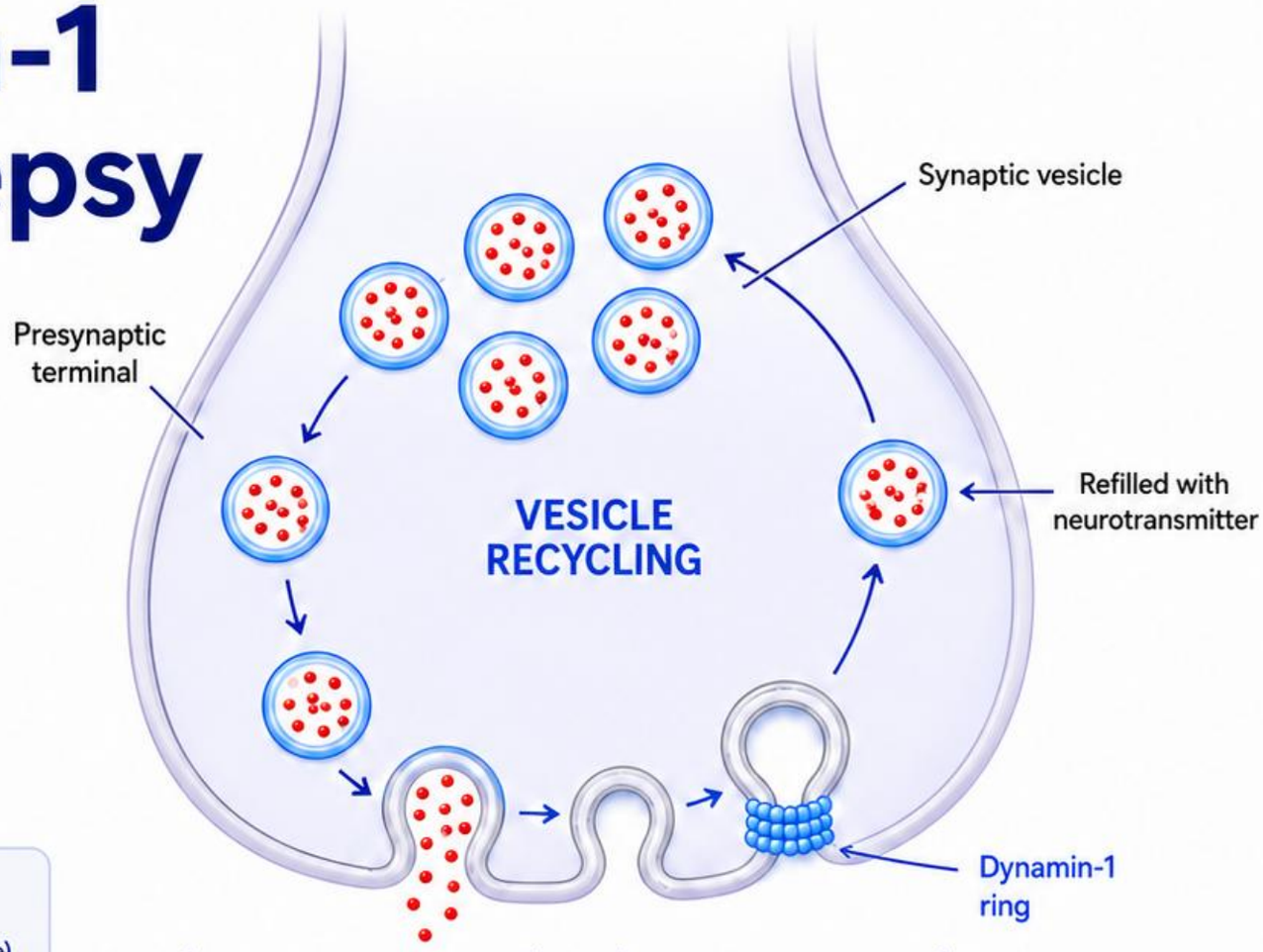
A visual guide

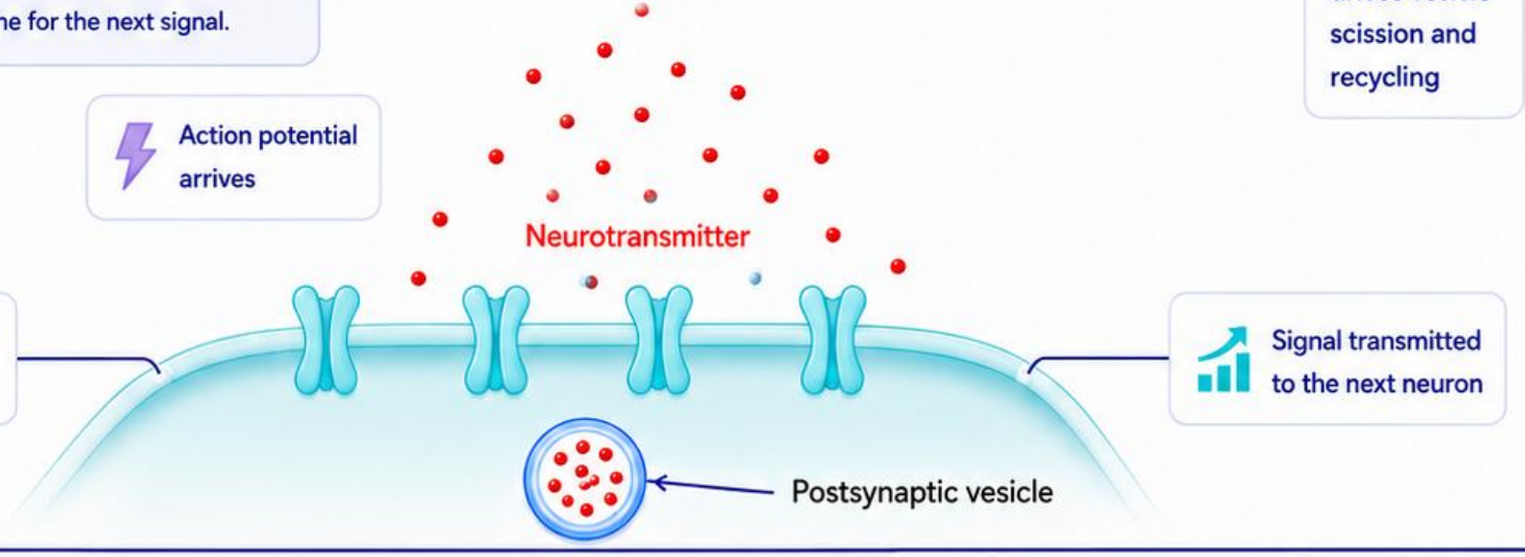
Dynamin-1 and Epilepsy

How autosomal dominant ***Dynamin-1*** variants disrupt synaptic vesicle recycling and lead to epilepsy.

Dynamin-1 is a **GTPase** that oligomerizes to form a necklace-like ring around presynaptic vesicles to excise them from the membrane during endocytosis.



Dynamin-1 (GTPase)
Oligomerizes into a ring (necklace) that wraps around budding vesicles to pinch them off and recycle membrane for the next signal.



Swipe to learn how ***DNM1*** variants can act in an autosomal dominant manner

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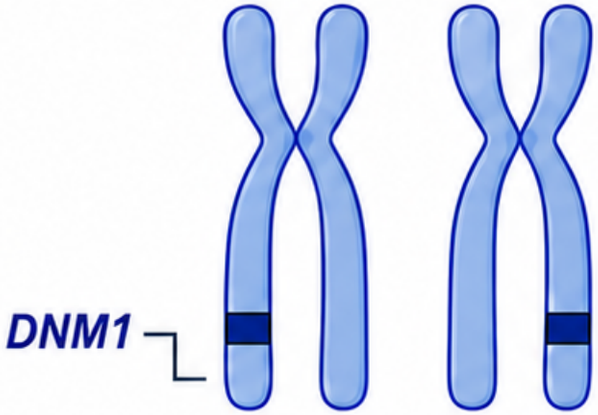
Most disease-causing *DNM1* variants are *heterozygous*, *de novo* and act in an autosomal dominant manner.

Wild type

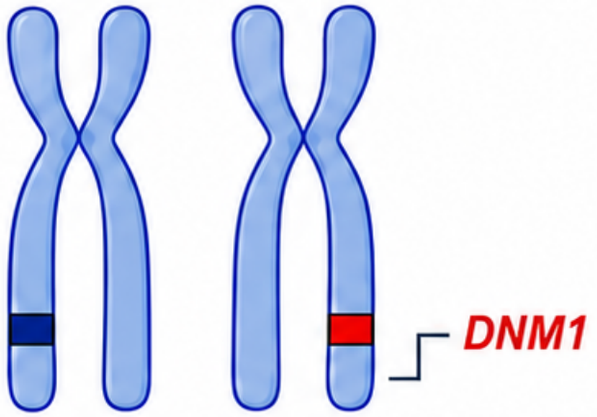
Chromosome 9



Both *DNM1* copies are normal.

Heterozygous *DNM1* variant

Chromosome 9



One altered copy (heterozygous) can be enough to disrupt function.

Most disease-causing ***DNM1*** variants are **heterozygous** and arise ***de novo*** (new in the child), meaning they are usually not inherited from a parent.

Swipe to learn about the predicted global incidence of ***DNM1***-DEE

A visual guide

Predicted global incidence of DNM1-DEE

According to López-Rivera et al. (Brain, 2020), *DNM1*-associated neurodevelopmental disorders caused by *de novo* variants are predicted to occur in about 3.78 per 100,000 births.

3.78 in 100,000 births

Predicted incidence worldwide

Supplementary spreadsheet value for DNM1: 3.78198 per 100,000 births

~5,000 new cases/year worldwide

Approximate projected annual births affected worldwide

Observed patient sources (July 2025)

177	79	27	>70
DNM1 Global Community (Facebook group)	GeneDx	Labcorp	Clinical publications

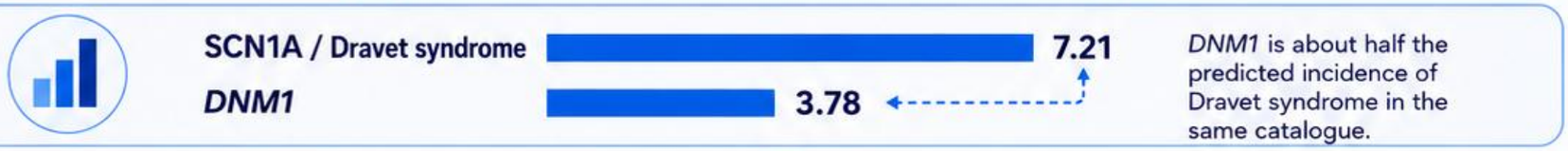
These sources may overlap and should not be interpreted as unique patients.

Total >250 identified individuals

Oldest reported individual is around 33 years old.

Still underdiagnosed

Diagnosis is increasing as exome/genome sequencing becomes more widely used globally.



DNM1 is about half the predicted incidence of Dravet syndrome in the same catalogue.

How this estimate was generated

This is a model-based estimate from López-Rivera et al. It was inferred from *de novo* variant data in large sequencing cohorts and gene-specific mutational models / variant-intolerance metrics. It is not a direct population-based epidemiology estimate from newborn screening, registries, or complete case counting.

Why this estimate is useful

These modeled estimates help approximate the expected birth incidence of *DNM1-DEE*, especially for an underdiagnosed disorder.

Source: López-Rivera et al., Brain (2020)
doi.org/10.1093/brain/awaa051

Takeaway: Even though only a fraction of patients are currently recognized, the predicted birth incidence suggests *DNM1-DEE* is substantially underdiagnosed worldwide.

*Swipe to learn more about the ClinVar landscape of **DNM1** variants*

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A visual guide

ClinVar landscape of DNM1 variants

ClinVar tracks submitted variants and their interpretations; these counts do not represent unique patients.

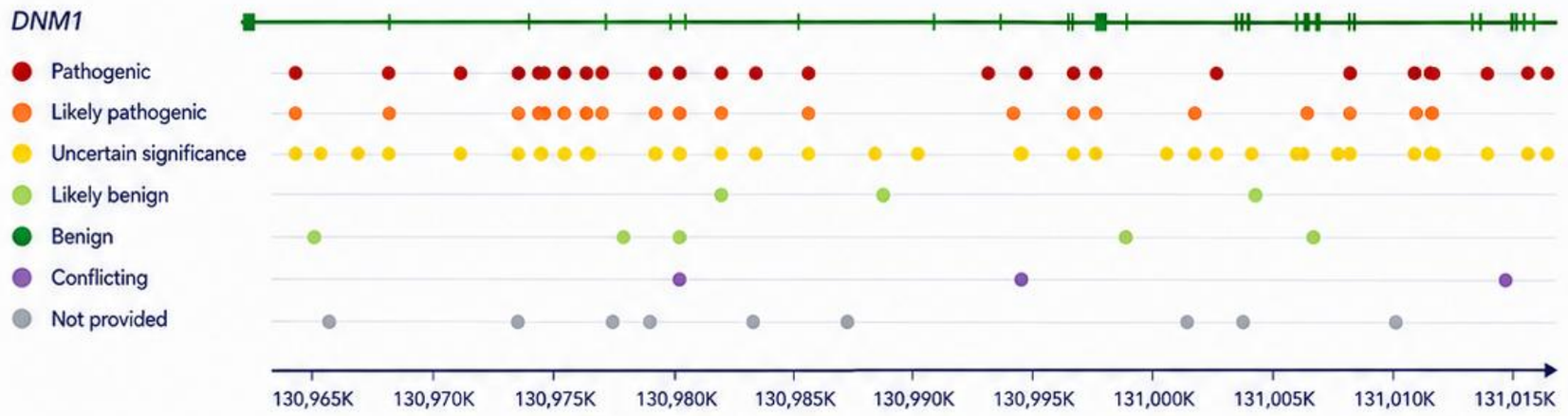
ClinVar variation search snapshot for:

DNM1[gene] AND single gene[PROP]

906
total ClinVar results

398
results with molecular consequence annotation

ClinVar graphical view (*DNM1* on GRCh37)



Takeaway

ClinVar shows a broad spectrum of *DNM1* variants across the gene, including pathogenic / likely pathogenic variants and variants of uncertain significance.

Why this matters

ClinVar helps families, clinicians and researchers track known *DNM1* variants, interpretation categories and reported molecular consequences.

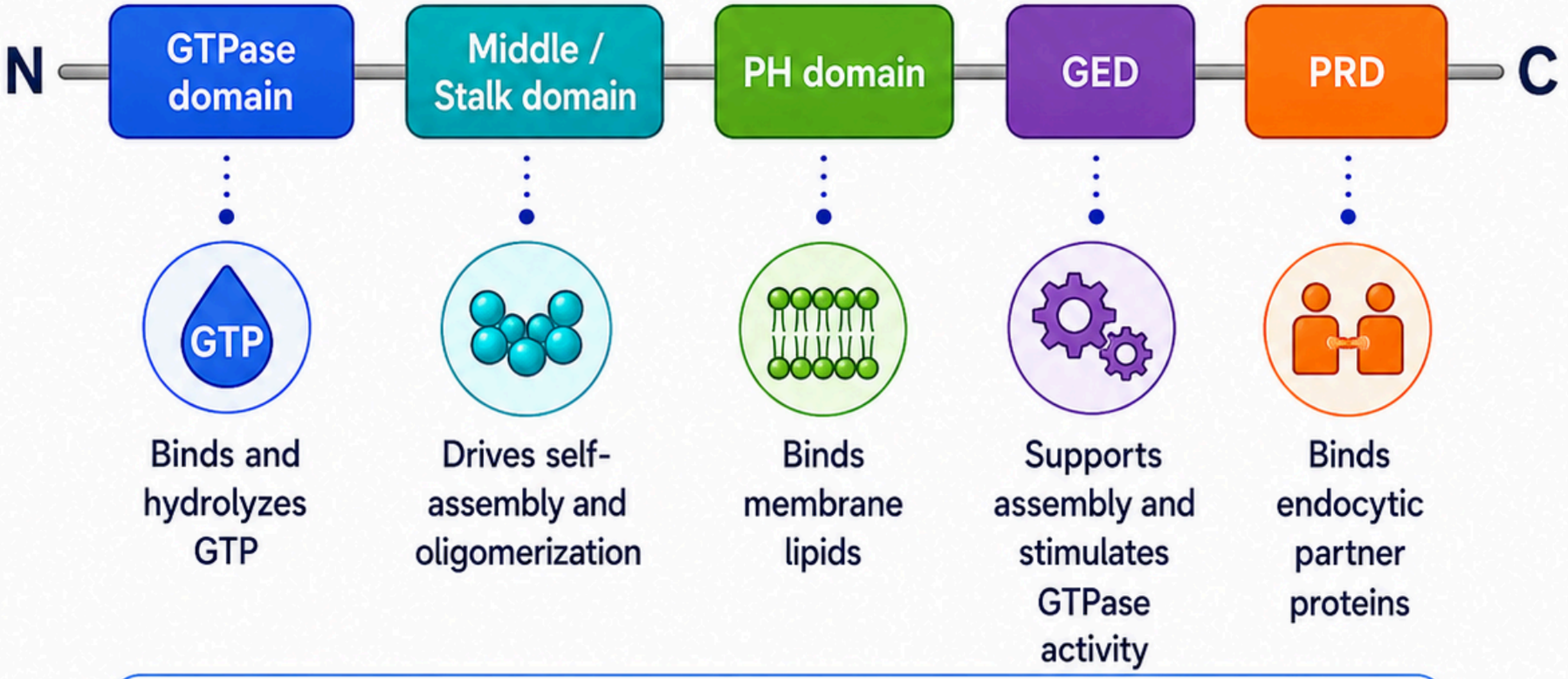
Source: ClinVar Variation Search (NCBI)
ncbi.nlm.nih.gov/clinvar/search

Swipe to learn about *Dynamin-1's specialized domains*

A visual guide

Dynamin-1 has specialized domains

Dynamin-1 is a large GTPase built from five domains, each with a unique job.



Together, these domains allow Dynamin-1 to oligomerize into a necklace-like collar wraps around presynaptic vesicle necks and excises vesicles during recycling.

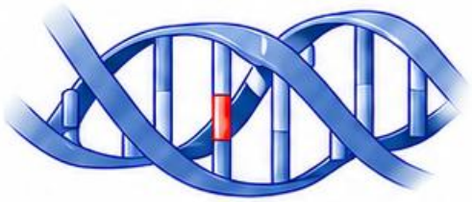
Swipe to learn how missense mutations can disrupt ***DNM1*** protein structure

A visual guide

Most pathogenic *DNM1* variants are missense mutations.

A missense mutation is a one-letter DNA change that alters one amino acid in the protein.

1 DNA point mutation



Point mutation in DNA

WT	G	A	A
Mutant	G	T	A

single base change

2 DNA to mRNA to protein translation

DNA (codon)

G	T	A

mRNA (codon)

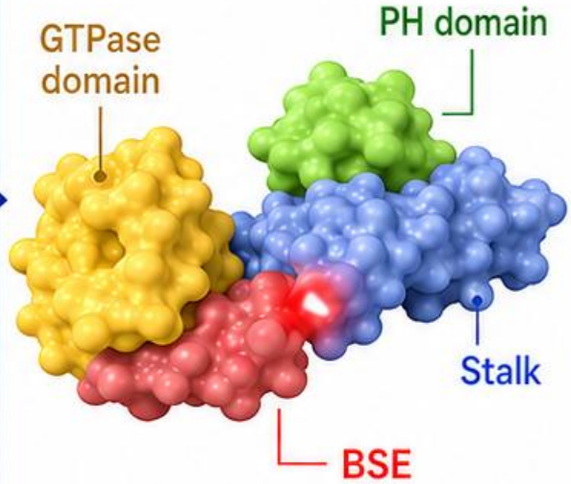
C	A	U

Protein (amino acids)

Leu — His — Lys

Missense mutation changes one amino acid.

3 3D *DNM1* protein structure



Altered amino acid can disturb *DNM1* structure and function.

Because protein shape determines function, even a single amino acid change can impair *DNM1* activity.

Swipe to learn about the most recurrent *DNM1* variants

A visual guide

Most recurrent *DNM1* variants

R237W and c.1197-8G>A together account for about **30%** of *DNM1* developmental and epileptic encephalopathy (DEE) cases.

1 R237W (GTPase domain)

Exonic point mutation

Exon 7

WT (Arg237) 5’ … C G G … 3’

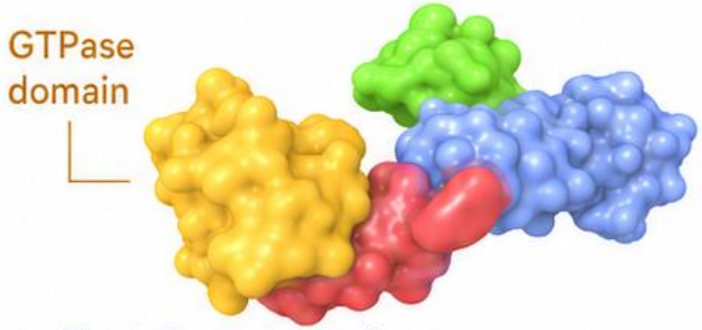
Arg

c.709C>T

Mutant (Trp237) 5’ … T G G … 3’

Trp

p.Arg237Trp (R237W)



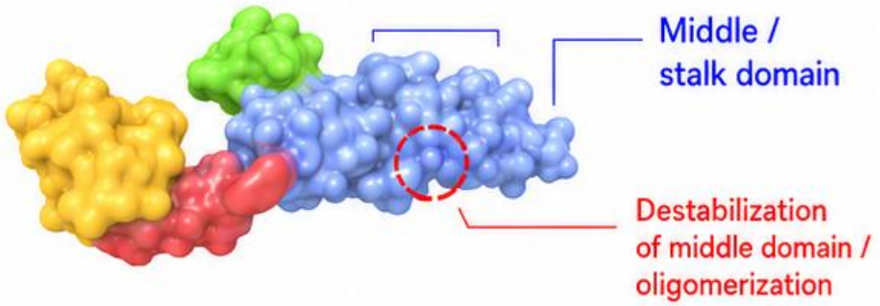
- Single base change in an exon
- Changes one amino acid in the GTPase domain

2 c.1197-8G>A (splice acceptor / middle domain)

Intronic splice-site variant

Abnormal splice acceptor

+CR insertion between Arg399 and Thr400 (2 amino acids)



- Intronic variant affects the splice acceptor
- Adds amino acids and destabilizes the middle domain

Although one variant is **exonic** and the other is **intronic**, both disrupt ***DNM1*** protein function and contribute to severe ***DNM1-DEE***.

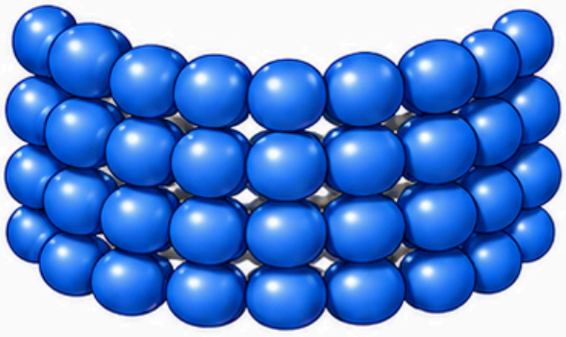
Swipe to learn how mutant ***DNM1*** destabilizes the oligomer

A visual guide

Mutant DNM1 destabilizes the oligomer

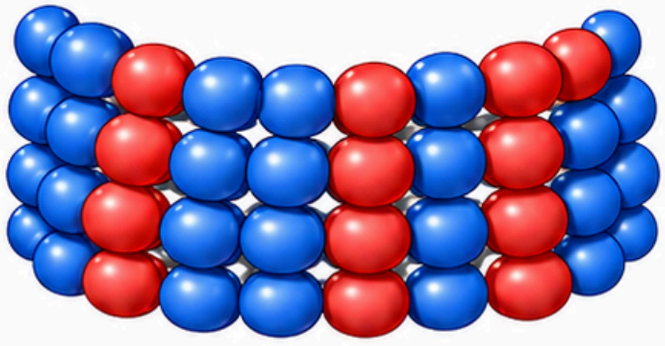
Mutant *DNM1* can incorporate into the oligomer and interfere with the whole protein complex, creating a **dominant-negative effect**.

WT oligomer



- Stable complex
- Efficient vesicle scission and recycling

WT + mutant oligomer



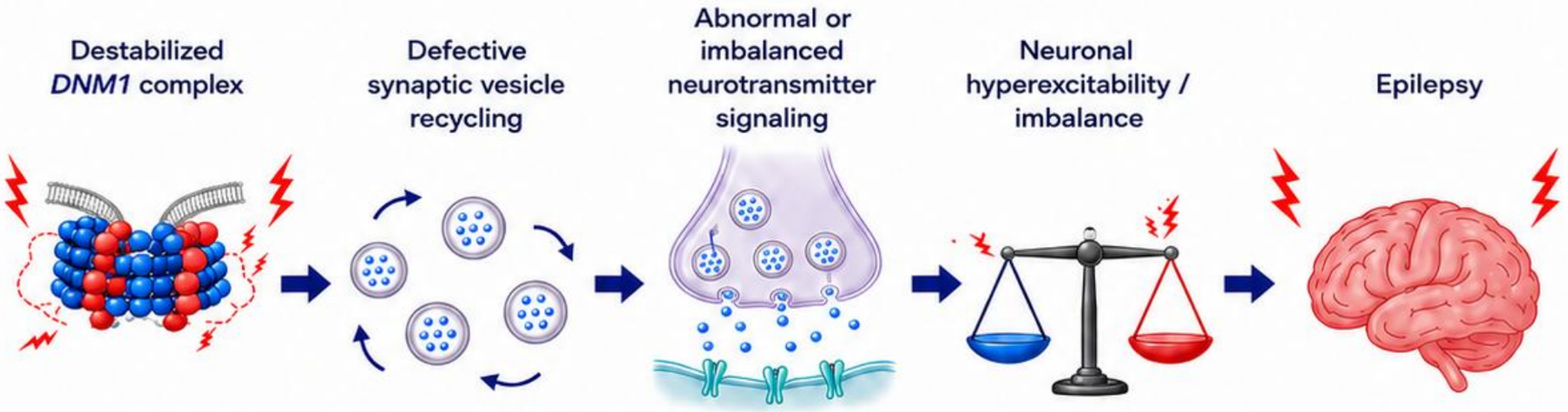
- Destabilized complex
- Dysfunctional vesicle fission / recycling

By disrupting the oligomer's stability, **mutant *DNM1*** impairs vesicle fission, undermining synaptic recycling and neuronal signaling.

Swipe to learn how impaired recycling can lead to epilepsy

A visual guide

Impaired recycling can lead to epilepsy



This results in DNM1 Developmental and Epileptic Encephalopathy

Hallmark phenotype:

- Infant-onset epilepsy
- Epilepsy mainly infantile spasms, frequently evolving to Lennox–Gastaut syndrome
- Severe to profound intellectual disability
- Hypotonia

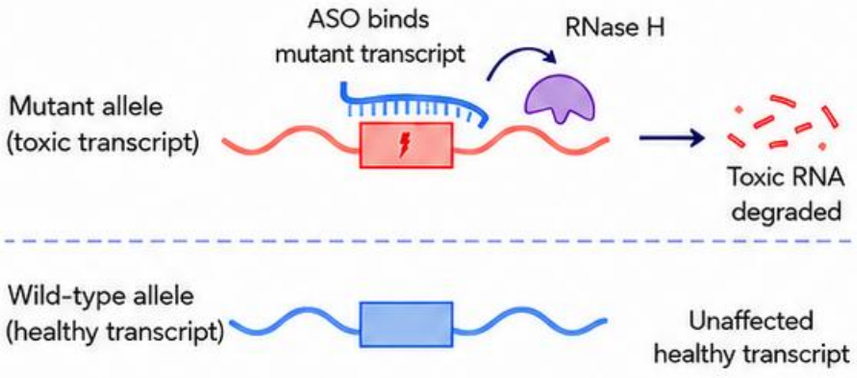
A visual guide

Therapeutic strategies under development for DNM1-DEE

Four therapeutic approaches are being explored to reduce the effects of pathogenic *DNM1* variants.

1. Allele-specific ASO

Most advanced personalized approach

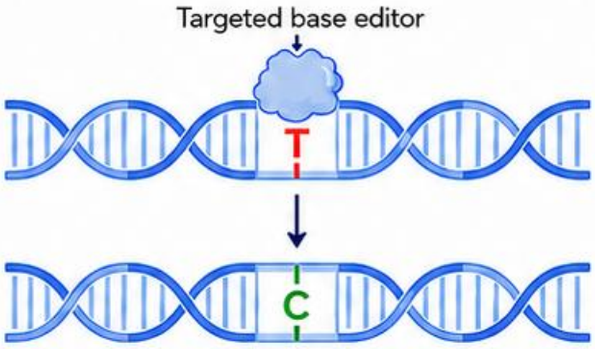


SNP-based allele-specific ASO

- Direct allele-specific ASO
- SNP-based allele-specific ASO
- **Goal:** selectively lower the mutant transcript while preserving the healthy copy
- **Status:** ongoing personalized / n-of-1 therapy development

2. Base editing

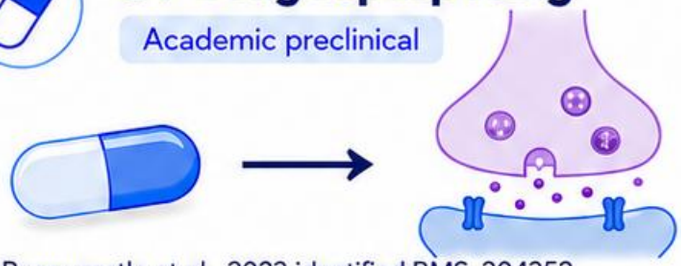
Personalized / n-of-1 concept



- Aims to directly correct selected pathogenic variants at the DNA level
- Best suited to specific variants
- **Status:** under development

3. Drug repurposing

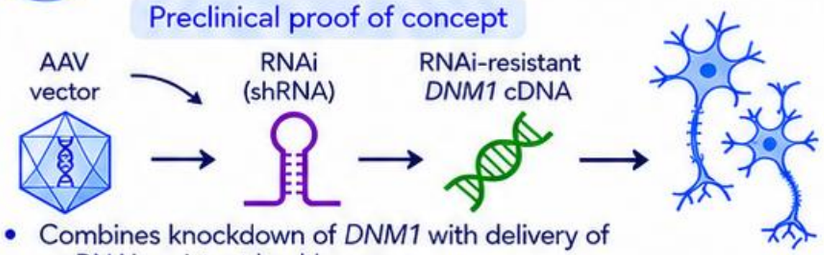
Academic preclinical



- Bonnycastle et al., 2023 identified BMS-204352 as a promising repurposing candidate
- In a *DNM1* mouse model, it accelerated endocytosis and reversed cell, circuit and seizure phenotypes
- **Status:** academic preclinical

4. Knockdown-replace gene therapy

Preclinical proof of concept



- Combines knockdown of *DNM1* with delivery of an RNAi-resistant healthy copy
- In a mouse model, this strategy improved survival, growth and synaptic function
- **Status:** preclinical proof of concept

Swipe to see selected *references and resources*

A visual guide

Selected references & resources

Key sources used throughout this DNM1 visual guide

1. **Daumke Lab (MDC Berlin) — 3D dynamin**
   mdc-berlin.de/daumke
2. **DNM1 research publications database**
   clinical cases included
   dnm1epilepsy.org/professionals
3. **Helbig team — latest publication**
   pmc.ncbi.nlm.nih.gov/articles/PMC13086092/
4. **Orphanet — DNM1 gene page**
   orpha.net
5. **ClinVar — DNM1 variation search**
6. **Human DNM1 3D structures**
   dnm1epilepsy.org/drugdevelopers_under_professionals
7. **OMIM — DNM1 (602377)**
   omim.org/entry/602377
8. **GeneCards — DNM1**
   genecards.org/card/DNM1
9. **GenCC submission SGC-119874.1**
   thegencc.org
10. **Ensembl — ENSG00000106976**
    ensembl.org

Additional resources and updates:
dnm1epilepsy.org

rare dynamos
THERAPIES | RESEARCH
GLOBAL COMMUNITY
DNM1 EPILEPSY