



Dravet syndrome :

Clinical presentation, genetic investigation  
and anti-seizure medication

Bradley Osterman MD, FRCPC, CSCN

# Objectives

- Learn about the typical early clinical presentation of Dravet syndrome
  - with the help of a case study
- Gain knowledge about the genetic causes of Dravet syndrome
- Become familiar with the common anticonvulsant medication used to treat the different seizures in Dravet syndrome



# Case study



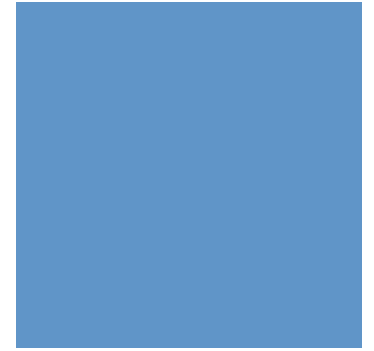
# Case study

- 2 ½ year girl
- Born at 35 weeks gestation, normal pregnancy and delivery
- Fam Hx:
  - 1 paternal aunt known to have had seizures as an teenager
- Normal early development
  - Until the age of 18 months



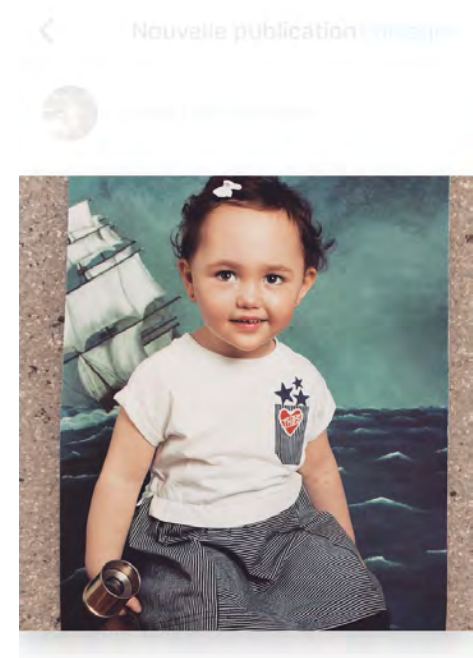
# Case study

- At 8 months
  - Episode of excessive “shivering” during a viral illness (common cold)
- At 10 months
  - First generalised seizure (< 5 minutes), provoked by swallowing water in a wading pool and choking
  - EEGs (x 2) – no epileptic activity



# Case study

- At 13 months
  - 3 x generalized febrile seizures over a 72 hr period
    - Longest being 7 minutes
    - In the context of another viral illness (38.6 C)
  - This time the EEG showed evidence of several generalised epileptic discharges
  - Also noted were several myoclonic jerks (5-6 x/day)
    - Accompanied by generalised epileptic discharges on the EEG
  - Brain MRI Normal



# Case study

- At 14 months
  - Significant increase in the frequency of the myoclonic seizures, despite introduction of anticonvulsant medication (clobazam, levetiracetam, valproic acid)
  - During a several day period, she was having over 100 myoclonic sz/day
    - With a fluctuation in her level of alertness







# Case study

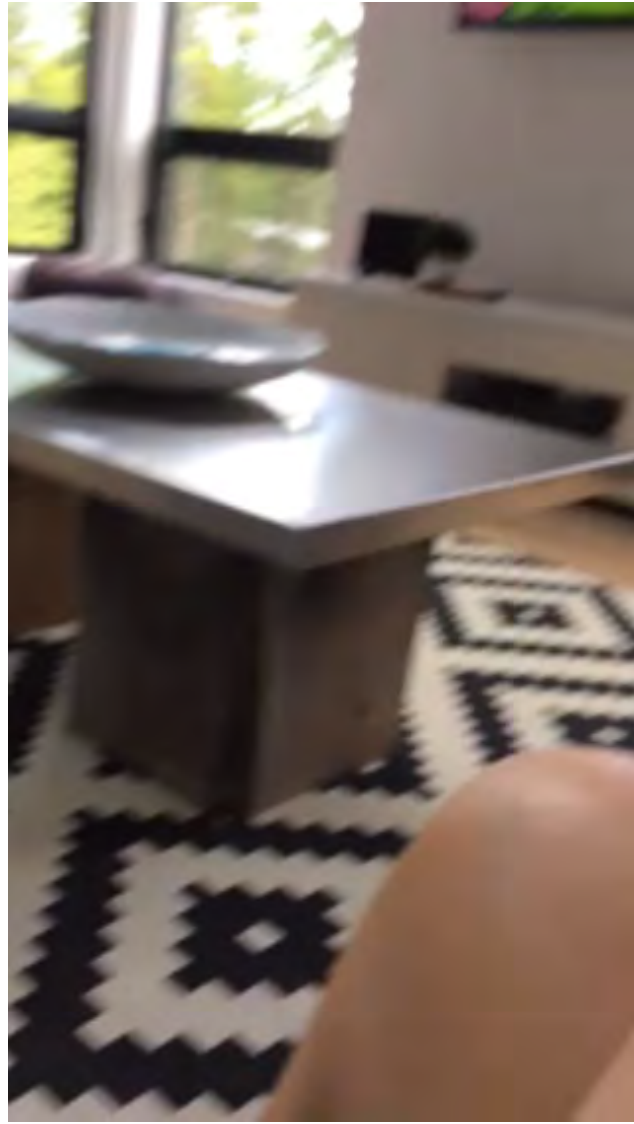
- At 15 months
  - Sz were better controlled
  - With higher doses of valproic acid, levetiracetam and diazepam
  - She did not respond well to lamotrigine
- Metabolic work-up Normal
- Genetic testing was ordered, but unfortunately not properly done during this admission and therefore had to be re-ordered at a subsequent follow-up visit



# Case study

- At 24 months
  - She was walking well even running
  - 100 word vocabulary, but did not put 2 words together
  - Normal social development
- Epilepsy better controlled, but still had daily occasional myoclonic jerks that interfered with her fine motor development
- EEG still showed generalised, but now also occasional multi-focal epileptic aN





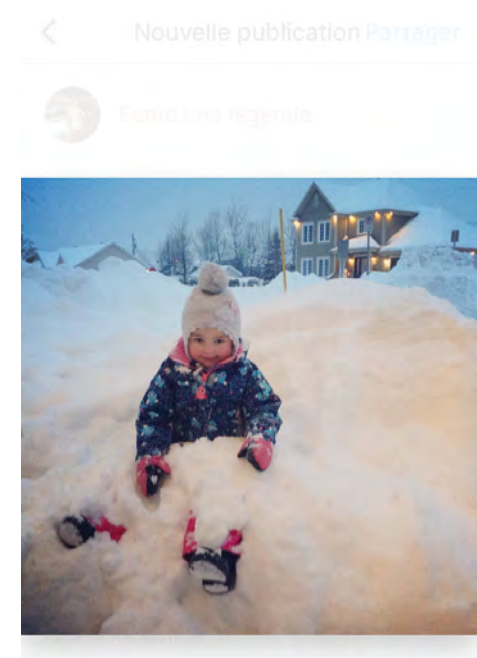
# Case study

- At 25 months
  - Epilepsy gene panel re-ordered
    - Pathogenic mutation was found in the SCN1A gene



# Case study

- Now at 27 months
  - Language delay more evident
    - Certain regression in language development
  - Walking has become more difficult
    - Often unstable, falls
- Epilepsy stable
  - But continues to have frequent daily myoclonic jerks, especially when tired
  - CBD added recently to anti-seizure medication
  - Stiripentol next to be tried if need be



# Classic clinical presentation

- Normal child development at onset
  - Universally normal development in the first year of life
  - Speech begins at a normal age
    - First words often by 12 months
  - Majority of patients are able to walk unsupported by 16 months
  - As seizures become more varied and frequent, there is often developmental regression
    - Generally by 2 years of age



# Classic clinical presentation

- Febrile seizures
  - Between 6 and 12 months of age
  - Recurrent episodes of prolonged febrile seizures
    - Known as febrile status epilepticus (> 15 minutes)
  - Commonly frequent
    - Ie. More than 5
  - Hot water or heat induced seizures
  - Seizure can also occur without fever (10-35%)



# Seizure types

- Multiple seizure types begin in the 2<sup>nd</sup> year of life
- Classic generalized tonic-clonic seizures
- Hemi-convulsion and focal seizures
- Myoclonic
  - Brief, shock-like jerks of a muscle or group of muscles
  - Typically begins between 1-5 years of age
- Atypical absence
- “Obtundation” status epilepticus





# Obtundation status epilepticus

- Fragmentary and erratic segmental or bilateral myoclonus involving the limbs and face
- Variable impairment in the level of consciousness
  - With waxing and waning in alertness
- Can resemble a typical prolonged GTC seizure
  - but remains a “non-convulsive” status epilepticus
- May last hours to days
- Hospitalisation may be required for effective treatment

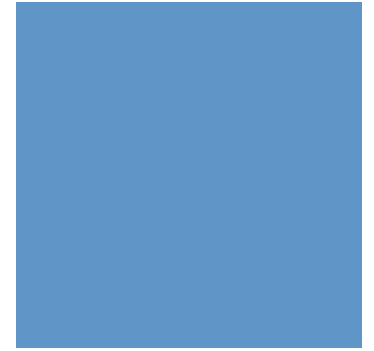


# Seizure types

- Seizures can often be triggered by changes in body temperature, not just with fever secondary to an infection
  - Hot water, warm weather and vaccinations
- Photo-sensitivity is common
  - ie. Flashing lights, patterns or other photic triggers
- Seizures can often be worsened by specific anticonvulsants
  - ie. Carbamazepine, phenytoin, fosphenytoin, oxcarbamazepine, lamotrigine, and rufinamide
  - Myoclonic seizures can be worsened by vigabatrin and tiagabine



# Developmental plateau



- By 2 years of age, children may begin to lose certain developmental milestones, or at least not progress as quickly as compared to other children their age
- This developmental plateau or regression can be severe, and often lasts until the age of 6 years old
- After 6 years of age, cognitive problems in children may stabilize or start improving
- The degree of cognitive impairment is commonly associated with seizure control
  - Better seizure control can promote better cognitive function

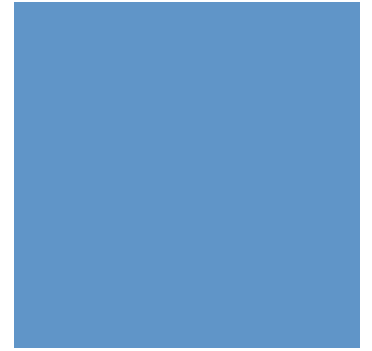
# Other common issues

- Delayed language and speech issues
- Unsteady gait
  - Ataxia, crouched gait in older children and adults
- Hyperactivity, behavioural issues, autistic traits
- Chronic infections
- Growth and nutritional problems
- Parkinsonism in adult patients
- Increased risk of SUDEP
  - Approximately 15-fold higher than with other childhood epilepsies



# Investigations

- Electroencephalography (EEG)
- Brain imaging
  - MRI
- Metabolic work-up
- Genetic testing



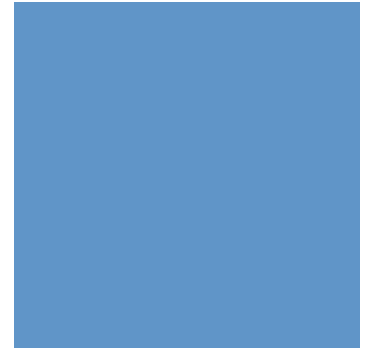
# EEG

- Normal in the first (sometimes second) year of life
- Then, generalised and multi-focal epileptic activity progressively appear
- Photosensitivity in many patients
- Background slowing

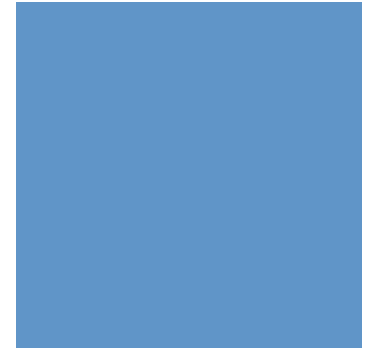


# Brain MRI

- Normal at onset
- Cortical atrophy can be seen in older children



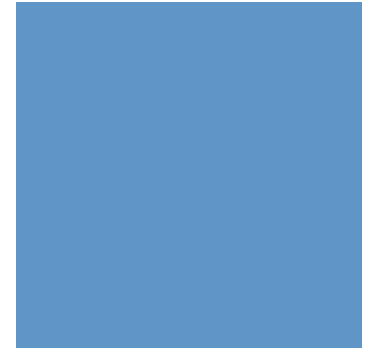
# Metabolic work-up



- Normal
- Commonly performed to rule-out other potential rare forms of early myoclonic epilepsies
  - Ie. Non-ketotic hyperglycinemia



# Genetic testing

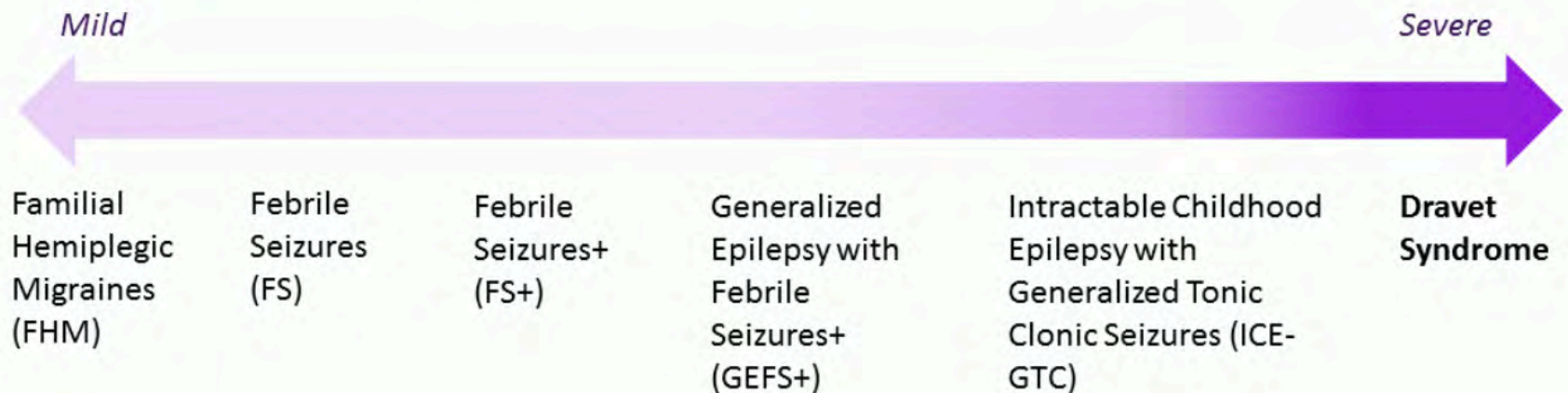


- Epilepsy gene panel
  - Includes testing for mutations in the gene *SCN1A*
- Dravet syndrome is caused by alterations in the *SCN1A* gene in > 80% of patients
  - *De novo* in 95% of patients
- Over 1,250 different disease-causing variants have been reported throughout *SCN1A*

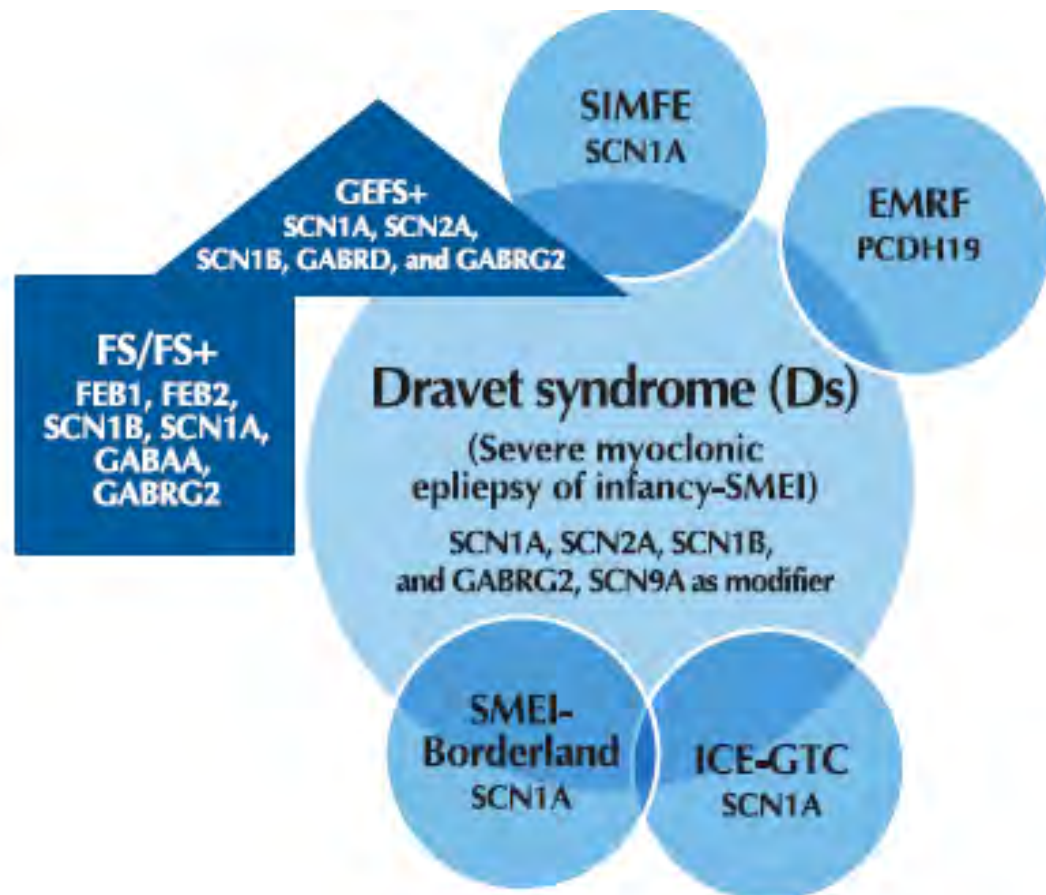
# SCN1A-related disorders



## The Spectrum of SCN1A Disorders



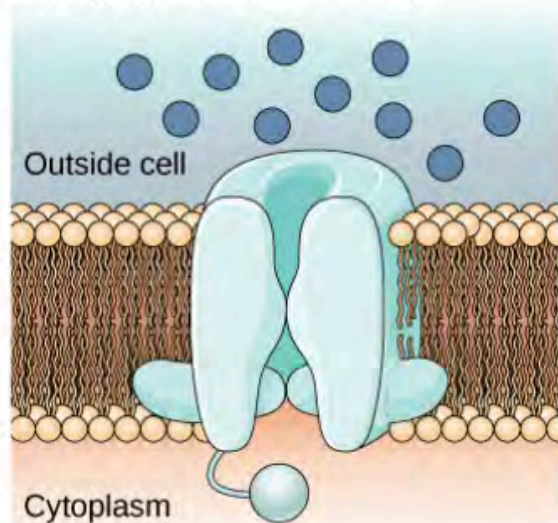
## Genetic Febrile Epilepsies and Associated Mutations



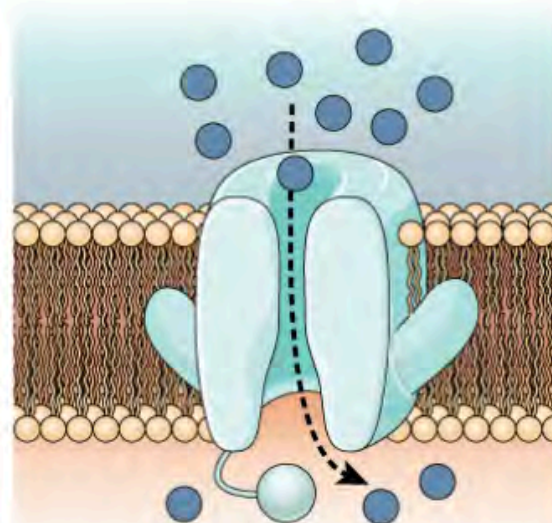
# The voltage-gated sodium channel



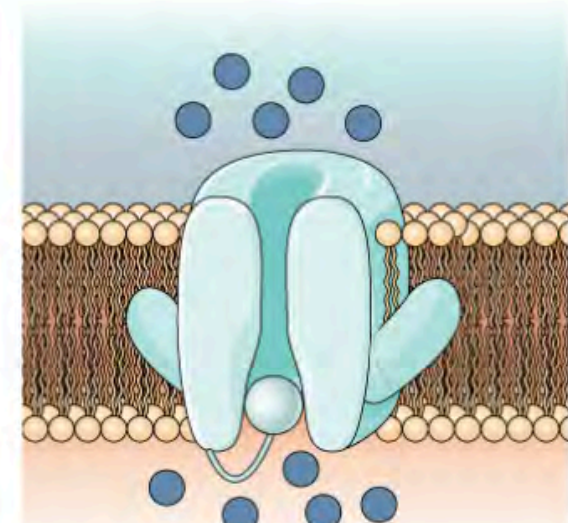
## Voltage-gated Na<sup>+</sup> Channels



**Closed** At the resting potential, the channel is closed.

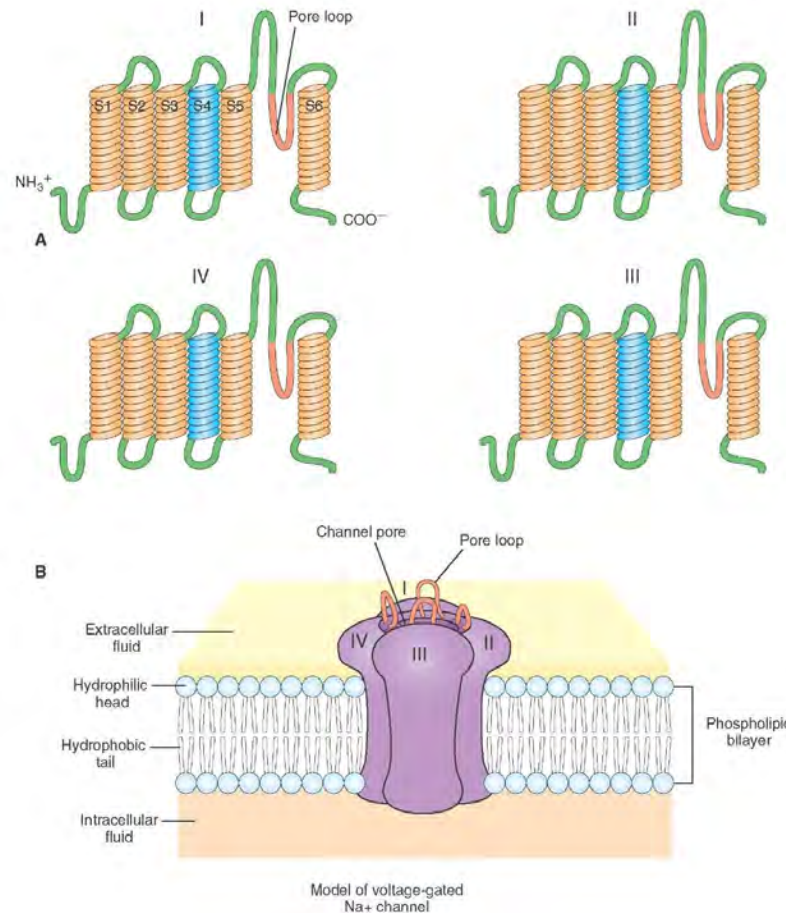


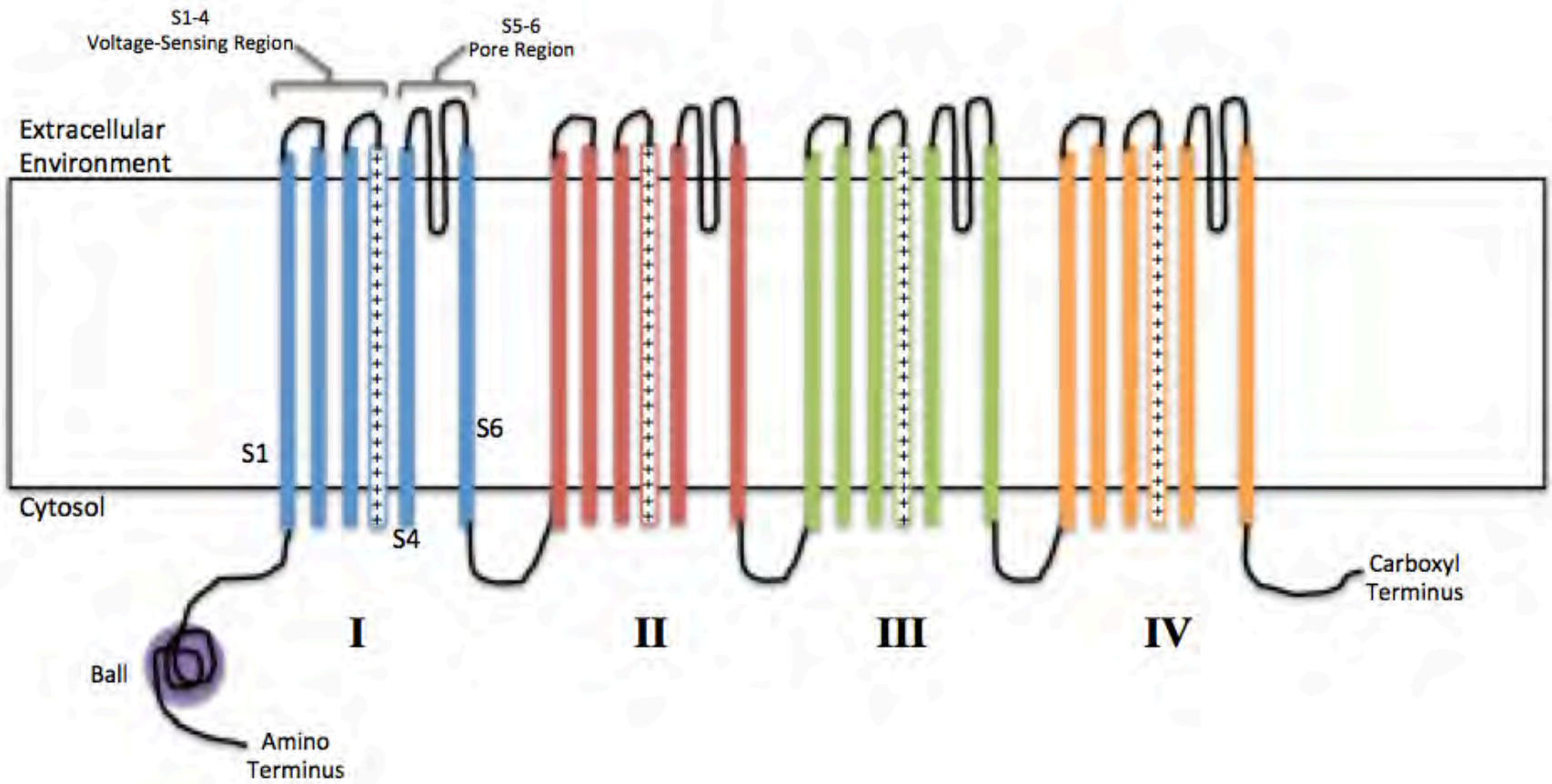
**Open** In response to a nerve impulse, the gate opens and Na<sup>+</sup> enters the cell.

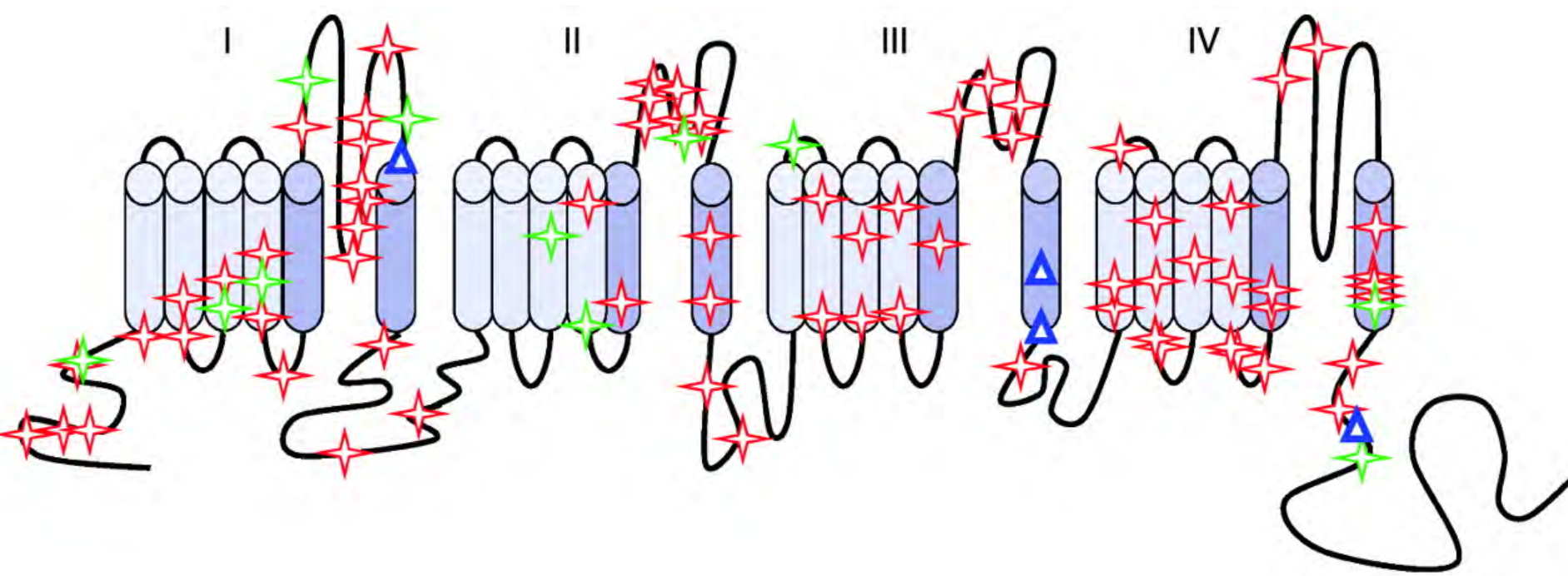


**Inactivated** For a brief period following activation, the channel does not open in response to a new signal.

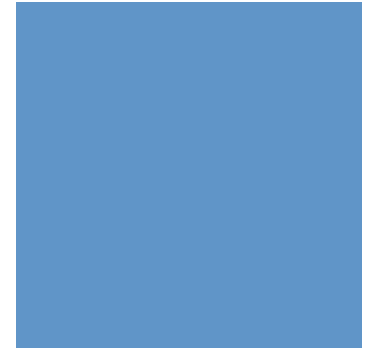
# The alpha subunit of Na<sub>v</sub>1.1







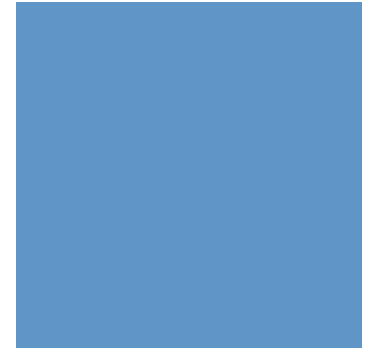
# SCN1A gene



- The SCN1A gene mutation was discovered in 2001
- Codes for the alpha subunit of the voltage-gated sodium channel ( $\text{Na}_v1.1$ )
  - This ion channel is highly concentrated in the brain and critical to the generation and propagation of action potentials
  - An abnormal or mal-functioning sodium channel causes neuronal dysfunction and hyper-excitability



# SCN1A gene



- Variants that truncate or completely disrupt the *SCN1A* protein are more likely to be found in patients with Dravet syndrome than in patients with GEFS+


# Treatment options

- Multidisciplinary team
- Anticonvulsant therapy
- Rescue medication
- Ketogenic diet
- Vagal nerve stimulator
- Cannabidiol (CBD)



# Anticonvulsants

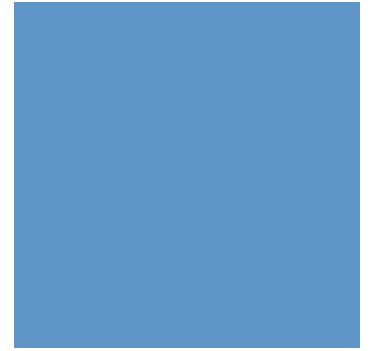


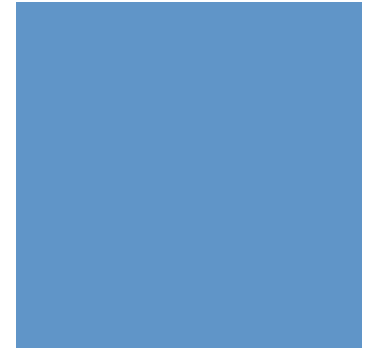
Maintenance Antiepileptic Medications	
First Line	<b>clobazam</b> (Onfi, Frisium, Urbanyl) and <b>valproic acid</b> (Depakote, Depakene, Epilim, Epival)
Second Line	<b>stiripentol</b> <sup>†</sup> (Diacomit), <b>topiramate</b> (Topamax), <b>ketogenic diet</b> (positive effect on cognition)
Third Line	<b>clonazepam</b> (Klonopin, Rivotril), <b>levetiracetam</b> (Keppra), <b>zonisamide</b> , <b>ethosuximide</b> (for atypical absences), <b>VNS</b>
 Contraindicated	<b>carbamazepine</b> (Tegretol, Celepsin, Cargagen), <b>oxcarbazepine</b> (Trileptal), <b>lamotrigine</b> (Lamictal), <b>phenytoin</b> <sup>††</sup> (Dilantin, Epanutin), and <b>vigabatrin</b> (Sabril, Sabrilan, Sabrillex)

† In combination with valproic acid and clobazam. Stiripentol currently has Orphan Drug Status classification in the US, but not full FDA-approval, which can make insurance coverage difficult. Importation of stiripentol requires documentation of medical necessity. †† Phenytoin and Fosphenytoin, while not recommended for daily use, are often used in emergency treatment of prolonged seizures with varying success in patients with Dravet syndrome. Caution is advised.

# Rescue medication

- Diazepam (Diastat)
- Midazolam (Versed)
- Lorazepam (Ativan)





Thank you