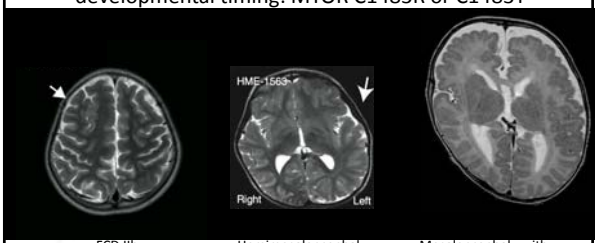


- FCD is most common cause of intractable epilepsy in children
- FCD's can occur anywhere from front to back, and from medial to lateral
- FCD's are typically the size of a gyrus or a sulcus: 1-2 cm in each direction
- Emerging genetics suggests that FCD and Hemimegalencephaly are allelic disorders
  - differing size and shape of lesion reflect developmental timing

Isolated focal cortical dysplasia shows same mutations as hemimegalencephaly

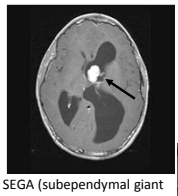
- AKT3 triplication; AKT3 E17K;
- PIK3CA E545K, H1047L, others;
- MTOR C1483Y
- Same mutation but present in a smaller fraction of cells, and a smaller region of the cortex

Same mutation causes distinct MCDs based on developmental timing: MTOR C1483R or C1483Y

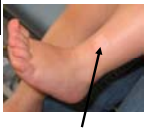


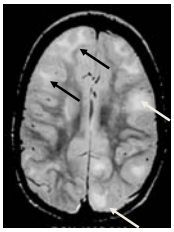
FCD IIb	Hemimegalencephaly	Megalencephaly with Polymicrogyria
C1483R	C1483Y	C1483Y
12.8% of cells	19.4% of cells	*De novo* germline
Not in saliva	Not in blood	(blood sequenced)
Lim et al. 2015	Lee et al. 2012	Unpublished data, D'Gama et al

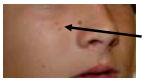
Tuberous sclerosis shows multiple FCD's (tubers) as well as other findings in CNS and elsewhere



SEGA (subependymal giant cell astrocytoma)







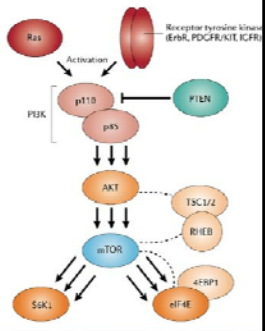
Shagreen patch
Facial angiofibroma

Cortical tubers

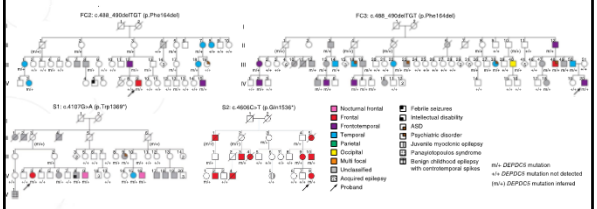
[Courtesy of Dr. Mustafa Sahin]

Tuberous sclerosis is paradigm of a dominantly acting mutation with lesions caused by "second hit"

- *TSC1* or *TSC2* mutation is inherited in one of these genes, and is detectable in peripheral blood, allowing diagnosis
- TSC1/2 negatively regulate MTOR
- Loss of TSC1/2 causes activation of MTOR, causing abnormal growth, proliferation and protein synthesis
- Typical brain contains> 20 cortical lesions along with other features
  - Subependymal heterotopia, subependymal giant cell astrocytoma
  - Lesions probably represent inactivation of the second allele
    - Examples confirm this



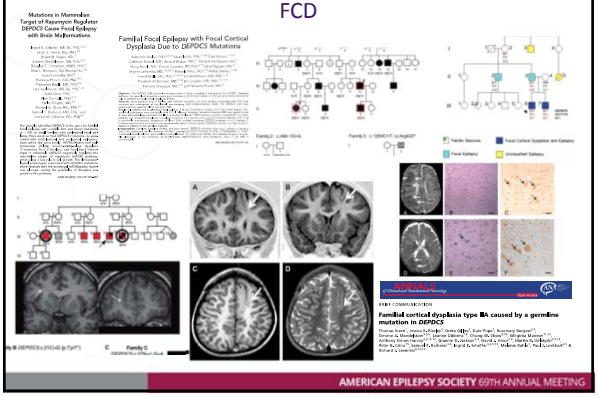
DEPDC5 mutations cause dominantly inherited focal epilepsy



Mutations in *DEPDC5* cause familial focal epilepsy with variable foci

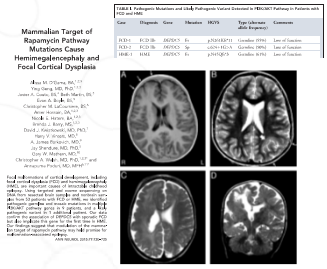
Mutations of *DEPDC5* cause autosomal dominant focal epilepsies

DEPDC5 mutations represent an inherited form of FCD



Familial cortical dysplasia type 8A caused by a germline mutation in *DEPDC5*

DEPDC5 mutations cause isolated FCD or hemimegalencephaly

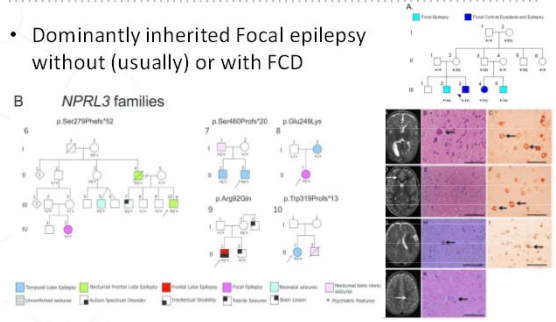


Mammalian Target of Rapamycin Pathway Mutations Cause Hemimegalencephaly and Focal Cortical Dysplasia

- *DEPDC5* mutations may act analogously to TSC mutations
- One inherited germline mutation predisposes to epilepsy and occasional dysplasia
- Much milder than *TSC*
- Second somatic mutation in specific lesions?
  - This mechanism not yet proven

NPRL2, *NPRL3* are the newest form of focal epilepsy with occasional FCD

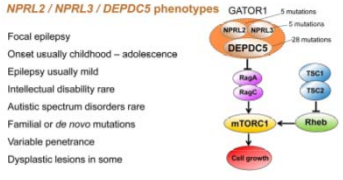
- Dominantly inherited Focal epilepsy without (usually) or with FCD



Ricos et al, Sim et al Annals of Neurology, (in press; available online)

NPRL2, *NPRL3* are the newest inherited forms of focal epilepsy with occasional FCD

- Dominantly inherited Focal epilepsy with or without FCD
  - *DEPDC5*
  - *NPRL2*, *NPRL3*



Ricos et al, Annals of Neurology, (in press; available online)

Impact on Clinical Care and Practice

- Genetic counseling impact
  - Most FCD's and Hemimeg reflect spontaneous somatic mutations of *MTOR*, *PIK3R2*, *PIK3CA*, *AKT3*
  - Some FCD's reflect inherited *DEPDC5*, *NPRL2*, *NPRL3* mutations
- Future treatment impact
  - A significant proportion of frontal epilepsy associated with mutations in MTOR pathway
  - Effective inhibitors of MTOR suggest potential mechanistic therapies of these frontal lobe epilepsies
  - *DEPDC5*, *NPRL2*, *NPRL3* mutations suggest a careful search for FCD is warranted in focal epilepsy, especially in the setting of a positive family history

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David Kwiatkowski, June Goto
Joe Madsen, Peter Black
Ed Yang

Seeking collaborations for analysis of focal cortical dysplasia specimens

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#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Neuroimaging of Malformations of Cortical Development

Ruben Kuzniecky, MD
Professor and Co-Director
NYU Epilepsy Center
NYU School of Medicine
New York

December 4, 2015

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Disclosure

Name of Commercial Interest	Name of Commercial Interest
Speaker/Lecturer	Sunovion, Esai, Lundbeck

Learning Objectives

- Review Imaging Findings and classification of MCD
- Review imaging Techniques for Diagnosis of MCD
- Describe Advances in Imaging techniques in MCD

Impact on Clinical Care and Practice

- Appropriate Diagnosis leads to:
  - Correct Treatment
  - Correct Prognosis
- Correct classification leads to:
  - Targeted Genetic testing
  - Counseling and family planning

MRI Characterization of MCD

- **First Level Characterization**

- Generalized Malformations
- Hemispheric Malformations
- Focal or multifocal Malformations
- Other Structures Findings
  - Corpus Callosum
  - Cerebellum
  - Brainstem

MRI Characterization of MCD

- **Second Level Characterization**

- Generalized
  - Cortical
  - Cortical/Subcortical
  - Lissencephalic Vs Pachygyric Vs PMG
- Hemispheric
  - Same as above
- Focal or Multifocal
  - Cortical vs BSCD vs Cortical/Subcortical
  - Abnormal white matter, Signal intensity
  - Abnormal vasculature

Classification System of MCD

- Malformations due to Abnormal Cell proliferation or Apoptosis
- Malformations due to Abnormal Cell Migration
- Malformations due to Abnormal Cortical Organization
- Malformations of Cortical Development not Classified

Barkovich, Kuzniecky, Guerrini, Jackson, Dobyns
Neurology, 2012

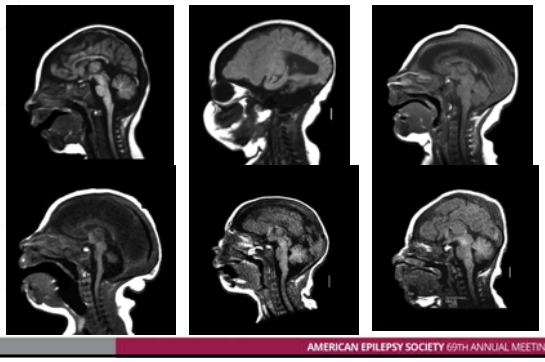
MCD due to Abnormal Cell Proliferation

Microcephalies

- Microcephaly with cerebellar anomalies
- Microcephaly with brainstem anomalies
- Microcephaly with normal cortex
- Microcephaly with smooth brain
- Microcephaly with other abnormalities

Several Genes involved spanning mitosis, microtubule formation, cell replication,

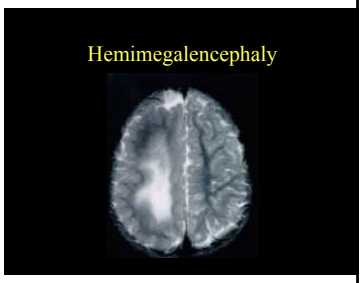
Microcephalies



MCD due to Abnormal Cell Proliferation

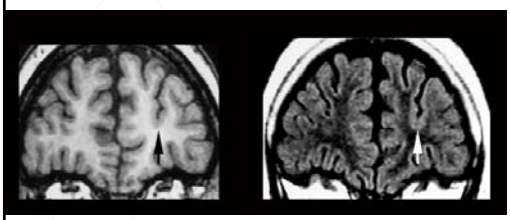
Intractable Seizures
Hemiparesis
Developmental Delay

Etiology : ?
Pathology: Variable
Treatment: Mostly effective



mTOR pathies (AKT3 and PIK3CA)

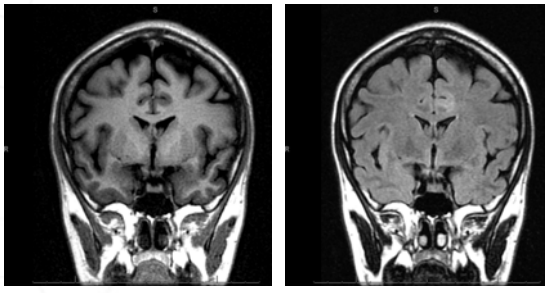
Focal Cortical Dysplasia



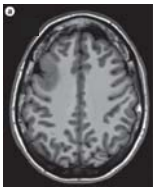
Bottom of Sulcus FCD

mTOR pathies

Focal Cortical Dysplasia (type IIb)



The Problem:50-80% of epileptogenic Developmental lesions escape routine visual inspection of MRI

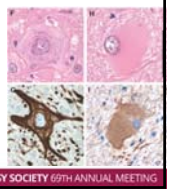


Kuzniecky &Barkovich, 2001; Lerner et al)

- Most common pathological finding in surgical specimen in cryptogenic patients

Potential reasons:

- Mostly represent subtle lesions
- May contain pathological features that are visually not appreciable on current MRI sequences
  - FCD *Type I*: 87% have normal MRI
  - FCD *Type II*: 37% have normal MRI
- Highly dependent on reviewer training
- Lot of information to process:
  - NYU MRI epilepsy protocol at 3T includes 10 sequences with 739 images
  - Time available for review: < 10 min



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Malformations due to Abnormal Cell Migration

Lissencephalies, Cobblestone and heterotopia

A.

- Microtubules mutations leading to abnormalities of cortical, subcortical, white matter, callosal, cranial nerves, etc
- Microtubule-associated-proteins (MAPs) such as DCX, LIS1, Kinesins and Dynein.

B.

- ARX
- REELIN

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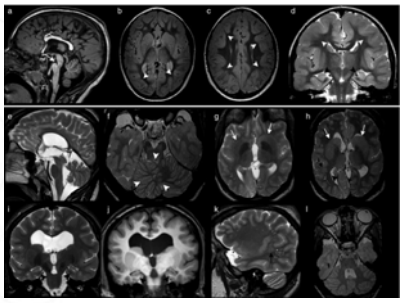
Tubulinopathies



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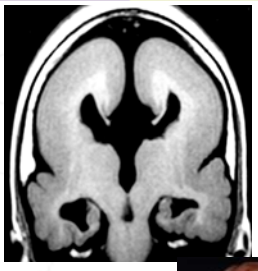

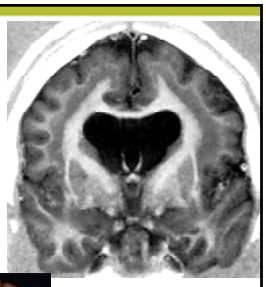

12 y/o brother

MAPS-DCX/LIS1

16 y/o Sister

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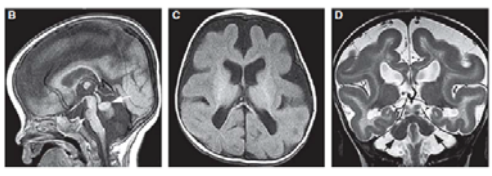
Malformations due to Abnormal Cell Migration

REELIN Mutation



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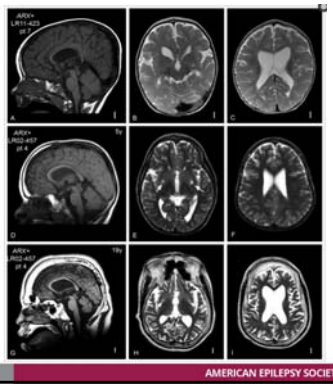
ARX Mutation



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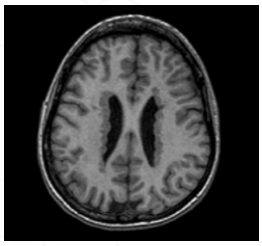
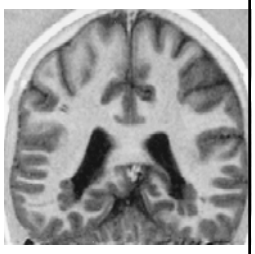
Heterotopia
PVNH



FLNA +



FLNA -

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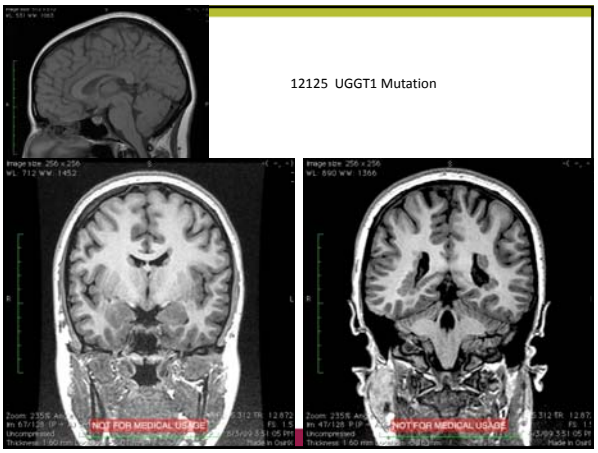
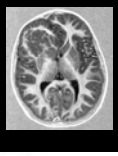
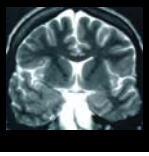


Malformations of Cortical Development

Focal Subcortial Heterotopia



Focal Subcortial Heterotopia



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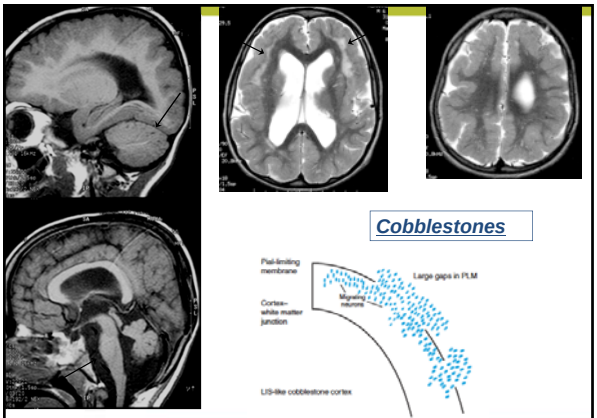

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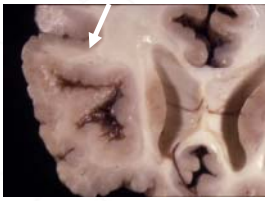
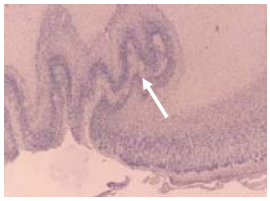
Malformations due to Abnormal Cortical Organization

Polimycrogyrias





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Classification of PMG/Schiz

2. Polymicrogyria Without Clefts Or Calcifications classified by location
Clinically defined bilateral PMG without clefts of unknown cause
- a. Generalized PMG
- b. Frontal PMG
- c. Perisylvian PMG
- d. Posterior PMG (lateral parieto-occipital)
- e. Parasagittal PMG
- f. Parasagittal mesial occipital PMG

Clinically defined unilateral PMG without clefts of unknown cause
- g. Hemispheric PMG
- h. Perisylvian PMG
- i. Focal PMG

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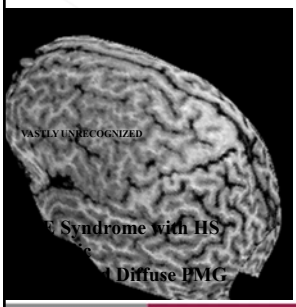
Syndromes with PMG

Syndromes With Polymicrogyria (neuropathology may differ from classic PMG)
Clinically defined syndromes with AD inheritance
a. Adams-Oliver syndrome AD form
Clinically defined syndromes with AR inheritance
b. Adams-Oliver syndrome AR form
c. Joubert syndrome and related disorders with PMG,
Clinically defined syndromes with XL inheritance (probable)
d. Aicardi syndrome
e. Oculocerebrocutaneous (Delleman) syndrome
Genetically defined with AD inheritance (new mutations)
f. Fronto-parietal PMG, variable ACC and delayed myelination of anterior limb internal capsule with *TUBB2B* mutations
g. Fronto-parietal PMG, variable with *TUBB3* mutations
h. Knobloch syndrome variable PMG with *COL18A1* mutations
i. Aniridia, variable temporal PMG, and CBL hypoplasia w *PAX6* mutations
j.k. Perisylvian PMG with deletion 1p36.3 or deletion 22q11.2
Genetically defined with AR inheritance
k. Goldberg-Shprintzen (megacolon) syndrome with mutations of *KIAA1279*
l. Joubert syndrome with variable (low penetrance) PMG and *AHI1* mutations
m. Meckel-Gruber syndrome.
n. Generalized (vs perisylvian) PMG, ACC and optic nerve hypoplasia with *TUBA8* mutations
o. Perisylvian PMG, ACC, delayed myelination of anterior limb internal capsule and cerebellar vermian hypoplasia with mutation of *TBR2* (*EOMES*)
Genetically defined with XL inheritance
s. Perisylvian PMG, Rolandic seizures and speech-language dyspraxia with *SRPX2* mutations
t. Perisylvian PMG, mild MIC and thin body habitus with *NSDHL* mutation
u,v. Perisylvian PMG with Xq27 or Xq28 locus

Polymicrogyria



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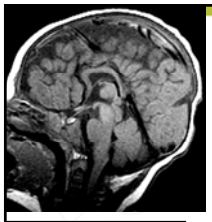
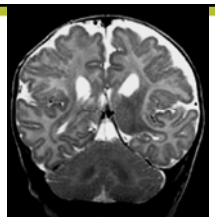
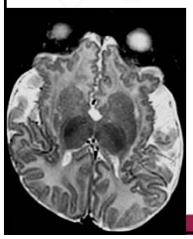
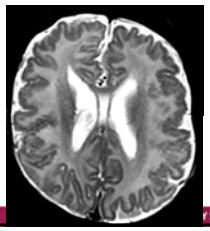

Multifocal Asymmetric PMG

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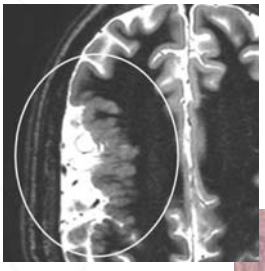
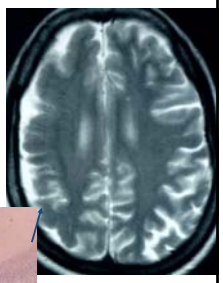
Unilateral Polymicrogyria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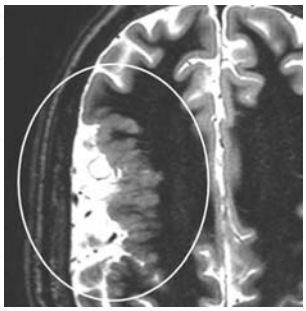

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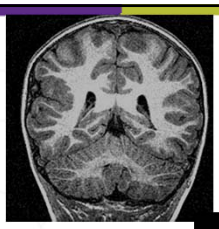
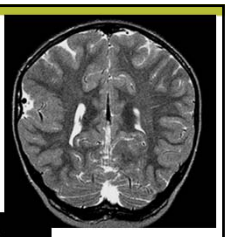
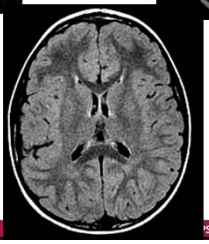

22 year old woman with partial epilepsy

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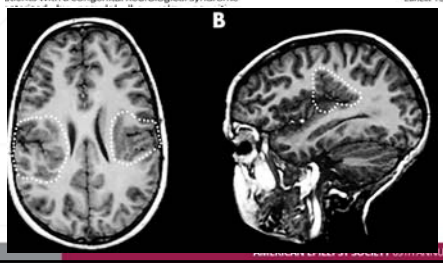
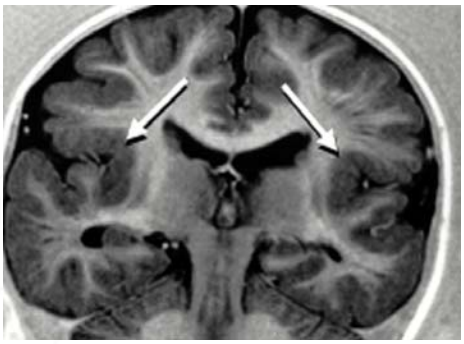
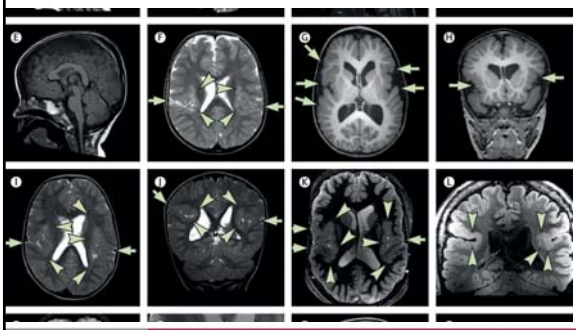
Congenital bilateral perisylvian syndrome: study of 31 patients

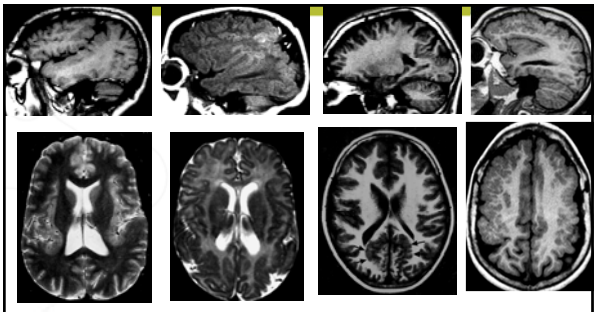
Ruben Kuzniecky Frederick Andermann Renzo Guerrini
and the CBPS Multicenter Collaborative Study*





PIK3R2 Mutations in CBPS

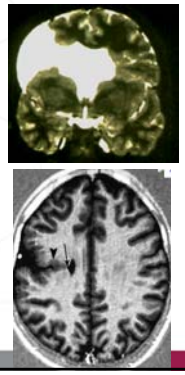


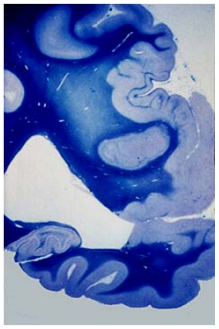


Perisylvian Parietal Par-Occ Frontal

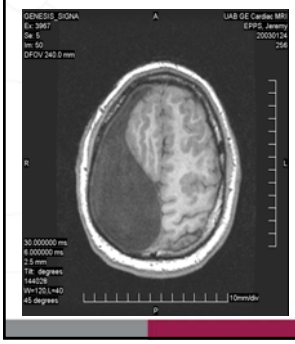
Bilateral PMG Syndromes

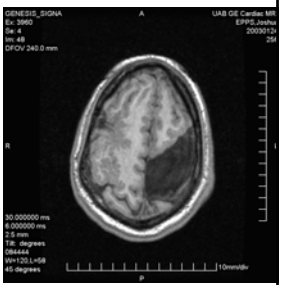
Schizencephaly/PMG





Familial SCH/PMG Syndrome

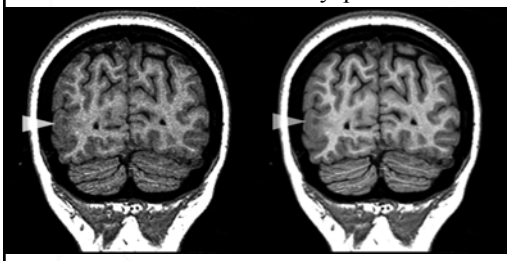




Improving Diagnosis of MCD's

- Better gray/white matter Contrast
- Higher in plane resolution
- Better SNR
  - Improved Coils
  - Higher Magnetic Field
- Computational Analysis
- Machine Learning
- Co-registration Multi-imaging Modalities PET/SPECT
- New Targets (inflammation, Receptors, etc)
- Network analysis
-

Image Averaging
Focal Cortical dysplasia

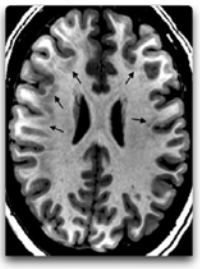


1 SPGR series

4 SPGR series

Knowlton et al

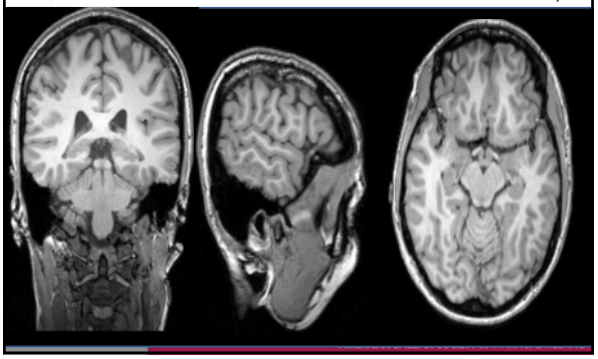
High Resolution 8S-coils



Grant et al 2004 MGH

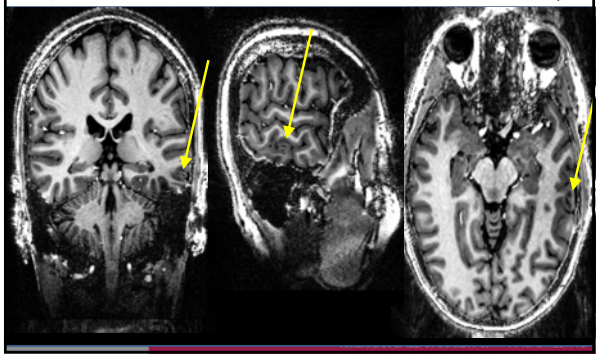
3T: best look

10/2015
University of Pittsburgh
New York University

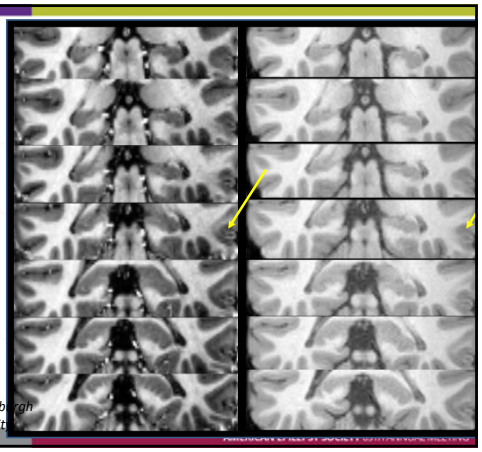


7T: best look

10/2015
University of Pittsburgh
New York University



7T images are re-angulated to approximately match 3T



10/2015
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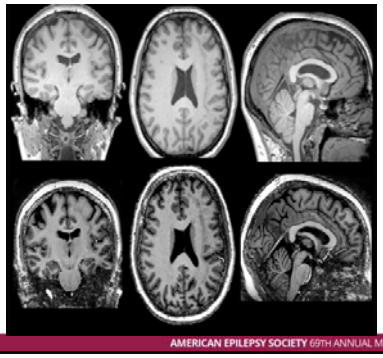
New York University

Subcortical heterotopia

3T

7T



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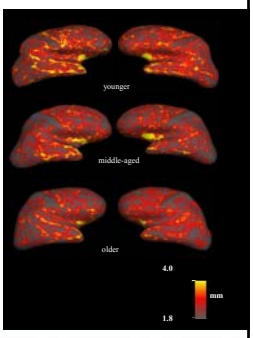
Cortical Thickness

- Distance between white and pial surfaces
- One value per vertex



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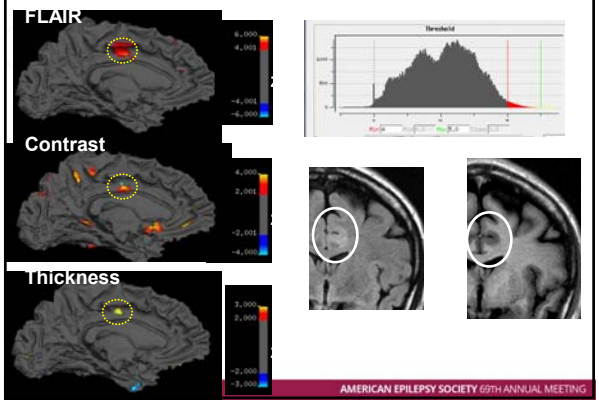

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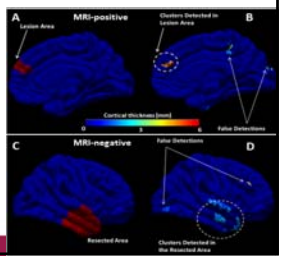
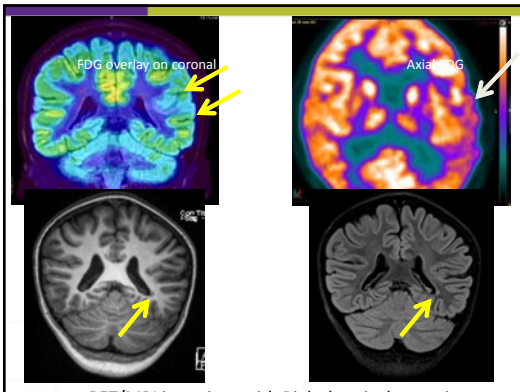
Machine Learning in MRI-negative patients

	Lesion detection accuracy	
	MRI-positive	MRI-negative
Z-score	6/7 patients (85%)	9/25 (37%)
Machine Learning classifier *	6/7 patients (85%)	**14/24 (58%)**



* Vertex-wise false positive rate was always below 2.5 %



PET/MRI in patient with Right hemisphere seizures.

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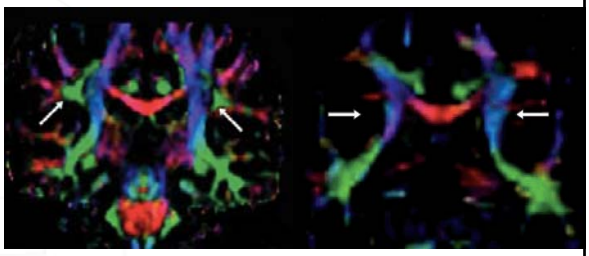
Abnormal Longitudinal Fasciculus CBPS



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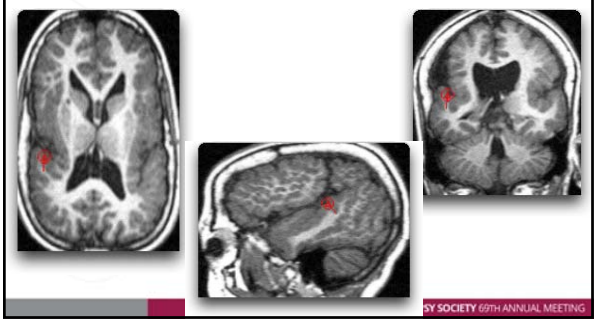
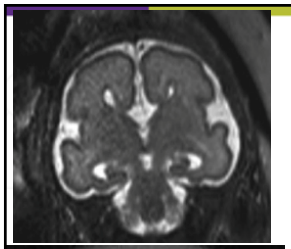
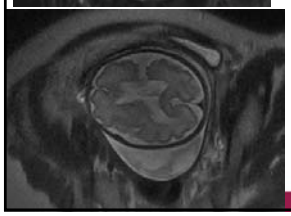
Unilateral Polymicrogyria
MEG/PET

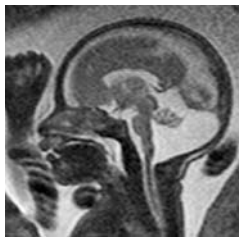
Polymicrogyria
MEG SSDL







Fetal MRI for diagnosis of MCD



#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Neurological Syndromes Associated with Cortical Malformations

Elliott H. Sherr M.D. Ph.D.
Professor of Neurology and Pediatrics
University of California, San Francisco

UCSF Benioff Children's Hospital San Francisco

December 4th, 2015

American Epilepsy Society 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

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Stock Ownership

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Jacaranda Biosciences
Stock Ownership

Learning Objectives

- Recognize brain malformation syndromes associated with epilepsy
- Understand neurologic manifestations of these conditions
- Appreciate extra-neurologic features of these disorders

Impact on Clinical Care and Practice

- Understand the neurologic manifestations of these syndromes
  - Neurologic outcomes
  - Seizure types
- Appreciate Role that advanced genetic techniques play in resolving epilepsy syndrome etiologies
  - Exome Sequencing vs. Epilepsy Panels
  - Range of phenotypes revealed by broad genetic investigation

Syndromes Associated with Brain Malformations

- Well recognized syndrome but with unclear genetics
- Newly recognized syndrome, with expanding phenotypic spectrum
- Syndrome with both CNV and single gene causes

"Think outside the box"

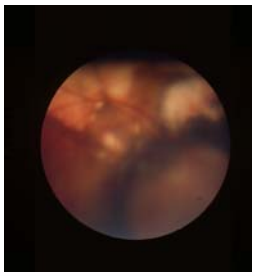
Aicardi Syndrome—well recognized, genetics unclear

- **Infantile Spasms**
- **Chorioretinal Lacunae**
  - And other eye findings (e.g. coloboma)
- **Agenesis of the Corpus Callosum**
- Extensive malformations of cortical development
- Association with cancer/tumors?

INFANTILE SPASMS

AL MEETING

CHORIORETINAL LACUNAE



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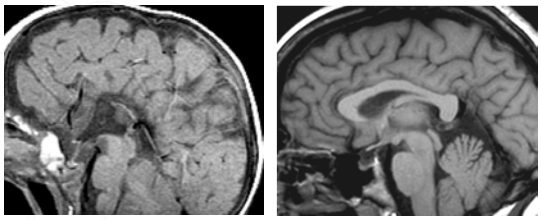
AGENESIS OF THE CORPUS CALLOSUM



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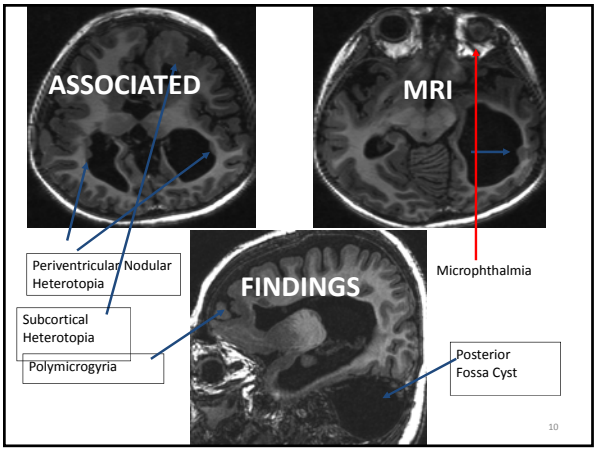

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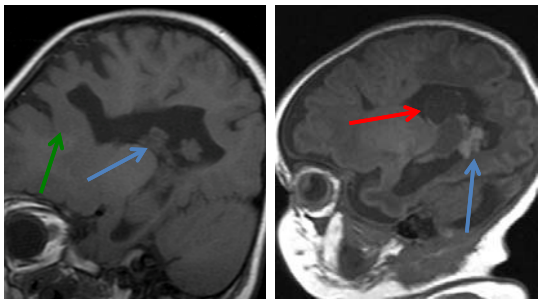
CHOROID PLEXUS PAPILLOMA



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DISTINCTIVE CLINICAL FEATURES

Unique Genetic/Epi Aspects

- Only found in females or in XXY Males
- Never recurs in the same family
- Two cases of discordant monozygotic twins
- No ethnic predilection
- 1-3% of cases of IS
- 1-3% of cases of ACC
- >1,000 cases worldwide

Additional Clinical Attributes

- Eye findings:
  - Coloboma or optic nerve and iris
  - Microophthalmia,
- Skeletal
  - Scoliosis
  - Butterfly vertebrae
  - Bifurcated or missing rib
- Tumors
  - Medulloblastoma
  - Hepatoblastoma
  - Hemangioma
  - Angiosarcoma
  - Embryonal carcinoma
  - Choroid Pexus Papilloma

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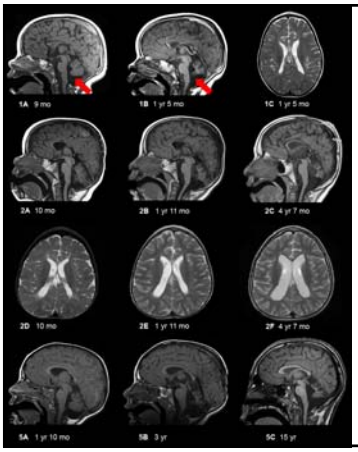
GENETIC INVESTIGATION

- No Cause yet identified
- One report of de novo mutation in gene TEAD1 , but only in one patient
- Given discordant twins and no recurrence in families, may be somatic mutation that causes disorder

Index Case

Newly identified genetic syndrome, expanding phenotypic spectrum

- Presented with developmental regression
- Optic atrophy
- Spastic paraparesis and peripheral neuropathy
- Seizures
- MRI showed progressive cerebellar and cerebral atrophy
- Exome Sequencing:
  - KIF1A
    - (R216H, c.647 G>A) de novo



Progressive Volume Loss In KIF1A de novo Dominant Mutation Carriers

Esmaeeli Nieh et al. Ann Clin Transl Neurol. 2015

PEHO Syndrome:

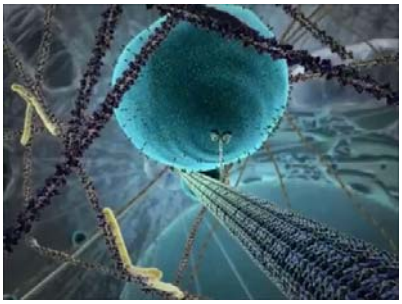
Progressive Encephalopathy, hypssarhythmia, hypertonicity and Optic atrophy

- Myoclonic Jerks and Infantile Spasms
- 4 patients with de novo T99M
- 2 patients with mutations at AA 215, 216
- Many reported KIF1A de novo mutations with regression, but without seizures, most have severe developmental impairment

Langlois, et al, *European Journal of Human Genetics* AOP 21 October 2015;

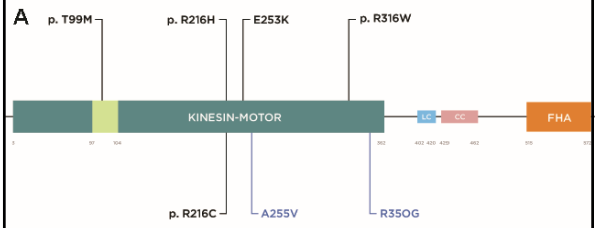
Kinesin Superfamily

Kinesin moving a vesicle on MT



Extracted from The Inner Life of a Cell by Cellular Visions and Harvard

KIF1A: Sites of Mutations



Spastic Paraplegia, Autosomal Recessive
Intellectual Disability, Autosomal Dominant

Esmaeeli Nieh et al. Ann Clin Transl Neurol. 2015

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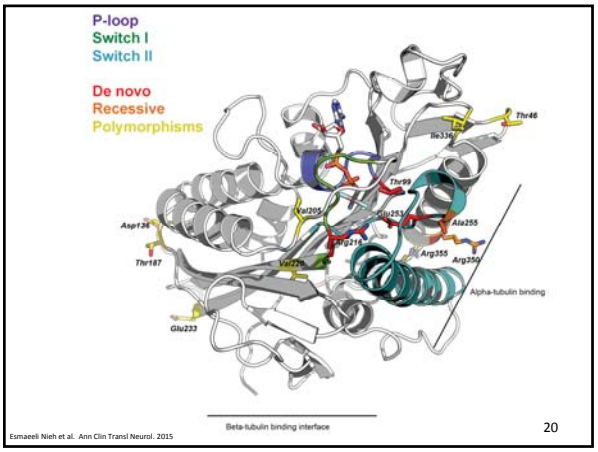

Esmaeeli Nieh et al. Ann Clin Transl Neurol. 2015

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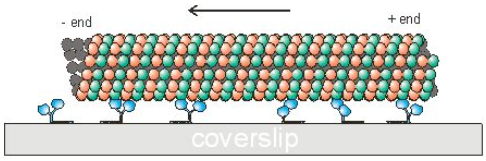
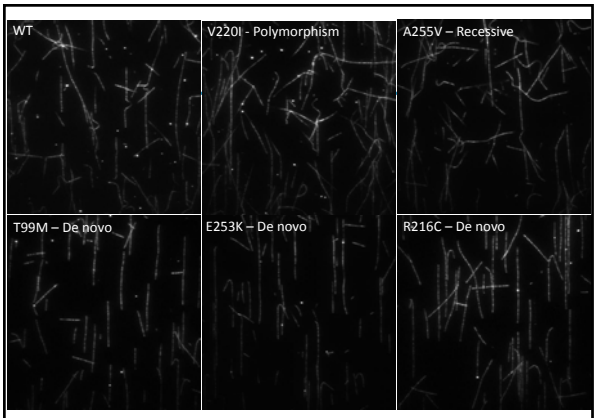
Gliding assay



https://valelab.ucsf.edu/images/movies/mov-invitmtglid.mov

21



Esmaeeli Nieh et al. Ann Clin Transl Neurol. 2015

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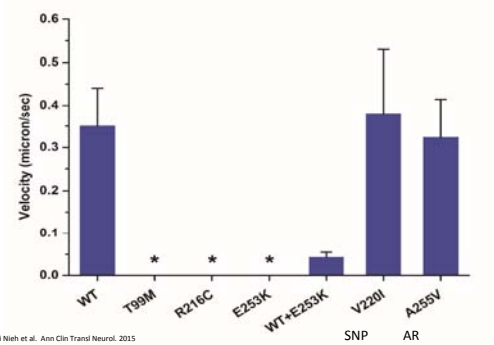
MT Speeds in WT and Mut KIF1A



Esmaeeli Nieh et al. Ann Clin Transl Neurol. 2015

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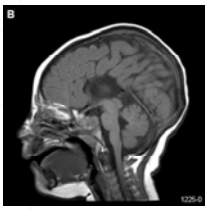
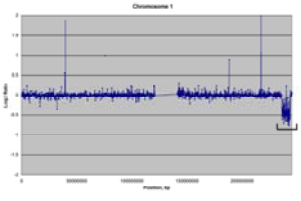
De Novo Deletion of 1qter





- Microcephaly, agenesis of the corpus callosum
- Epilepsy, Autism, Intellectual disability

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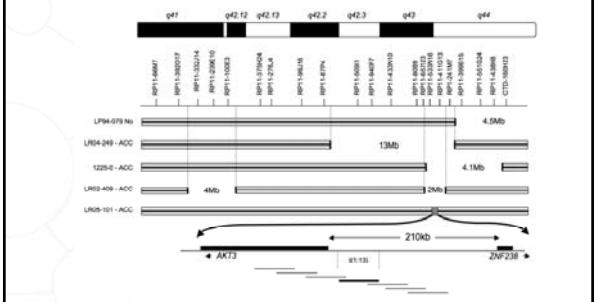
Deletion of 1qter; narrowing interval

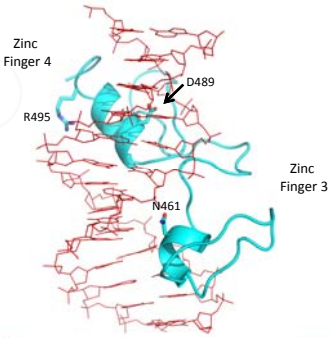


Boland et. al, Am J Hum Genet. 2007 Aug;81(2):292-303

Exome Sequencing Uncovers De Novo Mutations

- 4 year male patient
- Seizures, ASD, GDD, microcephaly (-2.5 SD)
- MRI: partial callosal agenesis, diminished white matter volume
- Whole Exome sequencing
  - c.1466A>T in ZNF238 (ZBTB18)
  - D489V (predicted pathogenic)

3-D Model of ZNF238 Binding DNA



Summary

- Aicardi Syndrome
  - Unique grouping of clinical and imaging findings
  - Likely de novo genetic, may be somatic mosaic
  - Involves other organ systems, may have linkage to cancer etiology
- PEHO syndrome
  - Epilepsy, progressive neurologic deterioration, brain atrophy on MRI
  - De novo mutations in KIF1A, impairing axonal transport of synaptic vesicles
- 1qter deletion syndrome
  - Epilepsy, autism, agenesis corpus callosum
  - Two likely genes: AKT3 and ZNF238
  - De novo missense mutations in ZNF238 replicate many features of syndrome

#AESmtg15

AMERICAN EPILEPSY SOCIETY

69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Medical Management of syndromes associated with MCD

Renée Shellhaas, MD, MS
University of Michigan

University of Michigan
C.S. Mott Children's Hospital

December 4, 2015

American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosures

Research Funding:
- NICHD
- American Sleep Medicine Foundation
- University of Michigan

Consultant:
- Epilepsy Study Consortium

Royalties:
- UpToDate

Learning Objectives

- Review the evidence (or lack thereof) that guides medical management for people with epilepsy related to MCD.
  - Tuberous Sclerosis Complex
  - Other syndromes

Impact on Clinical Care and Practice

- Medical management depends on patient's age and disorder.
  - Review TSC Surveillance & Treatment Guidelines
  - Review data relevant to the clinical syndrome
    (e.g. Infantile Spasms, Lennox Gastaut Syndrome)
- Ketogenic diet is often appropriate.
  - Review Ketogenic Diet Guidelines

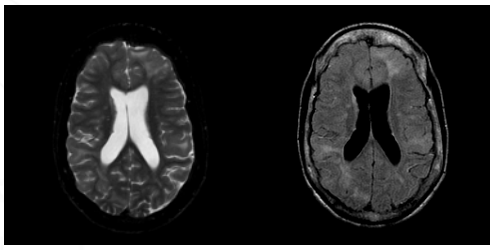
This is a tough topic.

We all know the best chance for a cure is surgery…
When the MCD is focal
When the MCD is resectable

What about those for whom surgery is not (currently) an option?

Evidence is sparse.

- For people with MCD, epilepsy is often very difficult to treat.
- For people with difficult to treat epilepsy, we try everything!



Treatment of TSC-associated epilepsy

Contents lists available at ScienceDirect
Pediatric Neurology
journal homepage: www.elsevier.com/locate/pnu

Original Article

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference

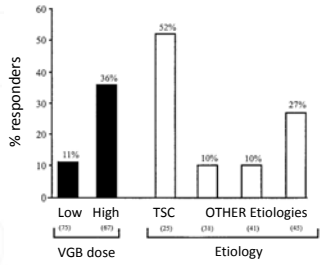
Darcy A. Krueger MD PhD [a,*], Hope Northrup MD [b], on behalf of the International Tuberous Sclerosis Complex Consensus Group

"Anticonvulsant therapy in TSC should generally follow that of other epilepsies."

Krueger, et al. Pediatric Neurology. 2013;49:255-265.

TSC + INFANTILE SPASMS = VIGABATRIN

- ~50% of people with TSC have infantile spasms.

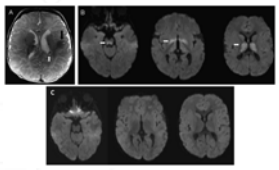


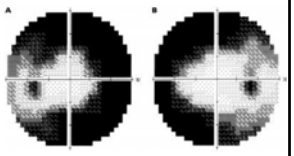
Elterman, et al. Neurology. 2001;57:1416-1421.

Why Vigabatrin?

- Vigabatrin ↑s GABA:
  irreversible inhibition of GABA transaminase.
- Inhibits mTOR pathway in mouse models.

Jülich & Sahin. Pediatr Neurol. 2014;50:290-296.
Zhang, et al. PLoS One. 2013;8;e57445.

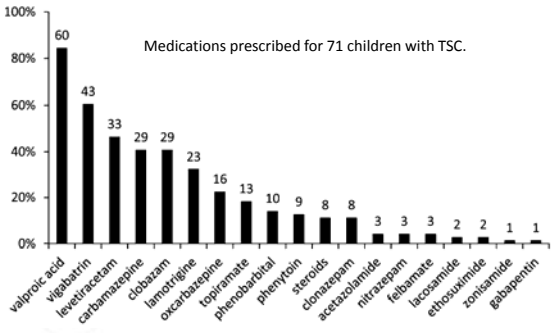




Hsieh & Thiel. J Pediatr. 2013;162:215.

Ravindran, et al. JNNP. 2001;70:787-789

What about other medications and seizure types?



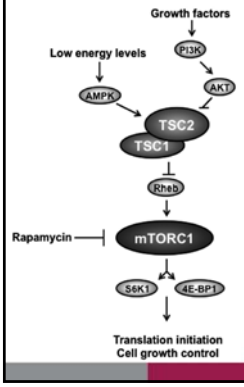
Overwater, et al. Epilepsia. 2015; 56:1239-1245.

Controversy: When should treatment begin?

- For infants with TSC…
  - Recommendation for screening EEG
    - Monthly until 6 months, then every 6-8 weeks
  - Treatment BEFORE seizures occur?
  - Could *prevention* of spasms ↑ neurodevelopment?

Krueger, et al. Pediatr Neurol. 2013;49:255-265.
Józwiak, et al. Eur J Paediatr Neurol. 2011;15:424-431.
Curatolo, et al. Eur J Paediatr Neurol. 2012; 16:582-586.

What about mTor inhibitors?



Animal TSC models:
- *Prevent epilepsy*
- *Improve myelination*
- *Improve synaptic function*
- *Improve learning*
- *Better seizure control*

Jülich & Sahin. Pediatr Neurol. 2014;50:290-296.

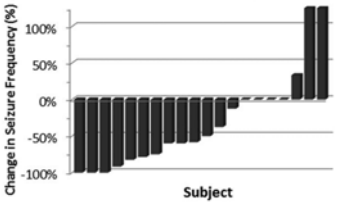
mTor inhibitors for *people* with TSC

- Everolimus for treatment of SEGA:
  - ↓ Seizure burden after 6 months of Rx in phase II study
  - Result not duplicated in phase III RCT
  - Not all subjects had seizures
  - Epilepsy Rx was not held constant during the trial

Krueger, et al. NEJM. 2010;363:1801-1811.
Franz, et al. Lancet. 2013;381:125-132.

mTor inhibitors for *people* with TSC <u>& epilepsy</u>

- Prospective, open-label
- Phase I/II
- Everolimus 5mg/m^2/day
- Goal level 5-15ng/ml



Response increased over time – duration-dependent mechanisms?
Better seizure control – ↑quality of life and behavior.

Krueger, et al. Ann Neurol. 2013;74:679-687.

Are mTor inhibitors ready for prime time?

- Side effects are common – *immunosuppression*

TABLE 2. Adverse Events

Category	Grade 1	Grade 2	Drug-Related	Terms (No.)[a]
Allergy	0	1	0	—
Hematologic	0	1	1	—
Constitutional	8	6	13	Fever (7); fatigue (4)
Dermatologic	11	3	4	Rash (4)
Gastrointestinal	34	2	29	Stomatitis/mucositis (18); diarrhea (6); nausea/vomiting (5); anorexia (4)
Infectious	2	29	29	Upper respiratory infection (19); otitis media (5); gastroenteritis (4)
Neurologic	3	4	1	—
Pain	1	1	0	—
Pulmonary	13	0	6	Congestion/rhinorrhea (7); cough (6)
Genitourinary	1	0	0	—
Total	73	47	83	

[a]Includes only event types with occurrence ≥2% of all reported adverse events.

Krueger, et al. Ann Neurol. 2013;74:679-687.

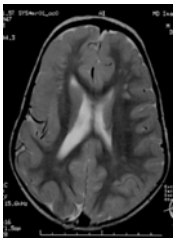
Are mTor inhibitors ready for prime time?

Stay tuned… many more data will be available soon!

What about patients who don't have TSC?

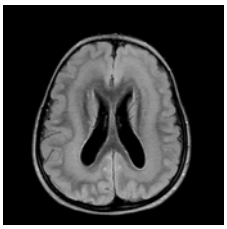
- 15-year-old with mild hemiparesis and rare focal clonic seizures.
- Chromosome 3p duplication
- Seizure-free on levetiracetam

- **Would you ever wean him off?**



Evidence is sparse

- 9-year-old with Lennox-Gastaut Syndrome
  - Ketogenic Diet
  - Clobazam
  - Felbamate
  - Zonisamide

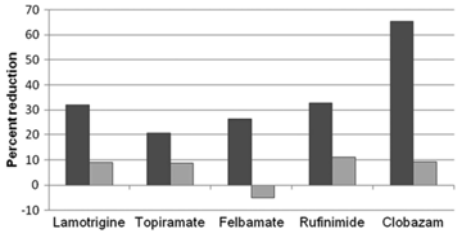


Still having daily seizures… what do you do?

Treating Difficult Epilepsy – the kitchen sink approach?

http://usscouts.org/usscouts/cartoons/knots_kitchen_sink.jpg

FDA-approved AEDs for Lennox-Gastaut Syndrome



Purcarin & Ng. Ther Adv Neurol Disord. 2014; 7: 169–176.

Non-pharmaceutical therapies

	Classic Ketogenic Diet	Medium chain triglyceride (MCT)	Modified Atkins	LGIT
Fat calories (% total)	90	70	70	45

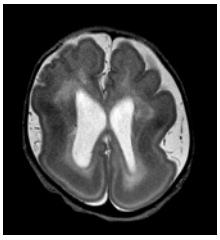
- ~50% have >50% seizure reduction after 3-6 months on the KD
- Benefits: better cognition & alertness, ? medication reduction.

(not FDA approved)

Lemmon, et al. Dev Med Child Neurol 2012;54:464–468.
Henderson, et al. J Child Neurol. 2006;21:193–198.
Farasat, et al. Epilepsy Behav 2006;8:406–410.

Evidence is sparse

- Presented with focal seizures @ 3 months
- Spasms @ 5 months.
- Now 3.5 yrs old – daily tonic seizures
  - Vigabatrin
  - Topiramate
  - Palliative care



Still having daily seizures… what do you do?

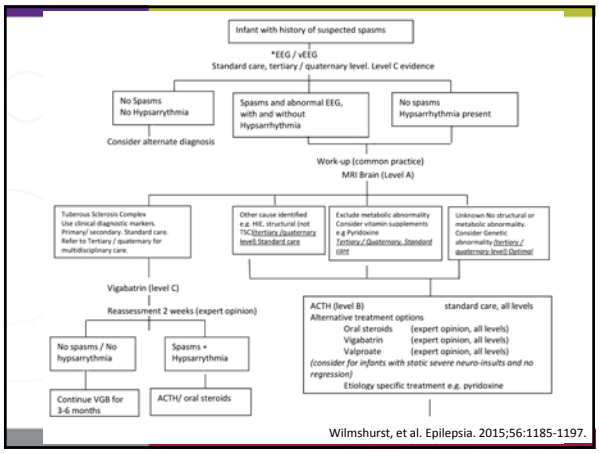
Summary of the evidence

SPECIAL REPORT

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics

Working Group: *Jo M. Wilmshurst, †William D. Gaillard, ‡Kollencheri Puthenveettil Vinayan, §Tammy N. Tsuchida, ¶Perrine Plouin, #Patrick Van Bogaert, **Jaime Carrizosa, ††Maurizio Elia, ‡‡§§Dana Craiu, ¶¶Nebojsa J. Jovic, ##Doug Nordli, ***Deborah Hirtz, †††‡‡‡Virginia Wong, §§§Tracy Glauser, ¶¶¶###Eli M. Mizrahi, and ****J. Helen Cross

Epilepsia, 56(8):1185–1197, 2015



Wilmshurst, et al. Epilepsia. 2015;56:1185-1197.

Summary

- People with MCD often have difficult epilepsy.
- They don't all need surgery.
- Sometimes medicine really works!
  - TSC + Spasms = vigabatrin.
- Lots of new options are being studied!

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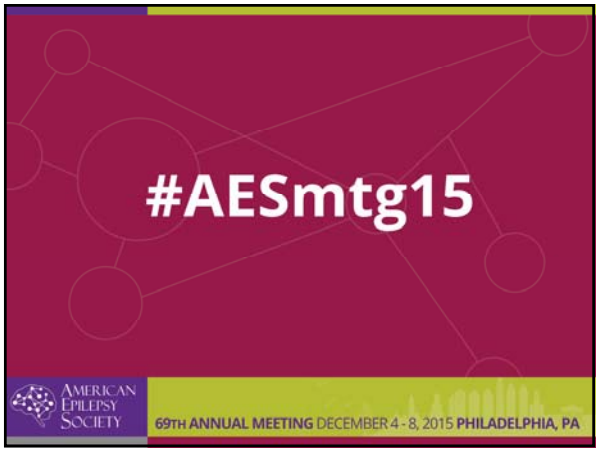


Surgical Management of Brain Developmental Anomalies

Dennis Spencer, MD
Harvey & Kate Cushing Professor of Neurosurgery
Director of Epilepsy Surgery Program
Yale University

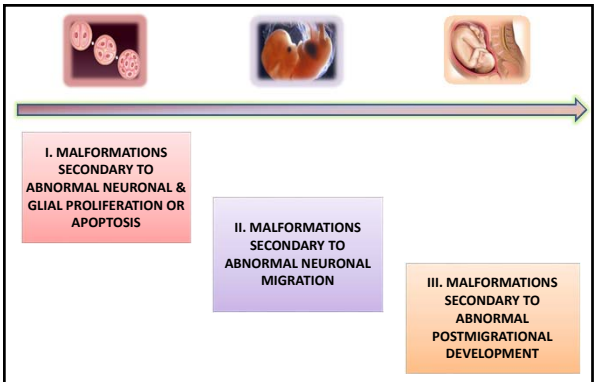
Yale University
School of Medicine

Disclosure

- Nothing to disclose.

Overview

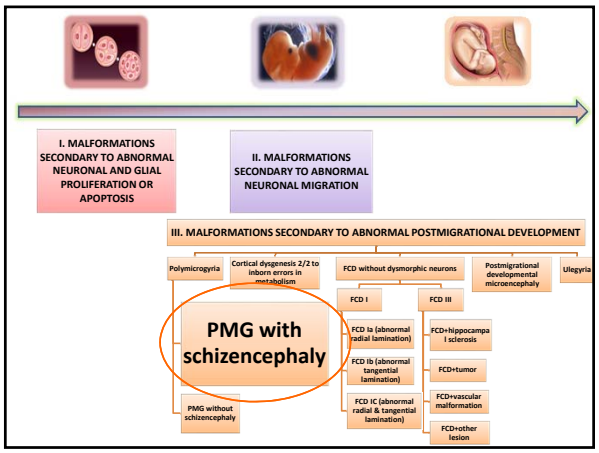
- Developmental anomalies from a surgical perspective
- Review of Yale's 30 year experience caring for patients with epilepsy in the setting of malformations of cortical development
- Case examples
  - Schizencephaly & Ulegyria
  - Periventricular Heterotopia
  - Neoplastic lesions
    - Ganglioglioma
    - Gangliocytoma
    - DNET
  - Cortical Dysplasias
    - Syndromic
    - Isolated
- Current controversies in the surgical management of focal cortical dysplasias
  - Intracranial EEG vs. intraop ECoG alone



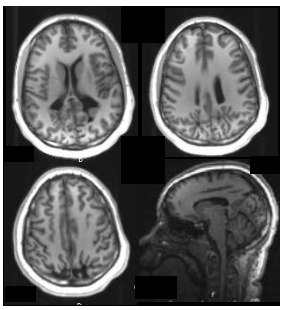
Yale's Experience: Surgery for Epilepsy in Brain Malformations

TYPE 3: MALFORMATIONS OF POST-MIGRATIONAL DEVELOPMENT

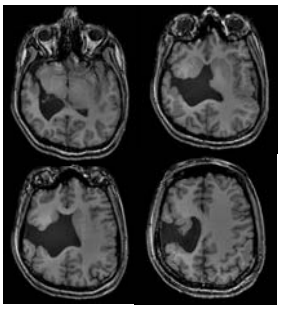
Schizencephaly & Ulegyria



Schizencephaly: Surgical Considerations



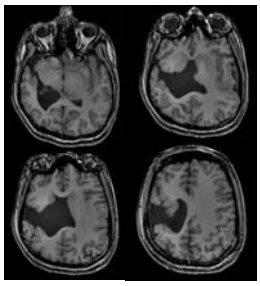
Case 1



Case 2

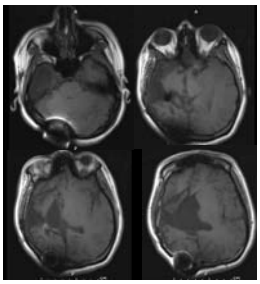
Schizencephaly

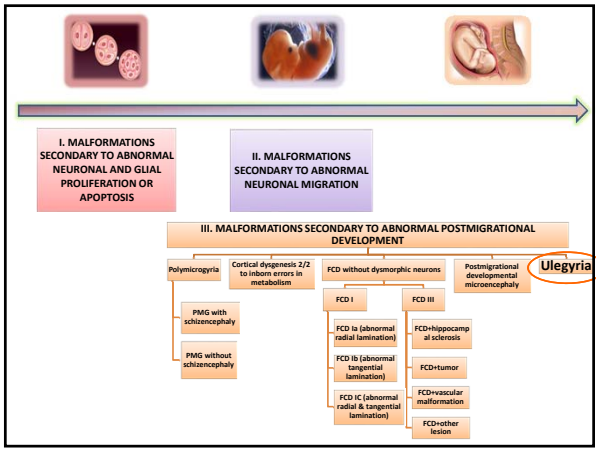
- 18 year old right handed developmentally delayed female with refractory complex partial epilepsy since age 15
- Seizure burden: 3-4 complex partial seizures weekly lasting 1-5 minutes each



Schizencephaly

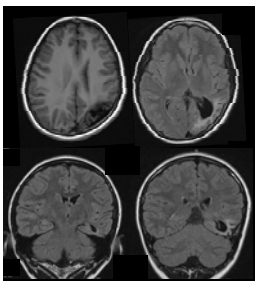
- Video EEG demonstrated primarily right hemispheric onset
- Right hemispherotomy with subsequent shunt placement
- Seizure free following surgery





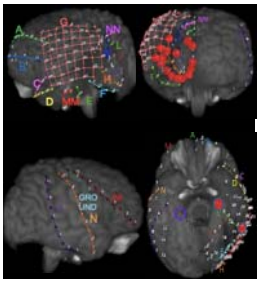
Ulegyria

- 17 year old ambidextrous developmentally normal male with refractory complex partial epilepsy since age 9 following a mild concussion
- Brief facial twitching in infancy following perinatal umbilical hemorrhage
- Seizure burden: 1 complex partial seizure monthly lasting 10-30 seconds each



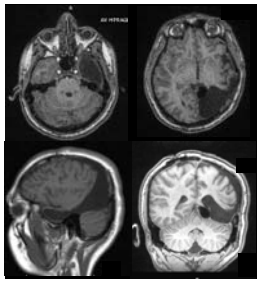
Ulegyria

- Left > right onset
- Left > right intracranial study
- Seizures localized to left encephalomalacia and left temporal lobe



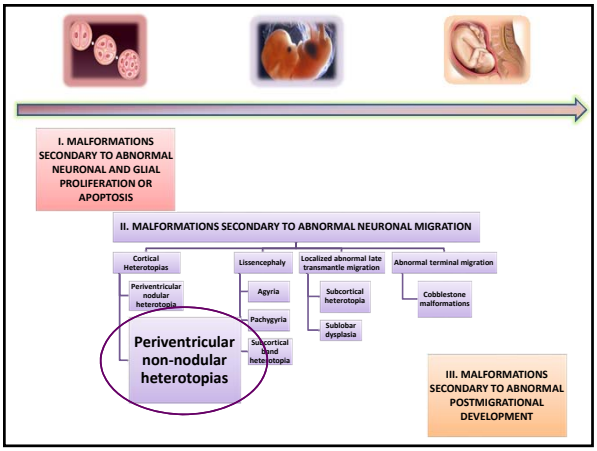
Ulegyria

- Generous left temporo-parietal-occipital resection
- Single seizure 8 months post op after stopping medications but currently seizure free back on AEDs



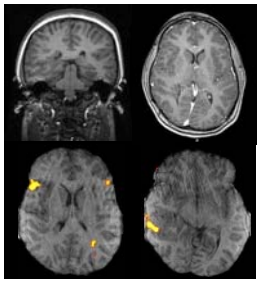
TYPE 2: MALFORMATIONS OF NEURONAL MIGRATION

Periventricular Heterotopias



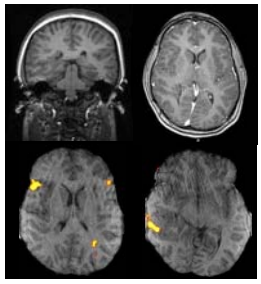
Periventricular Heterotopia

- 16 year old left handed developmentally delayed female with refractory epilepsy since age 12
- Significant co-morbid neuropsychiatric disease onset at age 8



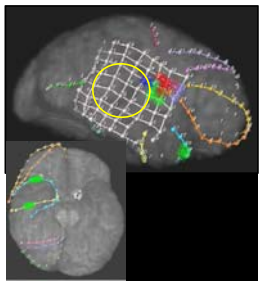
Periventricular Heterotopia

- Seizure burden: daily complex partial seizures lasting 1-3 minutes each
- fMRI and WADA both suggest mostly right sided dominance for language



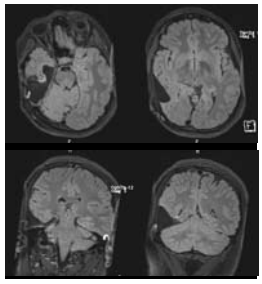
Periventricular Heterotopia

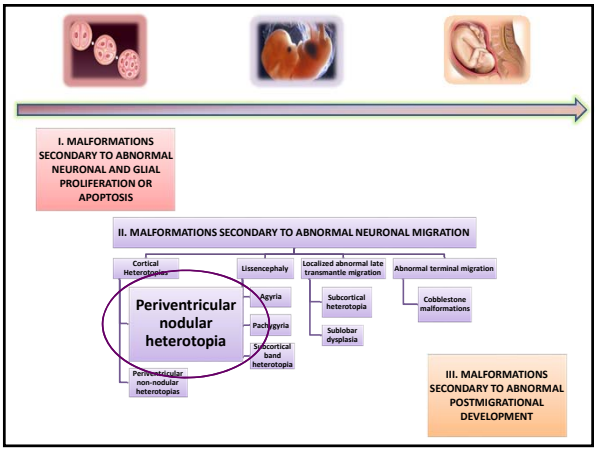
- Underwent implantation for extraoperative language mapping given fMRI and WADA findings
- Seizures localized mostly posterior to language but with some overalp



Periventricular Heterotopia

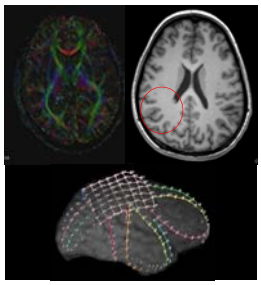
- Right posterior temporal resection
- Seizure frequency & behavior both improved post-operatively





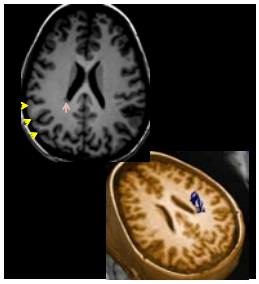
Periventricular Nodules

- 20 year old developmentally delayed right handed female with refractory complex partial epilepsy
- Infantile spasms treated w/ ACTH
- Seizure onset at 11 years of age with 5-7 seizures daily



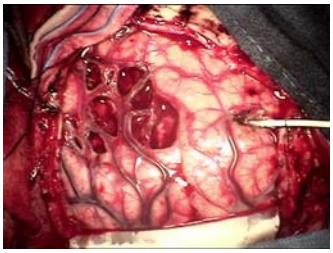
Periventricular Nodules

- Seizures localized to the cortex overlying the periventricular nodule and the nodule itself simultaneously
- Tractography identified the internal capsule descending immediately adjacent to the nodule



Periventricular Nodules

- Multi-focal resection to account for simultaneous, networked onset of seizure activity



Surgery for Epilepsy in the Setting of Periventricular Nodules

- Historically, patients with PVH were not considered surgical candidates due to
  - 1) the deep location of these lesions and
  - 2) the need to traverse normal cortex and white matter to reach these these lesions
- MR guided laser ablation has changed our management of these lesions by providing a novel technique to arrive at these deep lesions with minimal resulting en passage damage

Surgery for Epilepsy in the Setting of Periventricular Nodules

- Esquinazi et al., report the use of MR guided laser ablation for the treatment of epilepsy in two patients with PVN
  - Patient 1: Seizure free but requires AEDs
  - Patient 2: Briefly seizure free but seizures returned and he ultimately underwent temporal lobectomy and remains seizure free post-op

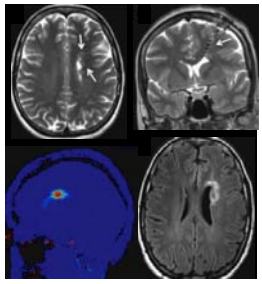
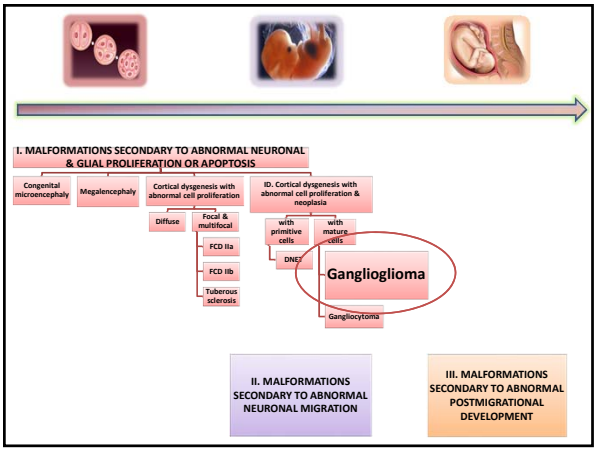


Figure adapted from Esquinazi et al., Epilepsy Research. 2014 Mar;108(3):547-54

TYPE 1: MALFORMATIONS OF NEURONAL PROLIFERATION

Neurodevelopmental Tumors (Ganglioglioma, Gangliocytoma & DNET) & Focal Cortical Dysplasias (Type II)



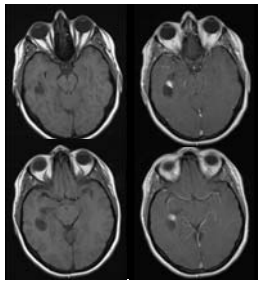
Neurodevelopmental Tumors

Ganglioglioma, Gangliocytoma & DNET

- No need for invasive intracranial EEG for seizure localization because pathology is more focal
- Instead, serial frozen sections to determine tumor margins
  - Gross total resection of the neoplastic tissue treats the epilepsy

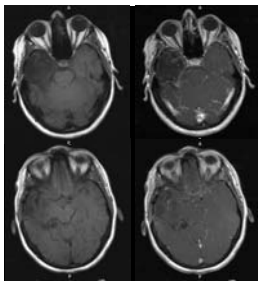
Ganglioglioma

- 44 year old left handed developmentally normal female with new onset complex partial epilepsy
- MRI demonstrates a partially solid, partially cystic lesion within the right temporal lobe



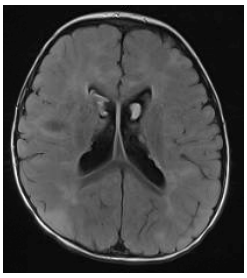
Ganglioglioma

- Patient went for surgical resection of this presumed glial neoplasm with interval resolution of her seizure activity



Epilepsy & Tuberous Sclerosis

- Characterized by multiple cortical tubers frequently occurring with radial glial bands
  - May also occur in conjunction with subependymal nodules and/or subependymal giant cell astrocytoma
- Tubers are histopathologically similar to FCD IIb



Focal Cortical Dysplasia

- Focal cortical dysplasias (FCDs) are localized regions of malformed cerebral cortex, which are intrinsically epileptogenic (Blumcke et al, 2011).
- Blumcke classification divides FCDs based on pathogical characteristics

FCD Type I: abnormal cortical lamination within radial microcolumns (isolated)	*Dysplastic cortex with abnormal radial cortical lamination (FCD Type Ia)*	*Dysplastic cortex with abnormal tangential cortical lamination (FCD Type Ib)*	*Dysplastic cortex with both abnormal radial & tangential cortical lamination (FCD Type Ic)*	
FCD Type II (isolated)	**Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)**		**Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)**	
FCD Type III (occurs in the setting of a primary lesion)	*Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)*	*Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb)*	*Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)*	*Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)*

Focal Cortical Dysplasia & Epilepsy

- Epilepsy surgery has become an increasingly successful treatment option that can provide freedom from seizures
  - However, patients with FCD may present with negative MRI scans (especially those with Blumcke FCD I)
  - Without knowing the exact location and borders of the lesion, complete removal is challenging

Focal Cortical Dysplasia & Epilepsy: Surgical Outcomes

- Meta-analysis of 37 studies demonstrates overall seizure freedom rates following surgery ranging from 40 to 73% in patients with all types of FCD (Moosa et al., 2014)
- Five factors correlated with good outcome
  - Partial seizures
  - Temporal location
  - Detectable lesion on the MRI
  - Type II dysplasia
  - Complete resection (absence of radiographic lesion and/or histologically proven clear margins)
- Secondary generalized seizures found to be predictive of poor outcome

Focal Cortical Dysplasia & Epilepsy: Optimizing Surgical Outcomes

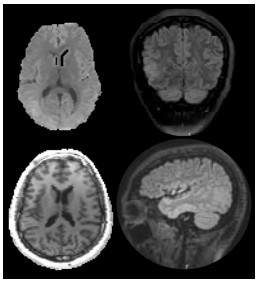
- Palmini et al., (1995) and others since describe distinct bursting and/or near-continuous rhythmic spiking patterns associated with FCD lesions
- Good seizure outcomes can be achieved when resecting these physiologic abnormalities as identified using intraoperative ECoG
- Incomplete resection of this physiologic phenomenon portends poor seizure outcome

Focal Cortical Dysplasia & Epilepsy: Optimizing Surgical Outcomes

- Ictal onset zone exceeds margin of rhythmic spiking area in many cases (Chassoux et al, 2000)
- Epileptogenicity is not necessarily limited to radiographic lesion and perilesional margins
- icEEG with depths can identify epileptogenic lesions not visible on MRI or surface EEG (Fauser et al, 2009)

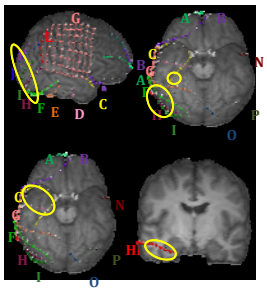
Focal Cortical Dysplasia

- 32 year old right handed, developmentally delayed female with refractory complex partial epilepsy since age 8
- MRI demonstrates right temporo-occipital FCD
- Seizure Burden: 2-3 seizures/night 2-3 nights/week



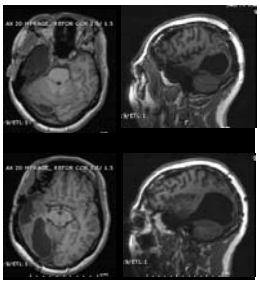
Focal Cortical Dysplasia

- R > L implantation
- Multiple foci of seizure onset identified
- Large temporo-parietal-occipital resection
- Seizure free



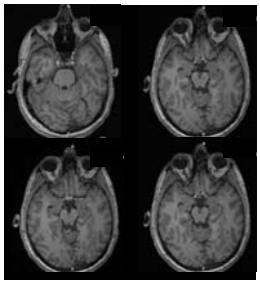
Focal Cortical Dysplasia

- Cortical dysplasia was identified in the radiographically normal anterior temporal cortex in addition to the MRI abnormality in the the temporo-occipital junction



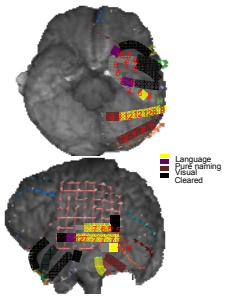
Focal Cortical Dysplasia

- 31 year old right handed, developmentally normal male with refractory complex partial epilepsy since age 17
- MRI demonstrates left temporo-occipital cortical malformation with polymicrogyria
- Seizure burden: 1-2 seizures/week lasting 30-60 seconds each



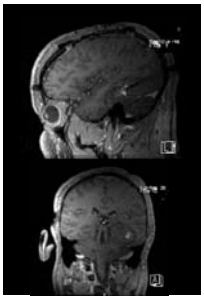
Focal Cortical Dysplasia

- L > R implantation
- Seizures localized simultaneously to both the anterior and posterior extents of the radiographic FCD
- Extraoperative mapping identified naming function localized to his basal temporal lobe limiting resection



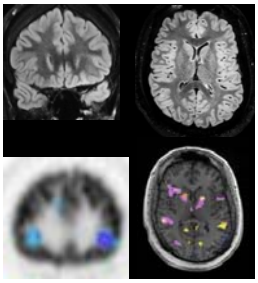
Focal Cortical Dysplasia

- Stereotactic laser ablation for preservation of language cortex and visual fibers
- Post-op neuropsych identifies stable verbal naming difficulties but improved non-verbal functions
- Seizure free



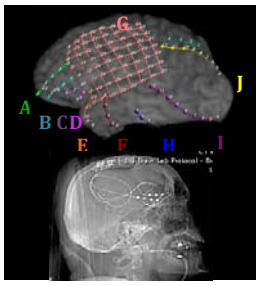
Focal Cortical Dysplasia

- 21 year old ambidextrous developmentally normal male with refractory complex partial epilepsy with secondary generalization
- MRI identifies left frontal FCD
- Seizure Burden: 2-3 seizures/night 2-3 nights/week



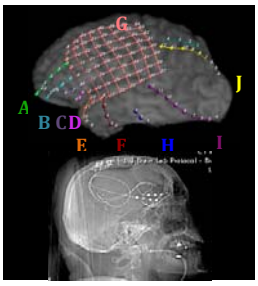
Focal Cortical Dysplasia

- L > R implantation
- Seizure onset localized to left operculum and orbito-frontal cortex with rapid spread to left lateral temporal cortex
- Opercular onset overlaps with Broca's area limiting resection



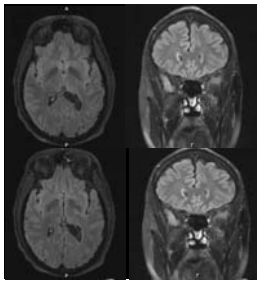
Focal Cortical Dysplasia

- Lateral temporal cortex resection and placement of RNS over left frontal operculum and orbito-frontal cortex
- No evidence of FCD in resected lateral temporal cortex



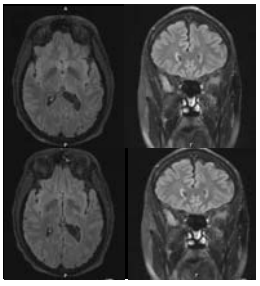
Focal Cortical Dysplasia

- 51 year old male with refractory complex partial epilepsy since age 7
- Multiple medical comorbidities including coronary artery disease s/p multiple stents on aspirin & clopidogrel
- Seizure burden: 1-2 seizures/week lasting 15-20 seconds each



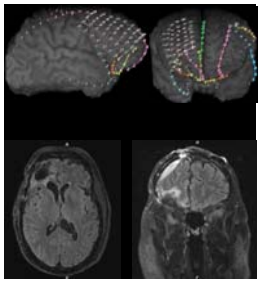
Focal Cortical Dysplasia

- MRI demonstrates right inferior frontal FCD
- Given his medical comorbidities, intraoperative ECoG attempted to spare the need for multiple surgeries



Focal Cortical Dysplasia (intraop ECoG)

- No definite epileptiform discharges identified so proceeded to implant for intracranial EEG
- Seizures localized to inferior orbito-frontal cortex overlying the FCD
- Seizure free



icEEG vs. Intra Op ECoG

- What can we learn about epilepsy in the setting of cortical dysplasia from chronic icEEG
  - Record *ictal* events, not just associated discharges
  - More comprehensive mapping possible
  - Combination of depths with surface monitoring useful for localization in deep and mesial brain regions
  - Overall, leads to more robust understanding of epileptic onset region in relation to surrounding cortex

Conclusions

- Surgery offers significant benefit to many patients with refractory epilepsy due to cortical malformations
- New classification scheme is complicated but helpful for understanding the broad range of cortical malformations that exist
- Intracranial EEG provides distinct advantages over intraoperative ECoG alone for both seizure localization and cortical mapping

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Malformations of Cortical Development and Epilepsy: Case Summary and Conclusions

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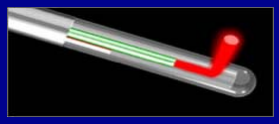
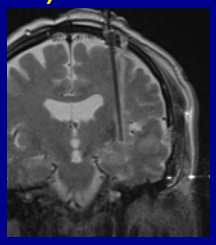
- Institutional sponsorship clinical trials
  - Upsher-Smith Pharmaceuticals
  - Eisai Pharmaceuticals
- Consultant
  - Upsher-Smith Pharmaceuticals

Minimally-invasive, MRI-guided, MRI-thermometry Laser Interstitial Thermal Therapy (LITT)





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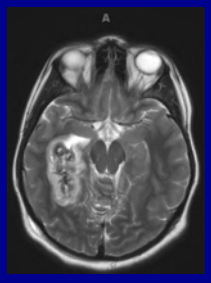
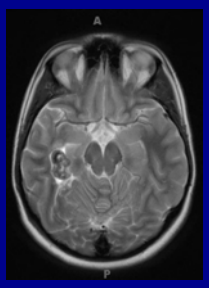
MRI



Peri-operative MRI



3 month post-operative MRI

Post-operative course

- The patient tolerated the procedure well, without visual, sensory or cognitive deficits
- She remains seizure free after surgery for 18 months.

Malformations of cortical development and epilepsy

- Genetics
- Neuroimaging
- Neurological Syndromes
- Medical Management
- Surgical Management of Brain Developmental Anomalies