Genetics 101: 

SCN1A

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Disclosures:

I have no financial interests or relationships to disclose.
Objectives

1. Review genetic concepts and terminology
2. Discuss the genetics of Dravet Syndrome
3. Understand how to interpret a genetic testing report
Who Are Genetic Counselors?

• Master’s-trained health care professionals who combine their knowledge of:
  - Basic science
  - Medical genetics
  - Epidemiological principles
  - Counseling theory

• With their skills in:
  - Genetic risk assessment
  - Education
  - Interpersonal communication and counseling

• To provide services to clients and their families for a diverse set of genetic or genomic indications
Dravet Syndrome

• **Seizures** beginning in the first year

• **Developmental delays**
  • Normal development prior to seizure onset
  • Developmental slowing, plateau, or regression

• **Other common features:**
  • Movement/balance issues, orthopedic conditions, growth and nutrition issues, sleeping difficulties, behavioral problems

• **Incidence of** 1:16,000 – 1:20,000

www.dravetfoundation.org
Cell

Chromosomes
Each chromosome is composed of one large continuous DNA molecule.

Gene
A gene is a segment of DNA that encodes a protein product.

Protein
A protein is a complex organic compound composed of hundreds or thousands of amino acids.

DNA

- Adenine
- Thymine
- Guanine
- Cytosine
Genes and Proteins

• A **gene** is a segment of DNA that codes for a protein

• A **protein** is a molecule that can have many different important roles in the body
  • provide structure and support
  • transport materials and sending signals
  • protect the body from viruses and bacteria
  • carry out chemical reactions

• Proteins are made up of smaller units called **amino acids**
  • 20 different types of amino acids
  • the sequence of amino acids determines each protein’s 3D structure and specific function
Exons and Introns

• An **exon** is a segment of DNA or RNA containing information coding for a protein
  • **EXpressed region**

• An **intron** is a non-coding region of DNA that is removed before a protein is made
  • **INTRagenic** or **INTeRvening region**
  • Can contain regulatory elements, such as enhancers
Genetic Variants

• A variant is any alteration in the DNA sequence that is different from what is seen in the majority of people
• A variant can be benign, pathogenic, or of uncertain significance (VUS)
• Pathogenic (disease-causing) variants are often referred to as mutations
Types of Mutations

• A **missense** mutation is a change in one DNA base pair that results in the substitution of one amino acid for another

• A **silent** mutation changes the DNA, but not the amino acid – this is possible because the code is redundant

• A **nonsense** mutation is a change in one DNA base pair that signals the cell to stop building the protein too early, causing a shortened protein, or **early truncation**

• An **insertion** adds a piece of DNA

• A **deletion** removes a piece of DNA

• A **duplication** is a piece of DNA that is copied one or more times

• If a deletion, insertion, or duplication alters the reading frame of the gene, this is called a **frameshift mutation**, and often results in an early truncation
Missense Mutation

THE CAT ATE THE RAT  →  THE CAT ATE THE BAT

Example: c.865G>A  
p.Glu289Lys
Missense Mutation

THE CAT ATE THE RAT  →  THE CAR ATE THE RAT
Silent Mutation

Example:
c.2712C>T
Silent
Nonsense Mutation

THE CAT ATE THE RAT $\rightarrow$ THE CAT $^*$

Example:
c.1455C>A
p.Cys485*
OR p.Cys485X
Insertion

THE CAT ATE THE RAT → THE **BAT** CAT ATE THE RAT

Example:
c.396insACT
p.132insThr
Deletion/ Duplication

THE CAT ATE **THE** RAT \( \rightarrow \) THE CAT ATE ___ RAT

THE CAT ATE **THE** THE RAT

Examples:
c.209_211CAAdel
p.Gln70del
c.209_211CAAdup
p.Gln70dup
Frameshift Mutation

THE CAT ATE THE RAT → THE CAT TET HER AT

Examples:
c.704delA  p.Tyr235*
c.227dupG  p.Met77Hisfs*12
The SCN1A Gene

- Made up of 26 exons
- Located on chromosome 2
- ~80% of patients with Dravet Syndrome have an identifiable mutation in SCN1A
- Over 1,250 different mutations have been reported
- Mutations in other genes can cause a Dravet Syndrome phenotype (SCN2A, STXBP1, PCDH19 and others)

https://ghr.nlm.nih.gov/gene/SCN1A#
Spectrum of SCN1A-Related Disorders

- Different mutations in SCN1A can cause different presentations
- The same mutation can sometimes cause different presentations in different people, even within the same family

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
Dravet syndrome phenotype

SCN1A

SCN2A

SCN9A

SCN8A

SCN1B

HCN1

KCNA2

GABRA1

GABRG2

PCDH19

STXBP1

CHD2
The NaV1.1 Sodium Channel

- **SCN1A = sodium voltage-gated channel alpha subunit 1**
- **NaV1.1 Sodium Channels**
  - Proteins found primarily in the brain
  - Control the flow of sodium ions into cells
  - Involved in **transmitting signals** from one neuron to another
  - Communication between neurons depends on chemicals called neurotransmitters
  - The flow of sodium ions through NaV1.1 channels helps determine when neurotransmitters will be released
  - Replaces the embryonic sodium channel subunit by the first year of life (which is why seizures typically start by that time)

https://ghr.nlm.nih.gov/gene/SCN1A#

Gataullina S, Dulac O. Eur J Epilepsy 2017
Types of SCN1A Mutations

- Mutations are spread throughout the entire gene
- 52% are early truncations that result in no functional protein
  - Typically cause Dravet Syndrome (94%)
- 27% are missense mutations in the pore-forming portion of the protein
  - Cause Dravet Syndrome in about 75% of patients
- 12% are missense mutations in the voltage sensor portion of the protein
  - Cause anything from febrile seizures to Dravet Syndrome
- Genotype-phenotype correlation is not perfect!
Where Did This Come From?

- 90% of *SCN1A* mutations are de novo, meaning they arose new in the patient and were not inherited from a parent.
- De novo mutations typically occur when DNA is being copied prior to cell division – they are changes that the cell’s “spell-check” missed.
- Not due to environmental exposures, or anything that parents did (or did not) do during the pregnancy.
- In up to 10% of cases, the mutation is inherited from a parent:
  - Parent is usually unaffected or has very mild symptoms.
  - In this case there is a 50% chance of passing the mutation on to any future children.
Autosomal Dominant Inheritance

• Each individual has two copies of most genes, one inherited from their mother and one from their father
• In **dominant** disorders, a pathogenic variant in just ONE of those two copies is enough to cause the disease
• One functional copy of the gene is not sufficient – this is called **haploinsufficiency**
• Individuals with a mutation in a single copy of a gene are referred to as **heterozygotes**
• An individual with a mutation in *SCN1A* has a 50% chance of passing it down to each child, and a 50% chance of passing down the typical copy
Reduced Penetrance & Variable Expressivity

- Factors that influence the effects of particular genetic changes
- *Reduced* or *incomplete penetrance* refers to a genetic condition in which some people with a mutation do not develop features of the disorder
- *Variable expressivity* refers to the range of signs and symptoms that can occur in different people with the same genetic condition
- Probably result from a combination of genetic, environmental, and lifestyle factors
- Can make it challenging to predict the risk of passing a genetic condition to future generations, and to predict how mild or severe that condition may be in other family members
Mosaicism

- Mutations that happen in a single cell early in embryonic development can lead to mosaicism.
- Genetic changes not present in parents or fertilized egg, but happen later in fetal development.
- As cells divide, cells that arise from the cell with the altered gene will have the mutation, while other cells will not.
- Depending on proportion of cells affected, a patient with SCN1A mosaicism may have a less severe presentation.
- Mosaicism can often be missed by genetic testing.
- May be present in 1% of patients with Dravet Syndrome.

Nakayama T et al. Am J Med Genet 2018
Greenwood Genetic Center Genetic Counseling Aids, 2013
Parental Testing

- Recommended for parents of children with an *SCN1A* mutation, even if they have no history of epilepsy
  - Especially if planning additional pregnancies
- Some labs offer free or reduced-cost parental testing
- If parental testing is negative, there is a very low chance of having another affected child
- Can not detect germline mosaicism
  - When a mutation is present in some of the egg or sperm cells, but not the rest of the body
  - Seen in about 10% of apparently de novo cases of Dravet Syndrome
- Prenatal/pre-implantation testing available
Example Test Report

Positive result. Pathogenic variant identified in SCN1A.

Clinical Summary

- A pathogenic variant, c.1278C>G (p.Tyr426*) was identified in SCN1A.
  - The SCN1A gene is associated with a spectrum of autosomal dominant SCN1A-related seizure disorders ranging from simple febrile seizures (MedGen UID: 338959) and genetic epilepsy with febrile seizures plus (GEFS+) (MedGen UID: 388117) to Dravet syndrome (MedGen UID: 148243) and intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) (MedGen UID: 148243). Other SCN1A-related conditions have been reported (OMIM: 607208).
  - This result is consistent with a predisposition to, or diagnosis of, SCN1A-related conditions.
  - SCN1A-related conditions are seizure disorders with varying severity and early childhood onset. Febrile seizures are childhood seizures that occur with fever and often resolve by six years of age. GEFS+ is also characterized by febrile seizures; however with GEFS+, both febrile and afebrile seizures may continue throughout an affected individual’s lifetime. Dravet syndrome is one of the most severe seizure disorders and is characterized by intractable seizures and usually associated with progressive dementia. ICE-GTC is considered a late-onset Dravet syndrome. Intrarafamilial variability in seizure type, persistence, and response to treatment has been documented, as has reduced penetrance (http://www.orpha.net/data/patho/GB/uk-GEFS.pdf).
  - Close relatives (children, siblings, and parents) have up to a 50% chance of being a carrier of this variant. More distant relatives may also be carriers. Parental testing may clarify the inheritance of this variant and may inform recurrence risk and risk for other close relatives. Testing for this variant is available.
Summary

• Dravet Syndrome is an autosomal dominant genetic condition caused by pathogenic variants (mutations) in the SCN1A gene.

• SCN1A mutations cause problems with the sodium channels in the brain, leading to epilepsy, developmental issues, and other symptoms of Dravet.

• Geneticists and genetic counselors can help to explain your child’s genetic testing and what it means for your family.
Online Resources

- Dravet Syndrome Foundation: https://www.dravetfoundation.org/
- Dravet Syndrome UK: https://www.dravet.org.uk/
- Genetics Home Reference: https://ghr.nlm.nih.gov/gene/SCN1A#
- Genetics Primer: https://ghr.nlm.nih.gov/primer
References

• Nakayama T et al. Somatic mosaic deletions involving SCN1A cause Dravet syndrome. American Journal of Medical Genetics 2018: 176A(3).
Questions?

Feel free to email me at kaitlin.angione@childrenscolorado.org with any specific questions regarding genetics or genetic testing.