Role of Genetic Exams in Pediatric Epilepsy

Reza Shervin Badv MD,
Associate Professor of Pediatric Neurology and Epileptology

Children’s Medical Center, Pediatrics Center of Excellence; Tehran University of Medical Sciences.
2021
Epilepsy definition

Any one of the following:

1. At least two unprovoked (or reflex) seizures occurring >24 hours apart.
2. One unprovoked (or reflex) seizure and a >60% chance of recurrent seizures over the next 10 years.
3. Diagnosis of an epilepsy syndrome.

ILAE 2017 Seizure Classifications

Focal-onset seizures

- “aware” vs “with impaired awareness”
- can progress from “focal to bilateral tonic-clonic”

(A) Motor
- Automatisms
- Atonic
- Clonic
- Epileptic spasms
- Hyperkinetic
- Myoclonic
- Tonic

(B) Non-motor onset
- Autonomic
- Behavioural arrest
- Cognitive
- Emotional
- Sensory

Generalized-onset seizures

- (A) Motor
- Tonic-clonic
- Clonic
- Tonic
- Myoclonic
- Myoclonic-tonic-clonic
- Myoclonic-atonic
- Atonic
- Epileptic spasms

- (B) Non-motor (Absence)
- Typical
- Atypical
- Myoclonic
- Eyelid myoclonia

Unknown-onset

- (A) Motor
- Tonic-clonic
- Epileptic spasms

- (B) Non-motor
- Behavioural arrest

Unclassified
- if there is insufficient information or inability to place in other categories
Genetic

Single gene epilepsies

Epilepsies with polygenic inheritance

Acquired

Epilepsies with a major acquired cause (trauma, hypoxia, vascular etc.)
Epilepsy Syndromes

Co-morbidities

Etiology
- Structural
- Genetic
- Infectious
- Metabolic
- Immune
- Unknown

Epilepsy types
- Focal
- Generalized
- Combined Generalized & Focal
- Unknown

Seizure types
- Focal onset
- Generalized onset
- Unknown onset

Unknown
Diagnostic considerations

MRI

MRI findings

- injury
- malformation

no MRI findings

metabolic testing

- positive
- negative
Diagnostic considerations

MRI

MRI findings

- injury
- malformation

no MRI findings

metabolic testing

positive

negative
Genetic *versus* idiopathic

- ‘Idiopathic’ = presumed hereditary predisposition

- **Genetic ≠ inherited**
  - Importance of *de novo* mutations in both mild and severe epilepsies

- Critical problem of stigma in some parts of the world
Genetic ≠ Gene testing

– Usually the mutation is *not* known
– Access to molecular genetic testing *not* necessary
– Diagnosed on clinical research eg. twin, family studies

JME pair; Lennox 1941

CAE pair; Lennox 1950
Benign

• Many epilepsies not benign
  – CAE – psychosocial impact
  – BECTS – learning concerns

• Replaced by terms:
  – Self-limited
  – Pharmacoresponsive

• No longer use
  – Malignant
  – Catastrophic
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| 0-3 months    | • Ohtahara syndrome (*STXBP1, KCNQ2, SCN2A*)  
• Neonatal onset, tonic seizures, burst suppression on EEG  
• Epilepsy of Infancy with Migrating Focal Seizures (*KCNT1, SCN2A*)  
• Refractory focal seizures, migrate from one region to another |
| 4 months – 2 years | • West syndrome (*CDKL5, STXBP1, ARX, DNM1*)  
• Infantile spasms with hypsarrhythmia on EEG  
• Dravet syndrome (*SCN1A*)  
• Prolonged febrile/afebrile sz, focal (hemiclonic), regression |
| 1-8 years     | • Lennox-Gastaut syndrome (*CDKL5, DNM1*)  
• Refractory seizures (tonic), generalized slow-spike wave on EEG  
• Myoclonic-atactic epilepsy/Doose syndrome (*SLC2A1, SLC6A1*)  
• Febrile seizures, myoclonic-atactic seizures, regression |
| 2-10 years    | • Landau-Kleffner syndrome (*GRIN2A*)  
• Acquired aphasia, previously normal devt, +/- seizures  
• Electrical status epilepticus during slow wave sleep |
## Pediatric Focal Epilepsy syndromes

### TABLE. FOCAL EPILEPSY SYNDROMES OF CHILDHOOD

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>EEG Findings</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign childhood epilepsy with centrotemporal spikes</td>
<td>Onset: 3-13 y  Peak: 7-8 y</td>
<td>Bilateral asynchronous high amplitude, sharp and slow-wave complexes, with horizontal dipole, negative in centrotemporal regions and positive in frontal regions</td>
<td>Remission by adolescence</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome</td>
<td>Onset: 3-10 y</td>
<td>Continuous diffuse slow spikes and waves at 1.5-2.5 Hz occurring at all slow-sleep stages</td>
<td>Remission by adolescence</td>
</tr>
<tr>
<td>Continuous spike-and-wave during sleep (CSWS)</td>
<td>Onset: 2-4 y</td>
<td>Infrequent spikes and waves; continuous diffuse slow spikes and waves at 1.5-2.5 Hz occurring at all slow-sleep stages, electrical status epilepticus in sleep (ESES)</td>
<td>Poor prognosis with long duration of ESES</td>
</tr>
<tr>
<td>Panayiotopoulos syndrome</td>
<td>Onset: 1-14 y  Peak: 3-6 y</td>
<td>Interictal EEG with occipital spikes and multifocal, high amplitude, sharp slow wave complexes</td>
<td>Remission approximately 3 years after onset.</td>
</tr>
<tr>
<td>Gastaut Type</td>
<td>Peak: 8 y</td>
<td>Bilateral occipital spike-wave discharges that activate with eye closure and diminish upon eye opening</td>
<td>Remission chance of 50-60% about 2-3 y after onset.</td>
</tr>
<tr>
<td>Genes Associated With Focal Epilepsy</td>
<td>Management Implications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SCN1A</strong></td>
<td>Avoid sodium-channel blocking antiepileptic drugs due to the risk of seizure aggravation; if surgery is considered, counsel patients about the potential risk of postoperative seizure recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SLC2A1</strong></td>
<td>Ketogenic diet as first-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TSC1, TSC2</strong></td>
<td>Consider mTOR inhibitors (e.g., everolimus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>POLG</strong></td>
<td>Avoid valproic acid due to risk of hepatic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GRIN2A</strong></td>
<td>Consider memantine?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DEPDC5, NPRL2, NPRL3</strong></td>
<td>Consider mTOR inhibitors?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>What is it?</td>
<td>Reference Genome</td>
<td>A Person’s Genome</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X X X X + Mitochondrial DNA</td>
<td>X X X X X X + Mitochondrial DNA</td>
<td></td>
</tr>
<tr>
<td>How many chromosomes?</td>
<td>24 (22 + X + Y)</td>
<td>46 (23 PAIRS)</td>
<td></td>
</tr>
<tr>
<td>How many letters?</td>
<td>~3.2 bn</td>
<td>~6.4 bn</td>
<td></td>
</tr>
<tr>
<td>How to think about it?</td>
<td>The Human Genome Project and its goal of a first draft of “the human genome”</td>
<td>The genome of a person</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serves as a standard for comparison</td>
<td>The genome within a person’s cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A “consensus” genome sequence</td>
<td>The whole genome sequence of an individual</td>
<td></td>
</tr>
</tbody>
</table>
GENOME

3.2 Gb

Chromosome

Gene

Intergenic region

Gene

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

From: Dixit, Abhijit; www.cewt.org.uk/CEWT/eig_files/Epilepsy.ppt
<table>
<thead>
<tr>
<th>No mutation</th>
<th>Point mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent</td>
<td>Nonsense</td>
</tr>
<tr>
<td></td>
<td>conservative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DNA level</th>
<th>mRNA level</th>
<th>Protein level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTC</td>
<td>TTT</td>
<td>Lys</td>
</tr>
<tr>
<td>AAG</td>
<td>AAA</td>
<td>Lys</td>
</tr>
<tr>
<td>ATC</td>
<td>UAG</td>
<td>STOP</td>
</tr>
<tr>
<td>TCC</td>
<td>AGG</td>
<td>Arg</td>
</tr>
<tr>
<td>TGC</td>
<td>ACG</td>
<td>Thr</td>
</tr>
</tbody>
</table>
### Wild-type mRNA and Polypeptide

<table>
<thead>
<tr>
<th>Wild-type mRNA</th>
<th>5'</th>
<th>GCU</th>
<th>GGA</th>
<th>GCA</th>
<th>CCA</th>
<th>GGA</th>
<th>CAA</th>
<th>GAU</th>
<th>GGA</th>
<th>3'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Ala</td>
<td>Gly</td>
<td>Ala</td>
<td>Pro</td>
<td>Gly</td>
<td>Gln</td>
<td>Asp</td>
<td>Gly</td>
<td>C</td>
</tr>
</tbody>
</table>

### Silent Mutation

<table>
<thead>
<tr>
<th>Silent Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCU GGA GCC CCA GGA CAA GAU GGA</td>
</tr>
<tr>
<td>Ala Gly Ala Pro Gly Gln Asp Gly</td>
</tr>
</tbody>
</table>

### Missense Mutation

<table>
<thead>
<tr>
<th>Missense Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCU GGA GCA CCA AGA CAA GAU GGA</td>
</tr>
<tr>
<td>Ala Gly Ala Pro Arg Gln Asp Gly</td>
</tr>
</tbody>
</table>

### Nonsense Mutation

<table>
<thead>
<tr>
<th>Nonsense Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCU GGA GCA CCA GGA UAA GAU GGA</td>
</tr>
<tr>
<td>Ala Gly Ala Pro Stop</td>
</tr>
</tbody>
</table>

### Frameshift Mutation

<table>
<thead>
<tr>
<th>Frameshift Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCU GGA GCC ACC AGG ACA AGA UGG A</td>
</tr>
<tr>
<td>Ala Gly Thr Arg Thr Arg Trp</td>
</tr>
</tbody>
</table>

Note: these are all substitutions

This one is an insertion
- **Substitution**: base is replaced by one of the other three bases
- **Deletion**: block of one or more DNA pairs is lost
- **Insertion**: block of one or more DNA pairs is added
- **Inversion**: 180° rotation of piece of DNA
- **Reciprocal translocation**: parts of nonhomologous chromosomes change places
- **Chromosomal rearrangements**: affect many genes at one time
Mutations are also classified by their impact on protein function:

**Loss of function**
Complete loss of the protein:
*null, loss-of-function, amorph*

Reduction of protein’s ability to work:
*hypomorph, reduction-of-function*

**Gain of function**
Increase in the protein’s function:
*hypermorph, gain-of-function*

A protein that interferes with the wild-type protein’s function:
*antimorph, dominant negative*

Acquisition of a new function (or ectopic expression of the function):
*neomorph, dominant gain-of-function*

These terms are frequently misused, and also context-dependent
The distinction between loss-of-function and gain-of-function is not always super-clear.

Loss-of-function usually means that less of a protein is made or that some function of the protein has been compromised.

Loss-of-function mutations are usually recessive, since in most cases, a single “good” copy of the gene will suffice.

2 common types of exceptions:

“Haploinsufficiency”:
One copy is not enough

“Dominant negative” or “antimorphic” mutations:
The defective gene interferes with the function of the wild-type copy. This is common with proteins that form polymeric structures, such as filaments.
Genetic testing algorithm for patients with unexplained epilepsy

1. Patient with unexplained epilepsy

Does this patient have epilepsy in conjunction with one or more of the following:
   - Developmental delay
   - Intellectual disability
   - Autism spectrum disorder
   - Infantile spasms
   - Congenital anomaly(ies)

- YES
  - Chromosomal microarray
  - UNINFORMATIVE
    - (Phenotype appropriate) epilepsy gene panel
    - UNINFORMATIVE
      - Whole Exome Sequencing

- NO
Genetic Testing in Epilepsy

Chromosomal Microarray
Gene Panel
Single Gene
Whole Exome Sequencing
Reported variants in Diagnostic versus Elective Testing.

**Diagnostic Testing**

- **Benign**
- **Likely Benign**

**Elective Testing**

- **VUS**
- **Likely Pathogenic**
- **Pathogenic**

**Clinical Report**

- **Inconclusive**
- **Positive**

---

**Pathogenic**
- Protein truncating variants
  - Nonsense OR
  - Frameshift OR
- Canonical splice site variants (<2 intronic basepairs from intron/exon boundary) OR
- Missense
  - Located in hotspot (E1705, D1709, G1809, D1810, E1813) OR
  - Variant reported in at least one publication

**VUS**
- In-frame deletion or insertion OR
- Stop loss OR
- Start gain OR
- Non-canonical splice site variants (>2 and <10 intronic basepairs from intron/exon boundary) OR
- Conflicting calls from ClinVar

**Likely Benign**
- Non-synonymous Missense
  - Located in non-hotspot AND
  - Bioinformatics pathogenicity prediction (MetaSVM = tolerated, CADD ≤ 30, or REVEL ≤ 0.75) OR
  - Synonymous variants
Copy number variation (CNVs)

- It was generally thought that genes were almost always present in two copies in a genome.
- However, recent discoveries have revealed that large segments of DNA, ranging in size from thousands to millions of DNA bases, can vary in copy-number.
- Genomic rearrangements
  - Deletions
  - Duplications
  - Inversions
  - Translocations

Copy number variation in the human genome
The 30,000 genes are usually present in two copies. New studies unveil a new map of the genome by cataloguing DNA and genes variable in copy number (those numbers other than 2 highlighted in red) across world-wide populations. Duplication of a gene (top) and deletion of two genes (bottom) are depicted.
One Third of Known Genes Linked to Epilepsy Encode Ion Channels

<table>
<thead>
<tr>
<th>Human</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nav1.1</td>
<td>NHE1</td>
</tr>
<tr>
<td>Nav1.2</td>
<td>Glyt1</td>
</tr>
<tr>
<td>Nav β1</td>
<td>Glut1</td>
</tr>
<tr>
<td>Kv1.1</td>
<td>KCC2</td>
</tr>
<tr>
<td>Kv3.2</td>
<td>ATP1A2</td>
</tr>
<tr>
<td>KCNQ2</td>
<td>NPY</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>GABA_B1</td>
</tr>
<tr>
<td>CACN α1a</td>
<td>GAD65</td>
</tr>
<tr>
<td>CACN β4</td>
<td>IP3R</td>
</tr>
<tr>
<td>CACN γ2</td>
<td>CamKII</td>
</tr>
<tr>
<td>CACN α2δ</td>
<td>PLC β1</td>
</tr>
<tr>
<td>CICN2</td>
<td>syn 1+2</td>
</tr>
<tr>
<td>HCN2</td>
<td>SV2a</td>
</tr>
<tr>
<td>GABA_A R α1</td>
<td>AP3δ</td>
</tr>
<tr>
<td>GABA_A R β3</td>
<td>TNAP</td>
</tr>
<tr>
<td>GABA_A R γ2</td>
<td>DCX</td>
</tr>
<tr>
<td>nAChR α4,</td>
<td>OTX</td>
</tr>
<tr>
<td>nAChR β2</td>
<td>EMX2</td>
</tr>
<tr>
<td>5HTR 2c</td>
<td>SOX1</td>
</tr>
<tr>
<td>GluR2</td>
<td>P35</td>
</tr>
<tr>
<td>Girk2</td>
<td>NeuroD</td>
</tr>
<tr>
<td>HCN2</td>
<td></td>
</tr>
</tbody>
</table>

UPAR  ARX  MECP2  EPM2a  FLN1  NCL 1,2,3,5,8  bmi-1
tRNA lys  lamR  RORα  PTEN  CBP-B  AMT  UBE3a  Cik kin
cystatin B  Gαo  myoVa  LGi1  TS 1, 2  NHLRC1
mDNA disorders

MELAS

MERRF

nDNA disorders

mtDNA depletion

POLG1
Epileptic channelopathies

I/E/I+E
Gain-of-Function Mutations

(e) Gain of function: Hypermorphic mutation

- Homozygous: XX
- Heterozygous: X

Excessive expression of the gene product leads to excessive gene action. The mutant phenotype may be more severe or lethal in the homozygous genotype than in the heterozygous genotype.

Hypermorphic = more function

(f) Gain of function: Neomorphic mutation

- Homozygous: XX
- Heterozygous: X

The mutant allele has novel function that produces a mutant phenotype in homozygous and heterozygous organisms, and may be more severe in homozygous organisms.

Neomorphic = new function
Loss-of-Function Mutations

(b) Loss of function: Null/amorphic mutation

Homozygous
Alleles

Heterozygous

Products
None

Null alleles produce no functional product. Homozygous null organisms have mutant (amorphic) phenotype due to absence of the gene product. Heterozygous organisms produce less functional gene product than homozygous wild-type organisms and may have mutant phenotype. See text for discussion of dominant versus recessive mutations.

Amorphic = no function

(c) Loss of function: Leaky/hypomorphic mutation

Homozygous
Alleles

Heterozygous

Products

Leaky mutant alleles produce a small amount of wild-type gene product. Homozygous organisms have a mutant (hypomorphic) phenotype. Heterozygous organisms may also be mutant.

Hypomorphic = less function
Epileptic Encephalopathy Genetic Pathways

Transcriptional Regulation:
- ARX
- CDKL5
- TBC1D24

Neuron Excitability:
- KCNQ2
- KCNT1
- SCN1A
- SCN1B
- SCN2A
- SCN8A

Synaptic Transmission:
- Presynaptic:
  - DNM1
  - LGI1
  - SNAP25
  - STX1B
  - STXBP1
  - SYN1
- Postsynaptic:
  - CHRN4
  - GABRB3
  - GABRG2

Cell Body
Axon
Synapse
The Spectrum of SCN1A Disorders

Familial Hemiplegic Migraines (FHM)
Febrile Seizures (FS)
Febrile Seizures+ (FS+)
Generalized Epilepsy with Febrile Seizures+ (GEFS+)
Intractable Childhood Epilepsy with Generalized Tonic Clonic Seizures (ICE-GTC)
Dravet Syndrome

Na\_\text{v}1.1 Mutation Severity

Mild
- missense
- Febrile Seizures

Moderate
- missense
- GEFS+
- Febrile seizures
- Generalized seizures

Severe
- missense

Truncation
- loss-of-function
- SMEI
- Febrile seizures
- Generalized seizures
- Myoclonic seizures
- Atypical seizures
- Ataxia
- Cognitive impairment
SCN1A related Epilepsies

Loss of function variants

Expression on inhibitory neurons => loss of inhibition => hyperexcitability

Not all SCN1A epileptic encephalopathies are Dravet syndrome: Early profound Thr226Met phenotype.

Sadleir LG\textsuperscript{1}, Mountier E\textsuperscript{1}, Gill D\textsuperscript{2}, Davis S\textsuperscript{2}, Joshi C\textsuperscript{2}, DeVile C\textsuperscript{2}, Kurian MA\textsuperscript{2}, DDD Study, Mandelstam S\textsuperscript{2}, Wirrell E\textsuperscript{2}, Nickels KC\textsuperscript{2}, Murali HR\textsuperscript{2}, Carvill G\textsuperscript{2}, Myers CT\textsuperscript{2}, Mefford HC\textsuperscript{2}, Schefer IE\textsuperscript{1}.

SCN1A gain of function in early infantile encephalopathy.

Berecki G\textsuperscript{1}, Bryson A\textsuperscript{1}, Jerhag J\textsuperscript{1}, Maljevic S\textsuperscript{1}, Gazina EV\textsuperscript{1}, Hill SL\textsuperscript{2}, Petrou S\textsuperscript{1,3}.

Depolarization block
SCN2A related epilepsies
The SCN2A protein

Epileptic encephalopathies
- Ohtahara Syndrome
- Unclassified EE with or without dystonia
- West Syndrome/Lennox-Gastaut Syndrome

BFNIS
- BFNIS

Autism/ID
- Truncating mutation
- Missense mutation

R853Q (3x)
Progress in Understanding and Treating SCN2A-Mediated Disorders

Stephan J. Sanders,1,* Arthur J. Campbell,2 Jeffrey R. Cottrell,2 Rikke S. Moller,3
Florence F. Wagner,2 Angie L. Auldridge,4 Raphael A. Bernier,5 William A. Catterall,6
Wendy K. Chung,7,8 James R. Empfield,9 Alfred L. George Jr,10 Joerg F. Hipp,11
Omar Khwaja,11 Evangelos Kiskinis,12,13 Dennis Lal,2 Dheeraj Malhotra,11
John J. Millichap,12,14,15 Thomas S. Otis,16 Steven Petrou,17 Geoffrey Pitt,16 Leah F. Schust,4
Cora M. Taylor,19 Jennifer Tjernagel,7 John E. Spiro,7 and Kevin J. Bender20,*

**De novo**
- GoF missense
- Increased
  - Infantile epileptic encephalopathy (IEE)
  - SCN8A/Na,1.6 excitability

**De novo or inherited**
- GoF missense
- Normal
  - Benign (familial) infantile seizures (BISs)
  - SCN8A/Na,1.6 excitability

**De novo truncating or de novo LoF missense**
- Reduced
  - Autism spectrum disorder (ASD) and/or intellectual disability (ID)
  - ± Childhood-onset seizures
# Epileptic Encephalopathies in Childhood: The Role of Genetic Testing

Johannes R. Lemke, MD¹  Steffen Syrbe, MD²

<table>
<thead>
<tr>
<th>Neuronal excitability</th>
<th>De novo gain-of-function missense</th>
<th>De novo or inherited gain-of-function missense</th>
<th>De novo truncating or de novo loss-of-function missense</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Infantile epileptic encephalopathy</td>
<td>Benign (familial) infantile seizures</td>
<td>Autism spectrum disorder and/or intellectual disability</td>
<td></td>
</tr>
</tbody>
</table>
Spectrum of SCN2A related epilepsies

- Onset < 3 months
  - BFNIS
  - Ohtahara, EIMFS, unclassified
- Response to sodium channel blockers (SCB)
- Missense mutations with **GOF** effect, correlating with clinical severity

- Onset > 3 months
  - West, LGS, MAE, focal E with ESES, unclassified
  - ID, autism
- Poor response to SCB
  - **LOF** mutations
Clinical and genetic spectrum of SCN2A-associated episodic ataxia.

- Neonatal-infantile onset sz
- Normal to mild ID
- Episodic ataxia onset 10m-14y
- Presumed GOF good effect of sodium channel blockers on sz
- Episodic ataxia
  - Majority did not respond to SCB
  - 50% response to acetazolamide
**KCNQ2 spectrum**

- Functional aspects: mutation + genetic background

BFNS

- Mostly Inherited

KCNQ2

KCNQ2 encephalopathy

- Mostly *de novo*
- Mozaicism described in inherited cases
KCNQ2 related epilepsy: mutational mechanisms

**BFNS** → **KCNQ2** → **KCNQ2 encephalopathy**

- **Mutation causes 25-50% loss of current**
- Most of the mutations are inherited

- **Mutation causes > 50% loss of current**
- Mutations mostly *de novo*
KCNQ2 encephalopathy

• KCNQ2 encephalopathy is characterized by severely abnormal EEG, neonatal-onset epilepsy and developmental delay.

• De novo Mutations (typically missense) in the KCNQ2 gene, encoding the voltage gated potassium channel Kv7.2
Spectrum of KCNQ2 related epilepsies

Neonatal nonepileptic myoclonus is a prominent clinical feature of KCNQ2 gain-of-function variants R201C and R201H

Infantile spasms and encephalopathy without preceding neonatal seizures caused by KCNQ2 R198Q, a gain-of-function variant.

In general: developmental delay from onset, Infantile onset or later onset seizures