



Mini
Q2



Gain-of-Function

What Does “Gain-of-Function” Mean?

In **gain-of-function (GoF)**:

- The potassium channel is **too active**
- It opens too easily or stays open too long
- Too much potassium leaves the cell

This makes neurons **less responsive**, disrupting communication between brain cells.

How is GoF KCNQ2 Different?

GoF variants are **less common** and often look different from typical KCNQ2-related disorders.

Seizure patterns

- May not begin immediately at birth
- May be milder or occur later
- Some individuals have abnormal EEG without frequent seizures

Developmental features

- Speech and language delays
- Learning differences
- Sometimes autism spectrum features

Other possible features

- Movement differences
- Sensory processing challenges

Studies show GoF variants are often associated with **non-neonatal phenotypes and developmental differences**, rather than classic neonatal epilepsy.

How is GoF KCNQ2 Different?

Normally:

- Potassium channels help regulate signaling

In GoF:

- Too much potassium leaves the neuron
- The neuron becomes **less responsive**
- Brain communication becomes less efficient

Recent research shows GoF affects **network-level brain signaling**, not just individual neurons.

What's Happening in the Brain?

Typically:

- Potassium channels help regulate signaling

In GoF:

- Too much potassium leaves the neuron
- The neuron becomes less responsive
- Brain communication becomes less efficient

Recent research shows GoF affects **network-level brain signaling**, not just individual neurons.

Treatments Currently Used

Anti-seizure medications

No single standard treatment exists.

Options may include:

- Levetiracetam
- Valproate
- Topiramate

Treatment is individualized.

Emerging Precision Treatments

Amitriptyline

- Most notable emerging option
- Shown to **block overactive KCNQ2/KCNQ3 channels**
- Studied in recent patient cohorts with GoF variants
- One of the strongest emerging targeted therapies
- Still not standard for all patients

New channel inhibitors

- Experimental compounds (e.g., Ebio3-like molecules)
- Designed to reduce overactive channel activity

Currently **preclinical (lab-stage)**.

Gene-targeted therapies

- ASOs to reduce overexpression
- Gene editing (CRISPR)

Still in research phases.

Key Takeaways

- GoF = channel **too active**
- Often presents with **different seizure and developmental patterns**
- **No standard targeted therapy yet**, but promising research is emerging

Key Sources (GoF)

- Nappi et al., 2022 — gain-of-function KCNQ2 phenotypes
- Sands et al., 2019–2024 — KCNQ2 spectrum reviews
- Recent cohort study (2025) — amitriptyline use in KCNQ2/KCNQ3 GoF
- Miceli et al., 2023–2025 — functional channel studies
- Early drug-development studies (2024–2025) — KCNQ inhibitors
- Precision medicine epilepsy reviews (2023–2025)
- caregiver handbook baseline explanation