

Temperature-dependent changes in neuronal dynamics in a patient with an *SCN1A* mutation and hyperthermia induced seizures

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Supplementary Material:

Supplementary Table S1

	WT 32°C			AV 32°C		
	Mean	StErr	N	Mean	StErr	N
G V_{1/2} (mV)	-12.6	2.1	11	-16.4	1.9	8
G z	3.73	0.28	11	3.62	0.18	8
SSFI V_{1/2} (mV)	-50.2	2.6	9	-58.9	1.6	9
SSFI z	-4.07	0.30	9	-3.12	0.37	9
FIrec τ1 (ms)	2.18	0.29	9	2.55	0.70	5
FIrec A1	0.597	0.030	9	0.508	0.046	5
FIrec τ2 (ms)	97	20	9	125	34	5
FIrec A2	0.357	0.024	9	0.400	0.025	5
-10mV, FIon τ (ms)	0.641	0.097	12	0.571	0.104	7
0mV, FIon τ (ms)	0.364	0.043	12	0.327	0.030	7
10mV, FIon τ (ms)	0.256	0.026	12	0.246	0.028	7
20mV, FIon τ (ms)	0.181	0.014	12	0.178	0.027	7
30mV, FIon τ (ms)	0.163	0.015	12	0.176	0.028	6
40mV, FIon τ (ms)	0.154	0.016	11	0.140	0.015	5
-20mV, 50% Act (ms)	0.303	0.011	11	0.304	0.016	9
-10mV, 50% Act (ms)	0.290	0.010	12	0.300	0.013	9
0mV, 50% Act (ms)	0.274	0.010	12	0.277	0.013	9
10mV, 50% Act (ms)	0.256	0.011	12	0.261	0.013	9
20mV, 50% Act (ms)	0.238	0.011	12	0.244	0.012	9
30mV, 50% Act (ms)	0.224	0.010	12	0.228	0.013	8
40mV, 50% Act (ms)	0.219	0.014	10	0.214	0.012	9
50mV, 50% Act (ms)	0.211	0.013	10	0.210	0.013	9
60mV, 50% Act (ms)	0.209	0.012	10	0.194	0.011	5

Table S1: Averages and standard errors of data at 32°C.

Conductance (G) and steady-state fast inactivation (FI) curves were fit with Boltzmann curves; V_{1/2} and z are the midpoint and apparent valence, respectively. Fast inactivation recovery curves (FIrec) at -90mV were fit with a double exponential equation; τ 1 and A1 are the fast time constant and fast amplitude, respectively, while τ 2 and A2 are the slow time constant and slow amplitude, respectively. Decay of macroscopic currents were fit with a single exponential equation to measure the time constant of open-state inactivation (FIon τ). The times between the voltage clamp of membrane potential and the time of 50% maximal current at a given membrane potential were used as measures of activation (50% Act).

Supplementary Table S2:

	NaV1.1, WT, 37°C			NaV1.1, A1273V, 37°C		
	Mean	StErr	N	Mean	StErr	N
-20mV, 50% Act (ms)	0.269	0.057	9	0.267	0.011	5
-10mV, 50% Act (ms)	0.250	0.008	9	0.266	0.008	5
0mV, 50% Act (ms)	0.227	0.006	9	0.257	0.012	5
10mV, 50% Act (ms)	0.211	0.005	9	0.237	0.012	5
20mV, 50% Act (ms)	0.199	0.004	9	0.218	0.011	5
30mV, 50% Act (ms)	0.191	0.004	9	0.204	0.010	5
40mV, 50% Act (ms)	0.185	0.004	9	0.194	0.009	5
50mV, 50% Act (ms)	0.181	0.006	6	0.187	0.008	5
60mV, 50% Act (ms)	0.182	0.006	6	0.180	0.010	5
	NaV1.1, WT, 40°C			NaV1.1, A1273V, 40°C		
-20mV, 50% Act (ms)	0.260	0.023	4	0.263	0.009	9
-10mV, 50% Act (ms)	0.261	0.019	7	0.270	0.010	10
0mV, 50% Act (ms)	0.238	0.016	7	0.256	0.011	10
10mV, 50% Act (ms)	0.222	0.015	7	0.239	0.012	10
20mV, 50% Act (ms)	0.206	0.013	7	0.225	0.010	10
30mV, 50% Act (ms)	0.196	0.011	7	0.211	0.009	10
40mV, 50% Act (ms)	0.189	0.010	7	0.200	0.005	10
50mV, 50% Act (ms)	0.182	0.008	7	0.183	0.006	8
60mV, 50% Act (ms)	0.181	0.013	6	0.186	0.007	8

Source Data for Figure 1 C and D:

The times between the voltage clamp of membrane potential and the time of 50% maximal current at a given membrane potential were used as measures of activation (50% Act).

Supplementary Table S3:

	NaV1.1, WT, 37°C			NaV1.1, A1273V, 37°C		
	Mean	StErr	N	Mean	StErr	N
G V^{1/2} (mV)	-14.1	3.1	9	-12.0	1.5	5
G z	3.43	0.24	9	4.08	0.21	5
SSFI V^{1/2} (mV)	-57.2	1.1	5	-54.8	3.7	5
SSFI z	-3.14	0.11	5	-3.73	0.63	5
	NaV1.1, WT, 40°C			NaV1.1, A1273V, 40°C		
G V^{1/2} (mV)	-10.0	2.0	7	-4.2	2.0	11
G z	3.39	0.19	7	3.07	0.19	11
SSFI V^{1/2} (mV)	-59.1	3.4	5	-45.5	3.1	6
SSFI z	-3.79	0.17	5	-3.38	0.49	6

Source Data for Figure 2:

Conductance (G) and steady-state fast inactivation (FI) curves were fit with Boltzmann curves; V^{1/2} and z are the midpoint and apparent valence, respectively.

Supplementary Table S4:

	NaV1.1, WT, 37°C			NaV1.1, A1273V, 37°C		
	Mean	StErr	N	Mean	StErr	N
FIrec τ_1 (ms)	1.62	0.44	5	1.42	0.23	5
FIrec A1	0.542	0.087	5	0.536	0.041	5
FIrec τ_2 (ms)	81	16	5	141	56	5
FIrec A2	0.418	0.022	5	0.337	0.023	5
	NaV1.1, WT, 40°C			NaV1.1, A1273V, 40°C		
FIrec τ_1 (ms)	1.27	0.21	6	1.24	0.13	5
FIrec A1	0.396	0.030	6	0.623	0.033	5
FIrec τ_2 (ms)	72	22	6	138	57	5
FIrec A2	0.503	0.034	6	0.285	0.033	5

Source Data for Figure 3 A and B:

Fast inactivation recovery curves (FIrec) at -90mV were fit with a double exponential equation; τ_1 and A1 are the fast time constant and fast amplitude, respectively, while τ_2 and A2 are the slow time constant and slow amplitude, respectively.

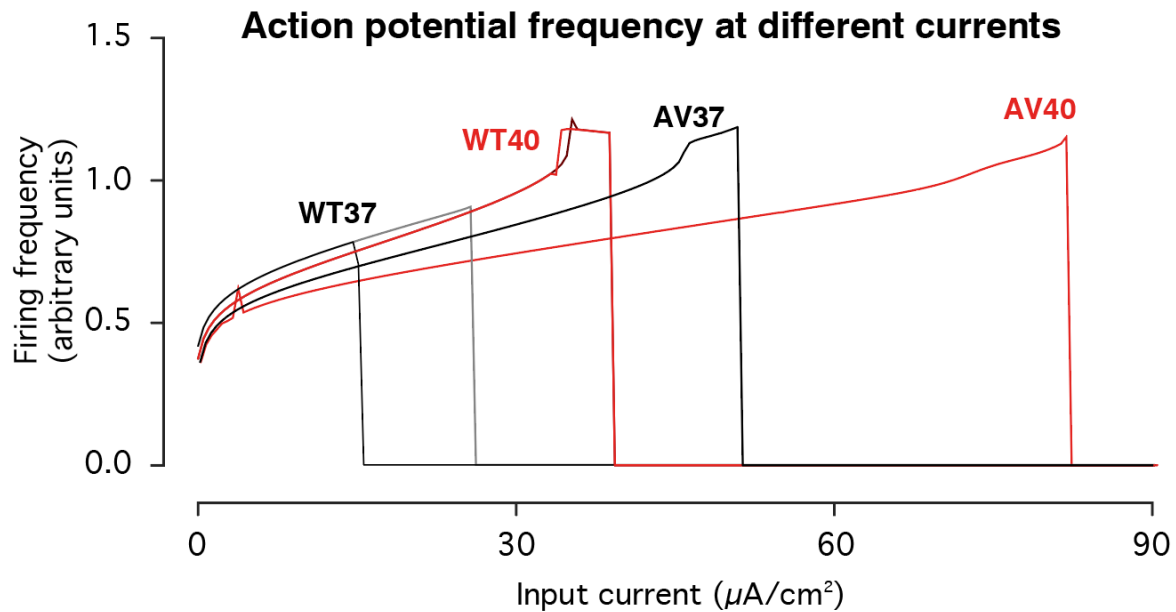
Supplementary Table S5:

	NaV1.1, WT, 37°C			NaV1.1, A1273V, 37°C		
	Mean	StErr	N	Mean	StErr	N
-10mV, F_{lon} τ (ms)	0.369	0.040	6	0.809	0.102	5
0mV, F_{lon} τ (ms)	0.249	0.024	6	0.429	0.017	5
10mV, F_{lon} τ (ms)	0.181	0.017	6	0.273	0.013	5
20mV, F_{lon} τ (ms)	0.188	0.022	6	0.209	0.017	5
30mV, F_{lon} τ (ms)	0.168	0.023	6	0.165	0.026	5
40mV, F_{lon} τ (ms)	0.134	0.010	5	0.158	0.033	5
	NaV1.1, WT, 40°C			NaV1.1, A1273V, 40°C		
-10mV, F_{lon} τ (ms)	0.494	0.100	7	0.686	0.117	9
0mV, F_{lon} τ (ms)	0.259	0.042	7	0.487	0.104	9
10mV, F_{lon} τ (ms)	0.170	0.026	7	0.245	0.037	9
20mV, F_{lon} τ (ms)	0.159	0.025	7	0.174	0.025	9
30mV, F_{lon} τ (ms)	0.127	0.016	7	0.150	0.014	9
40mV, F_{lon} τ (ms)	0.124	0.017	7	0.116	0.010	6

Source Data for Figure 3 C and D:

Decay of macroscopic currents were fit with a single exponential equation to measure the time constant of open state fast inactivation at a given membrane potential.

Supplementary Figure S1:



Modelled Action Potential Firing Frequency:

Action potential frequency is shown for the adapted Hodgkin-Huxley models for each of the four experimental conditions (i.e. wild type at 37°C [WT37] and 40°C [WT40], mutation at 37°C [AV37] and 40°C [AV40]). Modelling for all condition was performed in two directions (i.e. increasing, and decreasing values of stimulation currents), revealing hysteresis in the WT at 37°C only (grey – increasing stimulating currents; black – decreasing stimulating currents).

The plot shows the temperature-sensitive increase in stimulation tolerance across conditions. However, for any given stimulation current the predicted action potential frequency is lower for the low temperature vs high temperature conditions.