

Spectrins: molecular organizers and targets of neurological disorders

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Supplementary Table 1. Mouse models of spectrinopathies of the nervous system

Gene	Genotype	Cre recombinase or specific promoter	Expression	Lethality	Cortical and hippocampal morphology	Cerebellar morphology	Developmental Delay	Hyperactivity	Seizure	Motor deficits	Social deficits	Sensory and auditory function	Synaptic function	Other findings	Refs
Global knockout															
<i>Sptan1</i>	-/-	None	Global	E12.5-E16.5	+	U	In utero growth delay	N/A	N/A	N/A	N/A	N/A	N/A	Craniofacial, neural tube, and cardiac anomalies	92
<i>Sptan1</i>	+/-	None	Global	live 24 mo	-	U	-	U	U	U	U	U	U		92
<i>Sptbn1^{Eif}</i>	-/-	None	Global	E8.5-E16.5	U	N/A	In utero growth delay	N/A	N/A	N/A	N/A	N/A	N/A	Craniofacial, brain, liver, gut and cardiac anomalies	99
<i>Sptbn2</i>	-/-	None	Global	live 24 mo	-	Progressive ML thinning, PC loss	-	U	U	Progressive motor deficits, tremors	U	U	+	Hypomorph	104
<i>Sptbn2</i>	-/-	None	Global	live > 18 mo	U	ML thinning, PC degeneration, PSD deficits	-	-	Myoclonic seizures	Motor deficits	U	U	+	Hypomorph	72
<i>Sptbn2</i>	+/-	None	Global	live 24 mo	U	-	-	U	U	-	U	U	U		104
<i>Sptbn2</i>	+/-	None	Global	live > 18 mo	U	-	-	U	-	Deficits in the wire-hang test	U	U	U	Express a truncated fragment	72
<i>Sptbn4</i>	-/-	None	Global loss of full length Sptbn4 Σ I and Sptbn4 Σ VI. Might express N-terminal Sptbn4 Σ I products	live 6-10 mo	U	Impaired molecular clustering at the AIS of PC	U	U	U	Tremors, hind limb contraction and paralysis	U	U	U	Deficits in NoR organization	54
<i>Sptbn4 ΣI</i>	-/-	None	Global	live > 15 mo	U	Impaired molecular clustering at the AIS of PC	U	U	U	Juvenile tremors, gait and hind limb deficits	U	Auditory deficits	U	Deficits in NoR organization, impaired sexual behavior in males	51, 116
<i>Sptbn5</i>	-/-	None	Global	U, tested up to 2 mo	U	U	U	U	U	U	U	Auditory deficits	U	Reduction in SGN efferent and afferent fibers and in ABR wave 1 amplitudes	119
Conditional knockout															
	fl/fl	<i>Nestin</i>	Neural precursors in the CNS	<20 days	Disrupted cortical lamination and AIS development. Deficits in dendritic development	Fewer PC with disrupted AIS and altered dendrites axonal projections	Significant growth delay	U	generalized seizures	U	U	U	+	CNS neurodegeneration	52

<i>Sptan1</i> ^{fl/fl}	fl/fl	<i>Advillin</i>	PNS sensory neurons	live > 6 mo	U	U	-	U	U	Juvenile hindlimb clasping reflex, severe ataxia, impaired performance in wire-hang test	U	Reduced conduction velocity of large diameter PNS sensory axons	U	Deficits in NoR organization. Degeneration of large-diameter, myelinated PNS sensory axons	68	
<i>Sptbn</i> ^{null}	fl/fl	<i>Nestin</i>	Neural precursors in the CNS	U, tested up to 3 mo	-	-	-	U	-	-	U	-	-	-	58, 64	
	fl/fl	<i>Advillin</i>	PNS sensory neurons	U, tested up to 1.5 mo	U	U	-	U	-	-	U	-	-	-	64	
<i>Sptbn1</i> ^{null}	fl/fl	<i>Nestin</i>	Neural precursors in the CNS	<40 days	CC agenesis, loss of long-range axons, disrupted cortical lamination, AIS deficits	Loss of cerebellar white matter and projections	Significant growth delay	+	Generalized seizures	Severe ataxia with tremors, hindlimb clasping reflex, absence of rears	U	U	Reduced cortical dendritic complexity	Facial dysmorphism	41, 42	
	fl/+			live > 9 mo	CC dysgenesis, reduction in long-range axons, mild disruption in cortical lamination											U
	fl/fl	<i>Nex</i>	Forebrain excitatory neurons	<160 days	CC dysgenesis, reduction in long-range axons	U	Growth delay	U	U	U	U	U	U	U	42	
				fl/+	live > 12 mo	CC dysgenesis, reduction in long-range axons	U	-	U	U	U	U	U	U		
	fl/fl	<i>Advillin</i>	PNS sensory neurons	live > 4 mo	U	U	U	U	U	U	Motor coordination deficits, hindlimb clasping reflex, reduced grip	U	Normal thermal nociception	U	Deficits in NoR paranodes	67
	fl/fl	<i>Atoh1</i>	Auditory hair cells	live > 9 mo	U	U	U	U	U	U	U	U	Juvenile auditory deficits	U	Disorganized rootlet region of HC stereocilium	100
<i>Sptbn4</i> ^{null}	fl/fl	<i>Nestin</i>	Neural precursors in the CNS	live > 3 mo	Disrupted cortical AIS organization	U	U	U	U	Motor coordination deficits, tremors	U	U	U	Intact Na _v clustering at CNS NoR	58	
	fl/fl	<i>Advillin</i>	PNS sensory neurons	live > 3 mo	U	U	U	U	U	-	U	-	U	Intact Na _v clustering at PNS NoR	64	
<i>Sptbn4</i> ^{null} ; <i>Sptb</i> ^{null}	fl/fl	<i>Nestin</i>	Neural precursors in the CNS	live > 3 mo	Disrupted cortical AIS and CC NoR organization	U	U	U	Generalized seizures	Severe motor impairment	U	U	U	Gradual loss of Na _v clustering at CNS NoR	58	
	fl/fl	<i>Advillin</i>	PNS sensory neurons	live > 9 mo	U	U	U	U	Generalized seizures	Hindlimb clasping reflex	U	Severe defects in proprioception. Compromised myelinated sensory axon function	U	Gradual loss of Na _v clustering at PNS NoR and axon degeneration	64	
Knock-in																

<i>Sptan1</i> ^{R1098Q}	<i>Sptan1</i> ^{R1098Q/R1098Q}	None	Global	E18	Craniofacial and vascular defects	U	U	U	U	U	U	U	U	U	Presence of calpain-cleaved spectrin products	97
	<i>Sptan1</i> ^{R1098Q/+}	None	Global	live 24 mo	Neuronal loss and reactive gliosis in the cortex and hippocampus	Profound progressive atrophy of the cerebellum with gliosis, degeneration and loss of PC	U	U	Seizures observed in older ataxic mice	Progressive ataxia with tremors	Ataxic mice are more aggressive	U	Loss of PC. Severe loss of PC dendrites with fragmentation	Enhanced calpain activation and calpain-cleaved spectrin	97	
<i>Sptbn2</i> ^{E532_M544del}	<i>Sptbn2</i> ^{E532_M544del/+}	Express <i>Pcp2</i> TTA and TRE- <i>Sptbn2</i> transgenes	PC	live > 18 mo	U	Loss of PC dendrites. Decreased cerebellar NAA levels	-	U	-	Progressive motor coordination impairments	U	U	Loss of mGluR1α clustering at PC spines. Loss of mGluR1-mediated LTP	74		
<i>Sptbn4</i> ^{qv-1}	<i>Sptbn4</i> ^{R2079*/R2079*}	None	Global	< 5 months	U	U	U	U	U	Progressive ataxia with tremors. Hindlimb paralysis observed in 1 mo mice	U	Deafness	U	Eye infections	114	
<i>Sptbn4</i> ^{qv-2j}	<i>Sptbn4</i> ^{R1676fs*35/R1676fs*35}	None	Global	U	U	U	U	U	U	U	U	Abnormal auditory brainstem response	U	114		
<i>Sptbn4</i> ^{qv-3j}	<i>Sptbn4</i> ^{G2210fs*49/G2210fs*49}	None	Global	< 5 months	Abnormal morphology and Na _v clustering at NoR in the CNS	U	U	U	U	Progressive ataxia with tremors, hindlimb clasping reflex, and quivering. Decreased locomotion or paralysis in older mice	U	Abnormal auditory brainstem response	U	Infertility, mild morphological deficits in PNS NoR. Increased NF density and altered axon shape in the optic nerve	114, 116, 117	
<i>Sptbn4</i> ^{qv-4l}	<i>Sptbn4</i> ^{Q1359*/Q1359*}	None	Global	Reduced, age of death NA	Disrupted CNS nodes of Ranvier	U	U	U	U	U	U	Deafness	U	Disruption of NoR in the PNS	114, 116	
<i>Sptbn4</i> ^{qv-Ind}	<i>Sptbn4</i> ^{A480fs*12/A480fs*12}	None	Global	10 months	U	U	Decreased body size	U	U	Progressive abnormalities of gait, juvenile head tremors, paralysis	U	Significantly reduced or absent auditory brain response	U	Dystrophic axons in the low lumbar and sacral spinal cord levels. Male infertility	114	
<i>Sptbn4</i> ^{qv-Ind2j}	<i>Sptbn4</i> ^{R1675fs*35/A480fs*12}	None	Global	4 weeks	Abnormal auditory cortex morphology. Disrupted myelination of auditory neuron axons and KCNA1 clustering at NoR	U	U	U	U	U	U	Significantly reduced or absent auditory brain response	U	114		

ABBREVIATIONS: fl/+, floxed heterozygous; fl/fl, floxed homozygous; E, embryonic; U, unknown; ML, molecular layer of the cerebellum; PC, Purkinje cells; PSD, postsynaptic density; AIS, axon initial segment; CC, corpus callosum; NoR, nodes of Ranvier; -, no deficits detected; +, deficits detected; N/A, non-applicable; LTP, long-term potentiation; CNS, central nervous system; PNS, peripheral nervous system; NF, neurofilament; NAA, N-acetylaspartate; SGN, spiral ganglion neurons; ABR, auditory brainstem response.