Seizures and the Epilepsies, Epidemiology, Classification, and Genetics

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Infantile Spasms

This child is likely to have:

A. A hypoplastic vertebral artery
B. Dysplasia of the vertebral bodies
C. A Dandy-Walker cyst
D. Agenesis of the corpus callosum
Disclosures

- Scientific advisory board for Sunovion, Upsher-Smith
- Data safety monitoring board for Eisai, NHLBI
Definitions

- **Seizure**: a disturbance of brain function manifested as impairment/loss of consciousness, abnormal motor phenomena, psychic/sensory disturbances, or perturbation of the autonomic nervous system. Symptoms due to a paroxysmal disturbance of brain's electrical activity.

- **Epilepsy**: recurrent unprovoked seizures (i.e., not febrile seizures).

- **Epileptic syndrome**: complex of signs and symptoms that occur together, defining a unique epilepsy condition.

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**Epilepsy** is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

**Epileptic syndrome**: complex of signs and symptoms that occur together, defining a unique epilepsy condition.
Incidence of Unprovoked Seizures in Developed Countries

Classification of Seizures

- Focal (partial) seizures
- Generalized seizures
  - Tonic-clonic
  - Absence
    - Typical
    - Atypical
    - With special features
      - Myoclonic absence
      - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic atonic
    - Myoclonic tonic
  - Clonic
  - Atonic

Unknown
- Epileptic Spasms

Berg et al., 2010
Prevalence of Generalized and Partial Seizures

Pediatric Patients <15 Years

- Complex partial: 23%
- Tonic-clonic: 19%
- Absence: 13%
- Other partial: 7%
- Unknown/multiple: 9%
- Myoclonic: 7%
- Simple partial: 11%
- Other generalized: 11%

Adults 35-64 Years

- Complex partial: 49%
- Generalized tonic-clonic: 27%
- Myoclonic: 2%
- Simple partial: 13%
- Other partial: 6%
- Unknown/multiple: 3%
Epilepsy Etiology in Children

- Hypoxic-ischemic damages in perinatal period
- Developmental malformation of brain
- Craniocerebral injuries
- Neuroinfections in neonatal period
- Genetics

>50% etiology not determined
Etiology of Neonatal Seizures

**Day 1**
- Traumatic brain injury (subdural, subarachnoid, or intraparenchymal hemorrages)*
- Hypoxia and ischemia
- Stroke (arterial more likely than venous)
- Infection (bacterial or viral)*
- Severe inborn metabolic disorder (e.g., deficiency of sulfite oxidase or nonketotic hyperglycinemia)*
- Systemic hypoglycemia*
- Electrolyte disturbance (hypocalcemia or hyponatremia)*
- Intoxication (maternal substance abuse)*

**Day 2**
- Stroke (especially venous thrombosis)
- Traumatic brain injury*
- Inborn metabolic disorder (especially glucose-transporter defect)*

**Day 3**
- Partial defect in metabolism (e.g., organic acidemias or aminoacidopathies)*
- Benign neonatal convulsions
- Stroke (either arterial or venous)
- Withdrawal (from maternal substance abuse)*
- Traumatic brain injury*
- Inborn metabolic disorder*
A seizure is a specific color on a painter’s palette and the epileptic syndrome is the painting.

Fritz Dreifuss, 1990
Why Bother with Epileptic Syndromes?

- Effects diagnostic testing
- Effects treatment
- Provide prognostic information
- Very helpful in delineation of genetic defect
- Provides insight into pathophysiological mechanisms
A \ + \ B = \ = \:

A. Dravet Syndrome
B. Menkes Syndrome
C. West Syndrome
D. Ohtahara Syndrome
Benign Rolandic Epilepsy

- Is a genetic disorder that is confined to children and characterized by:
  - Nocturnal generalized seizures of probable focal onset or
  - Daytime partial seizures from the lower Rolandic area and
  - EEG patterns consisting of a mid-temporal-central spike foci

- Diagnosis of the syndrome allows the clinician to offer the patient and parents a rational plan for treatment, genetic counseling and prognosis.
Benign Rolandic Epilepsy

- The disorder always begins during childhood.
- The age range is from 3-13 years, with a peak of age incidence between the 7th - 8th years of life.
- The disorder occurs somewhat more frequently in boys than girls.
- Most children have normal neurological examinations and intelligence.
- Seizure frequency is typically low.
Benign Rolandic Epilepsy – Clinical Phenomenon

- Somatosensory aura is common.
- Attacks most frequently involve the face, although the arm and leg may be involved.
- Motor aphasia
- Consciousness is rarely impaired during the daytime attacks.
- Seizures rarely generalize during wakefulness.
- Sensory or motor phenomenon may alternate sides.
- Post-ictal confusion and amnesia are unusual following the seizure.
Interictal spikes in BECTS

- Vast majority of studies have found that children with BECTS have a variety of cognitive impairments.
- Some of the variability in function may be explained by fluctuations in interictal frequency and cognitive performance (Ewen, 2011).
- When spikes disappear, cognitive and behavioral deficits improve.
Panayiotopoulos Syndrome

- Occurs in otherwise normal children
- Manifests with infrequent autonomic epileptic seizures and autonomic status epilepticus.
- Onset of seizures is from age 1 to 14 years with 76% starting between 3–6 years.
- Autonomic seizures consist of episodes of disturbed autonomic function with nausea and vomiting as predominant symptoms.
- In approximately one fifth of the seizures the child becomes unresponsive and flaccid before or often without convulsions.
- Often have occipital spikes.
Epileptic Encephalopathies

- Concept is that the seizures, EEG abnormalities, or both, contribute to the encephalopathy in children.

- Conditions
  - Landau-Kleffner
  - Continuous spike-wave of sleep (ESES)
  - Infantile spasms
  - Lennox-Gastaut syndrome
Key Features

- Seizures - often frequent
- Interictal spikes/sharp waves
- Background abnormalities – slowing, disorganization
- 24/7 abnormalities
Hypsarhythmia
What Else Do You Want To Know?
Always Take A Family History
Benign Familial Neonatal Seizures

- Autosomal-dominantly inherited epilepsy of the newborn.
- Onset of epilepsy is typically on days 2-4. Spontaneous remission of seizures occurs between 2-15 weeks.
- Seizures typically start with a tonic posture, ocular symptoms and other autonomic features, which often progress to clonic movements and motor automatisms.
Benign Familial Neonatal Seizures

- Neonates are normal between the seizures.
- Evaluation for structural, infectious, metabolic disease is negative.
- Clinical and EEG features suggest the seizures are generalized in type.
- Seizures recur later in life in approximately 16% of cases, compared to 2% of normal population.
Benign Familial Neonatal Seizures

- Two loci have been identified:
  - EBN1 (epilepsy benign neonatal type 1) to chromosome 20q13.3
  - EBN2 to chromosome 8q24

- Genes encode voltage-gated \( K^+ \) channels (KCNQ2 and KCNQ3) which regulate “M-currents” which play important role in regulation of neuronal excitability by reducing current.
K⁺ Currents In BFNC

A. BFNC

5 bp Insertion

N - C

Graph:
- Wild type only
- 1/2 mutant + 1/2 wild type
- Mutant only

1(μA)

1/sec

0 1 2 3 4 5
KCNQ2 Encephalopathy: Emerging Phenotype of a Neonatal Epileptic Encephalopathy

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Dominique Audenaert, PhD,
Tine Deconinck, MSc,
Lieve R.F. Claes, PhD,
Liesbet Deprez, PhD,
Katrien Smets, MD,
Iglica Yordanova, MSc,
Albena Jordanova, PhD,
Berten Ceulemans, MD, PhD,
An Jansen, MD, PhD,
Danièle Hasaerts, MD,
Filip Roelens, MD,
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Simone Yendle, BSc (Hons),
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Samuel F. Berkovic, MD, FRS,
Ingrid E. Scheffer, MBBS, PhD,
and Peter de Jonghe, MD, PhD

Objective: KCNQ2 and KCNQ3 mutations are known to be responsible for benign familial neonatal seizures (BFNS). A few reports on patients with a KCNQ2 mutation with a more severe outcome exist, but a definite relation has not been established. In this study we investigated whether KCNQ2/3 mutations are a frequent cause of epileptic encephalopathies with an early onset and whether a recognizable phenotype exists.

Methods: We analyzed 80 patients with unexplained neonatal or early-infantile seizures and associated psychomotor retardation for KCNQ2 and KCNQ3 mutations. Clinical and imaging data were reviewed in detail.

Results: We found 7 different heterozygous KCNQ2 mutations in 8 patients (8/80; 10%); 6 mutations arose de novo. One parent with a milder phenotype was mosaic for the mutation. No KCNQ3 mutations were found. The 8 patients had onset of intractable seizures in the first week of life with a prominent tonic component. Seizures generally resolved by age 3 years but the children had profound, or less frequently severe, intellectual disability with motor impairment. Electroencephalography (EEG) at onset showed a burst-suppression pattern or multifocal epileptiform activity. Early magnetic resonance imaging (MRI) of the brain showed characteristic hyperintensities in the basal ganglia and thalamus that later resolved.

Interpretation: KCNQ2 mutations are found in a substantial proportion of patients with a neonatal epileptic encephalopathy with a potentially recognizable electroclinical and radiological phenotype. This suggests that KCNQ2 screening should be included in the diagnostic workup of refractory neonatal seizures of unknown origin.
New antiepileptic drug targets

Depolarization
Robust excitatory signal

Enhanced excitability of neonatal brain

Mutations in potassium channels impair inhibition

Seizures in neonates
Generalized Epilepsy with Febrile Seizures +

Genetic and phenotypic heterogeneity suggesting that an autosomal dominant epilepsy susceptibility gene is highly penetrant and can be modified by other genes, giving rise to varied phenotypes.

Family members have multiple febrile seizures in infancy and persistence of afebrile generalized tonic-clonic seizures beyond 6 years of life.

- FS + absences
- FS + myoclonic seizures
- FS + atonic seizures

Scheffer and Berkovic, 1997
Generalized Epilepsy with Febrile Seizures +

- Linkage to multiple loci
- Mutation in the $\beta_1$ subunit of the voltage-gated Na$^+$ channel
  - Channel composed of an $\alpha$ subunit and one or more regulatory $\beta$ subunits
  - Essential in action potential upstroke
  - Some channels operate in the subthreshold range, modulating the threshold for action potentials
- Result of mutation leads to increased excitability

Scheffer and Berkovik, 1997
Progression of Dravet syndrome

- **Normal Dev.**
- **1st Seizures**: Frequent seizures: febrile, tonic-clonic, myoclonic, absence
- **Cognitive development declines**
- **Persistent cognitive impairment**
Cognitive development declines
Na⁺ current and AP firing is impaired in interneurons not pyramidal cells

Yu, et al., 2006
Locus Heterogeneity and Variable Expressivity

SCN1A — Severe myoclonic epilepsy of infancy
SCN1B — GEFS+
SCN2A — Childhood absence and FS
GABRG2 — Benign familial neonatal-infantile seizures

Ottman, 2002
The spectrum of SCNIA-related infantile epileptic encephalopathies

Louise A. Harkin,¹,² Jacinta M. McMahon,³ Xenia Iona,¹ Leanne Dibbens,¹,² James T. Pelekanos,³ Sameer M. Zuberi,⁴ Lynette G. Sadleir,⁵ Eva Andermann,⁶ Deepak Gill,⁷ Kevin Farrell,⁸ Mary Connolly,⁸ Thorsten Stanley,⁵ Michael Harbord,⁹ Frederick Andermann,⁶ Jing Wang,¹⁰ Sat Dev Batish,¹⁰ Jeffrey G. Jones,¹⁰ William K. Seltzer,¹⁰ Alison Gardner,¹ The Infantile Epileptic Encephalopathy Referral Consortium, Grant Sutherland,¹,² Samuel F. Berkovic,³ John C. Mulley¹,¹¹ and Ingrid E. Scheffer³,¹²,¹³
<table>
<thead>
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<td>SMEB-O</td>
<td>16</td>
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<td>SMEB-M</td>
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<td>ICEGTC</td>
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<td>Cryptogenic generalized epilepsy</td>
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<td>Cryptogenic focal epilepsy</td>
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<td>Myoclonic–astatic epilepsy</td>
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<td>Lennox–Gastaut syndrome</td>
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<td>Unclassified</td>
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<td><strong>Total</strong></td>
<td><strong>188</strong></td>
<td><strong>90</strong></td>
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</table>

SMEI, severe myoclonic epilepsy of infancy; SMEB-SW, SMEI borderland without generalized spike wave; SMEB-M, SMEI borderland without myoclonic seizures; SMEB-O, SMEI borderland lacking more than one feature of SMEI; ICEGTC, intractable childhood epilepsy with generalized tonic–clonic seizures.
<table>
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<th>Gene</th>
<th>Syndrome</th>
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<td>CHRNNA4</td>
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<td>Generalized Epilepsy Febrile Seizures +</td>
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<td>SCN1A</td>
<td>Generalized Epilepsy Febrile Seizures +/Dravet Syndrome</td>
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<td>CHRN2</td>
<td>Autosomal Dominant Nocturnal Frontal Lobe Epilepsy</td>
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<td>SCN2A</td>
<td>Benign Familial Neonatal-Infantile Seizures</td>
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<td>GABRA1</td>
<td>Generalized Epilepsy Febrile Seizures +/Dravet Syndrome/Childhood Absence Epilepsy</td>
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<td>CHRNA2</td>
<td>Autosomal Dominant Nocturnal Frontal Lobe Epilepsy</td>
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<td>Genes Linked to a channel activity</td>
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<td>LGH</td>
<td>Autosomal Dominant Partial Epilepsy with Auditory Features</td>
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<td>EFHC1</td>
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<td>ARX disorders</td>
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<td>Tuberous Sclerosis</td>
<td><em>TSC1; TSC2</em></td>
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<td>Angelman Syndrome</td>
<td><em>UBE3A</em></td>
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<td>Rett Syndrome</td>
<td><em>MECP2</em></td>
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<td>Fragile X</td>
<td><em>FXS</em></td>
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<td>Lissencephaly</td>
<td><em>DCX; LIS1</em></td>
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</table>

Merwick et al., 2012
Ohtahara Syndrome

Who is this man? Which gene?

- SCN2A
- STXBP1
- KCNQ2
Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome.


From the Department of Human Genetics (K. Nakamura, K. Nishiyama, H.K., M.N., Y.T., N. Miyake, N. Matsumoto, H.S.), Yokohama City University Graduate School of Medicine, Yokohama; Department of Pediatrics (K. Nakamura, M.K., K. Hayasaka), Yamagata University Faculty of Medicine, Yamagata; Division of Neurology (H.O., S.Y., M. Okuda, T.W.), Clinical Research Institute, Kanagawa Children's Medical Center, Yokohama; Department of Child Neurology (E.N.), National Center Hospital, National Center of Neurology and Psychiatry, Tokyo; Department of Pediatric Neurology (K. Haginoya), Takuto Rehabilitation Center for Children, Sendai; Department of Pediatrics (J.T.), Epilepsy Center, Niigata Chuo National Hospital, Niigata; Department of Pediatrics (S.S.), Osaka Medical College Hospital, Osaka; National Epilepsy Center (K.I.), Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka; Department of Pediatrics (S.T.), Yokohama City University Medical Center, Yokohama; Department of Pediatrics (H.I.), Tokyo Metropolitan Bokuto Hospital, Tokyo, Japan; Metabolic Neurogenetic Clinic (D.L., T.L.-S.), Wolfson Medical Center, Holon, Israel; Department of Human Genetics (D.E.C.-B., C.E.V.), National Institute of Pediatrics, Mexico City, Mexico, Division of Child Neurology (M. Ohfu), Okinawa Nanbu Medical Center and Children's Medical Center, Okinawa, Japan; Institute of Medical Genetics (K.W.), University Medical Center Ljubljana; Department of Child, Adolescent and Developmental Neurology (B.G.S.), University Children's Hospital, Ljubljana, Slovenia; Department of Neurology (S.H.), Nagano Children's Hospital, Nagano, Japan; Department of Obstetrics and Gynecology (D.C.), The Prenatal Diagnosis and Medical Genetics Program, Mount Sinai Hospital, University of Toronto, and Division of Clinical and Metabolic Genetics (D.C., D.M.R.), The Hospital for Sick Children, University of Toronto, Canada.
Infantile Spasms

- ARX
- CDKL5
- STXBP1
- TSC1/2
Myoclonic Seizures

- CSTB/EPM1 (Unverricht-Lundborg)
- EPM2A/EPM2B/NHLRC1 (Baltic Myoclonus)
- EFHC1 (Juvenile myoclonic epilepsy)
Incidence of Seizures in Common Genetic Syndromes

- Angelman: ~90% (0.003%)
- Tuberous Sclerosis: ~80% (0.02%)
- Rett Syndrome: ~80% (0.007%)
- Fragile X: ~25% (0.01%)
- Down syndrome: ~10% (0.14%)
Angelman Syndrome
Angelman Syndrome – Consistent Findings

- Developmental delay, functionally severe
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behavior; short attention span
Angelman Syndrome
Frequent Findings

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2
- Seizures, onset usually <3 years of age. Seizures and EEG abnormalities are very common (>80%)
- Differentiating seizures from non-seizure movements may be difficult
- Abnormal EEG, characteristic pattern with large amplitude slow-spike waves (usually 2-3/s), facilitated by eye closure
ANGELMAN Syndrome - EEG

- EEG is characterized by rhythmic triphasic delta waves of high amplitude with a maximum in the frontal area
- High amplitude 4-6 Hz rhythmic activity in older patients
- Multifocal paroxysmal spike and slow activity
- Posterior spikes
- EEG becomes more “organized” with age
- EEG abnormalities may precede seizures
Bifrontal/Frontocentral Spikes
Admixed 2-3 Hz Slow Spike and Wave
Case

- Patient with Angelman syndrome presents to the ED with a recent brief tonic seizure.
- Child seems more hyperactive yet less interactive than usual per parents report.
- Child noted to be ataxia.

Case courtesy of Jim Riviello and Patrick Brown.
Bifrontal/frontocentral spikes
Admixed 2-3 Hz high amp slow/spike and wave
again
Thoughts?

- No prior EEG, is this her baseline “Angelman” EEG or is it NCSE?
- She is behaving somewhat unusually, more “spacey and less interactive.
- Decided to give lorazepam to see if there is a response.
EEG after 2 mg IV lorazepam
ANGELMAN Syndrome

- Caused by genetic imprinting whereby the phenotype depends on the sex of the parent from whom the mutation is inherited

- Disorder involves dysfunction of the maternally inherited chromosome 15q11-q13
  - Large deletions of maternal 15q11-q13
  - Paternal uniparental disomy (both copies of chromosome 15 are inherited from the father)
  - Imprinting (genes are only active on the chromosome derived from the mother; it is silenced on the chromosome inherited from the father)
  - Mutation in the E3 ubiquitin protein ligase gene (UBE3A)
Diagrammatic representation of the mechanisms causing Prader-Willi syndrome (PWS) and Angelman syndrome (AS)

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press
15q11-13 deletion
- Severe epilepsy
- Mixed seizures

Uniparental disomy
- No or mild epilepsy

Imprinting abnormalities
- No or mild epilepsy

UBE3A mutations
- No or mild epilepsy

Minassian et al. 1998

Involvement of other genes in the 15q11-13 deletion, such as GABARβ3 may explain the severe epilepsy
Tuberous Sclerosis
Tuberous Sclerosis

- TSC2 gene was identified in 1993 at 16p13 which encodes the protein tuberin, containing a domain near the COOH-terminus with homology to a guanosine triphosphatase (GTPase) activating protein (GAP) for rapl, a Ras-related GTPase.

- TSC1 identified in 1997 at 9q34 which encodes the protein hamartin.

- In 2002 tuberin-hamartin complex found to inhibit mTOR (mammalian target of rapamycin) via the GTPase-activating protein.
Growth Factors

RECEPTOR

Insulin Family Receptors

P13K → P1P3 → PTEN → AKT → TSC2 → TSC1 → GAB → Rheb → mTOR

Rapamycin

p70S6-kinase/S6K → 4E-BP1 → Protein synthesis → Cell proliferation, growth, and survival
Tuberous Sclerosis Complex (TSC)

- 1 in 6,000 live births; more than 1 million worldwide
- TSC1 and TSC2
- 1/3 dominant inheritance
- 2/3 spontaneous mutation

Diagnosable at birth
- Hypopigmented macules

CT / MRI

Images:
- Hypopigmented macule
- 22 week MRI
- 36 weeks MRI
Special Issues in Patients With Tuberous Sclerosis

- High incidence of infantile spasms
- Often have multi-focal abnormalities
- Multiple seizure types
- Pharmacoresistant epilepsy is common
- At high risk for AED-related cognitive impairment
- Beware of carbamazepine-induced atrioventricular block in children with rhabdomyoma
Tuberous Sclerosis Complex
Seizure Remission and AED Discontinuation in TSC

- 122 children with TSC
- Epilepsy in 106 (86.9%)
- Remission in 15 (14.2%)
- 5 of 15 had relapse; 1 successfully tapered off AEDs

Remission Rate in TSC

Sparagana et al., 2003
Rett Syndrome

- Normal early development followed by:
  - Loss of purposeful use of the hands
  - Distinctive hand movements
  - Slowed brain and head growth
  - Gait abnormalities
  - Seizures
  - Mental retardation
  - Severe apraxia
  - Autism
Rett Syndrome

- Mutations in the MECP2 (X chromosome)
- MECP2 gene codes for methyl cytosine binding protein 2 (MeCP2)
- MeCP2 acts as a biochemical switch to turn off other proteins.
- Insufficient amounts or structurally abnormal forms of the protein are formed.
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<tr>
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<th>Rett syndrome</th>
<th>MECP2 duplication syndrome</th>
<th>CDKL5 mutations/deletions</th>
<th>FOXG1 mutations/ duplications/deletions</th>
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<td>Development</td>
<td>Regression at 1–3 years</td>
<td>Severe early delay</td>
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<td>Social interaction</td>
<td>Poor</td>
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<td>Muscle tone</td>
<td>Initially normal, evolving to hypotonia</td>
<td>Early hypotonia, evolving</td>
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<td>to spasticity</td>
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<td>Speech-language</td>
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<td>Absent or minimal</td>
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<td>Absent or impaired</td>
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</tr>
<tr>
<td>Breathing abnormalities</td>
<td></td>
<td>Absent or minimal</td>
<td>Absent or minimal</td>
<td>Absent or minimal</td>
</tr>
<tr>
<td>Autistic behavior</td>
<td>Often present</td>
<td>Often present</td>
<td>Poor eye contact, reduced social interaction</td>
<td>Poor eye contact, reduced social interaction</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Poor sleep pattern</td>
<td>Poor sleep pattern</td>
<td>Poor sleep pattern</td>
<td>Poor sleep pattern</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Acquired microcephaly</td>
<td>Absent</td>
<td>Mostly borderline (30%)</td>
<td>Borderline head size at birth, severe postnatal microcephaly</td>
</tr>
<tr>
<td>Facial dysmorphisms</td>
<td>Mostly absent</td>
<td>Mild, always present</td>
<td>Mostly absent</td>
<td>Only in patients with deletions</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Partial complex and GTC seizures</td>
<td>Multiple seizure types</td>
<td>Early onset epileptic encephalopathy with spasms, myoclonus and prolonged GTC</td>
<td>Infantile spasms in association with duplications; complex partial, GTC, myoclonic</td>
</tr>
</tbody>
</table>

+, least severe; ++, severe; ++++, most severe; GTC, generalized tonic-clonic.
Fragile X

- X-linked disorder which occurs in boys
- Characteristics include:
  - Global developmental delay
  - Speech and communication problems
  - ADHD
  - Autism
- Epilepsy in about 25%
- Dx often missed
Summary

- 11 genes identified for causing human idiopathic epilepsy
- All have been identified in Mendelian forms of inheritance
- All but one are voltage-gated or ligand-gated channelopathies
- Locus heterogeneity is extensive for most syndromes with identified genes
Summary (2)

- Epilepsy syndromes may be caused by multiple genes (final common pathway).
- Variable expressivity is extensive, the epilepsy syndromes resulting from specific mutations are often variable, even in same family.
- Genetics important in a variety of syndromes in which epilepsy is a major component, i.e. Angelman Syndrome, Tuberous sclerosis.
- Mutations in the genes identified thus far account for a very small proportion of all epilepsies.
Thank You!