Introduction to the Genetics of *CACNA1A*-Related Disorders

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February 10, 2021

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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 *CACNA1A*
  - Trinucleotide repeat expansion
  - Onset between 40-50 years of age (not pediatric)

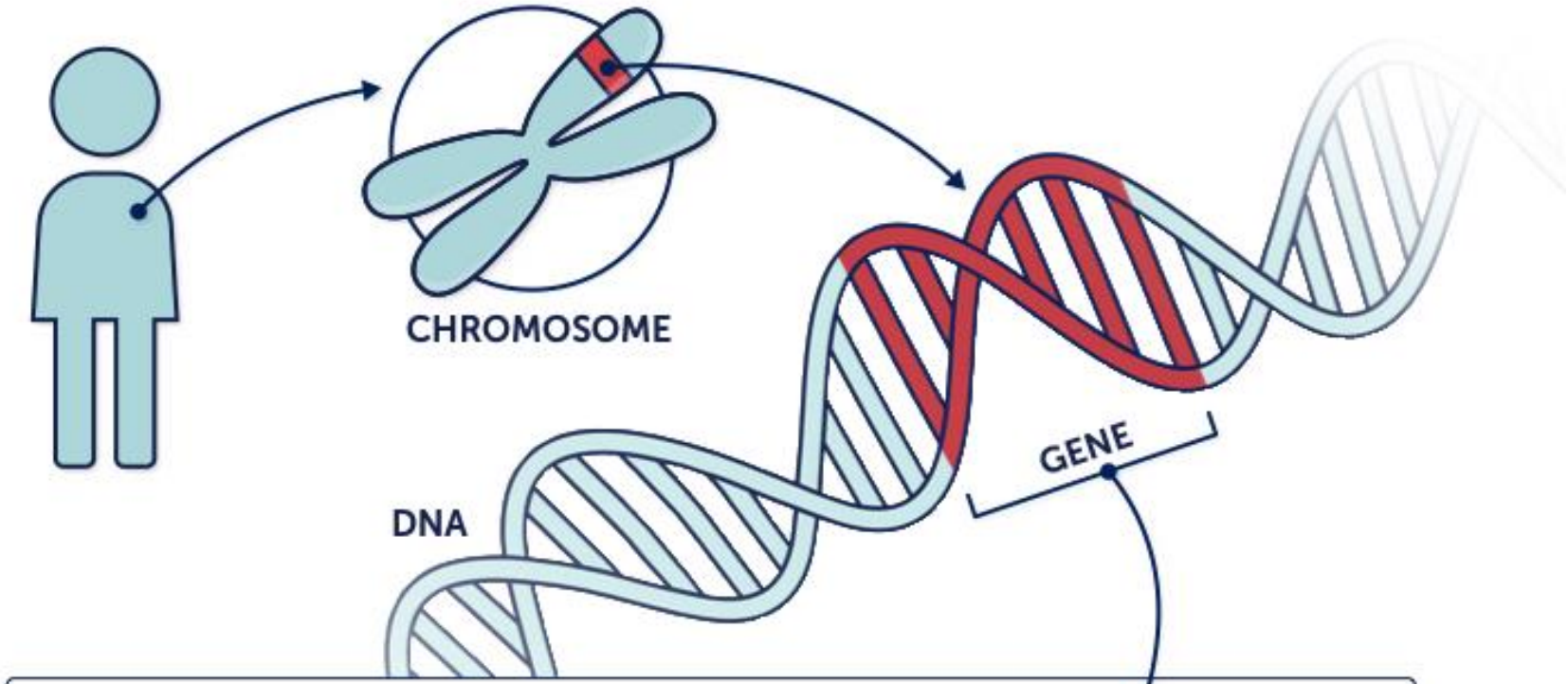
- Progressive neurological disorder
  - Increasing ataxia and issues with balance, tremor
  - Dysarthria (difficulty with speech)
  - Nystagmus (eye movements)

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.

Image from: Myriad Genetics

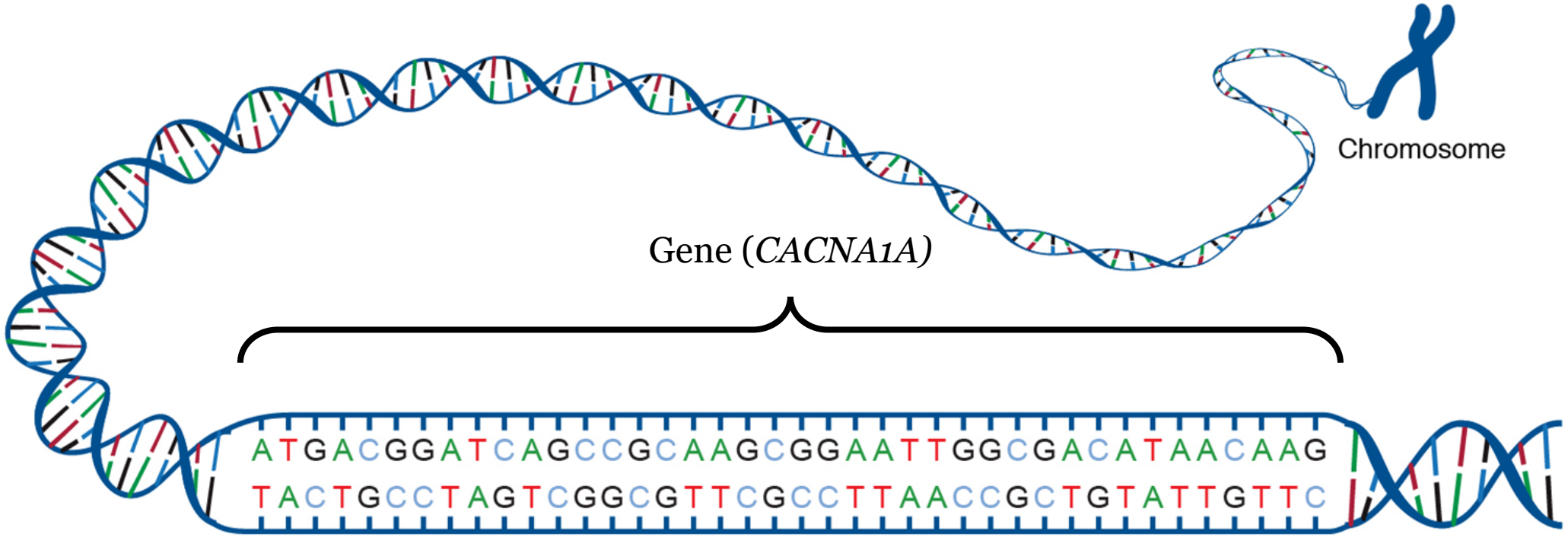


Image from: genome.gov

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WHAT HAPPENS WHEN THERE IS A GENETIC MUTATION?

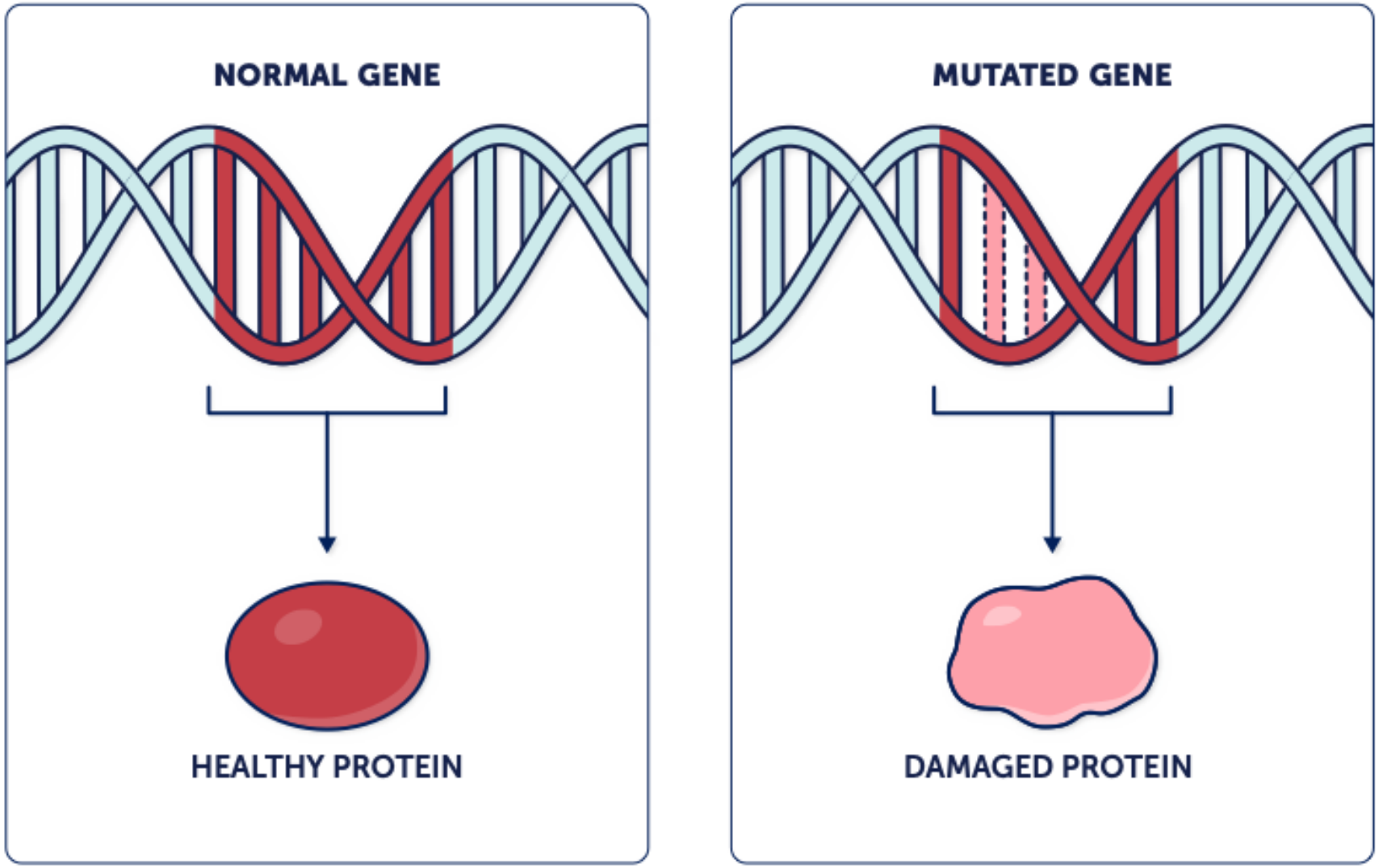
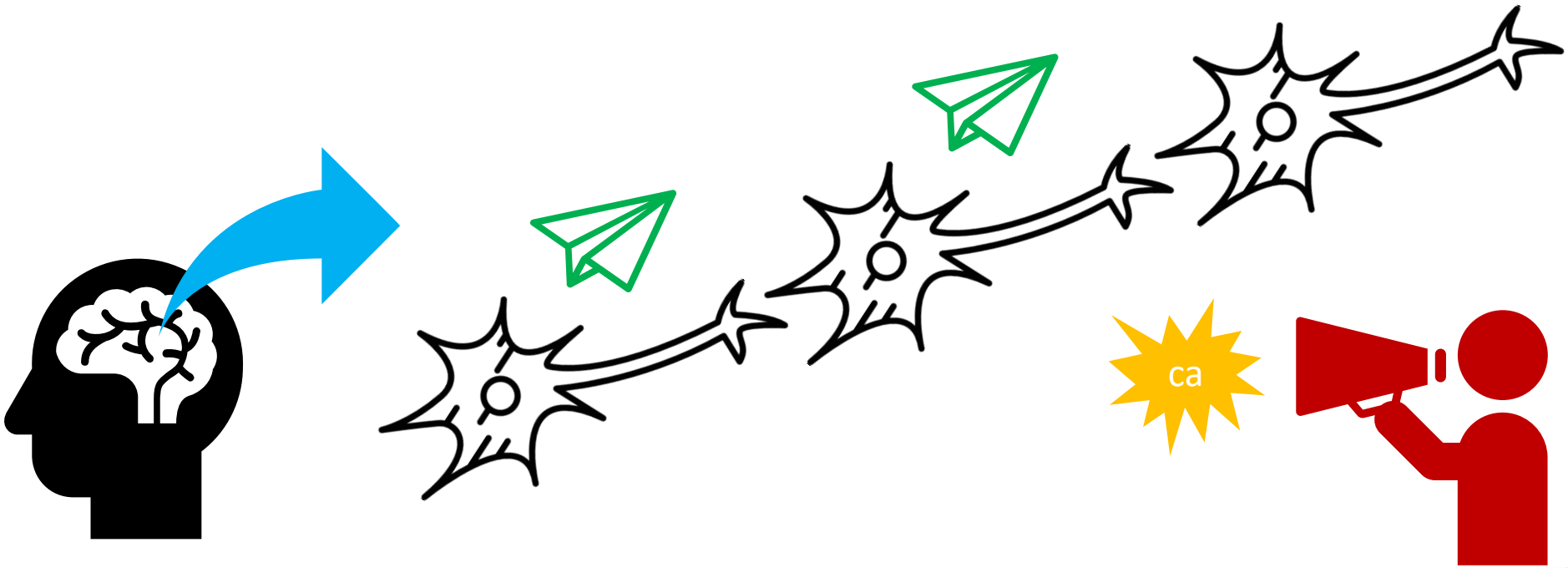


Image from: Myriad Genetics

What does *CACNA1A* do?

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



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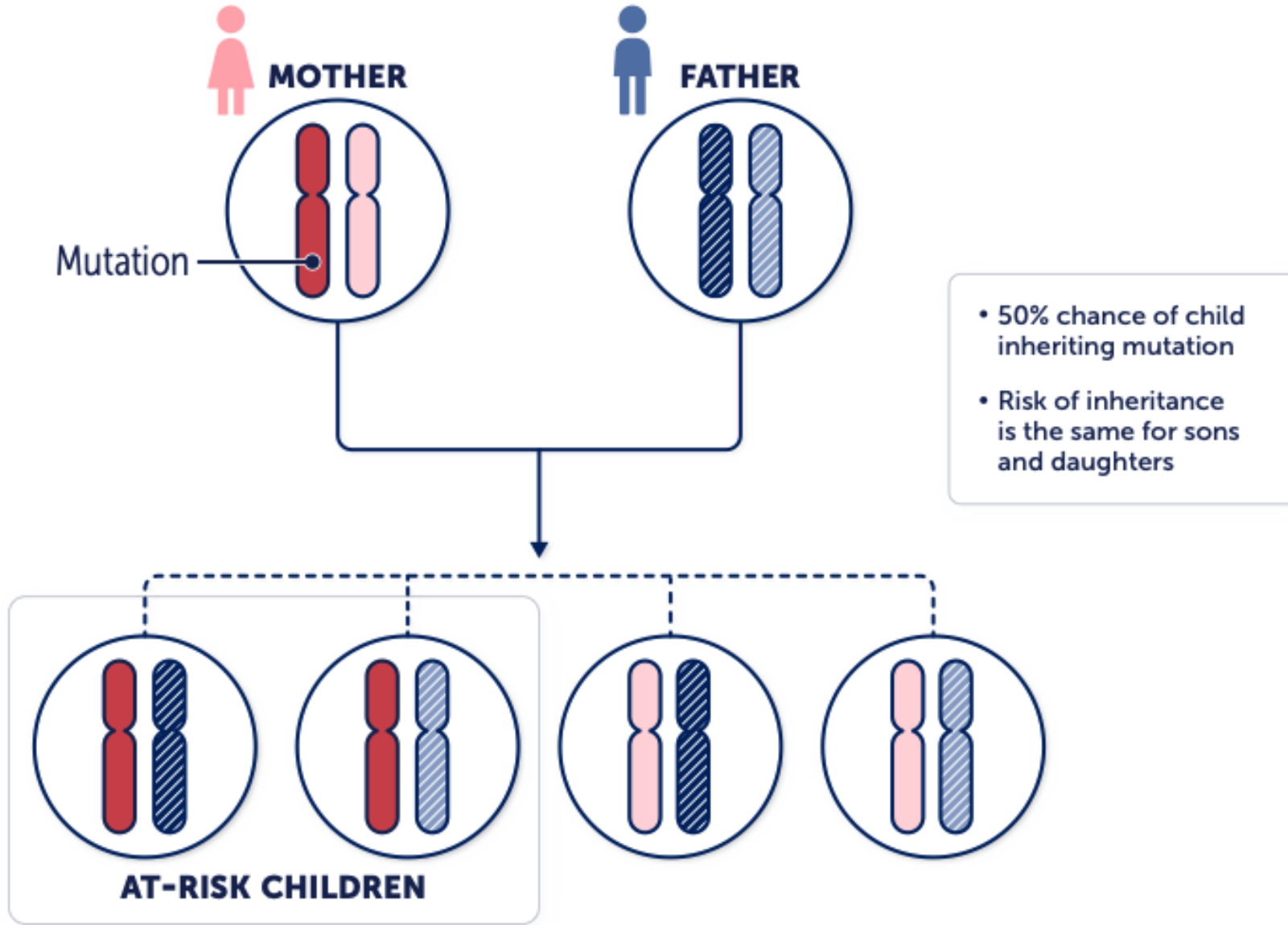
Inheritance of *CACNA1A* Disorders

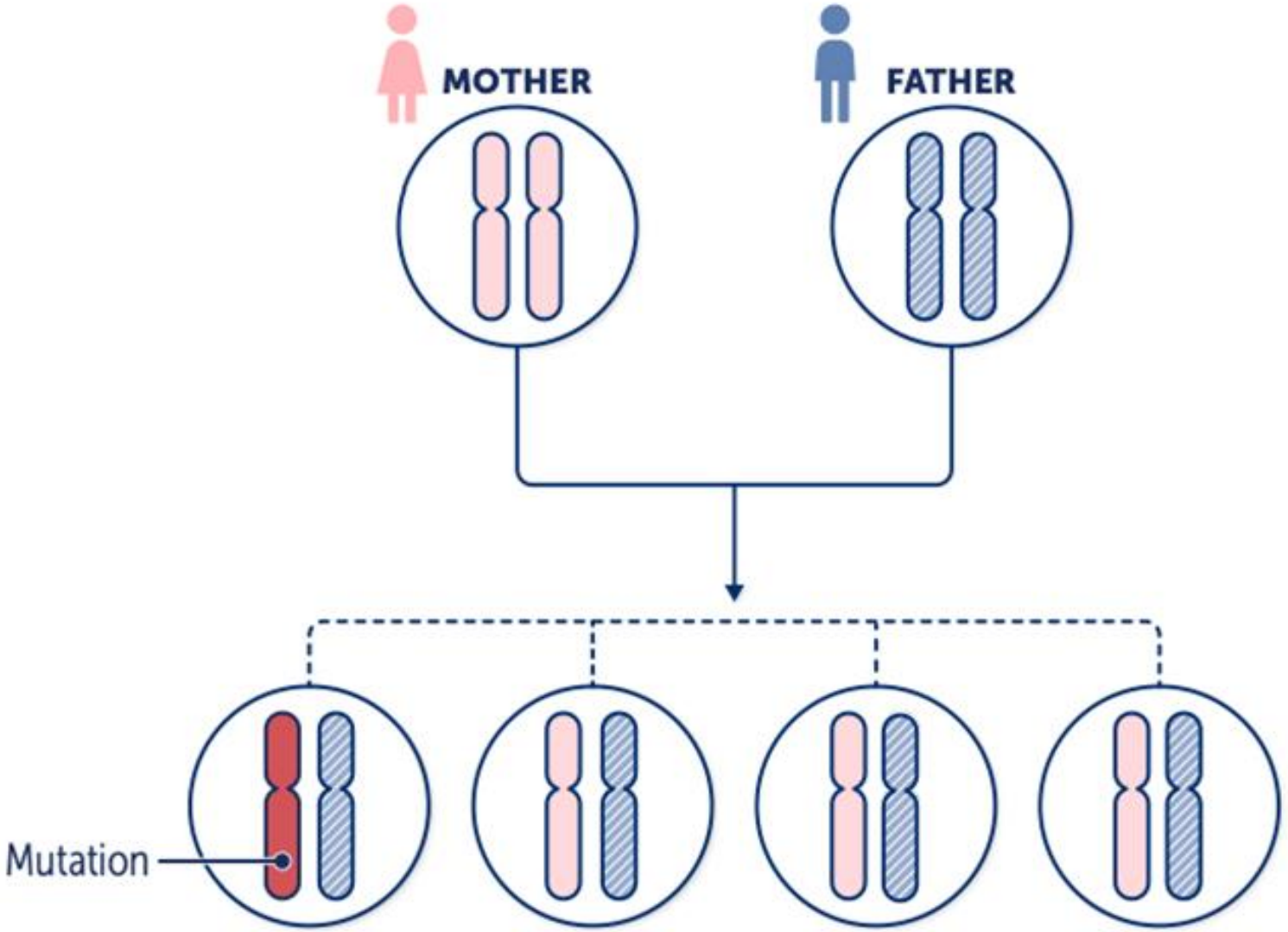
- Can be inherited from a parent or *de novo* (brand new in a child)
- Severe or early-onset *CACNA1A*-related disorders are more likely to be *de novo*

AUTOSOMAL DOMINANT INHERITANCE



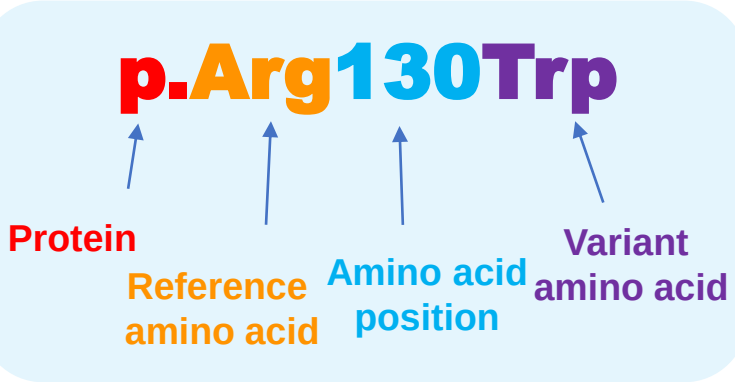
- 50% chance of child inheriting mutation
- Risk of inheritance is the same for sons and daughters

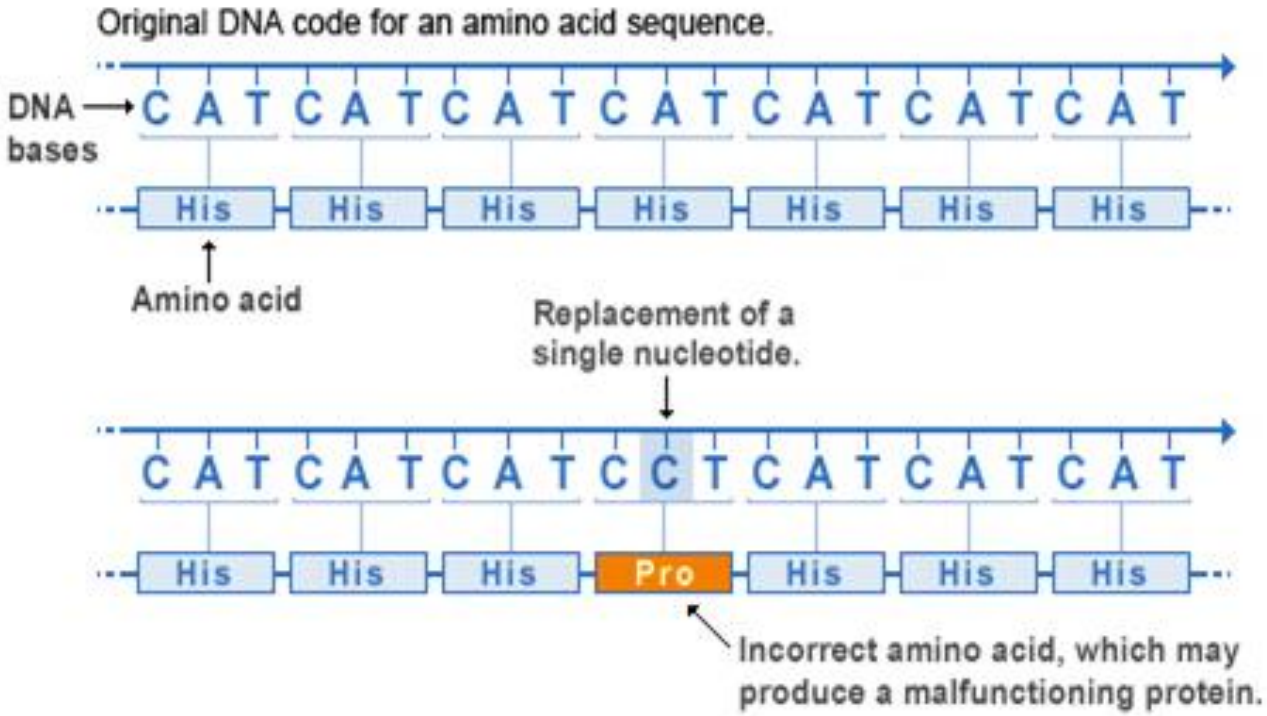
DE NOVO INHERITANCE



Types of Genetic Changes

Missense Variant





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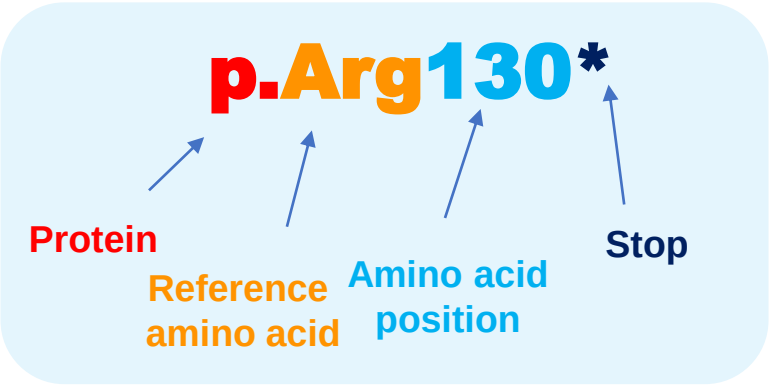
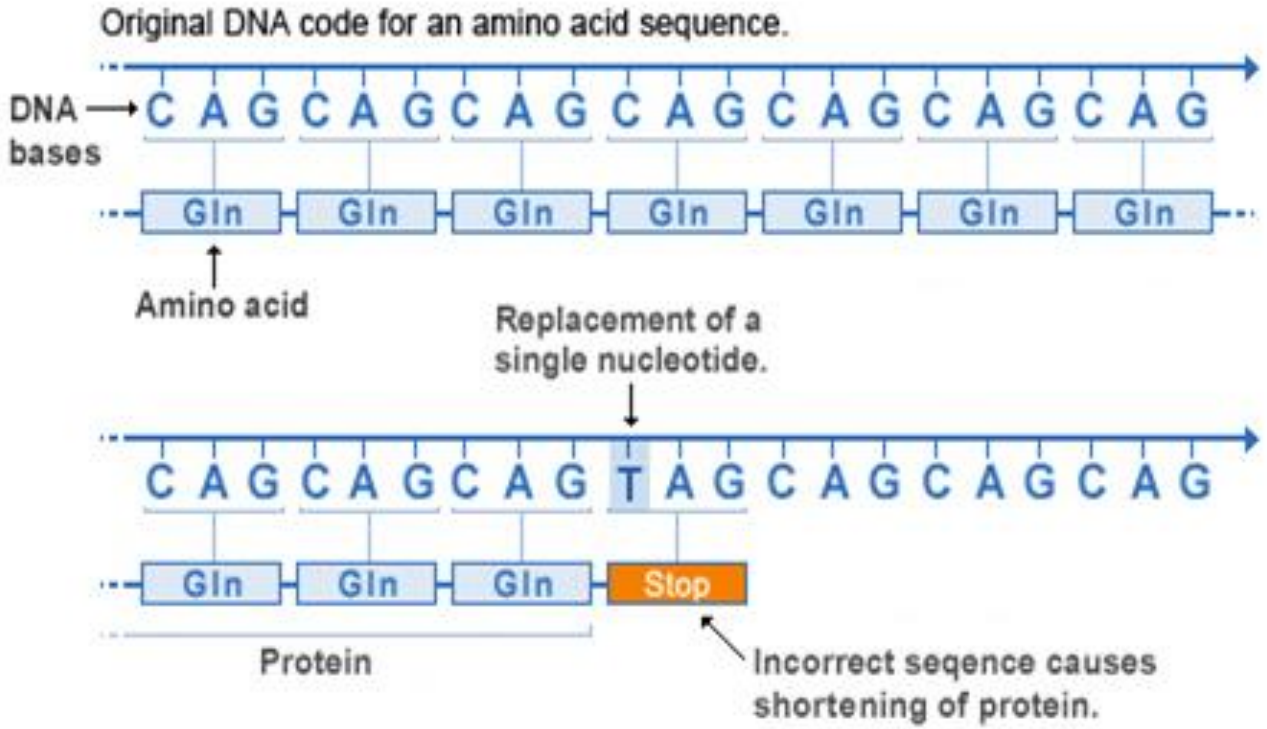
Nonsense Variant





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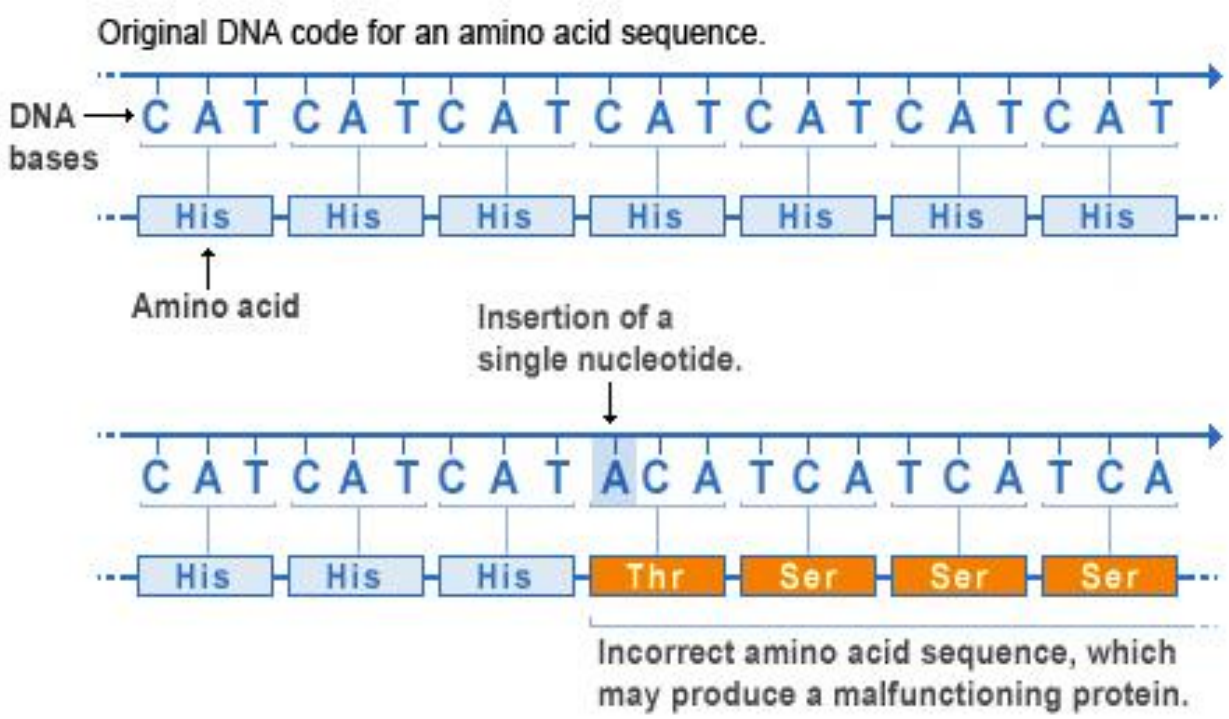
Frameshift Variant



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p.Leu130Aspfs*11

- **Protein**
- **Reference amino acid**
- **Amino acid position**
- **Variant amino acid**
- **Frameshift and STOP after 11 amino acids**

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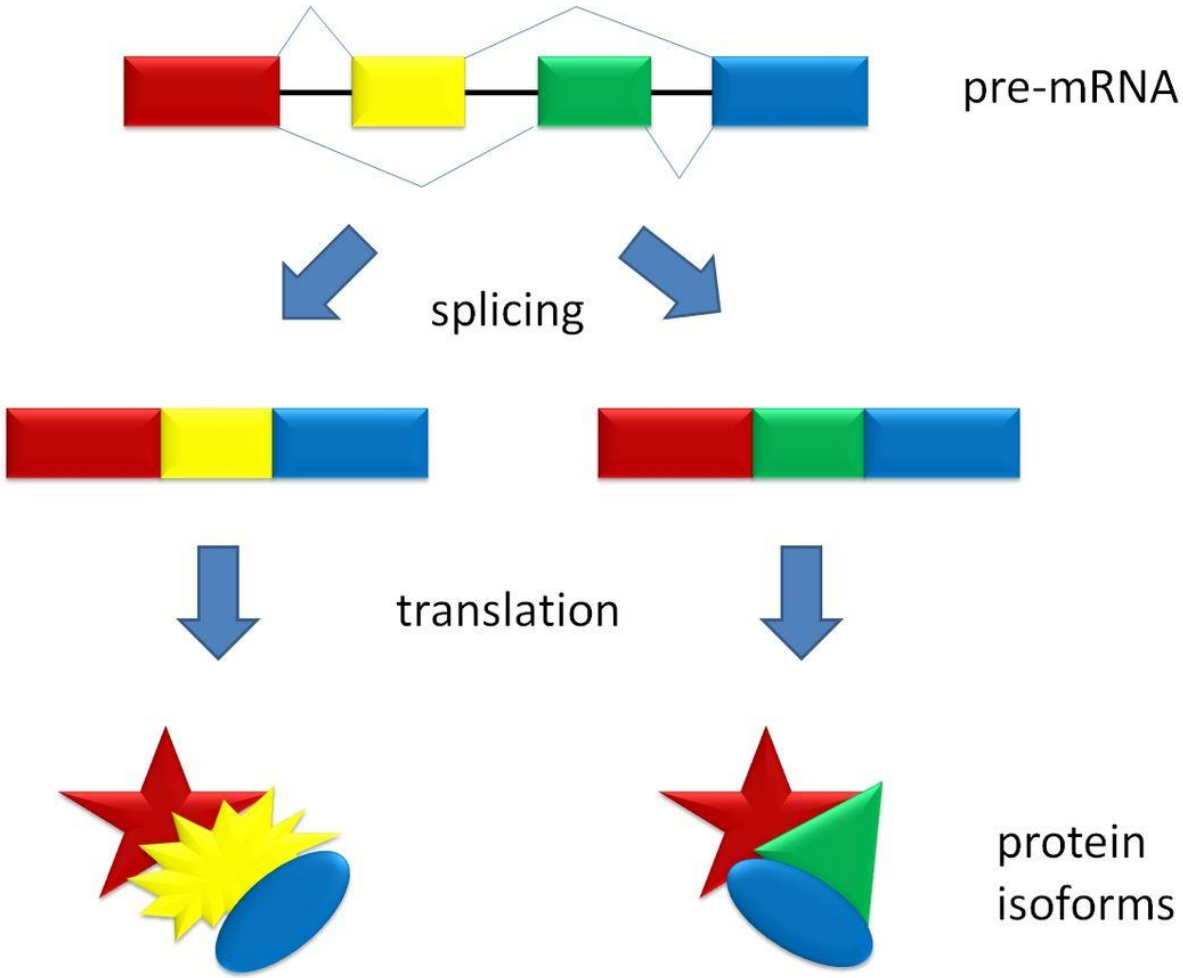
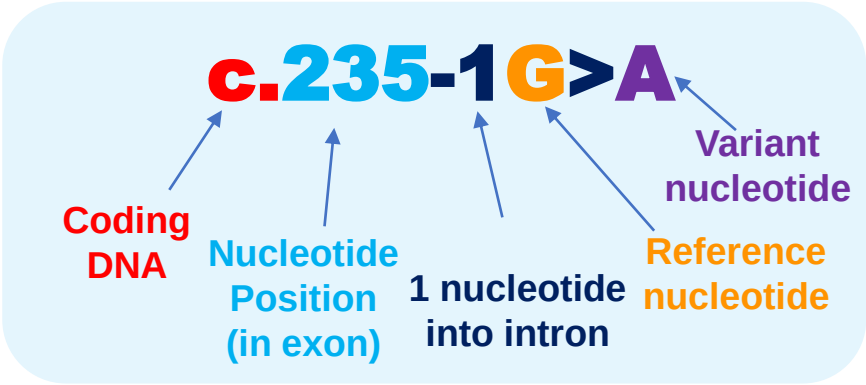
Splice Site Variant



Wiki Commons



Some splicing changes are normal—leads to different numbers in variant name

p.Val**1393**Met = p.Val**1396**Met

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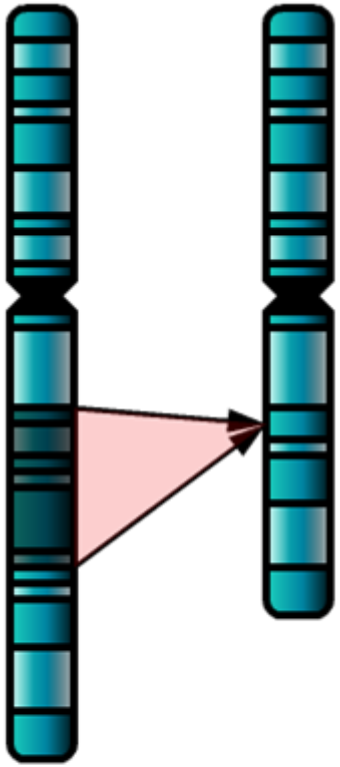
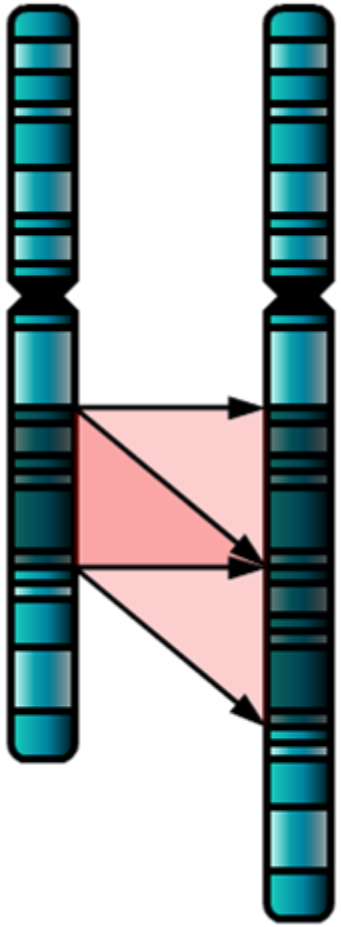
Deletions or Duplications of *CACNA1A*

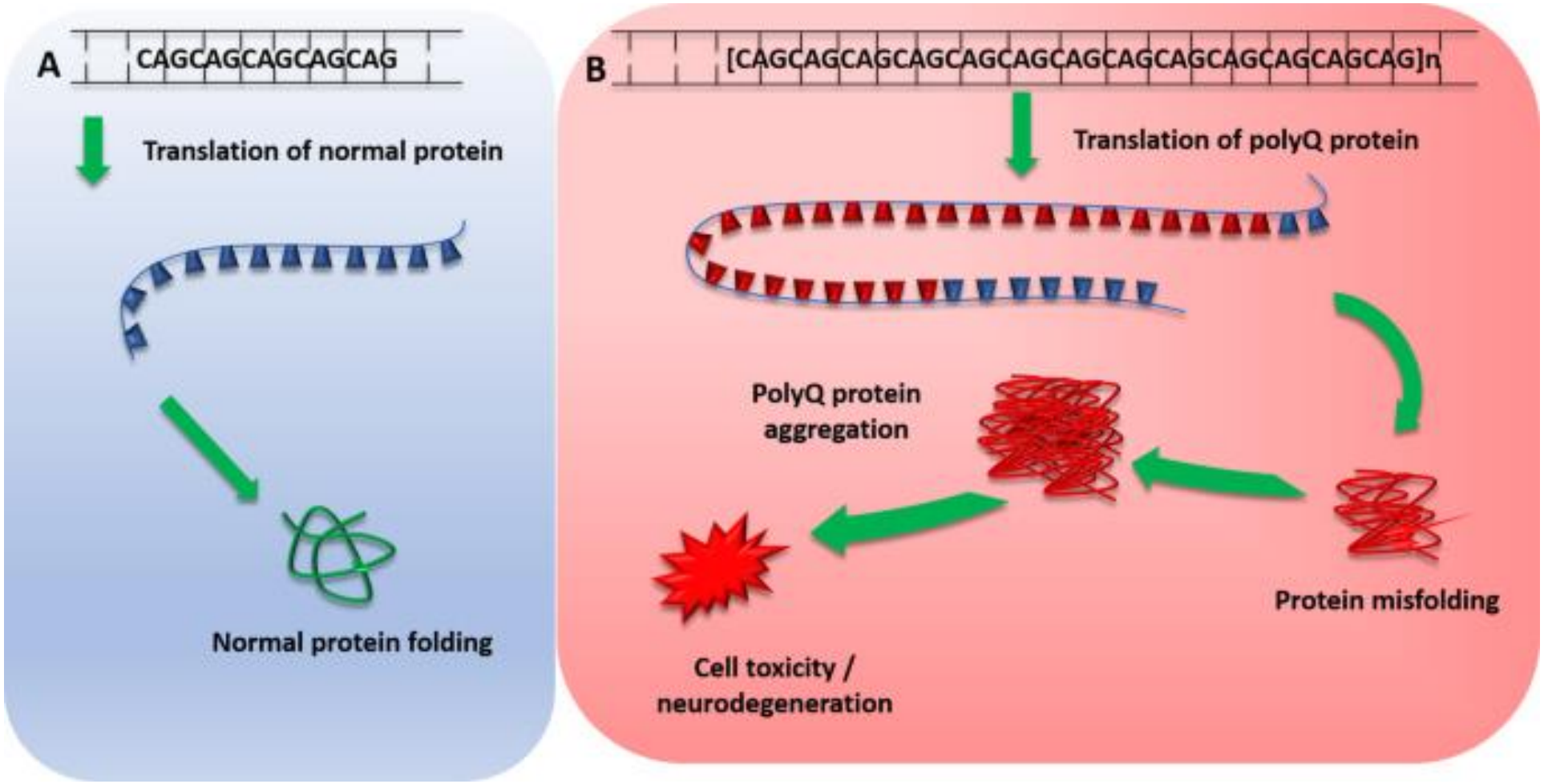


Deletion of *CACNA1A* on chromosome 19
May involve other genes



Duplication of *CACNA1A* on chromosome 19
May involve other genes

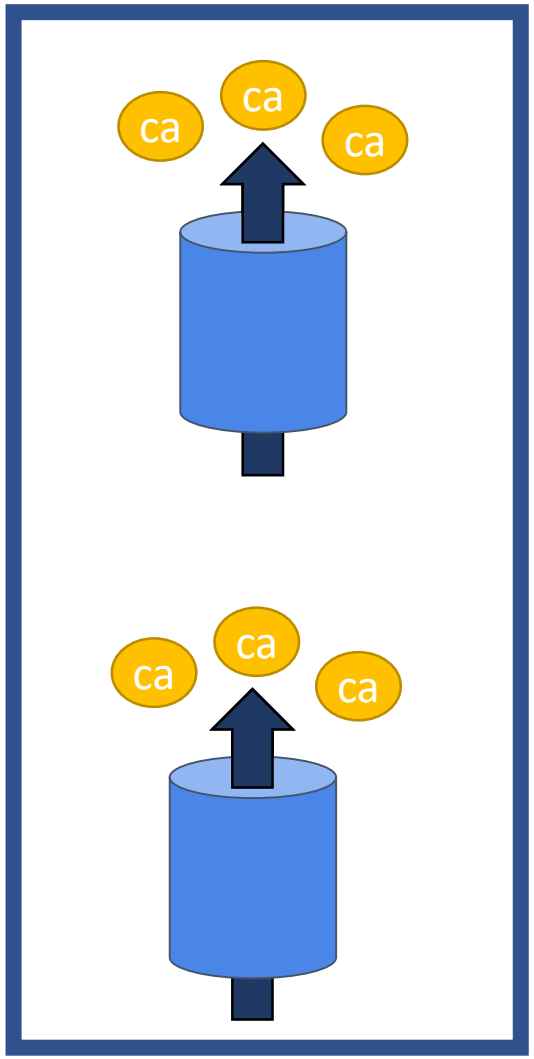
Spinocerebellar ataxia type 6



Sullivan, R., Yau, W.Y., O'Connor, E. *et al.* Spinocerebellar ataxia: an update. *J Neurol* **266,** 533–544 (2019).

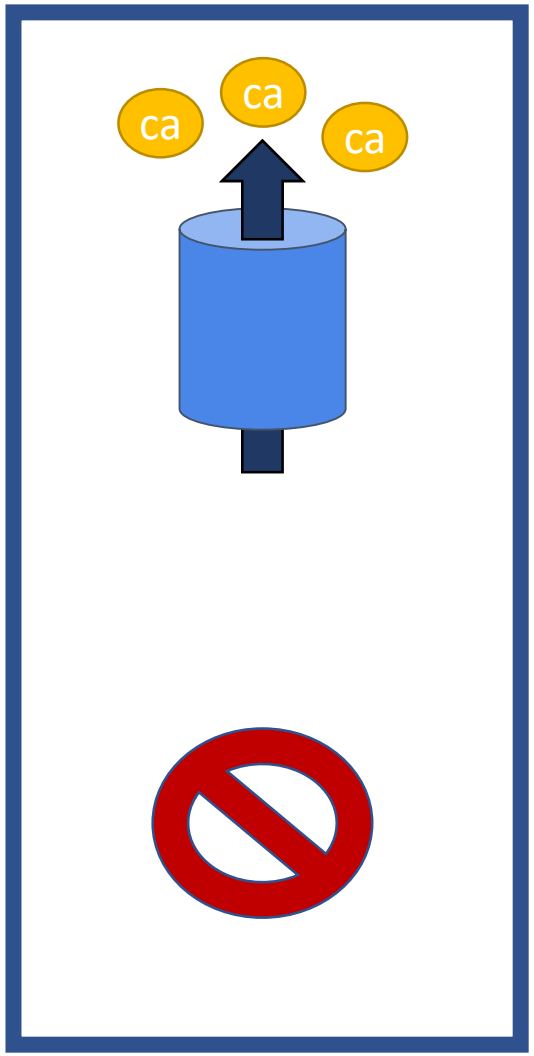
Normal

100% is functional



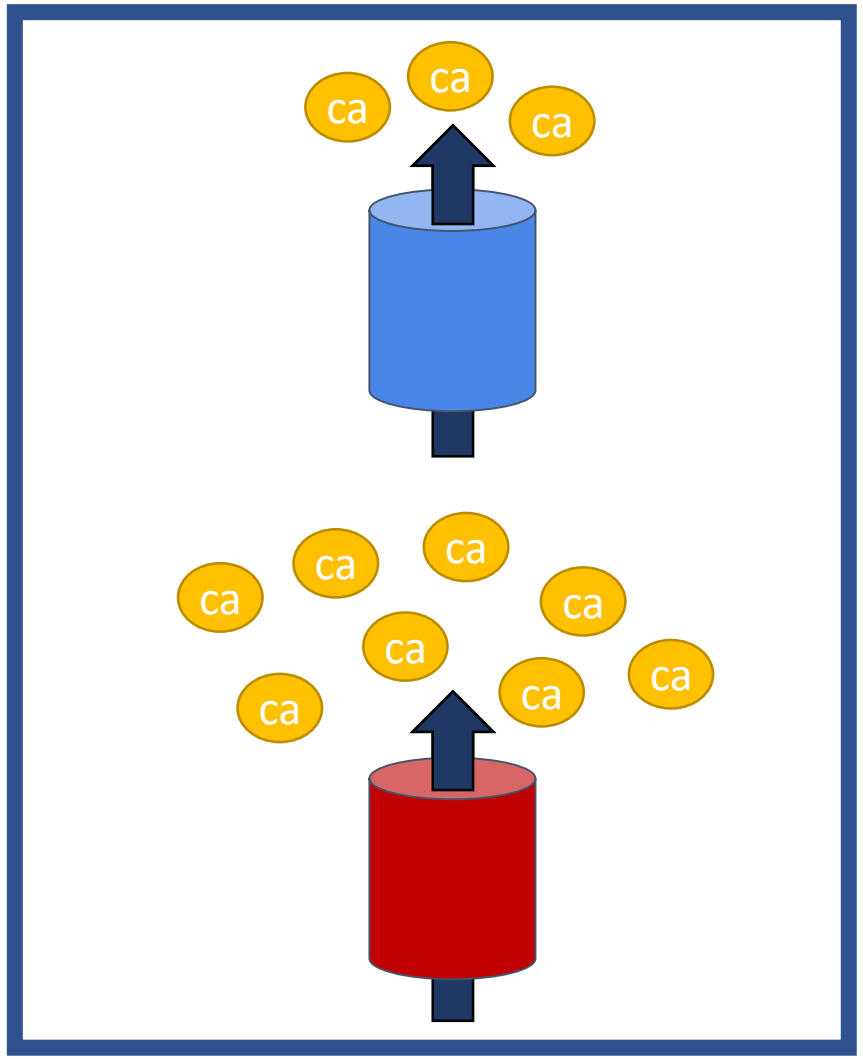
Loss of function

50% is functional



Gain of function

Added function



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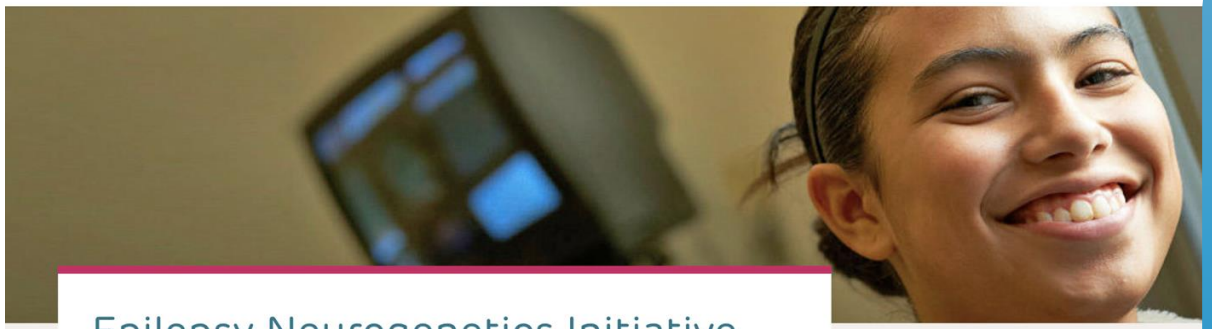
How is *CACNA1A* Diagnosed?

Chromosomal microarray	• Detects missing or extra pieces of a chromosome that include *CACNA1A*
Gene panel	• Test 10-1000 genes at once • Finds differences in the *CACNA1A* gene code sequence
Whole exome sequencing	• Tests exons of ~20,000 genes, compares to a child's parents
Trinucleotide repeat expansion	• Tests for total number of CAG repeats • In *CACNA1A*, only used to diagnose spinocerebellar ataxia • Cannot diagnose other *CACNA1A* disorders

ENGIN Frontier Program

CHOP Frontier Program



#1: Integrate genetics into epilepsy care

#2: Personalized plan for every patient

#3: Novel treatment and clinical trials

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Multidisciplinary Clinic

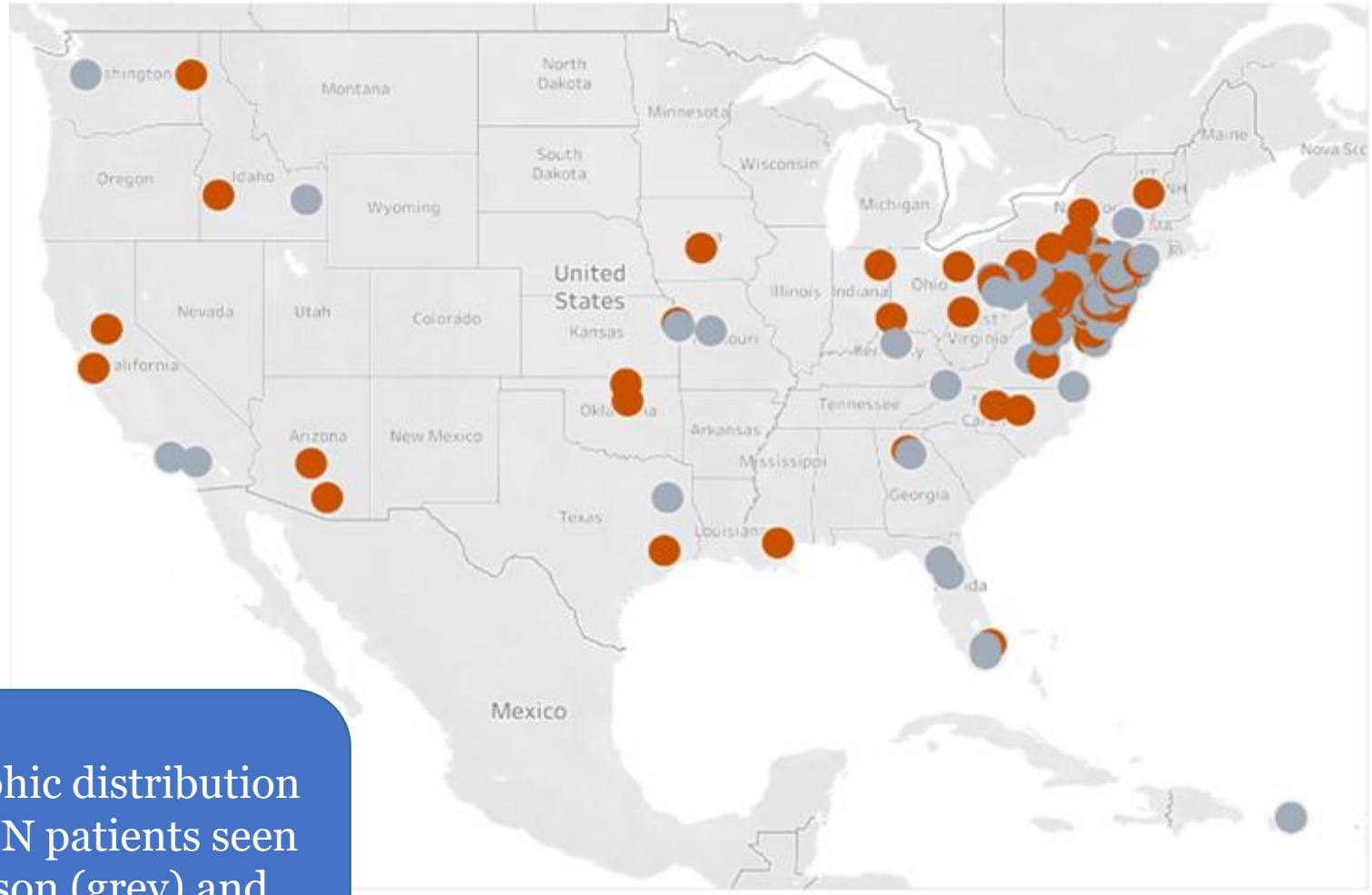
- ENGIN clinic consists of:
  - Child Neurologist
  - Genetic Counselor
  - Physical Therapist
  - Occupational Therapist
  - Social Worker
  - Research team

- 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)

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Research activities within ENGIN

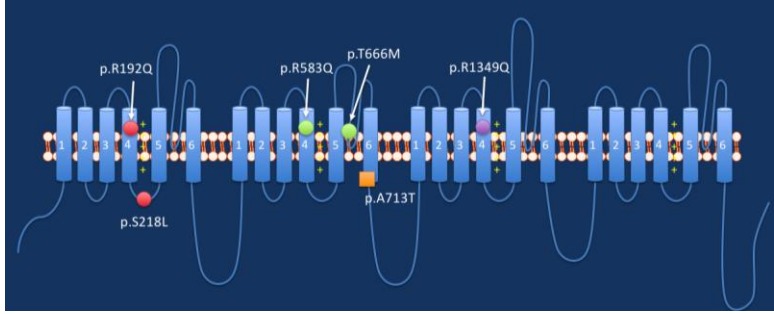
- Clinical presentations of *CACNA1A*-related disorders
  - Epilepsy features (international collaborations)
  - Understanding hemiplegic migraine presentations
- Functional analysis of *CACNA1A* variants
  - NIH Center Without Walls (U54)
- Data driven natural history/outcomes
  - Helbig Lab (data science 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

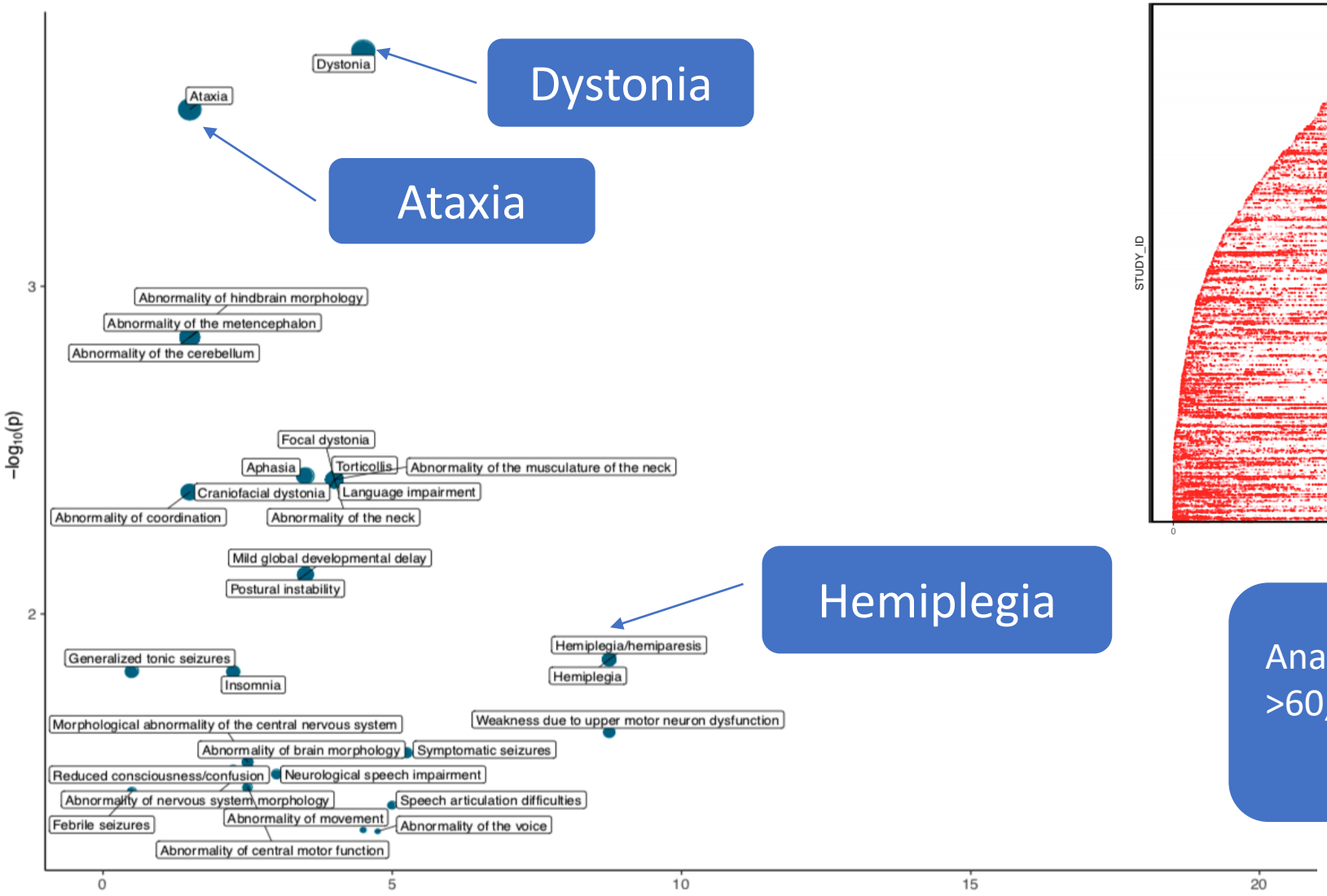


- ***CACNA1A*-related disorders**
  - One of the ”*most neglected common ion channel diseases*”
  - Knowledge on variant function behind other disorders
  - Disease variants result in wide range of functional changes

- **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

Helbig Lab
…make data speak

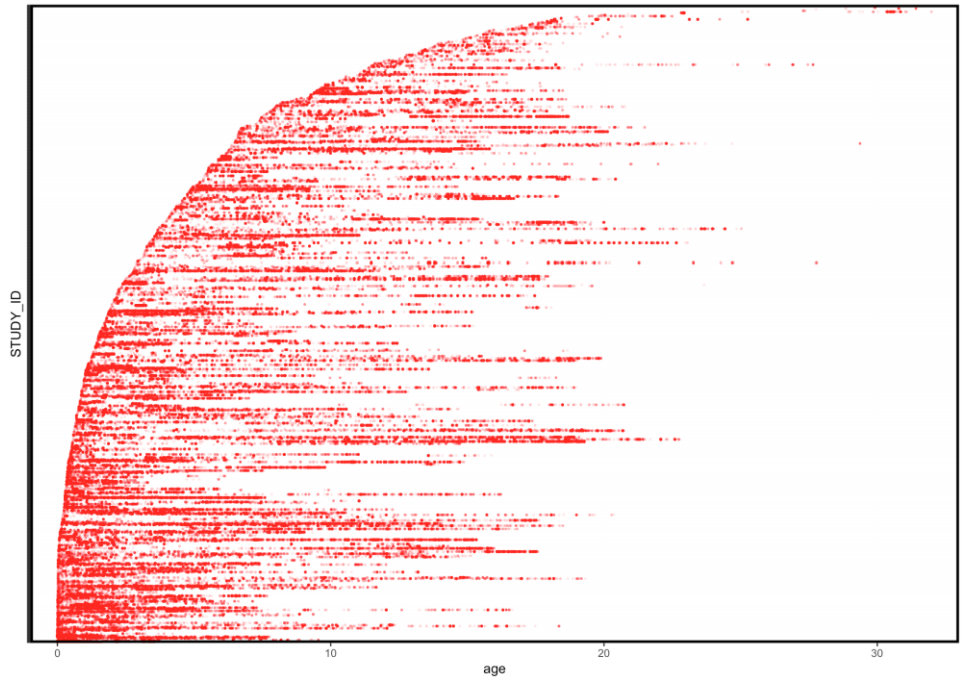
Data-driven natural histories



Dystonia

Ataxia

Hemiplegia



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

Genetic Counselors

- Sarah McKeown, MS, LCGC
- Holly Dubbs, MS, LCGC
- Laina Lusk, MMSc, LCGC
- Katie Helbig, MS, LCGC

Physical and Occupational Therapy

- 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

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