ION CHANNEL EPILEPSIES

Melanie Siv
Pharm D. Candidate
Wingate University
Objective

- At the end of the presentation, participants should be able to:
  - Describe what is intractable childhood epilepsy
  - Understand the mutations that occur to the ion channels
  - Explain the benefits of genetic testing
Brief History

- Over 50 million people worldwide have epilepsy
  - Epilepsy is having 2 or more unprovoked seizures
- Intractable epilepsy is epilepsy that is difficult to control or not controlled by medications
- Epilepsy associated with ion channel gene mutation was discovered in 1994
  - Mutations have been identified in 10 different channel subunits
Ion channels

- Membrane proteins
- 10nm in size
- Allows ions to enter or leave the cell

- Channelopathies = dysfunction in the ion channels
  - Gain or loss of ion channel function
Normal neuron function & AP

- Neurons send electrical signals via chemicals
- Not sending signal = resting state
  - Inside of the neuron is negative compared to outside
- Action potential occurs when neuron sends info down axon
Action potential
# Syndromes caused by gene mutation

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Voltage gated ion channelopathies</strong></td>
<td></td>
</tr>
<tr>
<td>SMEI</td>
<td>SCN1A</td>
</tr>
<tr>
<td>GEFS+</td>
<td></td>
</tr>
<tr>
<td>ICE-GTC</td>
<td></td>
</tr>
<tr>
<td>EA-1</td>
<td>KCNA1</td>
</tr>
<tr>
<td>BFNS</td>
<td>KCNQ2 &amp; KCNQ3</td>
</tr>
<tr>
<td><strong>Ligand gated ion channelopathies</strong></td>
<td></td>
</tr>
<tr>
<td>ADNFLE</td>
<td>nAchRs</td>
</tr>
<tr>
<td>JME</td>
<td>GABA-A &amp; CLCN2</td>
</tr>
</tbody>
</table>
Voltage gated channelopathies

- $\text{Na}^+$
- $\text{K}^+$
- $\text{Cl}^-$
- $\text{Ca}^{2+}$
Voltage gated sodium ion channel
Voltage dependent Na\(^+\) channels

- Initiates and propagates action potential
- Mutations in both $\alpha$ and $\beta$ subunits have been linked to epilepsy
Voltage gated sodium ion channel
SCN1A

- SCN1A gene mutation was discovered in 2001
- Codes for the alpha subunit (Na\textsubscript{\textit{v} 1.1})
  - Na\textsubscript{\textit{v} 1.1} is highly concentrated in the brain
- Abnormality causes neuronal dysfunction and hyperexcitability
Phenotypes associated with SCN1A

- Common phenotypes
  - FS
  - GEFS+
  - ICE-GTC
  - SMEB
  - SMEI

- Less common phenotypes
  - MAE/Doose syndrome, LGS, infantile spasms
- Proteins are made up of amino acids
- **Codons**
  - 3 positions
  - codes for specific amino acids
  - Ex. GUU codes for valine
• Missense & Nonsense mutation

  ▪ Single amino acid substitution

Missense mutation

Nonsense mutation

Original DNA code for an amino acid sequence.

Incorrect amino acid, which may produce a malfunctioning protein.

Original DNA code for an amino acid sequence.

Incorrect sequence causes shortening of protein.

U.S. National Library of Medicine
Frameshift & Deletion mutation

**Frameshift**
- Change in amino acid sequence from point of mutation

**Deletion**
- Deletion of a single nucleotide
Family findings for SCN1A related seizures

- ≥ 1 family member with epilepsy
- Febrile seizure before 1 year of age
- Febrile seizures after 6 years old
- Febrile seizure with unusual severity
- Febrile seizures that occur before an unproved seizure
Inheritance

- SNC1A related seizure disorders are inherited in an autosomal dominant manner.
- Most SMEI and ICE-GTC are due to new heterozygous mutation.
- The parent is thought to have the mutation that causes the disease if there is an additional family member who has seizures.
- A SCN1A seizure disorder may be a result of a de novo (new) mutation.
- As the severity of the phenotype increases, the likelihood that the parent has the mutation decreases.
Inheritance (cont) - Siblings

- Risk of development depends on genetic status of parents
  - There is a 50% chance the sibling may inherit the mutation is the parent has the mutation
  - If neither of the parents have the mutation then the risk is lower, but compared to the general population, there is still a risk
Inheritance (cont) - Offsprings

- Children of those with a SCN1A seizure disorder has a 50% chance of inheriting the mutation
  - Those how have GEFS+ may have children with more severe conditions
Type of mutation in SNC1A genes

- GEFS+ = missense and familial
- ICE-GTC = missense and familial
- SMEI = Truncating and missense mutations
SCN1A mutation map
FS and FS+

- **FS**
  - Childhood seizures occurring only with fever
    - On or after six months of age
    - Resolution by 5 years
    - Fever higher than 38°C (100°F)

- **FS+**
  - Subset of FS that presents with....
    - Occurs before 1 year of age
    - Present beyond 6 years of age
    - Unusual severity
    - Occurrence of unprovoked seizures
GEFS$^+$

- Generalized epilepsy with febrile seizures plus
  - Mutation in 4 channel genes have been indentified
    - SCN1A, SCN2A, SCN1B, and GABA receptors
  - Enhanced sodium current flow through channel
SMEB & ICE-GTC

- Intractable childhood epilepsy with generalized tonic-clonic seizure
  - Onset in infancy or childhood
  - ~70% have an SCN1A mutation
SMEI

- Severe Myoclonic Epilepsy of Infancy
  - Also known as Darvet syndrome
  - First described in 1978
  - Refractory seizures and cognitive decline
  - Onset is during first year
  - 33-90%
Mechanism of seizure in SCN1A

- Gain of function
- Loss of function
Voltage gated potassium channel
KCNA1

- Encodes the Kv1.1 channel
- Repolarise and shapes action potential
- Not regarded as a gene with major effects in the cause of epilepsy
- Risk factor for seizure if mutation exists
Episodic Ataxia with Myokymia

- Inherited disorder that involves the brain and peripheral nerves
- KCN1A is not present in all EA1 cases
- Severity of symptoms varies

Defective channel gating or a dominant negative reduction
KCNQ2 and KCNQ3

- Discovered in 1998
- They compose the ‘M current’
  - Regulates the firing rate of neurons
- Channels open slower and close faster
BFNC

- Benign Familial Neonatal Convulsions
  - Recurrent, brief, generalized seizures
  - Begins on the 4\textsuperscript{th} day of life
  - Remits after 1-3 months
  - 10-16\% chance of seizure recurrence later
  - Incidence of 1 in 100,000 in general population
Ligand gated channelopathies

- Nicotinic acetylcholine receptors
  - ADNFLE

- GABA receptors
  - JME
ADNFLE

- Autosomal-Dominate Frontal Lobe Epilepsy
  - Clusters of brief motor seizures during sleep
    - Often misdiagnosed as nightmare
  - Single amino acid changes at key positions within the $\alpha_4$ or $\beta_2$ helices
    - Gain or loss of function
Juvenile Myoclonic Epilepsy

- ~4-6% of patients with epilepsy
- Characterized by onset
- Bilateral myoclonic jerks
  - Single or repetitive
- Missense mutation in GABRA1
Screening/genetic testing

- SCN1A testing is available
- Testing of parents help to confirm the diagnosis of GEFS+ of SMEI
- In severe idiopathic childhood epilepsy a search for a channelopathy should be included in the diagnosis
- Knowing the genetics can aid in explaining the prognosis
- Discovery of the mutation can help in therapeutic decisions