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BRIEF COMMUNICATION

Genetic interaction between *Scn8a* and potassium channel genes *Kcna1* and *Kcnq2*

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Abstract

Voltage-gated sodium and potassium channels regulate the initiation and termination of neuronal action potentials. Gain-of-function mutations of sodium channel *Scn8a* and loss-of-function mutations of potassium channels *Kcna1* and *Kcnq2* increase neuronal activity and lead to seizure disorders. We tested the hypothesis that reducing the expression of *Scn8a* would compensate for loss-of-function mutations of *Kcna1* or *Kcnq2*. *Scn8a* expression was reduced by the administration of an antisense oligonucleotide (ASO). This treatment lengthened the survival of the *Kcn1a* and *Kcnq2* mutants, and reduced the seizure frequency in the *Kcnq2* mutant mice. These observations suggest that reduction of *SCN8A* may be therapeutic for genetic epilepsies resulting from mutations in these potassium channel genes.

KEYWORDS

ASO, epilepsy, potassium channel, sodium channel, therapy

1 | INTRODUCTION

Sodium and potassium channels concentrated at the axon initial segment (AIS) regulate the generation of neuronal action potentials.[1,2] Action potentials are initiated by excitatory stimuli that activate voltage-gated sodium channels, permitting the influx of sodium ions.[2] Subsequent activation of voltage-gated potassium channels permits the exit of potassium ions and repolarizes the neuron.[2] Potassium channels encoded by *KCNQ2* and *KCNQ3* modulate the subthreshold changes in membrane potential that influence neuronal excitability.[3,4] In genetic epilepsies, elevated sodium channel activity or reduced potassium channel activity can result in excess neuronal firing.[5,6] Emerging genetic therapies for seizure disorders include the reduction of sodium channel expression[7] or

the elevation of potassium channel expression.[8,9] Here we test the hypothesis that reduced expression of an AIS-concentrated sodium channel can compensate for loss of potassium channel activity.

Loss-of-function mutations of the potassium channel gene *KCNQ2* are a major cause of developmental and epileptic encephalopathy (DEE),[3,4] and loss-of-function mutations of potassium channel *KCNA1* are responsible for episodic ataxia type 1 and rare cases of DEE.[6] We used an antisense oligonucleotide (ASO) to reduce the expression of the sodium channel gene *Scn8a* in mouse models of *Kcnq2* and *Kcna1* epilepsy. *Scn8a* transcripts were reduced to 50% of wild-type level by administration of the ASO. Transcript levels return to normal 6 weeks after a single injection.[7] Our observations suggest that specific reduction of *SCN8A* expression may be a useful therapy for disorders of these potassium channels.

2 | MATERIALS AND METHODS

2.1 | Mice

Kcnq2$^{fl/fl}$ mice[10] on strain C57BL/6J were provided by Dr. Anastasios Tzingounis, University of Connecticut. *Kcna1*$^{+/-}$ mice[11] on a mixed Black Swiss genetic background (Tac:N:NIHS-BC) were provided by Dr. Edward Glasscock, Southern Methodist University. Emx1-Cre mice on strain C57BL/6J were purchased from the Jackson Laboratory (Jax #005628). Both male and female mice were used for the experiments. Mice were housed and cared for in accordance with National Institutes of Health (NIH) guidelines in a 12/12-hour light/dark cycle with standard mouse chow and water available ad libitum. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Michigan.

2.2 | Antisense oligonucleotides

The 20 bp *Scn8a* gapmer ASO (5′ GACGA TTAGT GACAT AGGCT 3′), synthesized by Ionis Pharmaceuticals, is complementary to the 3′ UTR of the mouse *Scn8a* transcript.[7] The control ASO (5′ CCTAT AGGAC TATCC AGGAA 3′) does not match any mouse transcript and is well tolerated in vivo.[7] ASOs were diluted in phosphate-buffered saline (PBS) for injection. On postnatal day 2 (P2), mutant mice received 45 μg ASO in 2 μL by intracerebroventricular (ICV) injection into the left lateral ventricle. Adult mice were anesthetized with isoflurane and received 100 ug ASO in a 3 μL manual ICV injection into the left lateral ventricle without a guide cannula, as described.[12]

2.3 | Electroencephalography (EEG) recording

Screw electrodes were implanted in *Kcnq2*$^{fl/fl}$, *Emx1-Cre* mice at postnatal week 6 ($n = 2$) and in *Kcna1*$^{-/-}$ mice at postnatal week 20 ($n = 2$). For surgery, mice were anesthetized with isoflurane and placed in a stereotaxic adapter. Bilateral screw electrodes were placed in the skull at approximately anteroposterior (AP) = −2.1, mediolateral (ML) = +/−1.7 and a common reference electrode was placed over the cerebellum (approximately AP = −6.0, ML = 0). The electrodes were connected to a 6-pin electrode pedestal and the headcap was secured using dental cement. After 1 to 7 days of recovery, simultaneous EEG recording and video monitoring were performed with a Natus recording system continuously for a minimum of 24 h and a maximum of 14 days. Signals were acquired at 256 Hz. Data were filtered with a 70 Hz low-pass filter and 1 Hz high-pass filter. Seizures and interictal background were assessed manually by an experienced reader. Seizures were defined as a sudden burst of electrographic activity consisting of rhythmic spike-and-wave discharges lasting >10 s and evolving in frequency and amplitude. Interictal epileptiform discharges were not quantified.

2.4 | Phenotypes

Hindlimb clasping in *Kcnq2* mutant mice was video recorded at P21. Mice were suspended by the tail for 1 min on three consecutive days. Videos were analyzed frame by frame to quantify the percent of time spent in hindlimb clasping. Myoclonic jerks in *Kcna1* mice were counted during a 5 min observation period at 11 a.m. on three successive days by two independent observers blinded to genotype.

3 | RESULTS

3.1 | *Kcnq2* mutant mice

KCNQ2 encodes the AIS-localized potassium channel Kv7.2, which regulates sub-threshold neuronal excitability and resting membrane potential.[3,4] Loss-of-function mutations of human *KCNQ2* cause a spectrum of disorders ranging from benign familial neonatal seizures to DEE, and it is the second most common gene mutated in DEE.[3,4]

Deletion of *Kcnq2* in forebrain excitatory neurons in *Kcnq2*$^{fl/fl}$, *Emx1-Cre* mice results in neuronal hyperexcitability and spontaneous seizures, as seen in human *KCNQ2* disorders.[10] The seizures and premature death in

these mice provide a useful end point for therapeutic intervention. We treated *Kcnq2*$^{fl/fl}$, *Emx1-Cre* mice with 45 μg of *Scn8a* ASO or control ASO by ICV injection on P2 (Figure 1A). After treatment with control ASO ($n = 12$), the first death was observed at 3 weeks of age, and 50% lethality was reached by 8 weeks of age (Figure 1B,C). In mice receiving the *Scn8a* ASO, the first death was delayed to 11 weeks of age, and 50% lethality was not reached until 15 weeks. A second dose of 100 μg ASO at 8 weeks of age further delayed the age of 50% lethality to 19 weeks (Figure 1B,C). Overall, 65% to 75% of mice exhibited premature lethality in mice receiving the *Scn8a* ASO and the control ASO (chi-square test of proportions, $\chi^2 = 0.36$, $df = 2$, $p = 0.83$). Reduction of *Scn8a* expression thus extended the lifespan of mice with *Kcnq2* deficiency but did not prevent premature lethality.

The reported frequency of spontaneous seizures in untreated *Kcnq2*$^{fl/fl}$, *Emx1-Cre* mice was 40 seizures in 67 days of observation[10,13] After treatment with *Scn8a* ASO, we did not observe any seizures or abnormal EEG activity in 16 days of observation ($p < .0001$, χ^2 test) (Figure 1D). However, the treated mice continued to exhibit hunched posture, scruffy appearance, and hindlimb clasping (Figure 1E). Reduction of *Scn8a* expression thus prevents seizures and delays premature death but does not correct other neurological phenotypes in *Kcnq2* mutant mice. Postnatal growth of *Kcnq2*$^{fl/fl}$, *Emx1-Cre* mice did not differ from wild-type littermates.

3.2 | *Kcna1* mutant mice

KCNA1 encodes Kv1.1, an inward rectifier potassium channel concentrated at the AIS.[6] Heterozygous loss-of-function mutations of *KCNA1* cause severe epilepsy and episodic ataxia type 1 that can be accompanied by seizures.[6] Homozygous *Kcna1*$^{-/-}$ null mice are a model of sudden unexpected death in epilepsy (SUDEP).[11]

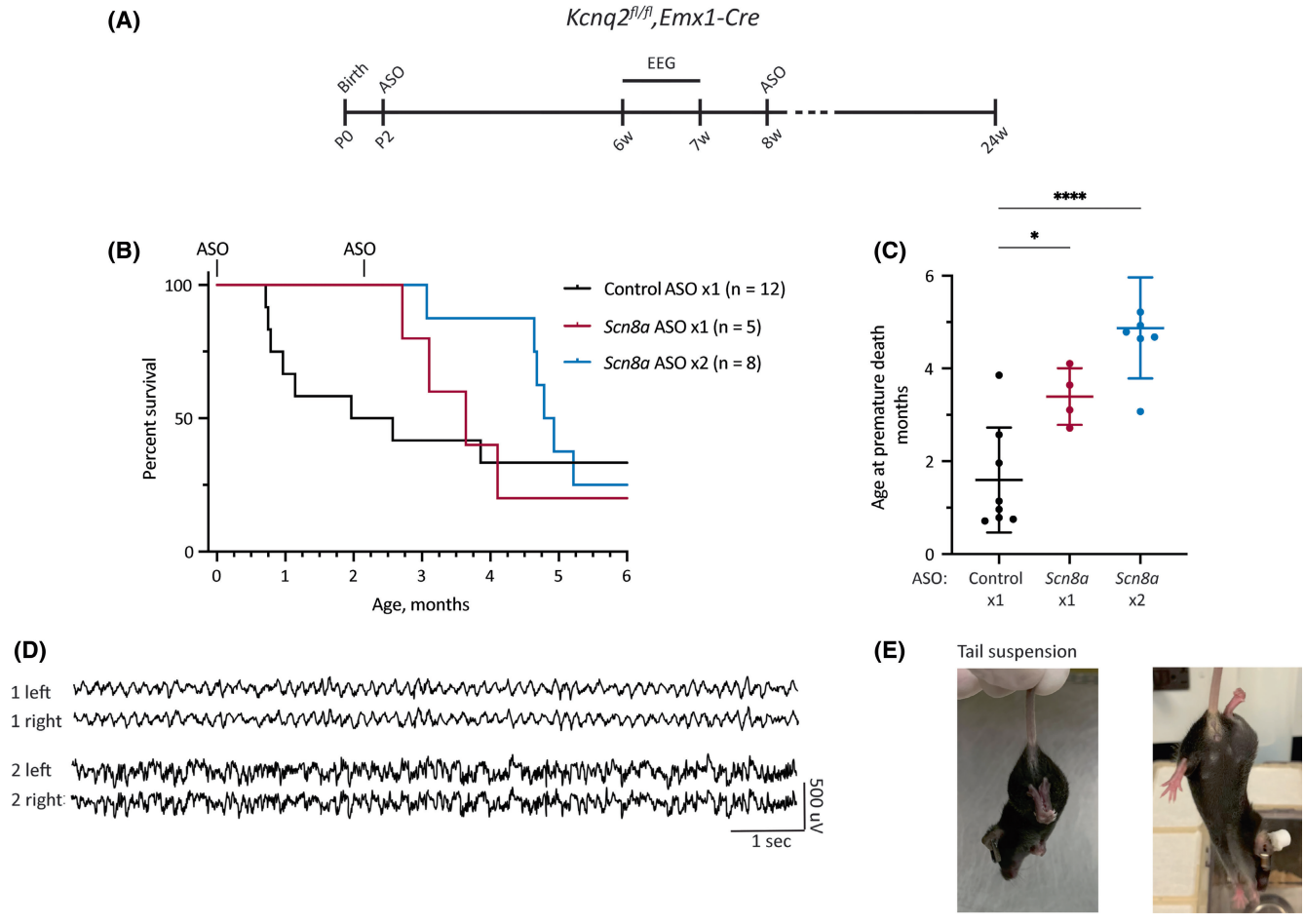


FIGURE 1 An antisense oligonucleotide (ASO) to *Scn8a* prolongs the survival of *Kcnq2* mutant mice. (A) Timeline for treatment. (B and C) *Kcnq2*$^{fl/fl}$, *Emx1*$^{Cre/+}$ mice treated with *Scn8a* ASO survive longer than mice treated with control ASO. A second treatment prolonged the effect. Asterisks indicate significance of Bonferroni's multiple comparisons test: *$p < .05$; ****$p < .0001$. (D) Sample electroencephalography (EEG) recordings demonstrating normal EEG background in two mutant mice. (E) Two abnormal hindlimb postures in *Kcnq2*$^{fl/fl}$, *Emx1*$^{Cre/+}$ mice after treatment with *Scn8a* ASO at postnatal day 2 (P2).

Kcna1$^{-/-}$ mice were treated with 45 μg *Scn8a* ASO or control ASO by ICV injection at P2 (Figure 2A). Mice that received control ASO at P2 ($n = 10$) died between 2 and 6 weeks of age with 50% lethality by 1 month of age (Figure 2B,C). A single dose of *Scn8a* ASO extended median lifespan to 3 months ($n = 9$) (Figure 2B,C). To evaluate repeated treatments, additional doses of 100 μg ASO were administered at monthly intervals between 1 and 4 months of age (Figure 2A). The repeated treatments delayed the earliest death to 13 weeks ($n = 9$), with <50% lethality at 6 months of age (Figure 2B,C). The penetrance of premature lethality was reduced from 70% (control ASO) to 20% (*Scn8a* ASO) (chi-square test of proportions, $\chi^2 = 5.05$, $df = 2$, $p = .025$).

Spontaneous seizures in untreated *Kcna1*$^{-/-}$ mice were reported to begin at 3 weeks of age[11] and occur 5–20 times per day.[11,14] We implanted electrodes at 20 weeks of age in *Kcna1* null mice that had been treated with five doses of ASO starting on P2 (Figure 2A). Electrographic and electroclinical seizures were detected with an average frequency of 13 seizures per day (Figure 2D).

Kcna1$^{-/-}$ mice also exhibit hunched posture, scruffy appearance, and impaired growth that was not corrected by the ASO (Figure 2E). *Kcna1*$^{-/-}$ mice exhibit myoclonic jerks that were not corrected by ASO treatment (Figure 2F). Thus reduction of *Scn8a* expression prolonged survival of *Kcna1*$^{-/-}$ mice but did not completely rescue the neurological abnormalities.

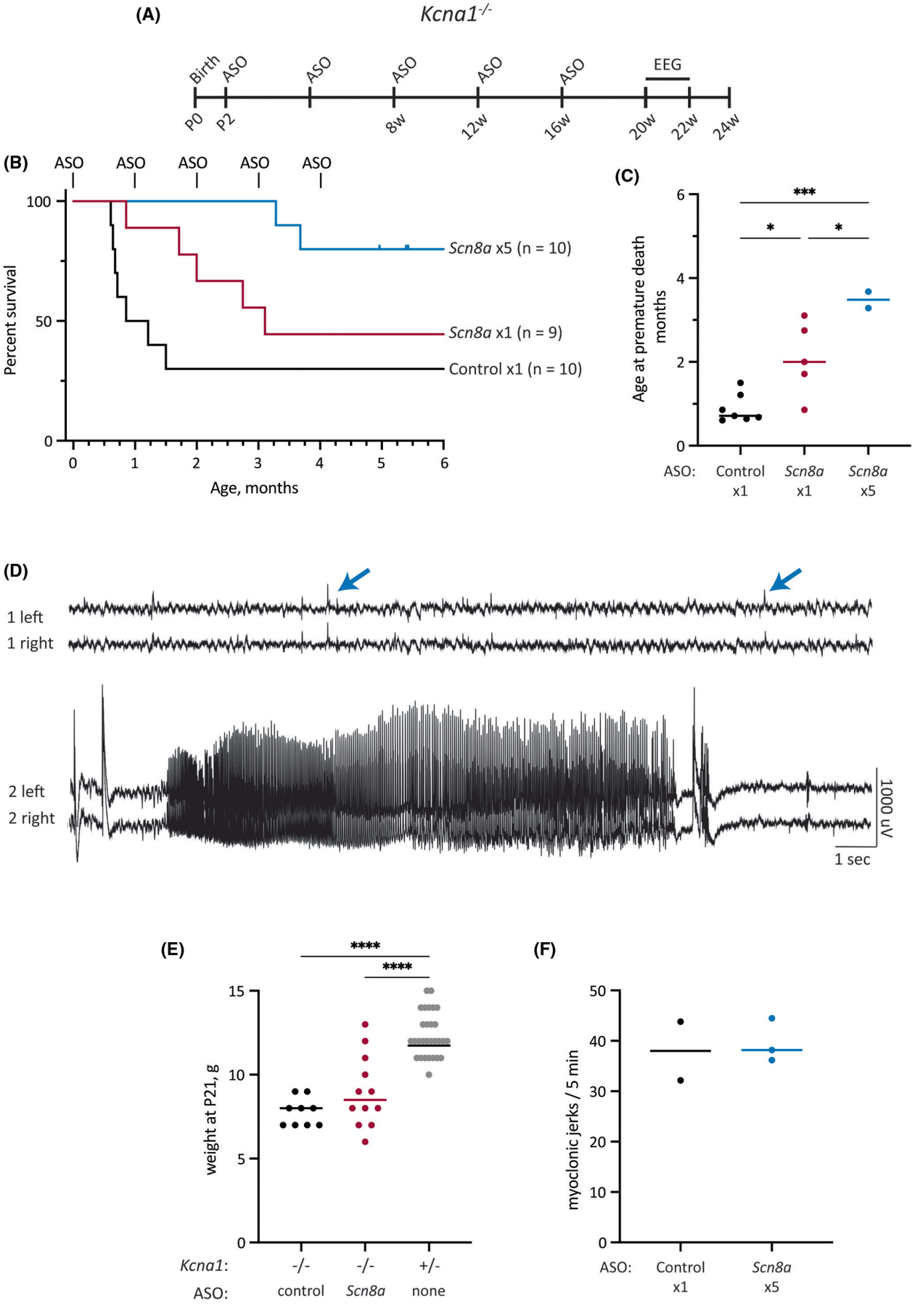
4 | DISCUSSION

Reduction of *Scn8a* expression had therapeutic benefits in two models of epilepsy caused by mutation of potassium channels localized at the AIS. *KCNQ2* is one of the most commonly mutated genes in childhood-onset epilepsy.[3,4] Reduced *Scn8a* extended the lifespan of *Kcnq2* mutant mice by 11 weeks and restored normal EEG activity but did not eliminate other neurological abnormalities. In the *Kcn1a* null mice, reduction of *Scn8a* expression significantly prolonged lifespan. The positive effect of reducing *Scn8a* is consistent with the therapeutic effectiveness of sodium channel blockers in some individuals with *KCNQ2* mutations[3] and in improving the symptoms of episodic ataxia in many individuals with null mutations of *KCNA1*.[15] $Na_v1.6$ is a major source of persistent current in mammalian brain, and reduction of persistent current led to reduced seizures in an in silico model of Kv1 deficiency.[16] In *Kcnq2* null neurons, pharmacological block of $Na_v1.6$ restored firing, leading to the prediction that Nav1.6 could be a therapeutic target in *KCNQ2* epilepsy.[17] The effectiveness of the *Scn8a* ASO demonstrates that the specific reduction of $Na_v1.6$ without changes in other sodium channels can be therapeutic for potassium channel deficiency.

Our results add to a growing body of evidence demonstrating genetic interactions between genes encoding ion channels.[5,18] The calcium channel genes *Cacna1a* and *Cacna1g* have been identified as modifiers of *Kcna1* epilepsy[19] and Dravet syndrome.[20] Quantitative variation in the γ-aminobutyric acid (GABA) receptor subunit *Gabra2* modifies the severity of *Scn8a* epilepsy and Dravet syndrome.[5] The current work demonstrates that quantitative variation in *Scn8a* modifies the severity of *Kcna1* and *Kcnq2* epilepsy in mouse models. *Scn8a* is also a modifier of Dravet syndrome.[7] *Scn2a* modifies the severity of *Kcna1*[21] and *Kcnq2* epilepsy.[22] In a human pedigree, an allelic variant of *SCN1A* was recently found to modify the severity of a null allele.[23] Neuronal excitability is evidently influenced by overall ion channel composition, and compensatory modulation of channel genes can restore the balance of excitation and inhibition that is disrupted in epilepsy.

The effects of *Scn8a* modulation shown here suggest that specific reduction of *Scn8a* might replace nonspecific sodium channel blockers in treating epilepsies caused by *KCNQ2* and *KCNA1*. In contrast to heterozygous affected patients, the mouse models studied here were homozygous for the potassium channel deficits, and the *Kcnq2* deficiency was expressed only in forebrain excitatory neurons. The side effects associated with non-specific sodium channel blockers are likely to be reduced by the specific reduction of *SCN8A*, for example with an Nav1.6-specific drug such as NBI-921352,[24] which is currently in phase 1 clinical trial for treatment of patients with gain-of-function mutations of *Scn8a* (https://clinicaltrials.gov/ct2/show/NCT03467100). Genetic therapies targeting *Scn8a* such as viral delivery of shRNA or CRISPR/Cas9 knockdown may also be applicable to the potassium channel disorders.

FIGURE 2 *Scn8a* antisense nucleotide (ASO) prolongs survival of *Kcna1* mutant mice. (A) Timeline for treatment. (B and C) *Kcna1*$^{-/-}$ mice treated with *Scn8a* ASO survive longer than mice treated with control ASO. Asterisks indicate significance of Bonferroni's multiple comparisons test: *$p < .05$; ***$p < .0005$. (D) Electroencephalography (EEG) recordings showing abnormal interictal discharges (arrows) and electrographic seizure. (E) *Scn8a* ASO does not correct the growth deficit in *Kcna1*$^{-/-}$ mice. (F) *Scn8a* ASO does not prevent myoclonic jerks in *Kcna1*$^{-/-}$ mice.


(A)
Kcna1-/-
Birth
ASO
ASO
ASO
ASO
ASO
EEG
P0
P2
8w
12w
16w
20w
22w
24w
(B)
ASO
ASO
ASO
ASO
ASO
Percent survival
100
50
0
Scn8a x5 (n = 10)
Scn8a x1 (n = 9)
Control x1 (n = 10)
0
1
2
3
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5
6
Age, months
(C)
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Age at premature death months
6
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ASO:
Control x1
Scn8a x1
Scn8a x5
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1 left
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Kcna1:
ASO:
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Scn8a
+/-
none
(F)
myoclonic jerks / 5 min
50
40
30
20
10
0
ASO:
Control x1
Scn8a x5

AUTHOR CONTRIBUTIONS

S.H., M.M., P.J-N., and F.R. contributed to the conception and design of the study; S.H. and J.Z. contributed to the acquisition and analysis of the data; S.H. and J.Z. contributed to the preparation of figures; S.H. and M.M. drafted the manuscript.

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CONFLICT OF INTEREST

P.J-N. and F. R. are employed by Ionis Pharmaceuticals, a for-profit company that develops antisense oligonucleotide (ASO) therapies. The remaining authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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