Computational modeling

The model of channel gating use in this study arises from previous work¹). Briefly the model consists of 12 states; 6 closed and 6 open, and two voltage sensor movements consistent with the growing knowledge of KCNQ1 gating features. The open states included states from different conformations of voltage sensing domains(O_0 - O_4) as well as a concerted final open state referred to in some literature as the activated open state(O_5)². Figure 1 shows the structure of the 12 state model and Table 1 shows the constants used for the simulations. The highlighted numbers represent changes from no-drug model.

$\begin{array}{c} \mathbf{C}_{0} \xleftarrow{4\alpha}{\beta} \mathbf{C}_{1} \xleftarrow{3\alpha}{2\beta} \mathbf{C}_{2} \xleftarrow{2\alpha}{3\beta} \mathbf{C}_{3} \xleftarrow{\alpha}{4j} \\ d \downarrow e/M d \downarrow eL/M d \downarrow eL^{2}/M d \downarrow eL^{3}/M \\ \mathbf{O}_{0} \xleftarrow{4\alpha'}{\beta'/L} \mathbf{O}_{1} \xleftarrow{3\alpha'}{2\beta'/L} \mathbf{O}_{2} \xleftarrow{2\alpha'}{3\beta'/L} \mathbf{O}_{3} \xleftarrow{\alpha}{4\beta} \end{array}$	$\begin{array}{c} \overset{\epsilon}{\to} \mathbf{C}_{4} \stackrel{\epsilon}{\to} \mathbf{C}_{5} \\ \overset{\epsilon}{\to} \mathbf{C}_{4} \stackrel{\epsilon}{\to} \mathbf{C}_{5} \\ \overset{\epsilon}{\to} $
α =c1*exp(c2*(V _m -V _{half}))	α'=c4* α
β =c1*exp(-c3*(V _m -V _{half}))	β '=c4 *β
ϵ =c5*exp(c6*(V _m -V _{half2}))	ε'=c4*ε
$\theta = c5^{*}exp(-c7^{*}(V_{m}-V_{half2}))$	θ '=c4* θ

Figure S1: Schematic of gating scheme for KCNQ1 along with equations for values that are not strict constants

KCNQ1	ML277	R-L3	Units
0.8559	0.8559	0.8559	
1 citmax	1.079 1.95 1. <u>1.95</u>	$1.24\frac{24}{24}81$	S ⁻¹
1.079	1.079	<mark>0.5681</mark>	S ⁻¹
0.021977	0.9659 0.02970 .9659	0.02957579	mV ⁻¹
0.027	0.027	0.027	mV ⁻¹
0.9.995.91	-30.56 0.9659-30.56	0.9 <u>65.9</u> 2	mVS ⁻¹
34.03	<mark>2.127</mark>	34.03	S ⁻¹
5.533	0.01413 0.3458 0.01413	5.5331413	mV§ ⁻¹
-30.56	-30.56	<mark>-52.12</mark>	mV
1.833	$^{98.11}_{1.399}$ 1.833 $^{98.11}_{1.399}$	1.833	mv
1.187	1.187	1.187	S ⁻¹
0.01413	Table S 0:04A18 s for par	amete fsQ34d3 n simu	lationsmV ⁻¹
0.01354	0.01354	0.01354	mV ⁻¹
98.11	98.11	98.11	mV
1.399	1.399	1.399	
	KCNQ1 0.8559 1 1.079 0.023 0.027 0.027 0.056 1.833 1.187 0.01413 0.01354 98.11 1.399	KCNQ1ML277 0.8559 0.8559 $1 [1,079]$ 1.95 1.079 1.079 0.027 0.9659 0.027 0.027 0.027 0.027 0.027 0.027 0.5659 $0.9659-30.56$ 34.03 2.127 5.523 0.01413 -30.56 -30.56 1.833 98.11 1.399 1.833 98.11 98.11 0.01354 0.01354 98.11 98.11 1.399 1.399	KCNQ1ML277 $R-L3$ 0.85590.85590.85590.85591 $i 179$ 1.95 $i 175$ 1.079 1.079 0.5681 0.02977 0.9659 $0.02977.9659$ 0.027 0.027 0.027 0.027 0.027 0.027 0.5681 $0.02977.9659$ $0.02957.92$ 34.03 2.127 34.03 5.563 0.01413 5.593413 -30.56 -30.56 -52.12 1.833 1.399 1.833 1.87 1.187 1.187 0.01413Table \$0.044412\$ for parameter \$04413\$ n simu0.01354 0.01354 0.01354 98.11 98.11 98.11 1.399 1.399 1.399

Table S1: Values for parameters used in simulations

BTX trafficking control experiments

For the flow cytometry experiments, three types of controls were performeduntransfected, BBS-KCNQ1 and KCNQ1-YFP constructs. These data are shown in Supplemental Figure S2.



Figure S2: Control flow cytometry results for BBS-KCNQ1 alone(left), KCNQ1-YFP alone (middle), after the sector of the sector of

	peak current	deactivation
WТ	119±8%	542±75%
L266W	93±3%	395±61%
Y267A	1±1%	-5±5%
G269L	12±5%	216±33%
G272C	99±10%	297±50%
V334L	78±4%	385±23%
F335I	41±4%	258±30%
F339I	23±5%	111±6%
F340A	-4±4%	298±25%

Table S2. R-L3 induced current increase (%) and Deactivation kinetics in all ML277 insensitive mutants



References

1. Peng, G., Barro-Soria, R. Sampson, K.J., Larsson, H.P. and Kass R.S. Gating Mechanisms underlying deactivation slowing by two KCNQ1 atrial fibrillation mutations. Sci Reports. 2017; 7:45911

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