Potassium channel dysfunction in genetic epilepsy

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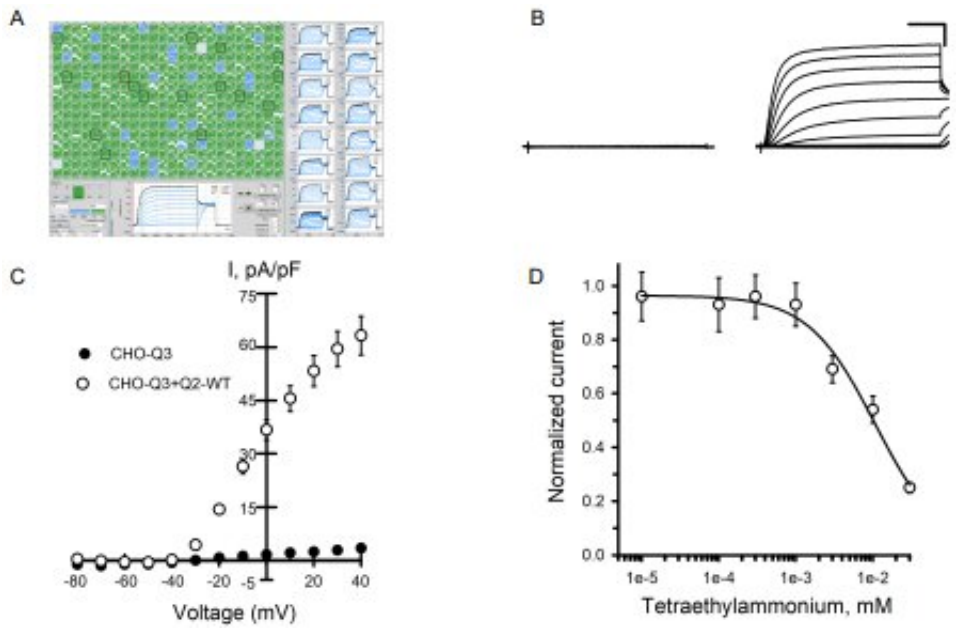

Figure 1. Functional analysis of KCNQ2/KCNQ3 channels by automated patch clamp. A) Screen display from automated patch clamp experiment illustrating whole-cell current recordings from CHO-Q3 cells transiently expressing KCNQ2 variants (6 variants, 4 columns per variant). B) Averaged XE991-sensitive whole-cell currents recorded from non-transfected CHO-Q3 cells, and CHO-Q3 cells electroporated with WT KCNQ2. C) Average current-voltage relationships measured from non-transfected (filled circles, n = 94) or KCNQ2-WT transfected (open circles, n = 124) CHO-Q3 cells. Current recorded from each cell was normalized to cell capacitance as a surrogate for cell size to calculate current density (I, pA/pF). D) Concentration-response relationship for TEA block of whole-cell currents recorded from CHO-Q3 electroporated with KCNQ2-WT (IC50 = 10.7 ± 4.2 mM, n = 51-82 for each concentration). Data shown in panels C and D are mean ± SEM (error bars are smaller than some data

symbols). Horizontal and vertical scale bars represent 200 ms and 20 pA/pF, respectively. Credit: *JCI Insight* (2022). DOI: 10.1172/jci.insight.156314

Northwestern Medicine scientists have discovered functional links between dozens of potassium channel gene variants and neonatal epilepsy, according to a study published in *JCI Insight.*

The findings represent a significant advancement in the understanding of the gene KCNQ2, according to Alfred George, Jr., MD, chair and Alfred Newton Richards Professor of Pharmacology and lead author of the study.

KCNQ2 was among the first genes linked to genetic forms of epilepsy. Loss-of-function pathogenic variants in KCNQ2 impair voltage-gated potassium channels in neurons, creating disturbances in the electrical current that regulates neuronal excitability. Just a small proportion of the hundreds of KCNQ2 variants discovered in patients with epilepsy have been functionally evaluated, with most variants classified as "variants of uncertain significance" (VUS).

In the current study, George, along with lead author Carlos G. Vanoye, Ph.D., research associate professor of Pharmacology, used high-throughput patch-clamp recording to measure the effects of 81 KCNQ2 variants in Chinese hamster ovary cells. These cells naturally lack KCNQ2, allowing the scientists to introduce variants of the gene and measure changes in currents passed through potassium channels.

"Prior to our study, the entire literature had only about 50 mutations studied for their functional consequences; we studied 81," said George, who is also director of the Center for Pharmacogenomics. "This helps demonstrate the molecular defect by which these variants contribute to

epilepsy."

Out of the 81 KCNQ2 variants studied, nearly 60 were associated with epilepsy while the remaining were found rarely in healthy populations, according to George. Normally, each potassium channel requires two copies of genes that code for KCNQ2 proteins, and many of the variants examined were "dominant-negative," impairing function even if paired with a normal KCNQ2 gene, poisoning the entire channel.

"Many of these variants caused a profound loss of function," George said.

A small number of the variants had little functional difference compared to normal KCNQ2, indicating their discovery in people with epilepsy may be incidental or that dysfunction may only be present in human neurons. For all studied variants, George and his collaborators plan to share findings with genetic testing companies and update entries on ClinVar, a public archive of genetic variants administered by the National Institutes of Health.

Further, preclinical tests suggested patients with some variants may respond to treatment with the FDA-approved drug ezogabine, also known as retigabine. Administering the drug to cells with pathogenic variants restored potassium channel function in some, but the effect was highly variable among variants. Ezogabine/retigabine was pulled from the market due to low uptake and side effects, but George said he believes it could be a useful tool for patients with certain KCNQ2 variants.

"There are infants and young children with pathogenic variants who might benefit," George said. "We want to partner with pharmaceutical companies to determine if the response of variants to retigabine that we found in the laboratory corresponds to clinical responses observed in

patients—that could help move precision epilepsy treatment forward."

More information: Carlos G. Vanoye et al, High-throughput evaluation of epilepsy-associated KCNQ2 variants reveals functional and pharmacological heterogeneity, *JCI Insight* (2022). DOI: 10.1172/jci.insight.156314

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