5 Things You Should Know About Genetics and Dravet

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5 Things You Should Know about Genetics and Dravet:

1. SCN1A codes for the sodium ion channel.
2. Mutations change the code.
3. Mutations are common in Dravet syndrome.
4. Mutations can be new or inherited.
5. You can decipher a lab report.
Seizures are Abnormal Electrical Impulses.

- Charged ions like sodium flow into and out of the cell membrane.

- When the ion channels don’t work properly, abnormal electrical impulses can result in a seizure.
SCN1A codes for the sodium ion channel.

Image adapted from National Human Genome Research Institute, www.genome.gov/pages/hyperion/DIR/VIP/glossary/illustration/codon.shtml

Image: Advances in Clinical Neuroscience and Rehabilitation, http://www.acnr.co.uk/2013/01/inherited-ion-channel-disorders-of-the-brain/

DNA (SCN1A)  Amino Acid Chain  Protein (Ion Channel)
SCN1A codes for the sodium ion channel.
Mutations change the code.

- **Missense** = change in one base
- *Can* alter shape and function of the protein.
- Can cause any phenotype

**Normal**

G
C
U
A
C
G
G
A
G

STOP

**Missense Mutation**

G
C
U
C
C
G
G
A
G

STOP

**Normal**

G
C
U
G
C
A
G
G

**Missense Mutation**

G
C
U
C
C
G
G
A
G

**Normal**

G
C
U
A
C
G
G
A
G

STOP

**Missense Mutation**

G
C
U
C
C
G
G
A
G

STOP
Mutations change the code.

- **Nonsense (truncation/termination)** = change in one base, makes a premature termination codon (PTC).
- Often non-functional ion channel
- Any phenotype, but often moderate-severe
2 Mutations change the code.

- **Insertion/Deletion** = usually changes the reading frame.
- All amino acids changed from that point on
- Any phenotype, but often moderate-severe

<table>
<thead>
<tr>
<th>Normal</th>
<th>Insertion Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>U</td>
<td>C</td>
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<tr>
<td>A</td>
<td>U</td>
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<td>C</td>
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<td>G</td>
<td>C</td>
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<td>G</td>
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<tr>
<td>A</td>
<td>G</td>
</tr>
<tr>
<td>G</td>
<td>A</td>
</tr>
</tbody>
</table>

Normal: GCU → Ala

Insertion: GAC → Asp

Tyr: UAC

Glu: GAG
Mutations change the code.

• **Splice Site** = mutations in the non-protein coding area

• **Large Deletions/Insertions** = Larger parts of the gene, or even the entire gene(s), are deleted or inserted
Mutations are common in Dravet.

SCN1A mutation (70-80%) (1)(2)

PCDH19 (2-5%) (2)

Other/No Known Mutation (15-20%)
Mutations are common in Dravet. But SCN1A mutation ≠ Dravet.

SCN1A Mutations:
- Dravet/SMEI Diagnosis: 75%
- Milder Diagnosis (GEFs+, FS, etc.): 24%

Dravet Mutations:
- Missense: 40%
- Nonsense/Termination: 20%
- Frameshift: 20%
- Splice Site: 10%
- Large Deletion: 7%

(4)
Mutations can be new or inherited.

90-95% appear to be “de novo” (new to the child). (1)(4)

- De novo mutations can happen spontaneously at or just after conception
- Mutations in eggs or sperm would also appear to be de novo.
4 Mutations can be new or inherited.

- One copy of SCN1A from each parent
- 50% chance of passing it on to each child.
- Children are often more severely affected than the parent. (reduced penetrance)
- 3-10% of DS mutations are inherited. (1)(4)

NIH: https://ghr.nlm.nih.gov/primer/inheritance/riskassessment
Mutations can be new or inherited.

**Mosaicism:** Mutation is not present in all cells of a person’s body.
- Chance of passing it along to children depends on location of mosaic cells.

- Up to 10% of mutations thought to be de novo may be inherited from a mosaic parent. (5)
- Up to 42% of inherited mutations may be from a mosaic parent. (4)
You can decipher a lab report.

**Example 1: Missense**

One “G” is replaced with a “T” at the 4073rd base pair.

Which is the 1358th codon ($4073 \div 3 = 1358$)

Changing one amino acid from Tryptophan to Leucine

Unknown significance because missense mutations can cause anything on the spectrum.
You can decipher a lab report.

Example 2: Nonsense/Termination

Substitution of a G for a C at nucleotide position 4521.
Changes the 1507th amino acid from Tyrosine (Y) to a termination codon (X).
Premature termination codons = nonsense mutations
“Deleterious” = disease-causing, not a deletion
Example 3: Frameshift

Sequence analysis detected the following:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon/Intron</th>
<th>Nucleotide change</th>
<th>Zygosity</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1A</td>
<td>Ex6</td>
<td>c.830delG</td>
<td>Heterozygous</td>
<td>Pathogenic</td>
</tr>
</tbody>
</table>

Although the c.830delG variant has not been reported in individuals with SCN1A-related disorders, it is of a type expected to cause disease.

One G is deleted at the 830th nucleotide.
The deletion is on Exon 6 (SCN1A has 26 Exons).
Pathogenic = likely disease-causing

This mutation has not been reported in published literature.
You can decipher a lab report.

**Example 4: Splice Site**

One G is replaced with an A one nucleotide before the 474\(^{th}\) position (474-1).

This substitution is at a splice site. Pathogenic = likely disease-causing

This mutation has been reported in published literature.
References


Questions?