

Supplemental Material

Age-dependent ataxia and neurodegeneration caused by an α II spectrin mutation with impaired regulation of its calpain sensitivity

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Supplemental Figure Legends

Figure S1: Coordination testing of R1098 and Q1098 mice.

Figure S2: In-utero comparison of fetal mice.

Figure S3: Comparison of WT vs. heterozygote cerebellum immunostained for β III-spectrin at postnatal day 7.

Figure S4: Secondary structure predictions

Figure S5: Compaction of the spectrin repeat unit relaxed in mutant

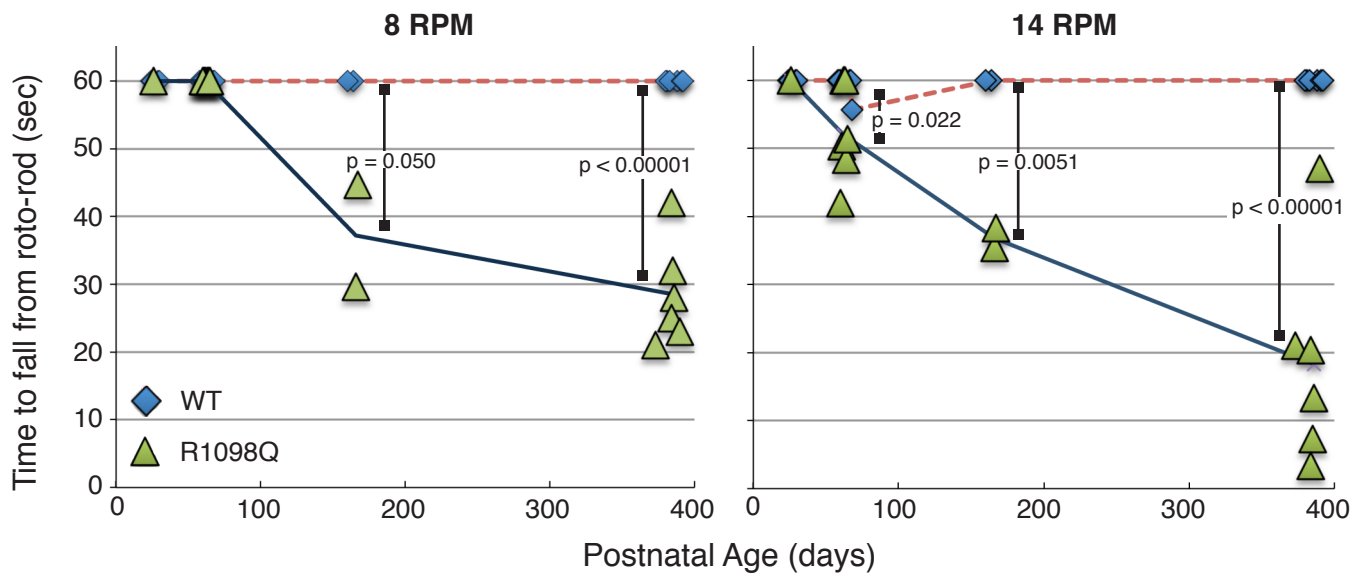
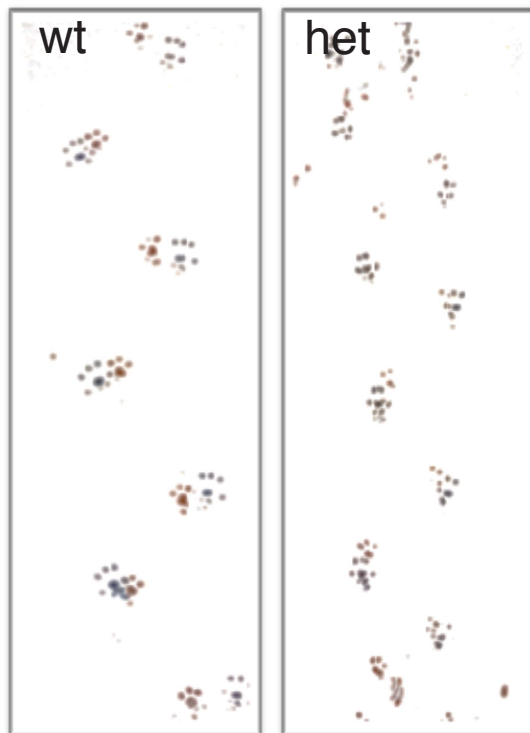
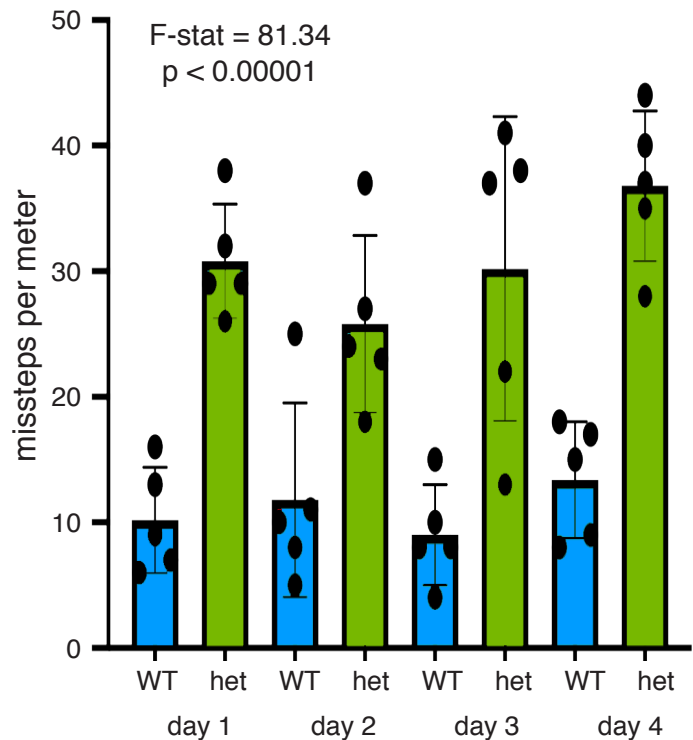
Figure S6: Original un-cropped Western blots used in Figure 3.

Figure S7: Measured cerebellar changes with age.

Table T1: Variants identified by WES

Movie M1: WT vs. R1098Q mice at 9 months of age.

Movie M2: Dynamics simulation of WT vs Q1098 spectrin \pm calmodulin; Y1176 (calpain cleavage site) is colored blue.

a**b****c**

Supplemental Figure S1: - Coordination testing of R1098Q mice

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Wild Type
 α II spectrin

R1098Q
 α II spectrin
homozygous

R1098Q
 α II spectrin
homozygous

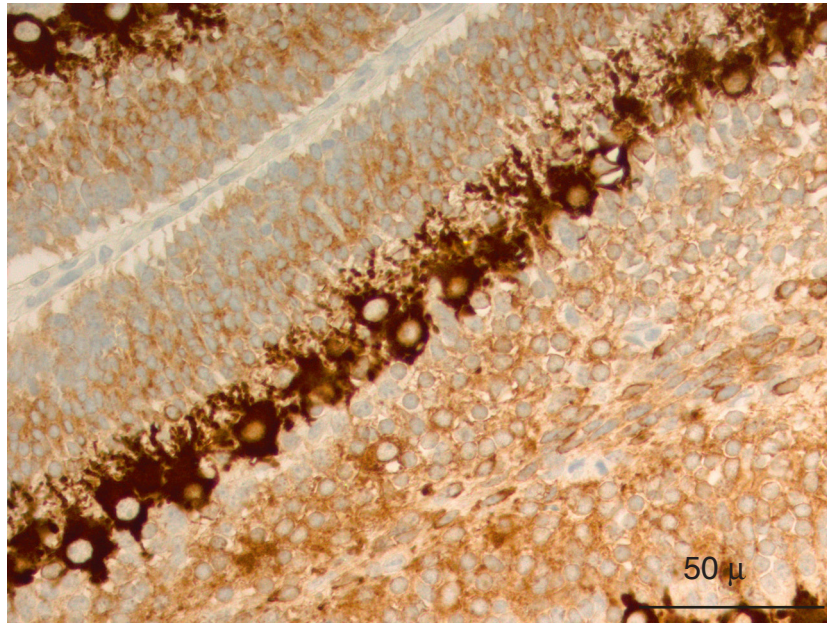
Supplemental Figure S2 - In-utero comparison of fetal mice

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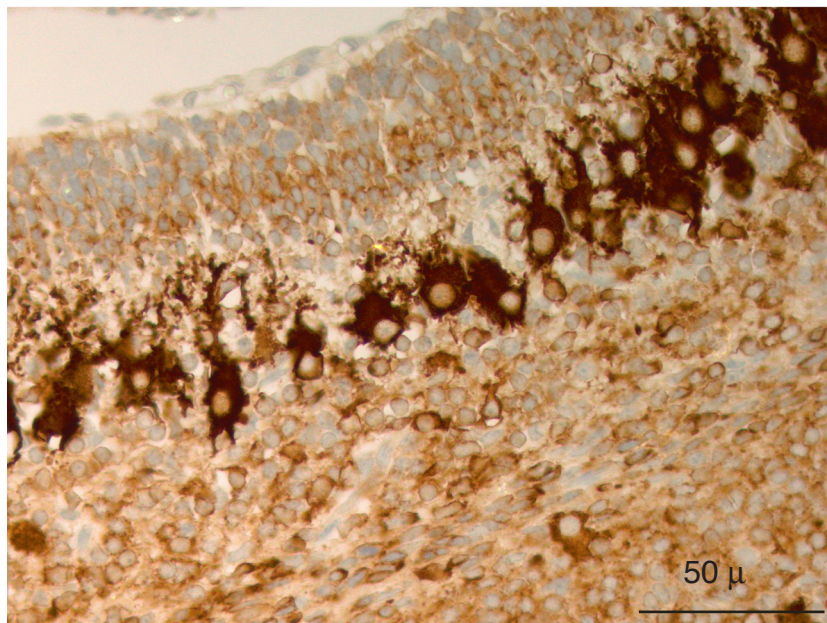
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P7 brain stained with anti- β III spectrin

WT



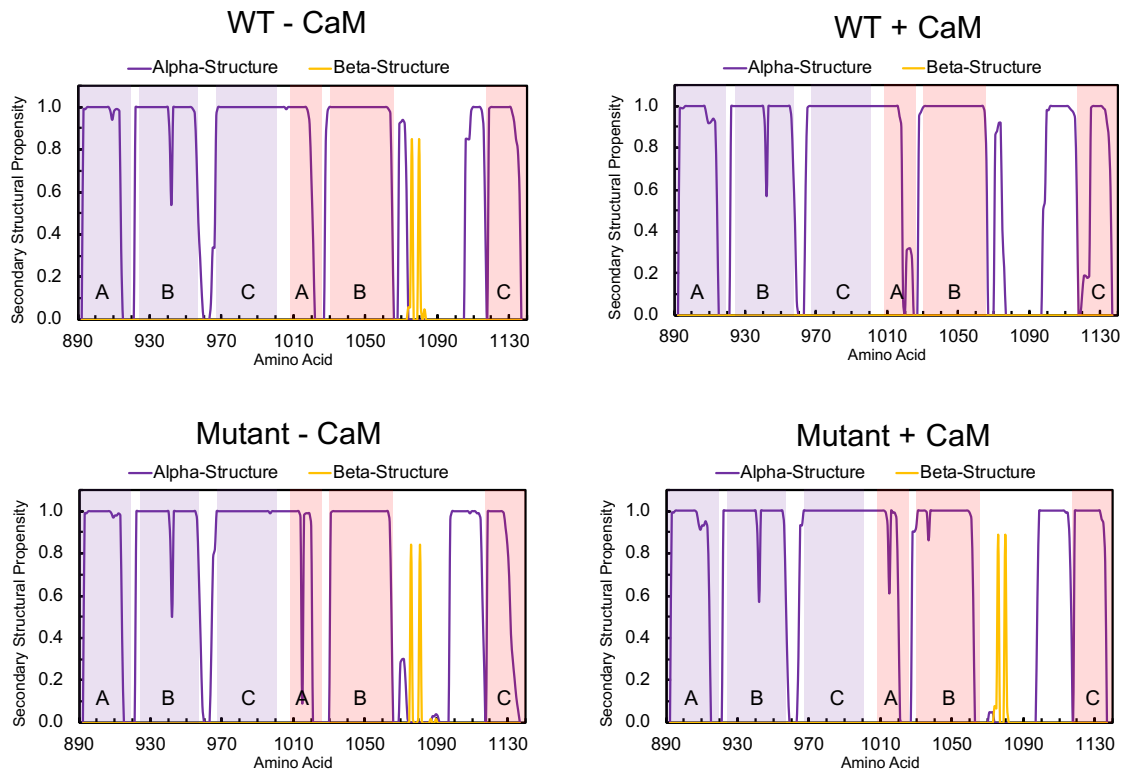
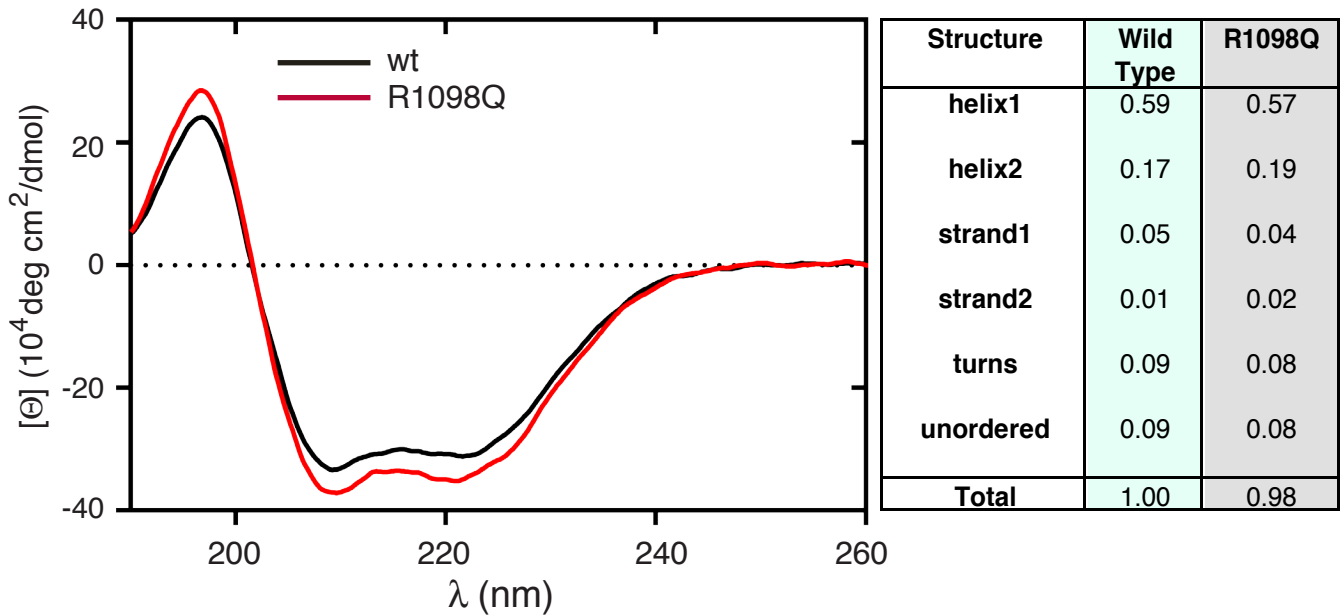
R1098Q
het



Supplemental Figure 3: Comparison of wt vs heterozygote cerebellum immunostained for β III-spectrin at postnatal day 7.

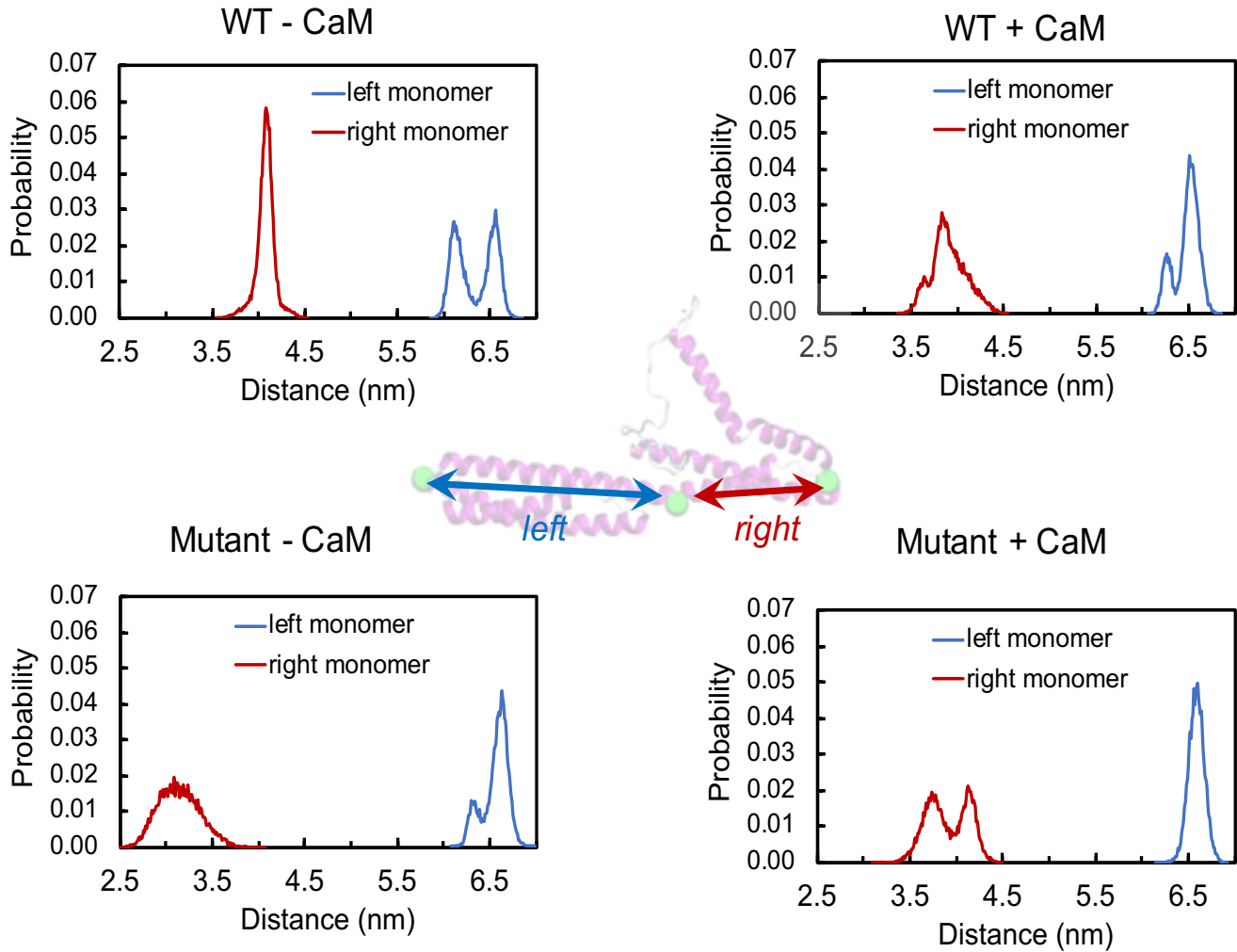
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a**b****Supplemental Figure S4** - Secondary Structure Predictions.

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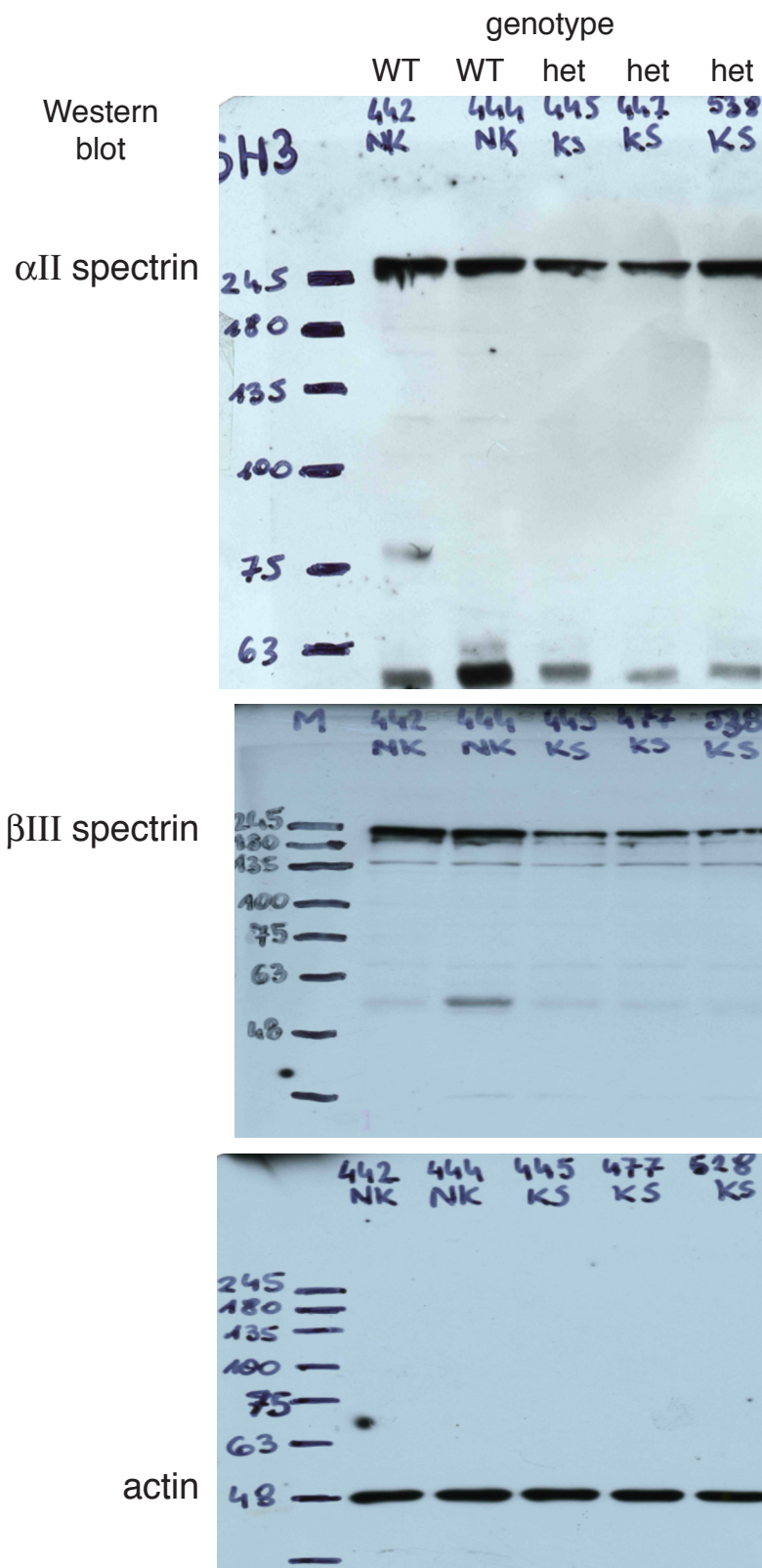
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Supplemental Figure S5 - Compaction of the spectrin repeat unit relaxed in mutant

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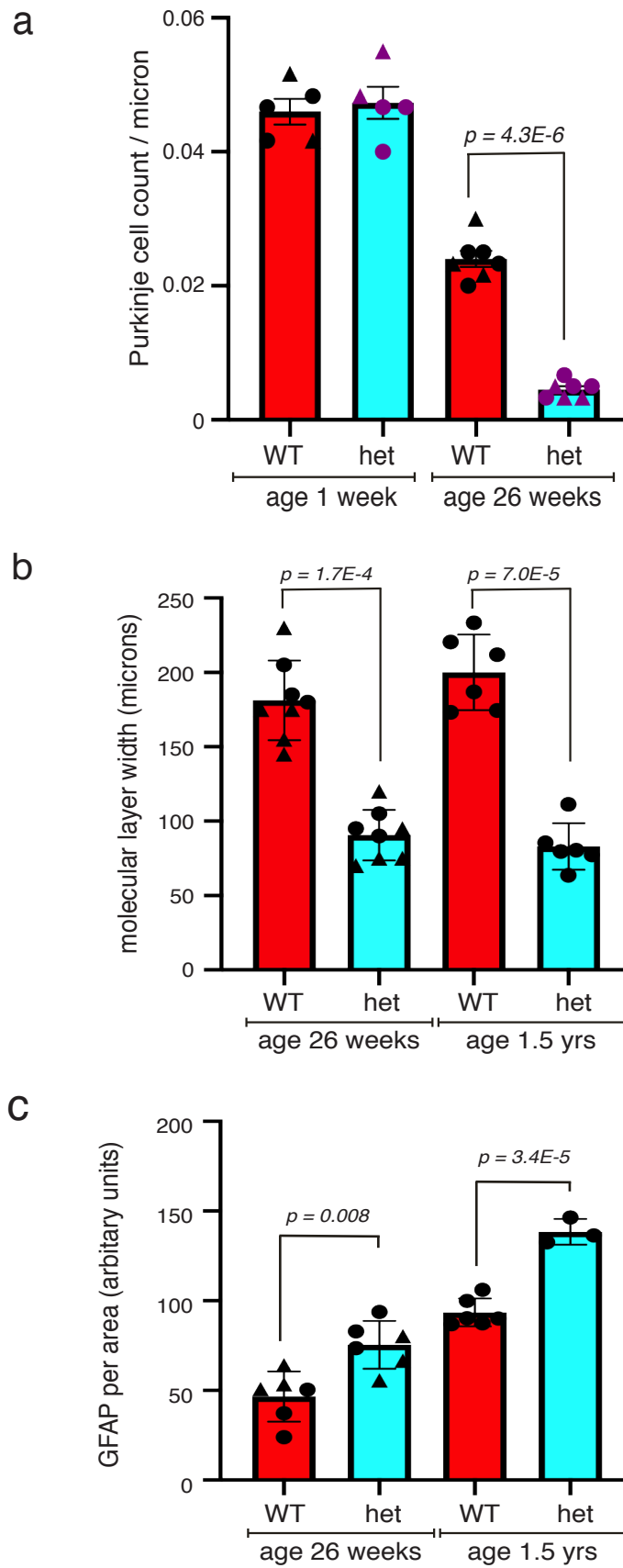
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Supplemental Figure 6: Original uncropped western blots used in Figure 3.

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Supplemental Figure 7: Measured cerebellar changes with age.

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Supplemental Table 1: Variants identified by WES in ataxia C57/B/6J mice but not in WT littermates.

Ch	gene	name	Putative function/association	SIFT
1	AC133103.1	BAC clone, not characterized		tolerated
1	AC168977.1	BAC clone, not characterized		deleterious
1	Hjrp	HJURP Holliday junction recognition protein	DNA binding; cellular component organization	tolerated
1	Mroh2a	MROH2A maestro heat like repeat family	uncharacterized	tolerated
1	Prg4	PRG4 proteoglycan 4	proteoglycan synthesis in cartilage	tolerated
1	Rrs1	RRS1 ribosome biogenesis regulator 1	protein synthesis	deleterious
1	Ugt1a1	UGT1A1 UDP glucuronosyltransferase family 1 member A1	Crigler-Najjar syndromes - metabolism of bilirubin	tolerated
2	Sptan1	Spectrin non-erythroid alpha1	West syndrome et al.	deleterious
3	Pias3	protein inhibitor of activated STAT 3 RPTN repetin	transferase; retinal phenotype Diminished serum repetin levels in patients with schizophrenia and bipolar disorder	deleterious
3	Rptn			tolerated
4	Zfp990	Zfp990 zinc finger protein 990	transcriptional regulator	tolerated
5	Gm17019	predicted gene, not characterized		deleterious
5	Tacc3	TACC3 transforming acidic coiled-coil	motor spindle protein that may play a role in	tolerated
6	Peg10	PEG10 paternally expressed 10	role in cell proliferation, differentiation and	deleterious
6	Phf14	PHF14 PHD finger protein 14	mitosis regulation and tumorigenesis	deleterious
7	Zfp936	Zfp936 zinc finger protein 936	transcription factor, low expression in brain	deleterious
8	Pkd1l3	PKD1L3 polycystin 1 like 3, transient receptor THAP1 THAP domain containing 1	cation channel pores proapoptotic factor that links PAWR to PML	tolerated
8	Thap1		nuclear bodies.	deleterious
10	Duxf3	Duxf3 double homeobox family member 3	DNA binding	tolerated
11	Gm11555	predicted gene, not characterized		tolerated
12	Gm2022	predicted gene, not characterized		tolerated
13	Nkapl	NKAPL NFKB activating protein like	polymorphic associatoin with schizophrenia	deleterious
14	Gm21103	predicted gene, not characterized		tolerated
15	Krt78	KRT78 keratin 78	structural protein in epithelial	tolerated
16	Muc13	MUC13 mucin 13, cell surface associated	epithelial mucin	tolerated
16	Muc4	MUC4 mucin 4, cell surface associated PRDM9 PR/SET domain 9	epithelial mucin histone methyltransferase activity that catalyzes	tolerated
17	Prdm9		histone H3 lysine 4 trimethylation (H3K4me3)	deleterious
17	Tbl3	TBL3 transducin beta like 3	WD40 repeat protein mediating protein-protein	tolerated
17	Vmn2r114	Vmn2r114 vomeronasal 2, receptor 114	pheromone receptor	deleterious
17	Vmn2r115	Vmn2r115 vomeronasal 2, receptor 115	pheromone receptor	deleterious
17	Vmn2r117	Vmn2r115 vomeronasal 2, receptor 117	pheromone receptor	tolerated
x	Cdr1	CDR1 cerebellar degeneration related protein 1	Cerebellar degeneration-related autoantigen 1	tolerated
x	Vmn2r121	Vmn2r121 vomeronasal 2, receptor 121	pheromone receptor	deleterious
y	Gm4064	predicted gene, not characterized		tolerated