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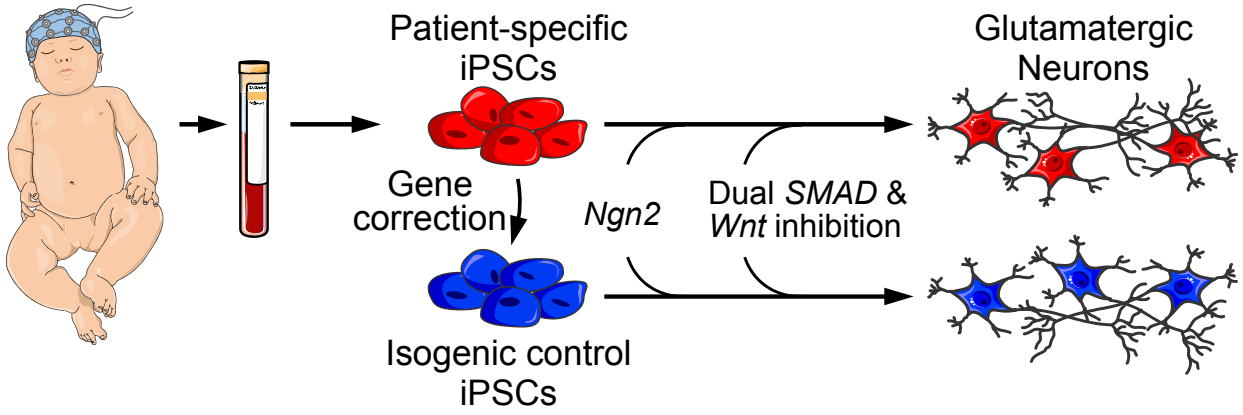
Mechanisms of maladaptive compensation in KCNQ2-related epilepsy in patient-specific iPSC-derived neurons

Dina Simkin[1]

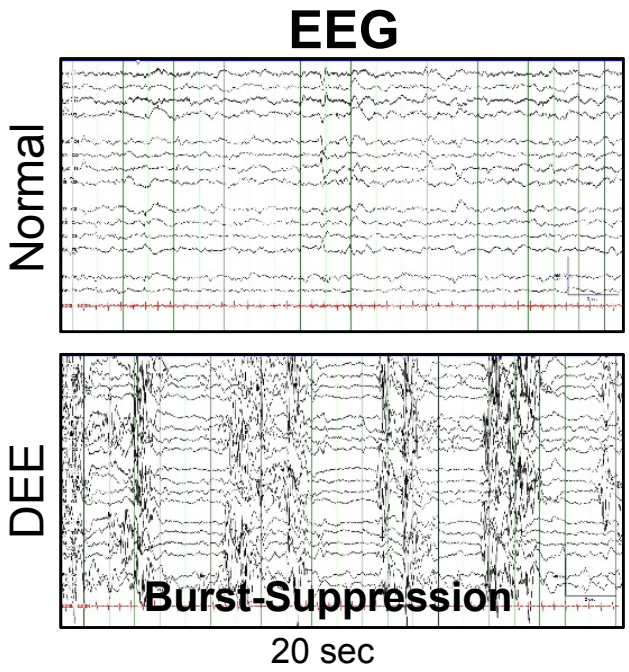
Adil Wafa[1], Mennat Gharib[1], Kelly Marshall[1], Alfred L. George[2] & Evangelos Kiskinis[1]

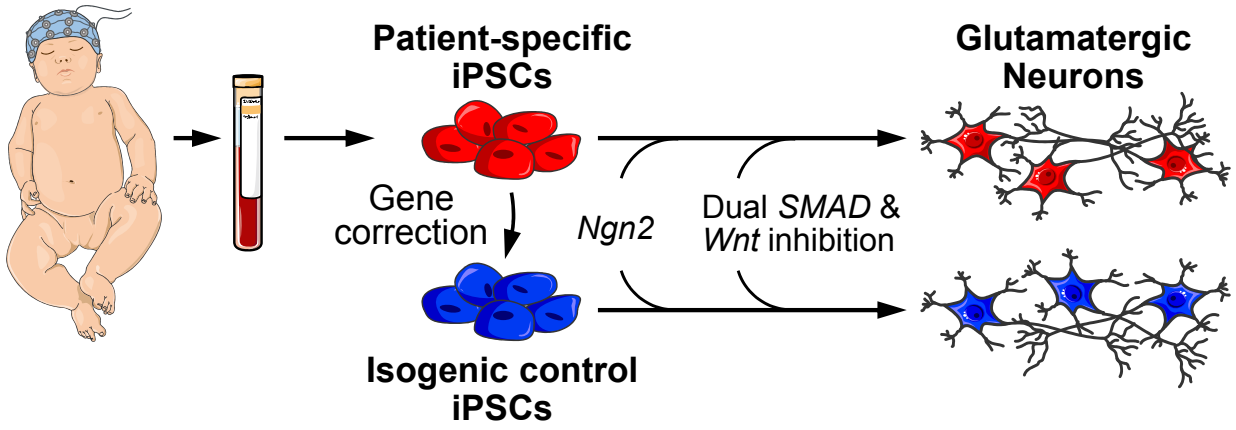
[1]Department of Neurology; [2]Department of Pharmacology,
Northwestern University, Feinberg School of Medicine, Chicago, IL

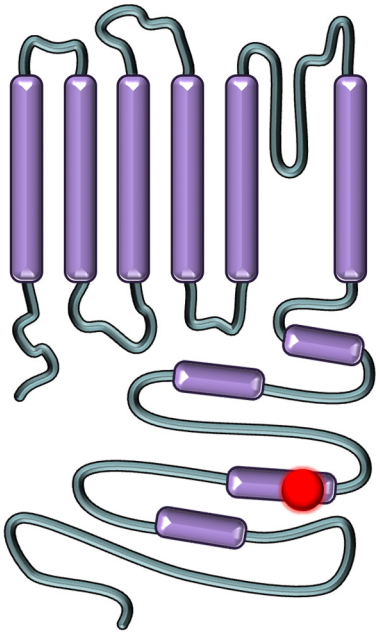


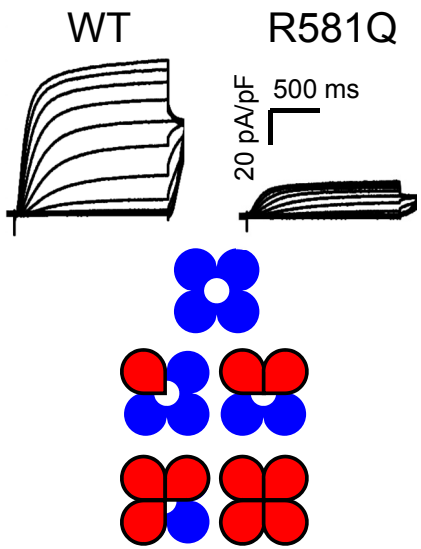
Simkin et al., 2021, eLife

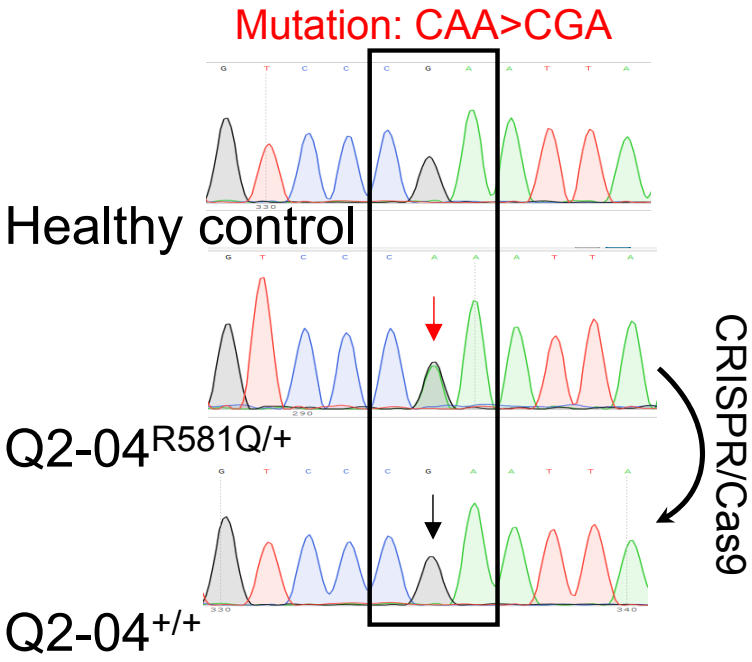
Developmental and epileptic encephalopathy (DEE) associated with KCNQ2-R581Q loss-of-function mutation





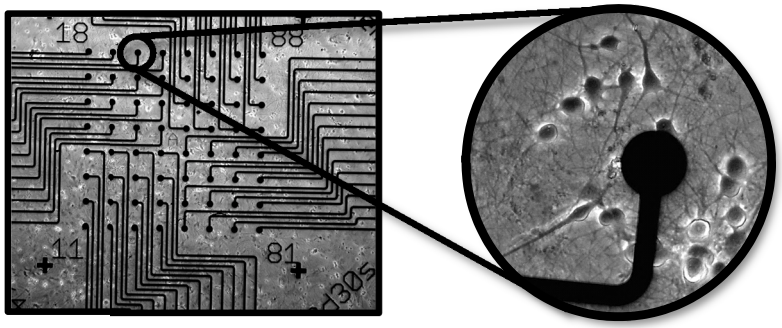


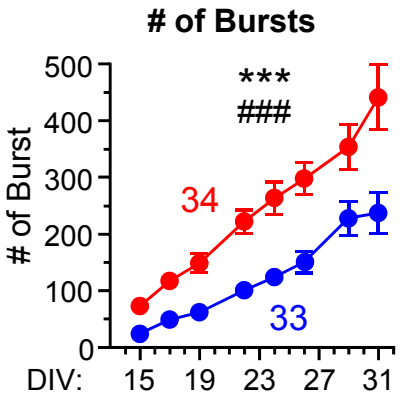


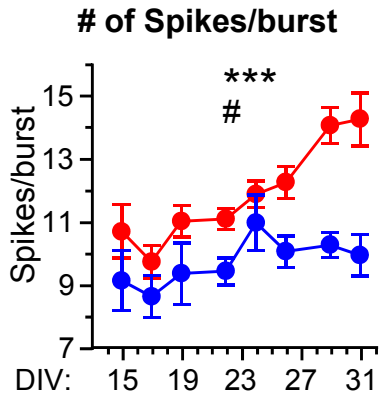


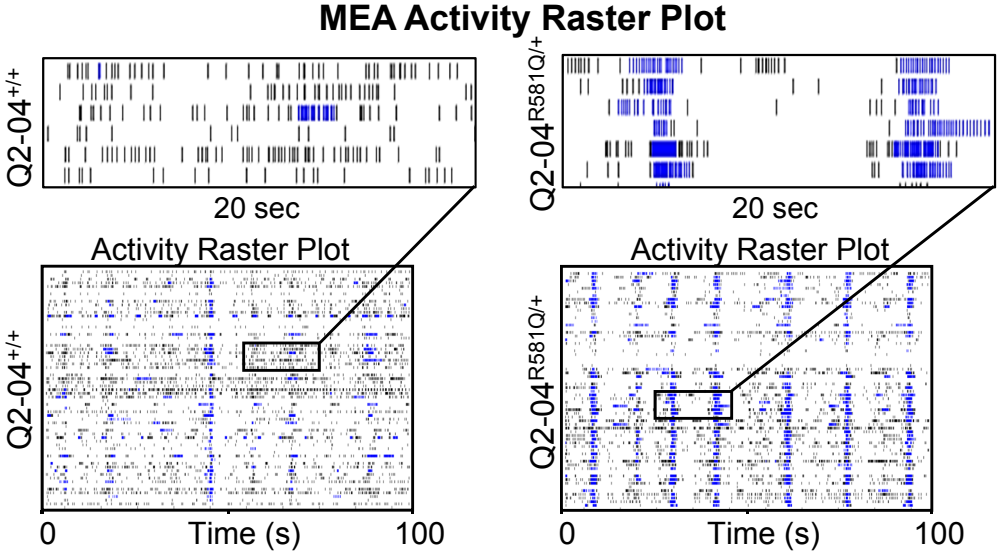
Simkin et al., 2021, eLife

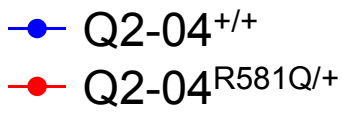
KCNQ2-DEE neurons exhibit enhanced spontaneous bursting on MEAs

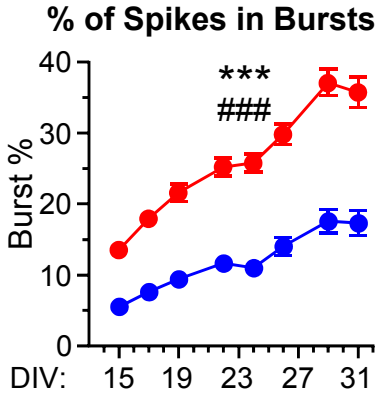


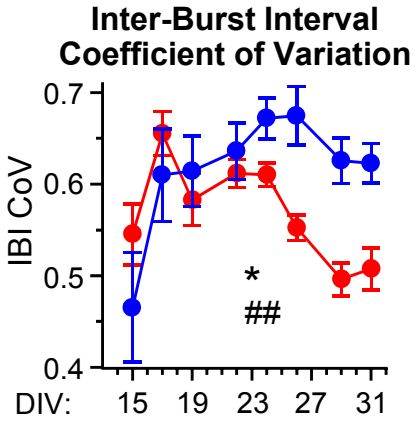


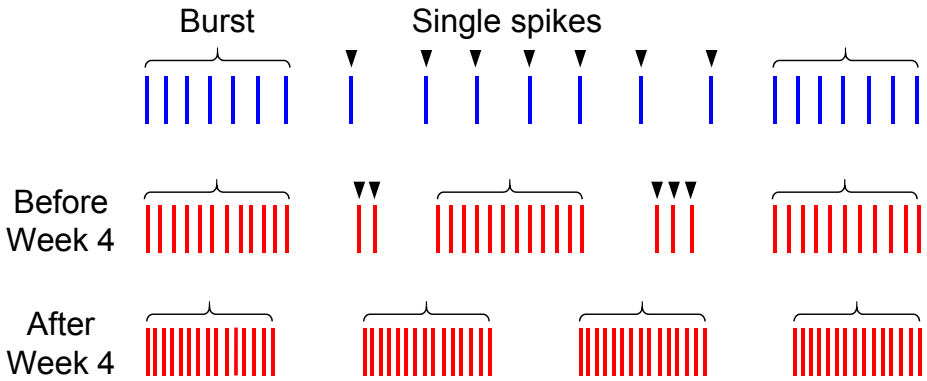






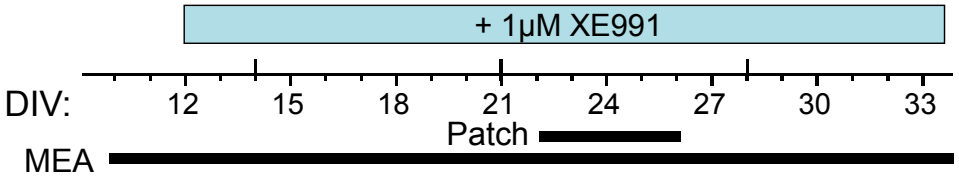




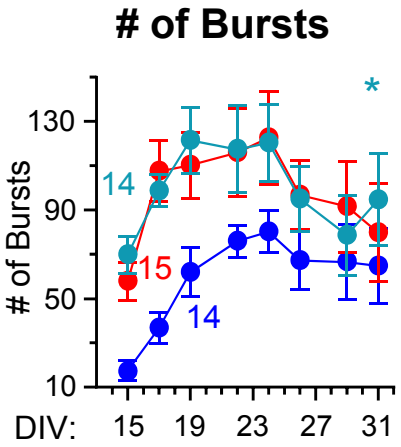


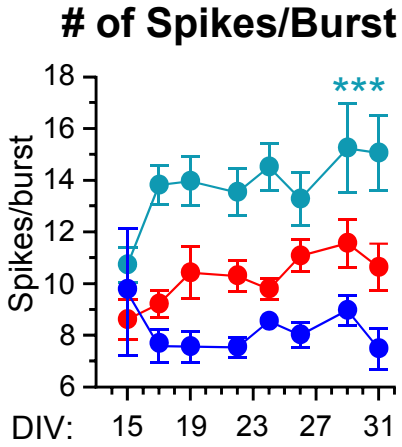
Simkin et al., 2021, eLife

Chronic inhibition of M-current in control neurons phenocopies KCNQ2-DEE

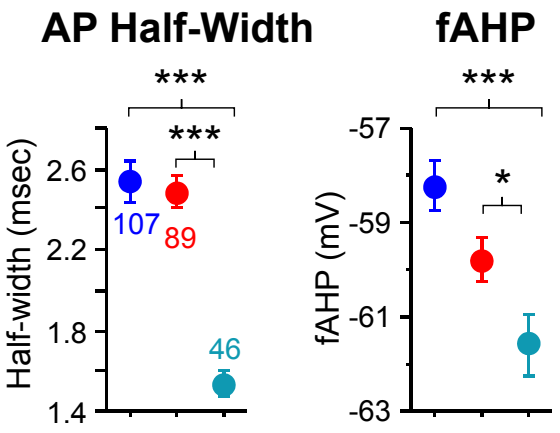


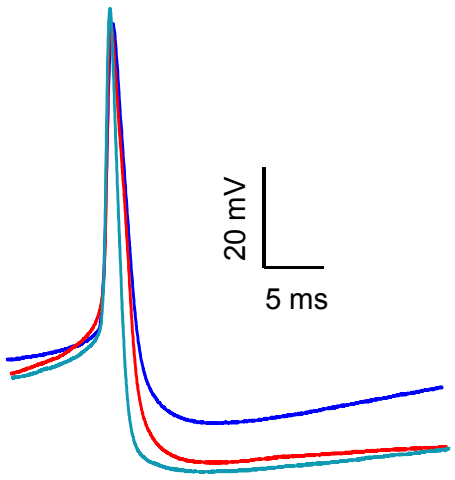
MEA activity

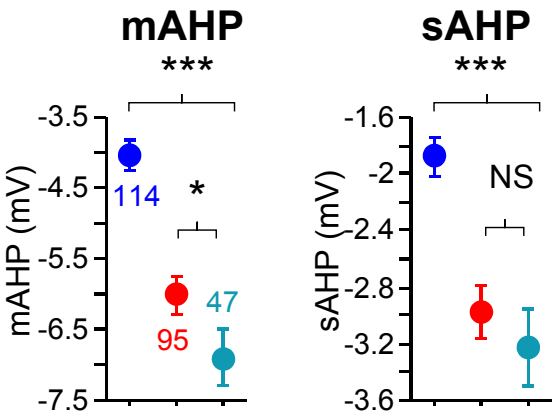


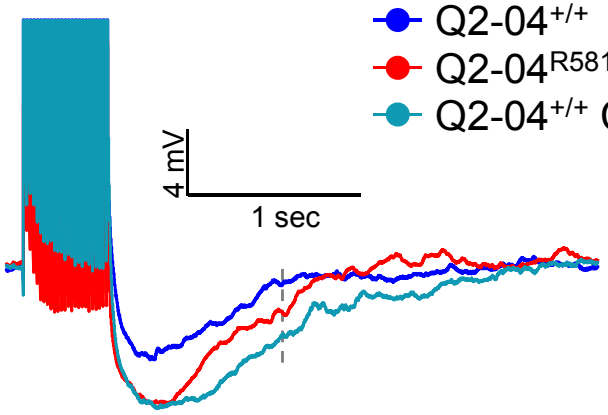


Current-Clamp

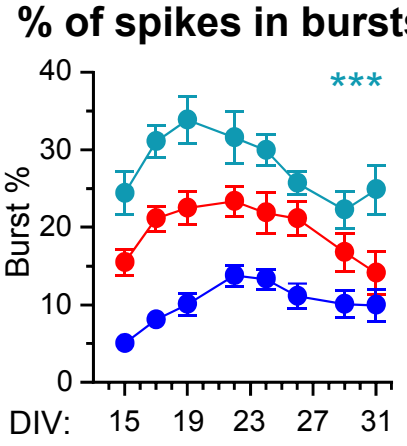








Q2-04$^{+/+}$
Q2-04$^{R581Q/+}$
Q2-04$^{+/+}$ Chronic XE991



KCNQ2-DEE neurons and control neurons chronically treated with XE991 exhibit faster AP repolarization and larger post-burst AHPs

KCNQ2-DEE neurons and control neurons chronically treated with XE991 exhibit enhanced bursting propensity

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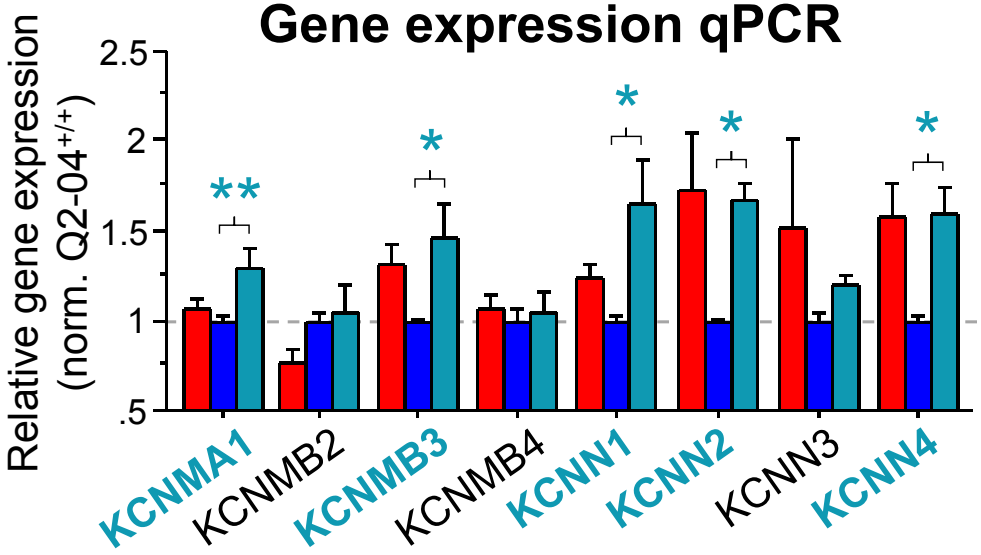
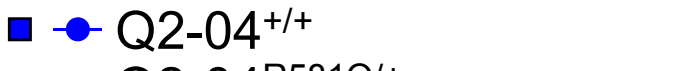
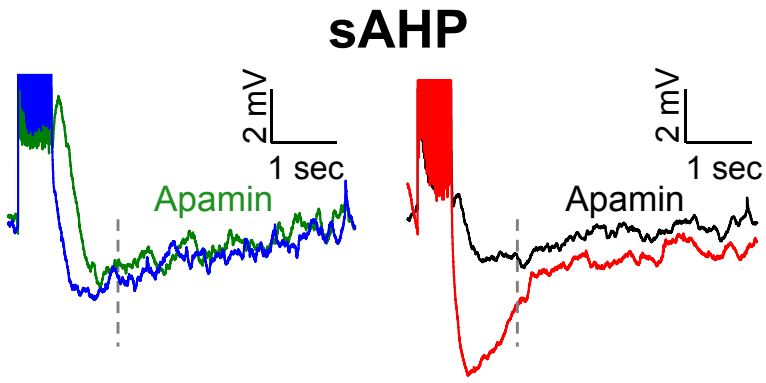
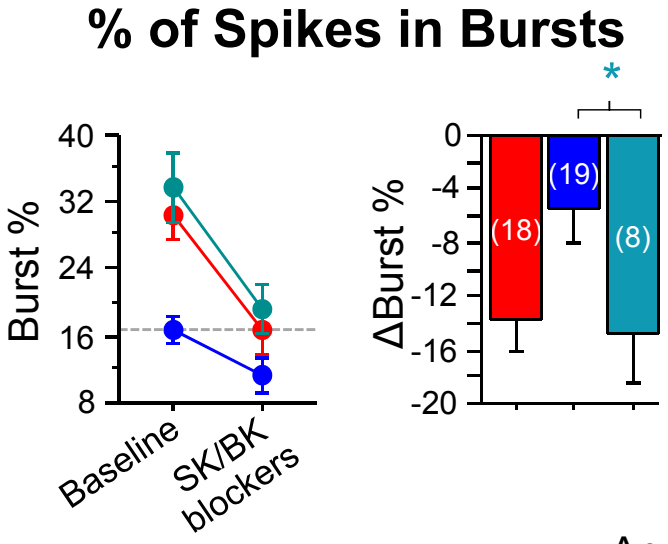
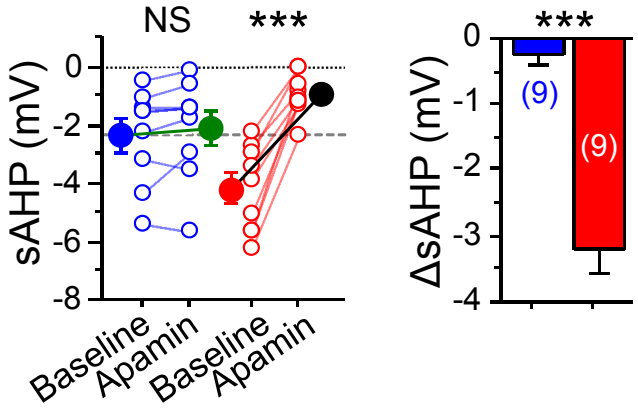
Maladaptive enhancement of SK/BK channels leads to enhanced AHPs and bursting in KCNQ2-DEE neurons and XE991 treated control neurons











Apamin (500nM): SK channel blocker

Paxilline (20μM): BK channel blocker

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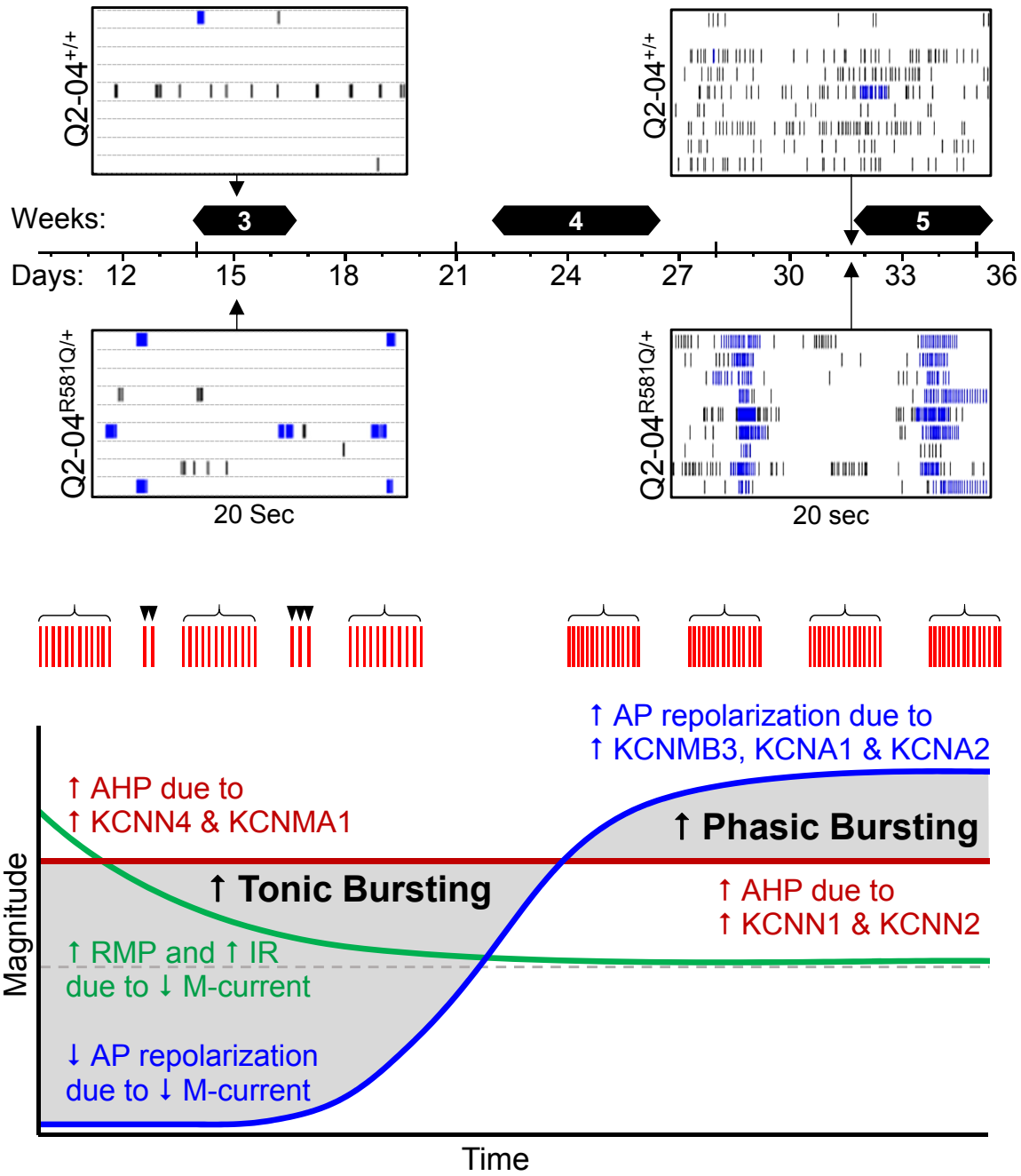
Developmental Time Course of KCNQ2-DEE Neurons



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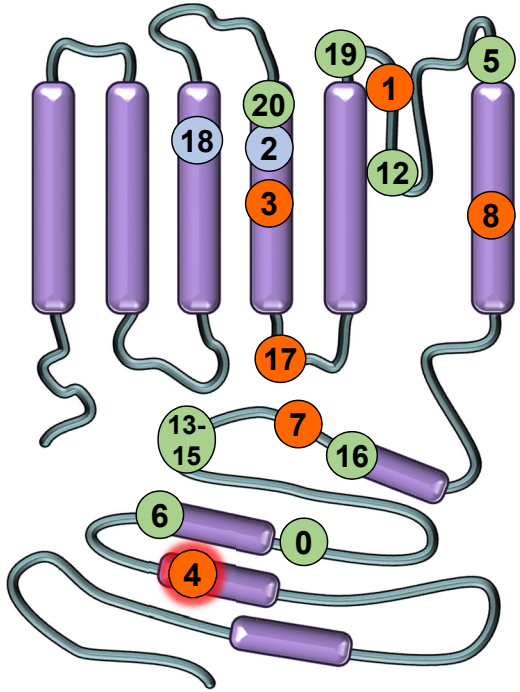
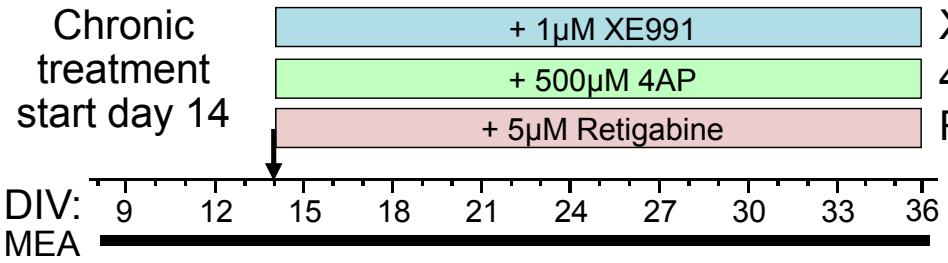
Unanswered questions:

1) Is maladaptive Ca^{2+}-dependent K^+ channel upregulation and bursting a result of reduced M-current specifically or the resulting hyperexcitability?



2) Is this bursting a common phenotype amongst KCNQ2-DEE patient neurons with other KCNQ2 mutations?

Chronic inhibition of K^+ channels and increased neuronal activity with 4AP does not phenocopy KCNQ2-DEE maladaptive phenotype



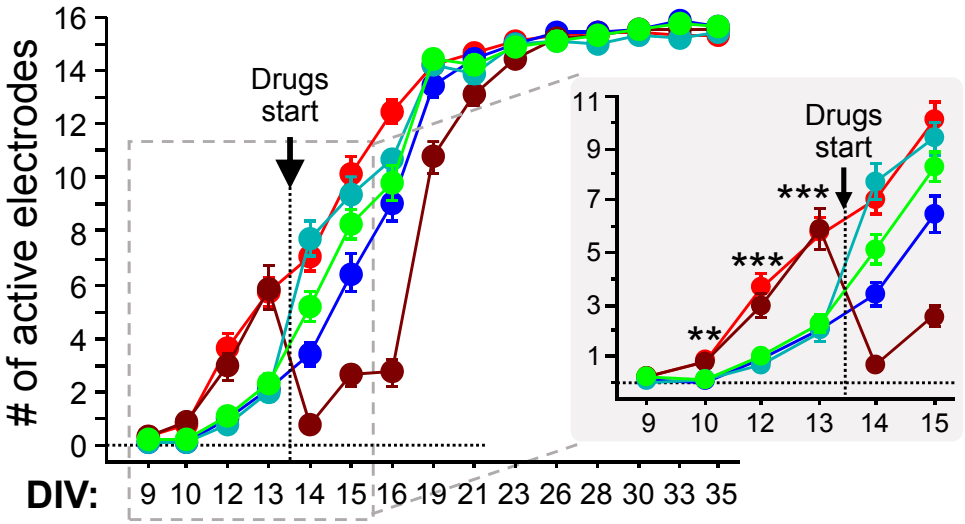
XE991: Blocker of M-current
4AP: Blocker of other K+ channels, ↑excitability
Retigabine: Activator of M-current, ↓excitability

N = 18 wells/condition averaged from 16 electrodes/well
(3 independent differentiations)

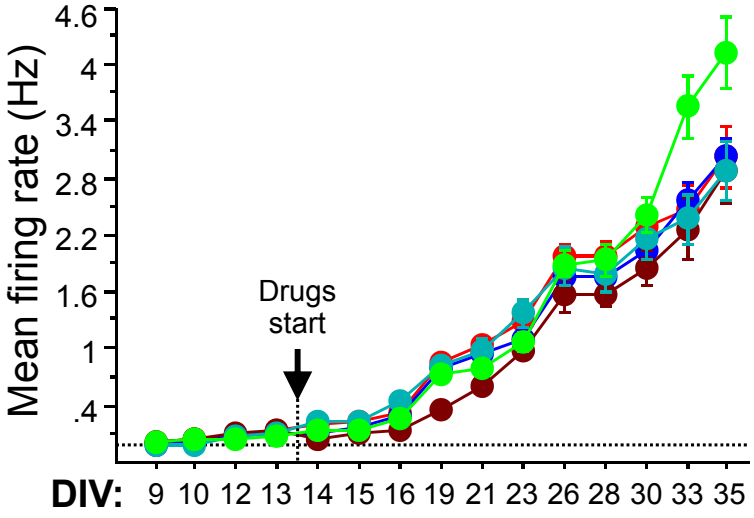
- $Q2\text{-}04^{+/+}$
- $Q2\text{-}04^{R581Q/+}$
- $Q2\text{-}04^{+/+}$ Chronic XE991
- $Q2\text{-}04^{+/+}$ Chronic 4AP
- $Q2\text{-}04^{R581Q/+}$ Chronic Retigabine

Early-onset of functional maturation

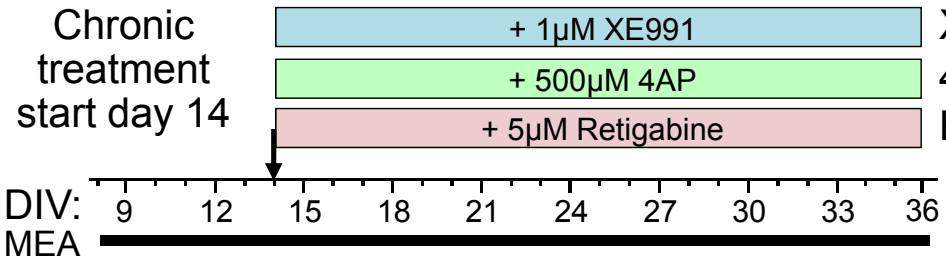
of Active Electrodes



Weighted Mean Firing Frequency



Chronic inhibition of K^+ channels and increased neuronal activity with 4AP does not phenocopy KCNQ2-DEE maladaptive bursting phenotype



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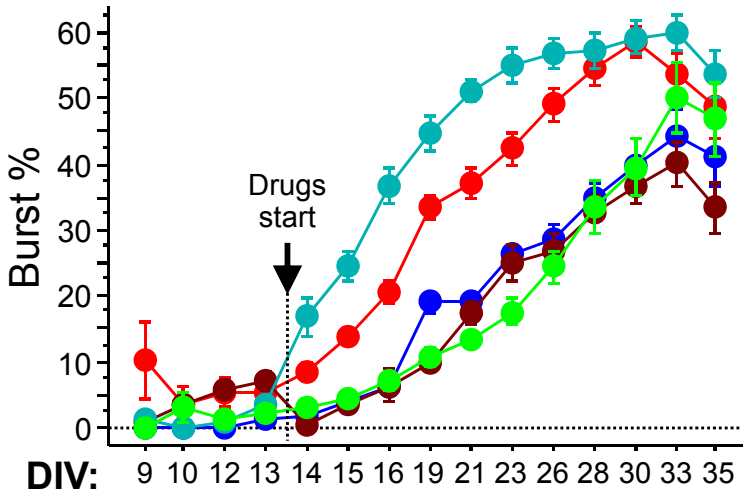
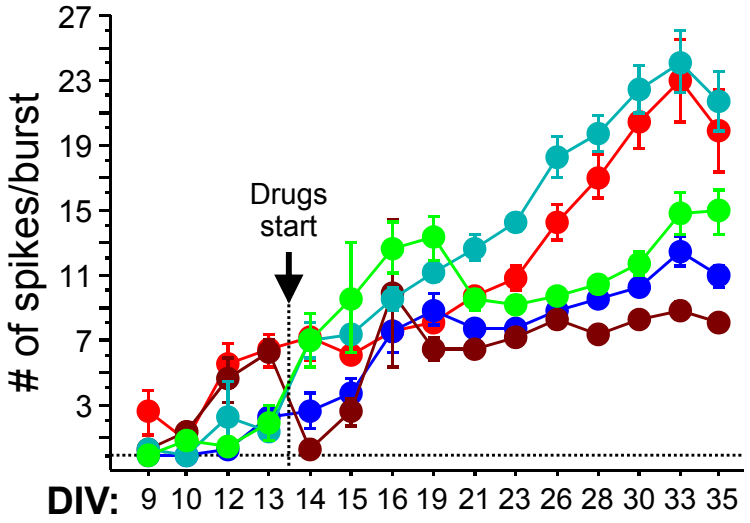
- $Q2\text{-}04^{+/+}$ Chronic XE991
- $Q2\text{-}04^{+/+}$ Chronic 4AP
- $Q2\text{-}04^{R581Q/+}$ Chronic Retigabine

Bursting Propensity

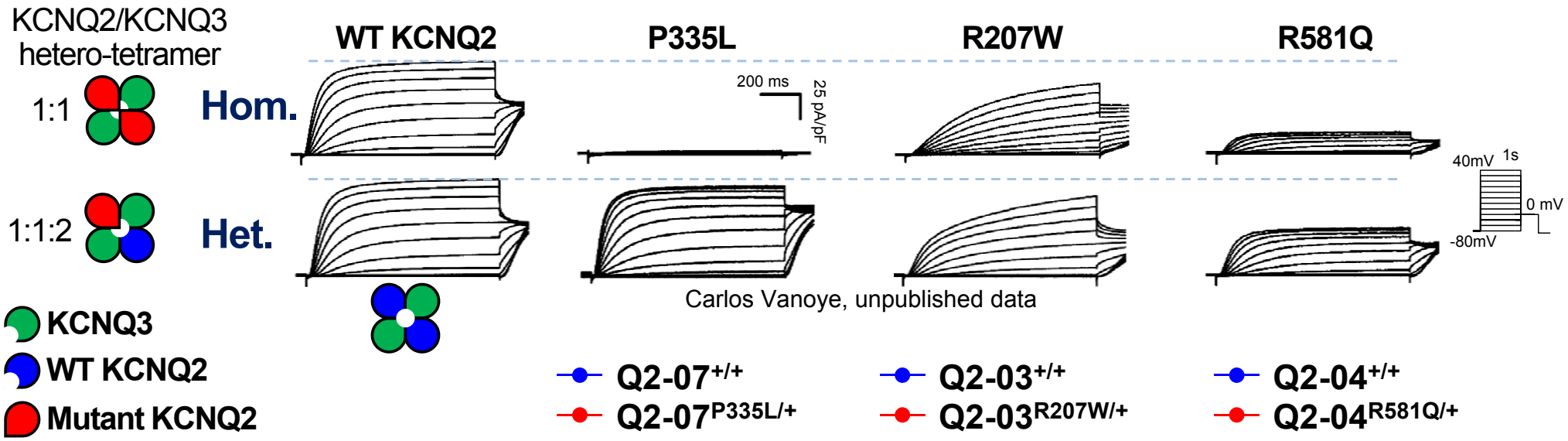
% of Spike in Bursts

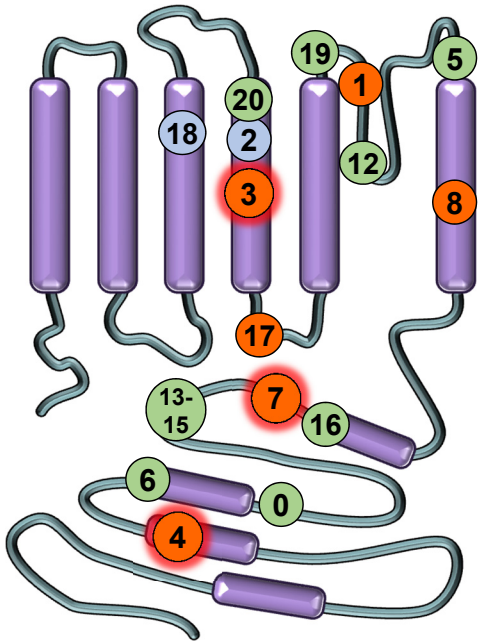


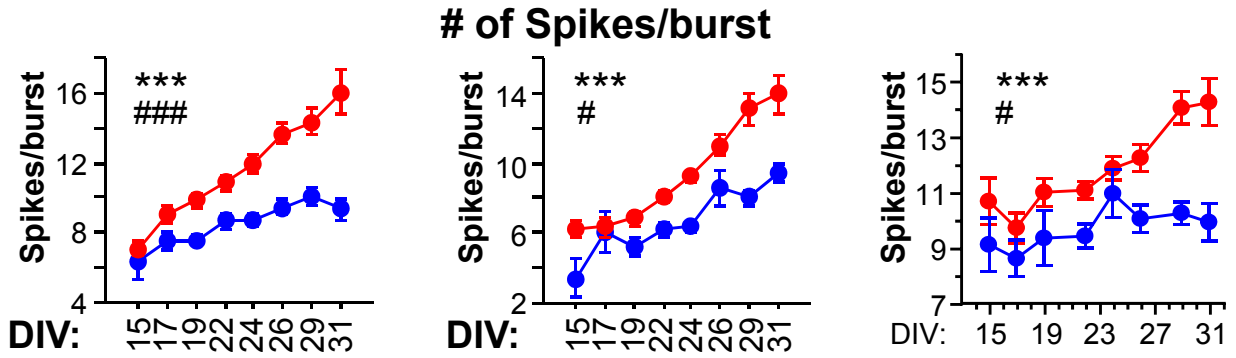
of Spikes per Burst

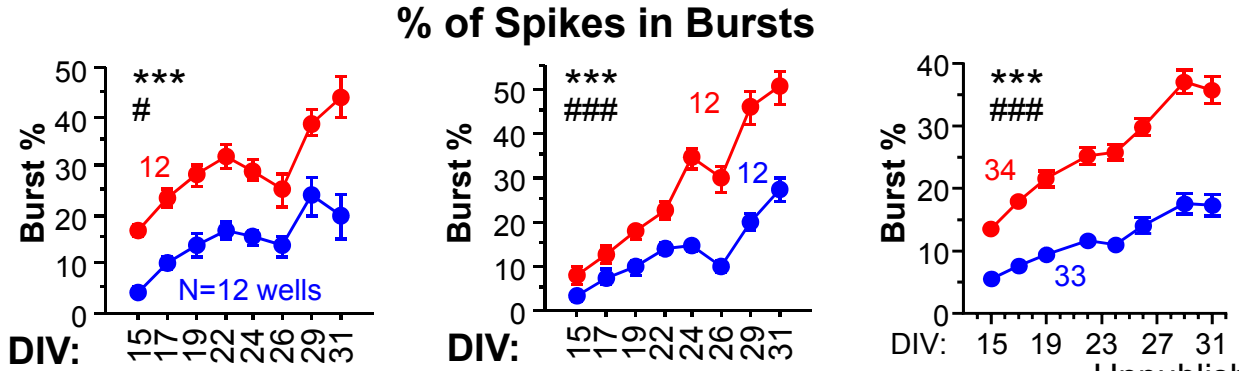


Common bursting phenotype amongst KCNQ2-DEE patient-specific iPSC-derived excitatory neurons with different KCNQ2 mutations









Unpublished data

Acknowledgments

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Kelly Marshall

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Mennat Gharib

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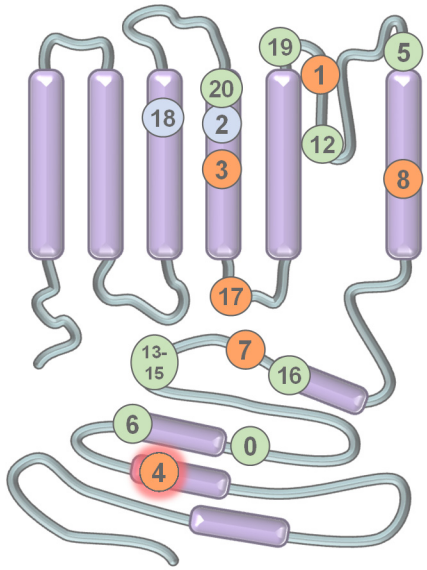

Dyshomeostatic modulation of Ca^{2+}-activated K^+ channels in a human neuronal model of KCNQ2 encephalopathy

eLife

Dina Simkin[1,2], Kelly A Marshall[1], Carlos G Vanoye[2], Reshma R Desai[2], Bernabe I Bustos[1], Brandon N Piyevsky[1], Juan A Ortega[1], Marc Forrest[3,4], Gabriella L Robertson[1], Peter Penzes[3,4], Linda C Laux[5], Steven J Lubbe[1], John J Millichap[5], Alfred L George Jr[2]*, Evangelos Kiskinis[1,3]*

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