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Sex-specific alterations of Purkinje cell firing in *Sgce* knockout mice and correlations with myoclonus

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Myoclonus is a hyperkinetic movement disorder characterized by sudden, brief, involuntary jerks of single or multiple muscles. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Myoclonus-dystonia (M-D) or DYT11 dystonia is an early-onset genetic disorder characterized by subcortical myoclonus and less pronounced dystonia. DYT11 dystonia is the primary genetic M-D caused by loss of function mutations in *SGCE*, which codes for ϵ -sarcoglycan. *Sgce* knockout (KO) mice model DYT11 dystonia and exhibit myoclonus, motor deficits, and psychiatric-like behaviors. Neuroimaging studies show abnormal cerebellar activity in DYT11 dystonia patients. Acute small hairpin RNA (shRNA) knockdown of *Sgce* mRNA in the adult cerebellum leads to motor deficits, myoclonic-like jerky movements, and altered Purkinje cell firing. Whether *Sgce* KO mice show similar abnormal Purkinje cell firing as the acute shRNA knockdown mice is unknown. We used acute cerebellar slice recording in *Sgce* KO mice to address this issue. The Purkinje cells from *Sgce* KO mice showed spontaneous and intrinsic excitability changes compared to the wild-type (WT) mice. Intrinsic membrane properties were not altered. The female *Sgce* KO mice had more profound alterations in Purkinje cell firing than males, which may correspond to the early onset of the symptoms in female human patients and more pronounced myoclonus in female KO mice. Our results suggest that the abnormal Purkinje cell firing in the *Sgce* KO mice contributes to the manifestation of the myoclonus and other motor symptoms in DYT11 dystonia patients.

KEYWORDS

Purkinje cells, dystonia, *SGCE*, DYT11, electrophysiology

Introduction

DYT11 dystonia is a major type of genetic M-D and is caused by mutations in *SGCE*, which codes for ϵ -sarcoglycan [1]. Many mutations in *SGCE*, such as nonsense, missense, and frameshift mutations, have been reported in M-D patients, suggesting that the loss of ϵ -sarcoglycan function causes DYT11 dystonia [2, 3]. The primary symptom of DYT11 dystonia is myoclonus; however, dystonia and psychiatric symptoms, such as depression, panic, and obsessive-compulsive disorder, have been reported in some patients [1, 4]. Interestingly, alcohol consumption in some patients can provide temporal relief of the symptoms [3, 5]. Treatment has been focused on symptom relief using various drugs and deep brain stimulation with limited success [2, 6]. Female individuals outnumber male individuals for both adult-onset idiopathic and early-onset monogenic dystonias [7]. The average age of onset for female DYT11 patients is 5 years versus 8 years for male patients [8].

Animal models are helpful to investigate the pathophysiology of genetic diseases and contribute to developing better treatments. Multiple mouse lines have been generated and characterized to model DYT11 dystonia [9–15]. *Sgce* is the mouse homolog of the human *SGCE* gene. *Sgce* is maternally imprinted and paternally expressed [11, 16, 17]. We generated paternally-inherited *Sgce* heterozygous KO mice lacking exon four and analyzed their behavioral and neurochemical phenotypes [11, 15, 18]. The *Sgce* KO mice, on average, exhibit 28 times more myoclonus than WT littermates and have deficits in motor learning, anxiety, depression-like behaviors, and fine motor coordination and balance. Furthermore, we found that the striatal dopaminergic system is impaired in the *Sgce* KO mice. The levels of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid; HVA) in the striatum of *Sgce* KO mice are significantly higher than those of wild-type (WT) mice [15]. *Sgce* KO mice exhibit a significantly low level of striatal dopamine receptor 2 (D2R) and a significant increase in dopamine release after amphetamine injection in comparison to WT littermates [18]. Finally, striatal medium spiny neurons and cerebellar Purkinje cells show abnormal nuclear envelopes in *Sgce* KO mice [9, 10].

Cerebellar circuits, especially Purkinje cells, are central players in movement and posture control, and there are multiple lines of investigations implicating their involvement in DYT11 dystonia pathogenesis [19–24]. Several brain imaging studies show the involvement of the cerebellum in

DYT11 patients [25–32]. DYT11 patients possess abnormal responses to cerebellar eye-blink classic conditioning [33, 34], which can be normalized by alcohol intake. Furthermore, DYT11 patients perform abnormally in a cerebellar saccadic adaptation task [35] but not in a limb adaptation task involving symptomatic body regions [36]. However, Purkinje cell-specific *Sgce* KO mice exhibit motor learning deficits but no myoclonus [10]. This suggests that *Sgce* KO in other cells inside and outside the cerebellum is needed to produce the myoclonus in mice. Interestingly, small hairpin RNA (shRNA) knockdown of *Sgce* mRNA in the adult cerebellum, but not basal ganglia, leads to motor deficits, spinning, and myoclonic-like jerky movements, which can be reduced by alcohol consumption. Moreover, the awake, head-restrained shRNA-treated mice show aberrant firing of Purkinje cells and deep cerebellar nuclei neurons *in vivo* [37]. The abnormal function of cerebellar circuits is likely involved in the pathogenesis of DYT11 dystonia. However, whether the *Sgce* KO mice, which have the *Sgce* gene inactivated constitutively throughout the lifespan, show similar aberrant Purkinje cell firing is unknown. Here, the Purkinje cells in the *Sgce* KO mice were characterized by electrophysiological recording of acute brain slices. The spontaneous firing, intrinsic excitability, and membrane properties of Purkinje cells were examined and compared to their myoclonus behavior published earlier [15].

Materials and methods

Animals

All experiments complied with the United States Public Health Service Guide for Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committees of the University of Florida. As described previously, *Sgce* KO mice and their WT littermates were prepared and genotyped by PCR [15]. Mice were housed under a 12-hour light and 12-hour dark cycle with *ad libitum* access to food and water. All experiments and initial data analysis were performed by investigators blind to the genotypes. This study followed the recommended heterogenization of study samples of various ages, and the data were analyzed with age as a covariate [38].

Brain slice electrophysiology

We used male and female mice to investigate the effects of sex on the phenotype. As described previously [39–43], electrophysiological recordings data for spontaneous firing, intrinsic excitability, and membrane properties of 105 Purkinje cells were obtained from 10 WT mice (5 males and 5 females) and 6 *Sgce* KO littermates (3 males and 3 females) at 80–165 days old. Briefly, the cell-attached recordings of

Abbreviations: CV: coefficient of variation; KO: knockout; M-D: Myoclonus-dystonia; PCR: polymerase chain reaction; RMP: resting membrane potential; SEM: standard error of the mean; *SGCE*: human gene codes for ϵ -sarcoglycan; *Sgce*: mouse gene codes for ϵ -sarcoglycan; shRNA: small hairpin RNA; WT: wild-type.

Purkinje cells were performed in the parasagittal 300 μm -thick cerebellar brain slices. After recording the spontaneous firing, whole-cell recordings were made by breaking through the membrane. Tonic Purkinje cells fire relatively constantly, while non-tonic Purkinje cells fire intermittently, with pauses separating the firing periods [44]. We define tonic Purkinje cells as those cells without pause of the spontaneous firing lasting for more than 300 msec during the cell-attached recording [45] and otherwise as non-tonic cells [40]. The intrinsic properties (resting membrane potential, capacitance, membrane resistance, and time constant) were measured in the whole-cell recording mode. Finally, current steps were injected to determine intrinsic excitability.

Myoclonus

The myoclonus data from 17 KO (9 males and 8 females) and 22 WT littermates (11 males and 11 females), 210–241 days old, were published previously [15]. The data were reanalyzed here to determine the effect of sex on the number of myoclonus.

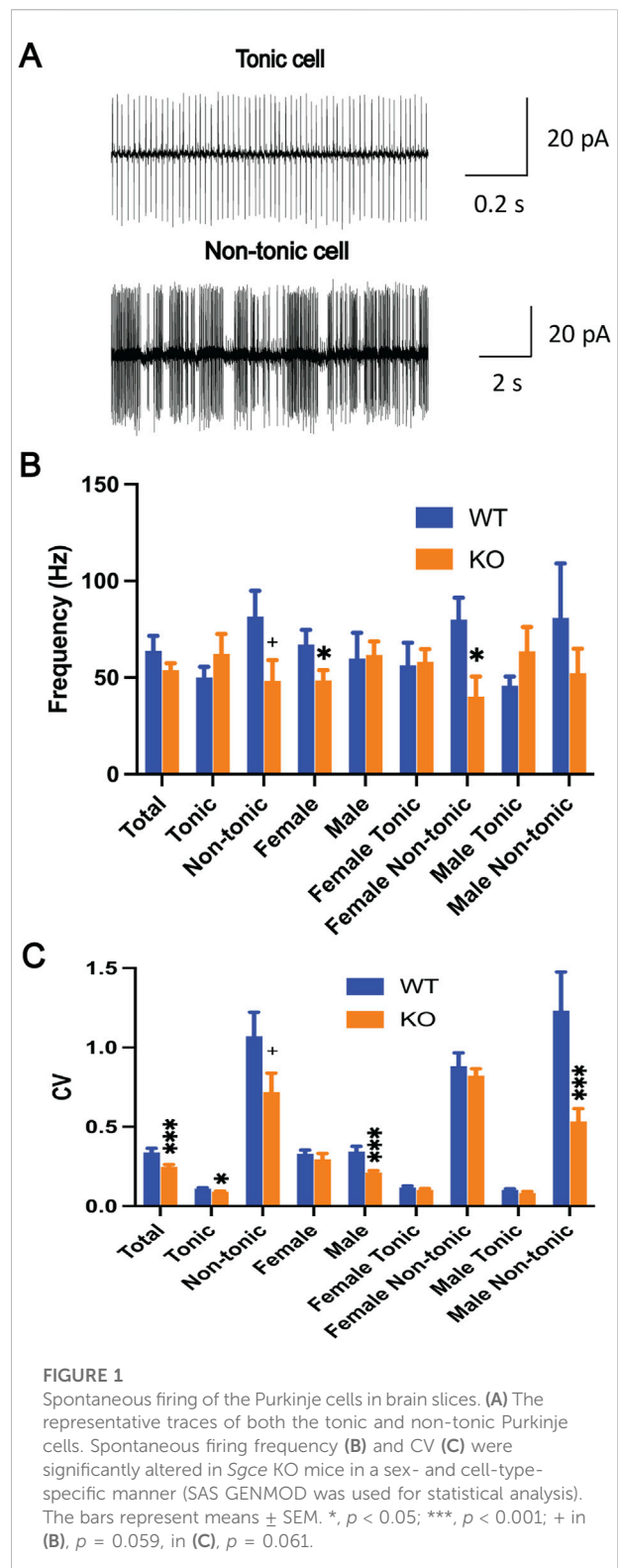
Statistics

Data were tested for normality first using the univariate procedure of the SAS statistical package. A generalized linear model (GENMOD) was used to compare the spontaneous firing, intrinsic excitability, membrane properties, and myoclonus. Age and body weight were used as continuous variables, and data from each cell were nested within individual animals and treated as repeated measurements. A negative binomial distribution was used for count data, i.e., the number of action potentials in the current injection and myoclonus. A gamma distribution was used for data that was not normally distributed. For tonic/non-tonic cell distribution analysis, chi-square was used. Significance was assigned at $p < 0.05$. A p -value between 0.05 and 0.1 was considered a trend. Data in the text are presented as “mean \pm standard error of the mean (SEM)” unless specified otherwise.

Results

Altered spontaneous firing frequency and coefficient of variation (CV) of the Purkinje cells in *Sgce* KO mice

Cerebellar Purkinje cells are the sole output of the cerebellar cortex, projecting into the deep cerebellar nuclei, which are the sole output of the cerebellum. They play an essential role in cerebellar function. The Purkinje cells in the *Sgce* KO mice were characterized by acute brain slice recording to understand their role in the pathogenesis of DYT11 dystonia. The spontaneous



firing of the Purkinje cells (WT, 59 cells/10 mice; KO, 45 cells/6 mice) was recorded by cell-attached recording mode with a voltage clamp. The representative traces of the Purkinje cells are

TABLE 1 Intrinsic properties of Purkinje cells.

	RMP (mV)	Capacitance (pF)	MR (MΩ)	Time constant (ms)
WT	-61.2 ± 0.6	97.8 ± 7.2	46.6 ± 12.8	1.39 ± 0.05
KO	-59.9 ± 0.6	108.0 ± 6.4	46.1 ± 7.8	1.68 ± 0.15
Z value	-1.70	-1.07	0.03	-1.94
P	0.09	0.29	0.98	0.053
WT ♂	-61.5 ± 1.1	99.8 ± 9.5	39.5 ± 8.7	1.40 ± 0.07
KO ♂	-59.9 ± 0.7	96.5 ± 10.3	44.4 ± 16.6	1.49 ± 0.11
Z value	-1.23	0.23	-0.27	-0.72
P	0.22	0.82	0.79	0.47
WT ♀	-61.1 ± 0.3	100.4 ± 10.5	52.7 ± 22.2	1.38 ± 0.07
KO ♀	-59.8 ± 0.9	113.3 ± 4.5	48.0 ± 7.3	1.82 ± 0.25
Z value	-1.35	-1.05	0.21	-1.92
p	0.18	0.29	0.83	0.054

RMP, resting membrane potential; MR, membrane resistance.

shown in Figure 1A. Although the firing frequency (WT, 63.8 ± 7.7 Hz; KO, 53.8 ± 3.6; $p = 0.22$, Figure 1B) was not altered, the CV (WT, 0.338 ± 0.026; KO, 0.249 ± 0.013; $p = 0.0009$; Figure 1C) was significantly decreased in *Sgce* KO mice compared to WT mice. CV is an indication of firing regularity. A decreased CV suggests increased firing regularity. Purkinje cells can be grouped into tonic and non-tonic types [40, 43, 45]. When analyzed separately by the cell types, tonic cells showed no change in the frequency (WT, 35 cells/10 mice, 50.1 ± 5.5 Hz; KO, 22 cells/6 mice, 62.3 ± 10.2; $p = 0.27$, Figure 1B) but a significant decrease in CV (WT, 0.110 ± 0.005; KO, 0.090 ± 0.007; $p = 0.026$; Figure 1C), while non-tonic cells showed decreases both in the frequency (WT, 24 cells/10 mice, 81.5 ± 13.4 Hz; KO, 23 cells/6 mice, 48.3 ± 10.7; $p = 0.059$, Figure 1B) and CV (WT, 1.071 ± 0.151; KO, 0.720 ± 0.118; $p = 0.061$; Figure 1C). When separated by sex, female Purkinje cells showed a significant decrease in the frequency (WT, 27 cells/5 mice, 67.2 ± 7.5 Hz; KO, 20 cells/3 mice, 48.6 ± 5.2; $p = 0.036$, Figure 1B) but no change in CV (WT, 0.330 ± 0.024; KO, 0.295 ± 0.037; $p = 0.43$; Figure 1C), while male Purkinje cells showed no change in the frequency (WT, 32 cells/5 mice, 59.8 ± 13.4 Hz; KO, 25 cells/3 mice, 61.7 ± 7.0; $p = 0.90$, Figure 1B) but a significant decrease of CV (WT, 0.344 ± 0.033; KO, 0.212 ± 0.010; $p < 0.001$; Figure 1C). When separated by both sex and cell type, there were significant decreases in frequency of female non-tonic Purkinje cells (WT, 12 cells/5 mice, 80.0 ± 11.3 Hz; KO, 13 cells/3 mice, 40.1 ± 10.5; $p = 0.02$, Figure 1B) and in CV of male non-tonic Purkinje cells (WT, 12 cells/5 mice 1.232 ± 0.244; KO, 10 cells/3 mice, 0.534 ± 0.081; $p = 0.0008$; Figure 1C), while the frequency and CV of the rest remained unchanged (Figures 1B, C).

Finally, the relative ratio of the tonic and non-tonic cells was analyzed, and there was no significant difference between the WT and *Sgce* KO mice (WT: tonic = 35, non-tonic = 24; KO: tonic = 22, non-tonic = 23, $p = 0.29$). Overall, *Sgce* KO mice had normal cell type distribution and sex-specific alteration of spontaneous firing of Purkinje cells both in frequency and CV, especially in the non-tonic cell types.

Altered intrinsic excitability of the Purkinje cells in *Sgce* KO mice

After recording the spontaneous firing by cell-attached mode, the intrinsic membrane properties were measured in whole-cell recording mode. The resting membrane property of the Purkinje cells was determined from 10 WT (56 cells) and 6 *Sgce* KO mice (46 cells). There was no significant difference in the membrane capacitance, membrane resistance, and resting membrane potential (RMP) between the WT and *Sgce* KO mice (Table 1). However, the *Sgce* KO mice showed increased membrane constants compared to the WT mice ($p = 0.053$), largely derived from females ($p = 0.054$). Male and female mice did not differ in the other 3 parameters (Table 1).

The intrinsic excitability of the Purkinje cells in the brain slices was measured with current step injections. The recorded neurons showed typical electrophysiological responses of the Purkinje cells (Figure 2A). The number of action potentials fired overall (WT, 56 cells/10 mice, 32.9 ± 2.1; KO, 46 cells/6 mice, 31.7 ± 1.8; $p = 0.67$, Figure 2B) and at each current step (Figure 2C) were similar between WT and *Sgce* KO mice. When analyzed separately by sex, female Purkinje cells showed a

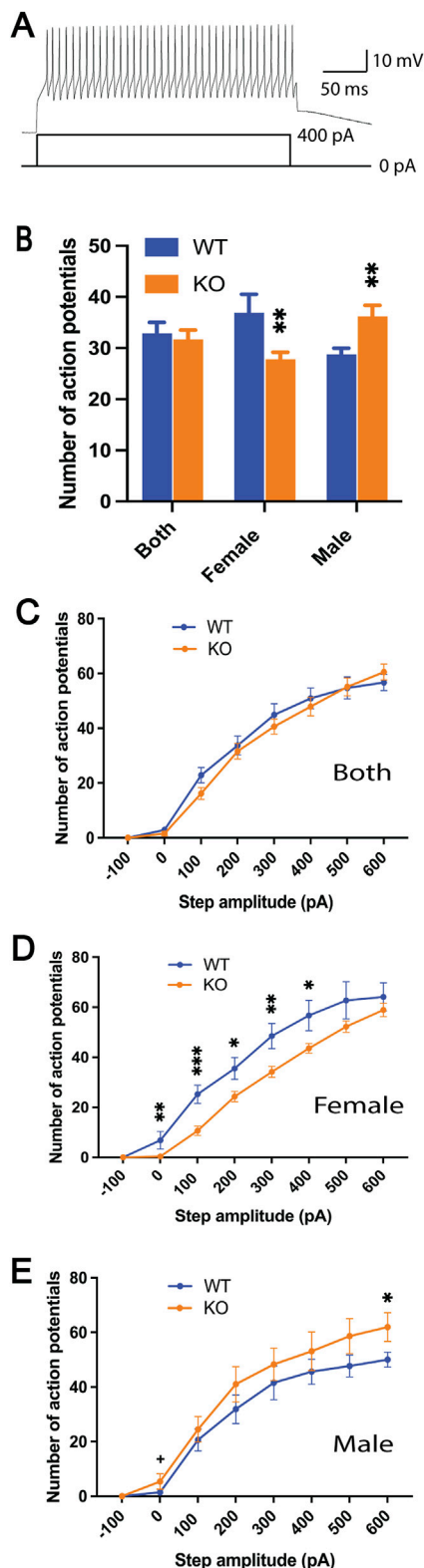


FIGURE 2
Intrinsic excitability of Purkinje cells as measured by current steps in the brain slices. Representative trace of the action (Continued)

FIGURE 2 (Continued)

potential firing in response to the current injection (A). The number of action potentials of all eight steps combined (B) and at each current step (C–E) were significantly altered in *Sgce* KO mice in a sex-specific manner (SAS GENMOD was used for statistical analysis). Means ± SEM were plotted. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

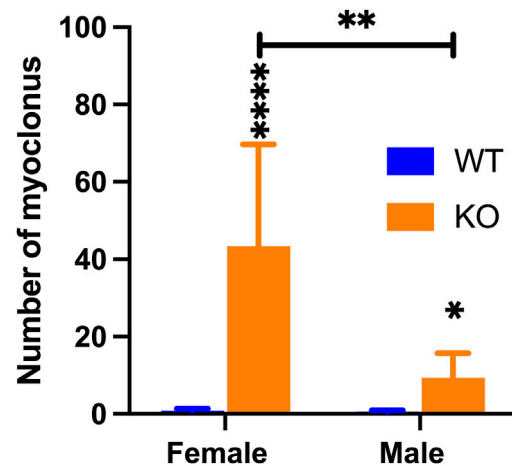


FIGURE 3

Comparison of the numbers of myoclonus in male and female WT and *Sgce* KO mice. While WT males and females did not differ, female *Sgce* KO mice showed 4 times more myoclonus than male *Sgce* KO mice (SAS GENMOD was used for statistical analysis). Means ± SEM were plotted. *, $p < 0.05$; **, $p < 0.01$; ****, $p < 0.0001$.

significant decrease in the number of action potentials (WT, 30 cells/5 mice, 36.9 ± 3.6 ; KO, 24 cells/3 mice, 27.8 ± 1.4 ; $p = 0.0096$, Figure 2B), while male Purkinje cells showed a significant increase (WT, 26 cells/5 mice, 28.8 ± 1.2 ; KO, 22 cells/3 mice, 36.2 ± 2.2 ; $p = 0.0019$, Figure 2B). When separated by both sex and current steps, there were significant decreases in the number of action potentials from steps 2 to 6 in the female KO mice compared to the WT mice (Figure 2D). In contrast, the male KO mice had a significant increase at the 8th step and a potential increase at the 2nd step (Figure 2E). These results suggest that the intrinsic excitability of the Purkinje cells is altered in the *Sgce* KO mice in a sex-specific manner.

Increased myoclonus in *Sgce* KO mice and sex difference

We previously reported that *Sgce* KO mice, on average, exhibit 28 times more myoclonus than WT littermates [15]. Here, we reanalyzed the data separately by each sex or genotype. Both male and female *Sgce* KO mice showed significantly

increased numbers of myoclonus compared to the WT mice (Females: WT, $n = 11$, 0.8 ± 0.5 ; KO, $n = 8$, 43.4 ± 26.3 ; $p = <0.0001$; Males: WT, $n = 11$, 0.5 ± 0.4 ; KO, $n = 9$, 9.4 ± 6.3 ; $p = 0.014$, Figure 3). While WT males and females showed no difference ($p = 0.29$), the KO females showed four times more myoclonus compared to the KO males ($p = 0.0048$), suggesting female KO mice have a more pronounced myoclonus phenotype compared to male KO mice.

Discussion

We aimed to determine whether there was abnormal Purkinje cell firing in the *Sgce* KO mice, a model for DYT11 dystonia or M-D. For spontaneous firing, the *Sgce* KO mice showed a significantly decreased CV and no change in the frequency. Interestingly, the female *Sgce* KO mice showed significantly decreased frequency, especially in non-tonic cells, while male *Sgce* KO mice had significantly decreased CV, derived mainly from non-tonic cells. For intrinsic excitability, female *Sgce* KO mice showed a significant decrease, consistent with their decreased spontaneous firing frequency. In contrast, male *Sgce* KO mice showed a modest increase that did not lead to increased spontaneous firing. Membrane properties remained unchanged except for the membrane constant, which showed an increasing trend in females. Female *Sgce* KO mice showed profound electrophysiological changes in the Purkinje cells compared to male *Sgce* KO mice. To correlate myoclonus behavior with sex-dependent changes in Purkinje cell firing, we reanalyzed the myoclonus data we published previously [15]. The female *Sgce* KO mice showed four times more myoclonus than male *Sgce* KO mice. These results suggest that the abnormal Purkinje cell firing in the *Sgce* KO mice contributes to myoclonus phenotype.

Our results expand the existing research on Purkinje cell firing in DYT11 dystonia from the shRNA-mediated knockdown [37]. The *Sgce* knockdown mice show a reduced firing rate similar to *Sgce* KO female mice and an increased CV opposite to the *Sgce* KO mice. It should be noted that the reported *Sgce* knockdown mice data are from *in vivo* recordings, and we used brain slice recording with both GABAergic and glutamatergic transmission blocked. Furthermore, shRNA knockdown is introduced in adult mice, while the *Sgce* gene was inactivated constitutively throughout the animals' lifespan in *Sgce* KO mice. These differences could contribute to the discrepancy. Although the knockdown experiments used both males and females, the effect of sex on the Purkinje cell firing property was not investigated. Furthermore, we compared tonic and non-tonic cells in the current study, which is lacking in the study of *Sgce* knockdown mice. We extended their results by showing that female non-tonic Purkinje cells showed decreased firing frequency, likely due to decreased intrinsic excitability, and male non-tonic Purkinje cells showed a reduced CV.

Our results showed sex-specific alternations in Purkinje cell firing in the *Sgce* KO mice. Female *Sgce* KO mice showed greater changes than male *Sgce* KO mice. Interestingly, reanalysis of the myoclonus data showed a similar differential change in the myoclonus data. Female *Sgce* KO mice showed 4 times more myoclonus than male *Sgce* KO mice. This is consistent with the finding that the average age of onset for female DYT11 patients is 5 years versus 8 years for male patients [8] and other dystonia patient databases in general [7].

Past studies have shown that the cerebellum is critically involved in DYT11 dystonia pathogenesis [19–23]. This is further supported by brain imaging studies in DYT11 patients [25–32]. DYT11 patients show abnormal responses to cerebellar eye-blink classic conditioning [33, 34] and perform abnormally in a cerebellar saccadic adaptation task [35]. shRNA knockdown of *Sgce* mRNA in the cerebellum leads to motor deficits, spinning, and myoclonic-like jerky movements [37]. Our results here further support a direct role of cerebellum involvement. However, Purkinje cell-specific *Sgce* KO mice have no myoclonus phenotype and only exhibit motor learning deficits [10]. This suggests that myoclonus may not originate from the cerebellum but downstream of the brain network, which leads to the pathogenesis of DYT11 dystonia.

What might be the upstream brain network abnormality that drives Purkinje cell abnormality and myoclonus in DYT11 dystonia? The basal ganglia and the cerebellum are interconnected at the subcortical level with disynaptic pathways. The subthalamic nucleus in the basal ganglia connects to the cerebellar cortex via pontine nuclei [46]. We previously conditionally knocked out *Sgce* in the striatal medium spiny neurons using *RGS9-cre* mice [47, 48], and the mutant mice failed to exhibit the myoclonus phenotype [9], suggesting striatum may not be the origin. Future studies should analyze the conditional *Sgce* KO mice restricted to the cerebral cortex, dopaminergic neurons, and striatal cholinergic neurons, to determine the origin of myoclonus generation in DYT11 dystonia.

There are limitations associated with the current study. We used glutamatergic and GABAergic antagonists to block synaptic transmission in brain slice recording. Synaptic inputs to Purkinje cells were not measured and compared. Furthermore, we did not investigate whether altered Purkinje cell firing leads to any physiological changes elsewhere. Finally, although profound Purkinje cell firing changes in female *Sgce* KO mice correlate with their more pronounced myoclonus phenotype, correlation does not mean causation. Further direct experimental manipulations are needed to demonstrate the relationship.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by the Institutional Animal Care and Use Committees of the University of Florida. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

HX, PG, and FY conducted the experiments, and HX and YL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Author disclaimer

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