Epileptic Encephalopathies with focus on Genetics of Epilepsy
Childhood Epilepsy - Etiology

**Idiopathic – 60%**
- No clear etiology
- Presumed genetic
- Normal or near normal neurologically
  - Idiopathic Generalized Epilepsy
    - Childhood Absence Epilepsy
    - Juvenile Absence Epilepsy
    - Juvenile Myoclonic Epilepsy
  - Idiopathic Partial Epilepsy
    - Childhood Epilepsy with centro-temporal spikes
    - Occipital Epilepsy of Childhood

**Cryptogenic – 10%**
- No clear etiology
- Abnormal neurologically
- Probable genetic etiology
  - Severe Epilepsies of Childhood – the epileptic encephalopathies
    - Infantile spasms
    - Lennox Gastaut Syndrome

**Symptomatic – 30%**
- Identifiable etiology
  - Variety of causes
    - Structural brain abnormalities
      - Developmental
      - Genetic
      - Acquired
    - Complex epilepsy syndromes
      - Genetic disorders affecting brain development and associated neurologic and systemic manifestations
Idiopathic – 60%

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    - Childhood Epilepsy with centro-temporal spikes
    - Occipital Epilepsy of Childhood
Idiopathic Epilepsies

- Idiopathic Generalized/Partial Epilepsies
  - *Genetically complex*
    - Polygenic, inheritance of susceptibility genes (vast majority)
      - Rapidly diminishing risks beyond first degree relatives
      - High concordance between monozygotic twins
      - Likely modify ion channels
  - *Monogenic with variability in phenotypic presentation (less frequent, inherited or de novo)*
    - GEFS + (SCN1A, SCN1B, GABRG2, GABRD)
    - GRIN 2A (Glutamate receptor, ionotopic, NMDA)
    - Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (CHRNA4, CHRNB2, CHRNA2)
## Childhood Epilepsy - Etiology

<table>
<thead>
<tr>
<th>Symptomatic – 30%</th>
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<tbody>
<tr>
<td>• <strong>Identifiable etiology</strong></td>
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<tr>
<td>• <strong>Variety of causes</strong></td>
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<tr>
<td>• <strong>Structural brain abnormalities</strong></td>
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<tr>
<td>• <strong>Developmental</strong></td>
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<td>• <strong>Genetic</strong></td>
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</tr>
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<td>• <strong>Genetic disorders affecting brain development and associated neurologic and systemic manifestations</strong></td>
</tr>
</tbody>
</table>
Symptomatic Epilepsies

- Complex single gene disorders and epilepsy
  - Tuberous Sclerosis (AD or sporadic, TSC1, TSC2)
  - Neurofibromatosis (AD or sporadic, NF1)
  - Angelman Syndrome (sporadic 15 q11-q13 deletion with genomic imprinting)
  - Rett Syndrome (sporadic MECP2 mutation or CDKL5 mutation, X-Linked dominant)
  - Progressive Myoclonic Epilepsies
    - Unverricht-Lundborg Disease (CSTB on Ch 21)
    - Lafora Body Disease (AR, EPM2A, NHLRC1)
  - Protocadherin 19 (PCDH 19) mutation – affects heterozygous females, Hemizygous males unaffected
  - ARX Disorders
Cryptogenic – 10%

- No clear etiology
- Abnormal neurologically
- Probable genetic etiology
- *Severe Epilepsies of Childhood* – *the epileptic encephalopathies*
  - Infantile spasms
  - Lennox Gastaut Syndrome
In which the underlying epilepsy and abnormal electrical discharges contribute, at least in part, to the abnormal neurologic dysfunction – cognitive, motor dysfunction

Most epilepsies in children do not contribute to or cause neurologic dysfunction
Epileptic Encephalopathy

Underlying Neurologic Disorder
Onset in early childhood

- Severe Epilepsy
  - Devastating
  - Seizures are difficult to control
  - Relatively severe EEG abnormalities

Brain dysfunction
- Developmental delay, arrest of development and often regression
- Cognitive Dysfunction, Intellectual disability, Autism
- Motor Dysfunction – delayed milestones, coordination and balance difficulties, abnormal movements, features of cerebral palsy.
- Behavioral difficulties
Epileptic Encephalopathies

Critical Period of Brain Development

Age

Electrical abnormalities

Epileptic events and electrical abnormalities as seen on the EEG

Epileptic Encephalopathy
Genetic causes
- Monogenic – de novo mutations
  - Channelopathies
    - Pathologic affectation of membrane bound proteins
      - Voltage gated
      - Ligand gated
    - Gene mutations causing alterations of critical intracellular proteins

Acquired causes
- Autoimmune epilepsies
  - Anti-NMDA receptor encephalitis
  - Rasmussen’s encephalitis
Modes of Inheritance

- Polygenic inheritance
  - Idiopathic generalized epilepsies, Idiopathic focal epilepsies
  - Relatively benign disorders

- Monogenic inheritance
  - Epileptic Encephalopathies, severe epilepsies of childhood
  - Complex Epilepsy Syndromes, may also cause epileptic encephalopathies, may have variability of presentation
  - Epilepsy disorders of variable presentation (vary from relatively benign to severe disorders)
### Monogenic Inheritance – mutations of large effect

<table>
<thead>
<tr>
<th>Autosomal Dominant</th>
<th>Autosomal Recessive</th>
<th>X-Linked</th>
<th>Mitochondrial Disorders</th>
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</thead>
<tbody>
<tr>
<td>Variable presentation</td>
<td>Usually have significant neurologic impairment</td>
<td>Moderate to severe neurologic impairment often with severe epilepsy</td>
<td>Variety of disorders with significant variability in presentation.</td>
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<tr>
<td>- GEFS+</td>
<td>- GLUT1 deficiency</td>
<td>- Fragile X</td>
<td>- MERRF</td>
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<tr>
<td>- Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>- Various metabolic and CNS degenerative disorders</td>
<td>- Rett Syndrome</td>
<td>- MELAS</td>
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<tr>
<td>- Benign Neonatal convulsions</td>
<td></td>
<td>- CDKL5 encephalopathy</td>
<td>- POLG related syndromes</td>
</tr>
<tr>
<td>- Complex disorders such as Tuberous Sclerosis</td>
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<td>- ARX syndromes</td>
<td></td>
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<tr>
<td>De novo mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some variability in epilepsy presentation but usually severe epilepsies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Epileptic encephalopathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Early onset severe epilepsy with significant neurologic impairment</td>
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</tbody>
</table>
Comparative genetic architectures of susceptibility alleles in complex epilepsy, genes of large effect in monogenic epilepsy and epilepsy arising as a secondary feature of other Mendelian syndromes.

Model of Genetics of Epilepsy

Same model applicable to intellectual disability and autism

GEFS+ spectrum arising from mutations in SCN1A with quantitative representation of associated epilepsy subsyndromes.

Prolonged (45 mins) GTC seizure within 24 hours of 4-month immunization.

Prolonged (45 mins) GTC seizure within 24 hours of 6-month immunization – positctal left hemiparesis.

Over next few months developed recurrent, prolonged focal (hemiclonic) or generalized onset tonic-clonic seizures requiring hospitalization multiple times. Often intubated.

Seizures were both febrile and non-febrile, although often precipitated by an illness.

Seizures often unresponsive to rectal diazepam.
Pregnancy and birth history unremarkable

Early development till 6 months of age was normal. Subsequently - developmental delay, slowing of developmental progress, regression with seizure episodes.

Family history + for infantile spasms in first cousin

MRIs normal

EEG – initial EEGs were normal. EEGs abnormal from 11 months of age – multifocal, predominantly frontal, spikes and diffuse slowing

Lab tests – normal metabolic and routine genetic testing

Epileptic encephalopathy
Case 1

- Seizures refractory to medication therapy – Phenobarbital, valproate, zonisamide, levetiracetam,
- Seizure types – hemiclonic (left or right), frontal lobe seizures characterized by hypermotor activity, GTC, frequent episodes of status epilepticus
- Walked at 23 months – ataxic gait, rare words
- At 2 ½ years age – status epilepticus for 4 ½ hours, with evidence for continuing electrical seizures subsequently on EEG. Went into ARDS and subsequently died.
Epileptic Encephalopathy Syndromes Recognized by ILAE Commission on Classification and Terminology

Neonatal Period
- Early Myoclonic Encephalopathy
- Ohtahara Syndrome

Infancy
- Epilepsy of Infancy with Migrating Focal Seizures
- West Syndrome
- Dravet Syndrome
- Myoclonic Encephalopathy in non-progressive disorders

Childhood
- Epileptic Encephalopathy with Continuous Spike-And-Wave during Sleep (CSWS) (including Landau-Kleffner Syndrome)
- Lennox-Gastaut Syndrome
- Epileptic Encephalopathy
1 year of age

- Fever-induced, often prolonged, hemiclonic (shifting lateralization) or generalized tonic-clonic (GTC) seizures.
- Vaccine-induced seizures, vaccine encephalopathy
- Other triggers – mild fever, infections without fever, hot baths

Early childhood

- Fever-induced seizures may continue
- Afebrile myoclonic (massive and erratic), GTC, atypical absence and partial seizures
- Development regression – unsteady gait, speech language and cognitive deterioration, behavior problems

Later childhood

- Short tonic-clonic seizures, often with focal component, particularly in sleep
- Episodes of non-convulsive status
- Alternating clonic seizures, complex partial seizures
Dravet Syndrome

- **EEG**
  - Often normal in the first months/year of life
  - Second year of life – diffuse slowing, generalized fast spike-wave and polyspike-wave discharges, multifocal spikes
  - Later life – variable EEG changes including multifocal spikes, generalized spike and polyspike-wave discharges, diffuse frontally predominant slowing

- **Treatment**
  - Seizures often intractable, difficult to treat
  - Avoid medications that may worsen seizures – carbamazepine, lamotrigine, vigabatrin, phenytoin
  - Beneficial meds – valproate, levetiracetam, zonisamide, clobazam, topiramate, stiripentol
  - Alternative treatments – ACTH, prednisone, IV IgG, ketogenic diet, VNS
Channelopathy

- Mutation of sodium channel subunit alpha 1 (SCN1A) – 70-80%
  - Mostly de novo
  - Missense mutations
  - Nonsense mutations - truncated, incomplete, non-functional proteins
  - Higher proportion of mutations in the pore region of SCN1A.

- GABRG2

From SCN1A-Related Seizure Disorders, GeneReviews [Internet]
Severe Myoclonic Epilepsy of Infancy (SMEI, Dravet syndrome)

Genetic testing

- Direct sequencing of the SCN1A gene –
  - novel missense mutation found not previously reported.
  - Mutation resides in the region of the gene where other pathogenic mutations have been detected.
  - Parents have not been tested.

De novo mutations
Case Presentation

- 15-years old, female
- Seizure onset – 6-7 months of age
  - Brief generalized seizures
  - Staring, repetitive eye blinking
  - Synchronous clonic jerks of arms/hands
  - 2-10 seconds
  - 40-50 per day
- EEG: Brief bursts of GSW, bifrontal spikes
Clinical Manifestations

- **Treatment of Initial Seizures**
  - Did not respond to valproate and ethosuximide
  - Controlled on valproate and lamotrigine
  - Attempts to taper valproate unsuccessful
- **Seizures remained controlled till age of 3.75 years**
- **Global Developmental Delay**
  - Sitting 10 months, walking 35 months
  - Slow speech-language development
Clinical Manifestations

- Recurrence of seizures at 45 months
  - Coincided with attempt to taper meds
  - Loss of muscle tone, unresponsiveness, inability to sit up, staring, eye blinking
  - Few seconds
  - Only partially controlled with meds
- EEG at 46 months – Left centrotemporal spikes
Late-onset Epileptic spasms

- 4 ½ years
- Loss of tone, balance, up-rolling of eyes, tonic stiffening of arms for 1-2 seconds recurring in a cluster
- 5-60 mins
- Persisted for next 11 years
- Continued with complex partial seizures, sometimes preceding epileptic spasms
- Occasional tonic seizures
- Best response to Clobazam added to VPA + LTG
Physical Examination

- Decreased verbal abilities
- Diminished language comprehension
- Markedly diminished cognitive abilities
- Repetitive behaviors
- Slow slurred speech
- Hypotonia
- Scoliosis
- Coordination and balance difficulties, ataxia
- Jerky choreoathetotic movements
Investigations

- MRIs – Normal or nonspecific, non-diagnostic findings
- Metabolic workup – lactic acid, ammonia, amino acids, organic acids, acylcarnitine profile, plasma guandinoacetate, CSF neurotransmitters
- Genetic workup – High resolution chromosomes, Subteleomeric deletions, ARX mutation analysis, Rett syndrome sequencing
- PET scan - Normal
Clinical Manifestations And Outcome

- Regression of speech-language
  - Using 5-6 word phrases at age 4 ½ years
  - At age 5-6 years speech-language abilities slowly regressed
  - Initial regression was in expressive speech – to level of occasional single words
  - Some improvement at age 8 years, but limited, some fluctuation
- Regression in social skills
  - Decreased social interaction
  - OCD and repetitive behaviors
- Outcome
  - SUDEP at age 15 years
Trio Exome sequencing

- Vissers et al 2010 (Nat Gen) demonstrated the power of using trios (proband and parents) and Next Generation Sequencing (NGS)
- Identified 10 trios with unexplained MR
- Sequenced exomes of all individuals
- Assumed dominant *de novo* model

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A *de novo* paradigm for mental retardation

Lisenka E L M Vissers\(^1,2\), Joep de Ligt\(^1,2\), Christian Gilissen\(^1\), Irene Janssen\(^1\), Marloes Steehouwer\(^1\), Petra de Vries\(^1\), Bart van Lier\(^1\), Peer Arts\(^1\), Nienke Wieskamp\(^1\), Marisol del Rosario\(^1\), Bregje W M van Bon\(^1\), Alexander Hoischen\(^1\), Bert B A de Vries\(^1\), Han G Brunner\(^1,3\) & Joris A Veltman\(^1,3\)
Other exome screens in patients and their immediate families with neurological disorders have since demonstrated high rates of success.

However, exome screening still has a few disadvantages.

These can be improved by (more expensive) Whole Genome Sequencing (WGS).
WGS

Differences from the human reference genome
5,378,745

Found in exome
31,931

Potential functional effect
13,395

Appear de novo
34

Validated
1

Pathogenic dominant de novo variant
NGS still has a high error rate
- ~1 in every 100,000 nucleotides
Therefore most of our 34 are probably sequencing errors
We removed 10 candidate variants present in public databases (“normal” variation)
Performed Sanger sequencing on remaining 24
As expected, only 1 mutation was successfully validated
Variant found in **SCN8A**

- The validated *de novo* variant was in the *SCN8A* gene
  - c.5302A>G
- Causes a non-synonymous change in Na\(_v\)1.6
  - p.Asn1768Asp
- *SCN8A* not previously associated with any human epilepsy disorders
SCN8A/Nav1.6 is one of 9 voltage-gated sodium channel alpha subunits in humans
De Novo Pathogenic SCN8A Mutation Identified by Whole-Genome Sequencing of a Family Quartet Affected by Infantile Epileptic Encephalopathy and SUDEP


*The American Journal of Human Genetics* 90, 1–9, March 9, 2012
<table>
<thead>
<tr>
<th>Family</th>
<th>Variants</th>
<th>Functional Variants</th>
<th>De Novo Variants</th>
<th>Sanger Sequenced</th>
<th>Confirmed</th>
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<tr>
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<td>16,651</td>
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</table>
Candidate Pathogenic Variants

- 7 good candidate pathogenic de novo variants based on gene function
- 2 probands have de novo variants possibly related to phenotype
- 1 proband did not possess any de novo mutations in exomes
De novo mutations in Infantile Spasms and Lennox-Gastaut Syndrome (Epi4K/EPGP)

Exome sequencing 264 trios

Infantile Spasms
Lennox-Gastaut-Syndrome

Novel epileptic encephalopathy genes

Recurrent:
GABRB3, ALG13, HDAC4

Single hits:
CHD2, GABRA1, GRIN1, GRIN2B, HNRNPU, IQSEC2, MTOR, NEDD4L

Known epilepsy genes (subset):
SCN1A (n=7)
STXBP1 (n=5)
CDKL5 (n=3)
SCN2A (n=2)
SCN8A (n=2)
KCNT1, DCX (1 each)

Novel genes: ranking score for mutation intolerant genes
How likely is a given gene to mutate by chance?

Interpretation:
likely pathogenic de novo mutations in 15% of patients
(known and novel genes)

Courtesy: The Channelopathist @ EuroEPINOMICS
**GENOME**

3.2 Gb

**EXOME**

Protein-coding ‘exons’ of all genes
Just 1% of the genome

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Examining genes, chromosomes, exomes and genomes

Karyotype

ArrayCGH
1000X resolution

Sanger sequencing

Next-gen sequencing
ArrayCGH vs Next Gen Sequencing

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Benign familial neonatal seizures
KCNQ2; KCNQ3

Ohtahara syndrome
GNAO1, STXBP1, ARX, CASK, KCNQ2

Early myoclonic encephalopathy
ERBB4

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Migrating partial seizures of infancy  
**KCNT1**

West syndrome  
multiple

Dravet syndrome  
**SCN1A**

Benign familial infantile seizures  
**PRRT2**

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Early onset benign childhood occipital epilepsy (Panayiotopoulos type)

EE with continuous spike-and-wave during sleep (CSWS)
Landau-Kleffner syndrome (LKS)

Benign epilepsy with centro-temporal spikes

Childhood absence epilepsy

Complex

Autosomal dominant nocturnal frontal lobe epilepsy
CHRNA4; CHRN.B2; CHRNA2

Lennox-Gastaut syndrome
Multiple

Febrile seizures plus
SCN1A

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Progressive myoclonic epilepsies
Unverricht-Lundborg disease
   CSTB, PRIKLE1, SCARB2
Lafora disease
   EPM2A; EPM2B
Others- NCL

Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Complex

Autosomal dominant partial epilepsy with auditory features (ADPEAF)
   LGI1

Familial partial epilepsy with variable foci
   DEPDC5

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
Epilepsy Panels

- Panels directed at detecting gene mutations known to be associated with epilepsy
- Commercially available
  - GeneDx
  - Courtagen
  - Transgenomic
Genetic testing in epilepsy

- Chromosomal Microarray (ArrayCGH)
  - All patients with epilepsy plus intellectual disability and learning difficulties
- Epilepsy Gene Panel
  - Difficult to control seizures, intractable epilepsy often with other associated neurologic impairment
  - Epileptic encephalopathy
- Whole exome sequencing
  - Unexplained epileptic encephalopathy
  - Intractable epilepsy with associated neurologic impairment of unclear etiology
Many of the idiopathic childhood epilepsies have polygenic inheritance, with a few identified syndromes with monogenic inheritance

Monogenic inherited epilepsies
- Autosomal dominant conditions
- Autosomal recessive conditions
- X-linked disorders
- De novo mutations causing epileptic encephalopathies
Conclusions

- Epileptic encephalopathies are disorders in which intractable seizures and EEG abnormalities contribute to developmental and cognitive difficulties. *Look for slowing, arrest or regression in development.*
- Heterogeneous etiologies
- New genetic tests (Exome sequencing) will help to identify disorders not previously recognized
- Early recognition and treatment is important and helpful in some of the disorders.
Conclusions

- In epileptic encephalopathies seizures are often difficult to treat, may require treatment other than anti-epileptic medications.
- Appropriate diagnosis of channelopathies, genetic mutations with alteration of protein function, and acquired disorders (e.g. autoimmune disorders) will help guide future treatment directed specifically for the disorder.
1. The most common method of genetic inheritance in Idiopathic generalized epilepsies is
   a. **Polygenic inheritance**
   b. Monogenic inheritance
   c. De-novo mutations
   d. X-Linked inheritance

2. Autosomal dominant inheritance is seen in:
   a. Generalized seizures with febrile seizures PLUS (GEFS+)
   b. Tuberous Sclerosis
   c. Autosomal dominant nocturnal frontal lobe epilepsy
   d. **All of the above**

3. An epileptic encephalopathy is:
   a. A benign epilepsy of childhood
   b. A condition that usually starts in teenage years
   c. A **condition in which the abnormal EEG and ongoing seizures contribute to or cause neurologic deterioration**
   d. Is easy to treat