Supporting Information

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SI Allosteric Gating Scheme

The allosteric gating scheme in Fig. 6 is reproduced below in Fig. S1 and comprises the following equations for voltage-sensor movements and voltage-insensitive time constants for movements between closed and open states.

$$\alpha = c1{*}\exp\left(c2{*}\left(Vm - V_{1/2}\right)\right)$$
$$\beta = c1{*}\exp\left(-c3{*}\left(Vm - V_{1/2}\right)\right)$$
$$\alpha' = c4{*}\alpha$$
$$\beta' = c4{*}\beta$$

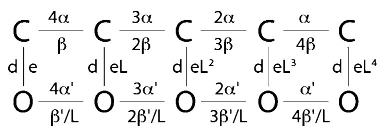

Fig. S1. Gating scheme used to model the KCNQ1 constructs in this study. See rates in Table S1.

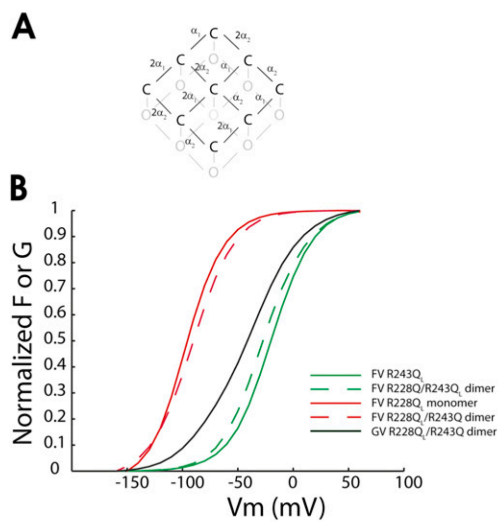

Fig. S2. Allosteric model simulated fluorescence and current for R228Q and R243Q coinjection experiments. (*A*) Schematic of a model for channels comprised of 2 subunits (R228Q and R243Q) with different voltage sensing domains. The closed to open transition maintain the same allostery as in the model equations given in Fig. S1. (*B*) Prediction for one voltage sensor with a $F_{1/2}$ of −98 mV and one at −20 mV, as for R228Q and R243Q, respectively. Solid lines show the model for each construct expressed alone and dotted lines show the effect they have on each other in a channel tetrameric complex comprising two subunits of each type. For this scenario, the allosteric model predicts a flattening and small shift (<7 mV) in the voltage sensors with the resulting current lying in between. This result is in good qualitative agreement with the experimental results in Fig. 1. In addition, in our coinjection experiments of R228Q and R243Q subunits the shifts are expected to be even smaller than this 7-mV shift. This is because a large fraction of the fluorescence will come from channels with more than two fluorescently labeled subunits, which will have an even smaller shift or no shift (in the case of four fluorescently labeled subunits coming together to form a channel). Therefore, our model is consistent with our data in Fig. 1.

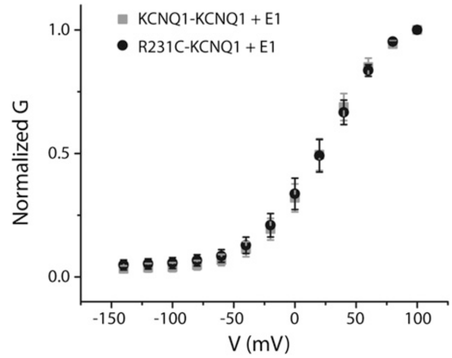

Fig. S3. KCNE1 keeps KCNQ1 channels closed even with two activated voltage sensors. Average G-V relationship for experiments coexpressing KCNE1 with either the linked dimer KCNQ1-KCNQ1 (gray squares) or R231C-KCNQ1 (black circles). Experiments are normalized to the maximum from Boltzmann fits to the data (see *Methods*). Experiments are performed in 98 mM extracellular potassium ("High K^+") (see *Methods*), and cells are held at −80 mV, pulsed to voltages between −140 and 100 mV for 5 s, followed by 3-s pulses to −120 mV to collect tail currents. Error bars represent SEM.

Table S1. Parameter sets for the best fit to each construct

Construct	c1	c2	c3	c4	d	e	$V_{1/2}$	L
K218C	1.61	0.022	0.036	0.58	21.4	2.26	−36.0	4.11
219C	1.33	0.012	0.037	0.56	82.6	2.26	−55.0	3.64
L251A	1.48	0.013	0.062	0.10	897.6	1.14	−23.6	6.08
I268A	1.24	0.011	0.044	0.92	18.2	6.98	−28.7	2.04

Time is in seconds. The allosteric coupling factor L was here associated with the backward rates in the model (Fig. S1), but allosteric models with L in the forward rate or L split between forward and backward rates could also reproduce our data. Future studies with more constraining data will be necessary to distinguish between these possible allosteric models.