Introduction to the Genetics of CACNA1A-Related Disorders

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Disclosures

• None

• Information discussed should **not** be considered medical advice
OVERVIEW

• Introduction to CACNA1A-related disorders

• Introduction to Genetics of CACNA1A
  • Important genetic concepts
  • Types of genetic changes

• The CHOP Epilepsy Neurogenetics Initiative (ENGIN)
  • Multidisciplinary clinical program
  • Ongoing research activities
Main categories of CACNA1A disorders

- Clinical features in individuals with CACNA1A
  - Neurodevelopmental disorders and epilepsy
  - Ataxia (congenital and episodic)
  - Hemiplegic migraine
  - [Spinocerebellar ataxia type 6]

Many individuals have symptoms across categories
Neurodevelopmental disorders

- Global developmental delay or intellectual disability
  - Mild to severe
  - Learning disabilities

- Autism spectrum disorder
  - Impairment of social interaction
  - May present atypically

- Hypotonia (low muscle tone)
  - May be developmental and improve over time
  - Often results in gross motor delay, may be related to ataxia
Epilepsy

• Mild to severe seizures
  • In earliest cases, seizures start soon after birth or 1st weeks of life
  • Some individuals have episodes of “status epilepticus”

• In some cases, severe enough to impact development
  • “Epileptic encephalopathy” – requires more intense treatment

• Many individuals with CACNA1A have few or no seizures
  • Early-onset epilepsy more likely with “gain-of-function” variants
Ataxia (developmental, episodic)

• Unsteadiness of movement and poor balance
  • Example: someone who can typically walk well suddenly struggles to keep balance or move as they normally would

• Can occur during constantly or during specific occasions
  • Episodic ataxia may be treated with acetazolamide
  • Assessing ataxia, specifically episodic ataxia is challenging in children
Eye movement abnormalities

• **Nystagmus**
  - Uncontrolled movement of the eyes from side-to-side or up-and-down
  - Affected person may not be aware of these movements

• **Paroxysmal tonic upgaze**
  - Periods where a person’s eyes stare upwards uncontrollably

• **These eye movements are NOT seizures**
  - Can occur with episodes of ataxia or migraine
Hemiplegic migraine

• Weakness and/or paralysis on one side of the body
  • Can be mistaken for a stroke
  • May occur with headache (”migraine”), but different mechanism

• Loss of consciousness due to minor head injury
  • Severe, but often self-limiting episodes

• Can be severe and require immediate medical attention
  • Brain swelling and extended hospital stays
Spinocerebellar ataxia type 6 (SCA6)

• Unique genetic difference within \textit{CACNA1A}
  • Trinucleotide repeat expansion
  • Onset between 40-50 years of age (not pediatric)

• Progressive neurological disorder
  • Increasing ataxia and issues with balance, tremor
  • Dysarthria (difficulty with speech)
  • Nystagmus (eye movements)
CACNA1A-related features

- Neurodevelopmental disorders
- Epilepsy
- Ataxia (congenital and episodic)
- Hemiplegic migraine
Important Genetics Concepts
WHAT IS A GENE?

A gene is made up of DNA. It carries instructions to make proteins.

The proteins have specific jobs that help your body work normally.
Gene (CACNA1A)

Image from: genome.gov
WHAT HAPPENS WHEN THERE IS A GENETIC MUTATION?

NORMAL GENE

HEALTHY PROTEIN

MUTATED GENE

DAMAGED PROTEIN

Image from: Myriad Genetics
What does CACNA1A do?

- Codes for part of a calcium channel
- Traffic cop in the brain for when messages should be sent
Inheritance of CACNA1A Disorders

• Can be inherited from a parent or *de novo* (brand new in a child)

• Severe or early-onset CACNA1A-related disorders are more likely to be *de novo*
AUTOSOMAL DOMINANT INHERITANCE

- 50% chance of child inheriting mutation
- Risk of inheritance is the same for sons and daughters

AT-RISK CHILDREN
Types of Genetic Changes
Missense Variant

- **Protein**
  - Reference amino acid
  - Position
- **Variant amino acid**
- **p.Arg130Trp**

Original DNA code for an amino acid sequence:

```
CATCATCATCATCATCATCATCATCATCATCAT
```

- **Amino acid**
  - Replacement of a single nucleotide.

Incorrect amino acid, which may produce a malfunctioning protein.

U.S. National Library of Medicine
Nonsense Variant

U.S. National Library of Medicine
Frameshift Variant

U.S. National Library of Medicine
Some splicing changes are normal—leads to different numbers in variant name

p.Val_{1393}^{\text{Met}} = p.Val_{1396}^{\text{Met}}
Deletions or Duplications of \textit{CACNA1A}

Deletion of \textit{CACNA1A} on chromosome 19
May involve other genes

Duplication of \textit{CACNA1A} on chromosome 19
May involve other genes
Spinocerebellar ataxia type 6

Normal
100% is functional

Loss of function
50% is functional

Gain of function
Added function
## How is CACNA1A Diagnosed?

<table>
<thead>
<tr>
<th>Method</th>
<th>Details</th>
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<tbody>
<tr>
<td>Chromosomal microarray</td>
<td>Detects missing or extra pieces of a chromosome that include CACNA1A</td>
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<tr>
<td>Gene panel</td>
<td>Test 10-1000 genes at once</td>
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<tr>
<td></td>
<td>Finds differences in the CACNA1A gene code sequence</td>
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<tr>
<td>Whole exome sequencing</td>
<td>Tests exons of ~20,000 genes, compares to a child's parents</td>
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<td>Trinucleotide repeat expansion</td>
<td>Tests for total number of CAG repeats</td>
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<td>In CACNA1A, only used to diagnose spinocerebellar ataxia</td>
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<td>Cannot diagnose other CACNA1A disorders</td>
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</table>
#1: Integrate genetics into epilepsy care

#2: Personalized plan for every patient

#3: Novel treatment and clinical trials
Multidisciplinary Clinic

• ENGIN clinic consists of:
  • Child Neurologist
  • Genetic Counselor
  • Physical Therapist
  • Occupational Therapist
  • Social Worker
  • Research team

• Team works together to create best plan of care for our patients
CACNA1A, Telemedicine, and COVID-19

• Drastic changes to the healthcare system

• A benefit: increased access to telemedicine
  • Video visits are now more widely available at many institutions
  • Especially beneficial for rare disorders, such as CACNA1A

• Advocating for increased access to telemedicine
  • Ongoing ability on our end to perform telemedicine visits

• Research focus on child neurology telemedicine
CACNA1A, Telemedicine, and COVID-19

Geographic distribution of ENGIN patients seen in-person (grey) and telemedicine (red)
Research activities within ENGIN

• Clinical presentations of CACNA1A-related disorders
  • Epilepsy features (international collaborations)
  • Understanding hemiplegic migraine presentations

• Functional analysis of CACNA1A variants
  • NIH Center Without Walls (U54)

• Data driven natural history/outcomes
  • Helbig Lab (data science approaches to natural history gap)
Understanding CACNA1A in 2021

• Epilepsy features in CACNA1A-related disorders
  • Insufficiently described, needed for better treatment
  • Ongoing international collaboration to outline specific features

• Hemiplegic migraine in CACNA1A-related disorders
  • Most cryptic feature in CACNA1A-related disorders
  • Clinical features of the p.V1396M (p.V1393M) variant
  • To participate, please contact Laina Lusk, CGC (LUSKL@chop.edu)
Large-scale variant analysis

- **CACNA1A-related disorders**
  - One of the "most neglected common ion channel diseases"
  - Knowledge on variant function behind other disorders
  - Disease variants result in wide range of functional changes

- **NIH Center Without Walls**
  - Channelopathy-associated Epilepsy Research Center (A. George)
  - Variant Curation Core (E. Cooper, I. Helbig)
  - Evaluation whether CACNA1A variants is feasible for screening
Data-driven natural histories

Analysis of >3,500 patient years with >60,000 data points in the Electronic Medical Records (EMR)
CHOP Epilepsy Neurogenetics Team

Child Neurologists and Epileptologists

- Ingo Helbig, MD
- Ana Cristancho, MD, PhD
- Colin Ellis, MD
- Mark Fitzgerald, MD, PhD
- Ethan Goldberg, MD, PhD
- Naomi Lewin, MD, PhD
- Eric Marsh, MD, PhD
- Shavonne Massey, MD, MSCE
- Xilma Ortiz-Gonzalez, MD, PhD
- Pamela Pojomovsky McDonnell, MD

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- Helen Milligan, PT, MPT
- Samuel Pierce, PT, PhD, NCS
- Kristin Girardi Cunningham, MS, OTR/L
- Anne-Ashley Field, MOTR/L

Contact: LUSKL@chop.edu or ENGIN@chop.edu
Seeing Us in ENGIN

- Contact ENGIN@chop.edu
  - Alternatively, contact us through CHOP website

- Indicate that you would like to see us for CACNA1A
  - We will have you scheduled with our CACNA1A team
  - Dr. Ingo Helbig; Laina Lusk, CGC; Sarah McKeown, CGC

- Video visits available for families within US
  - Regulations vary state by state