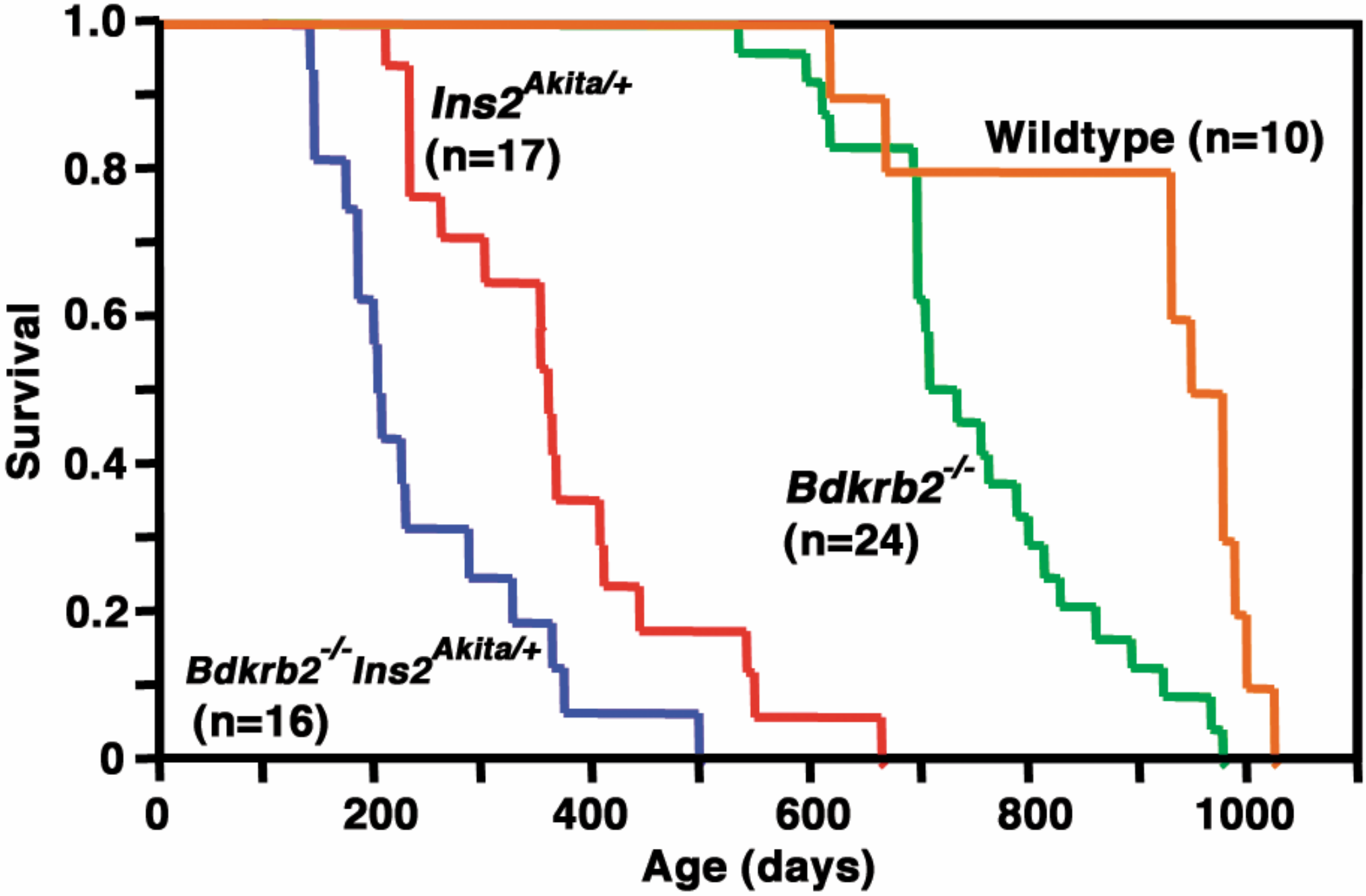
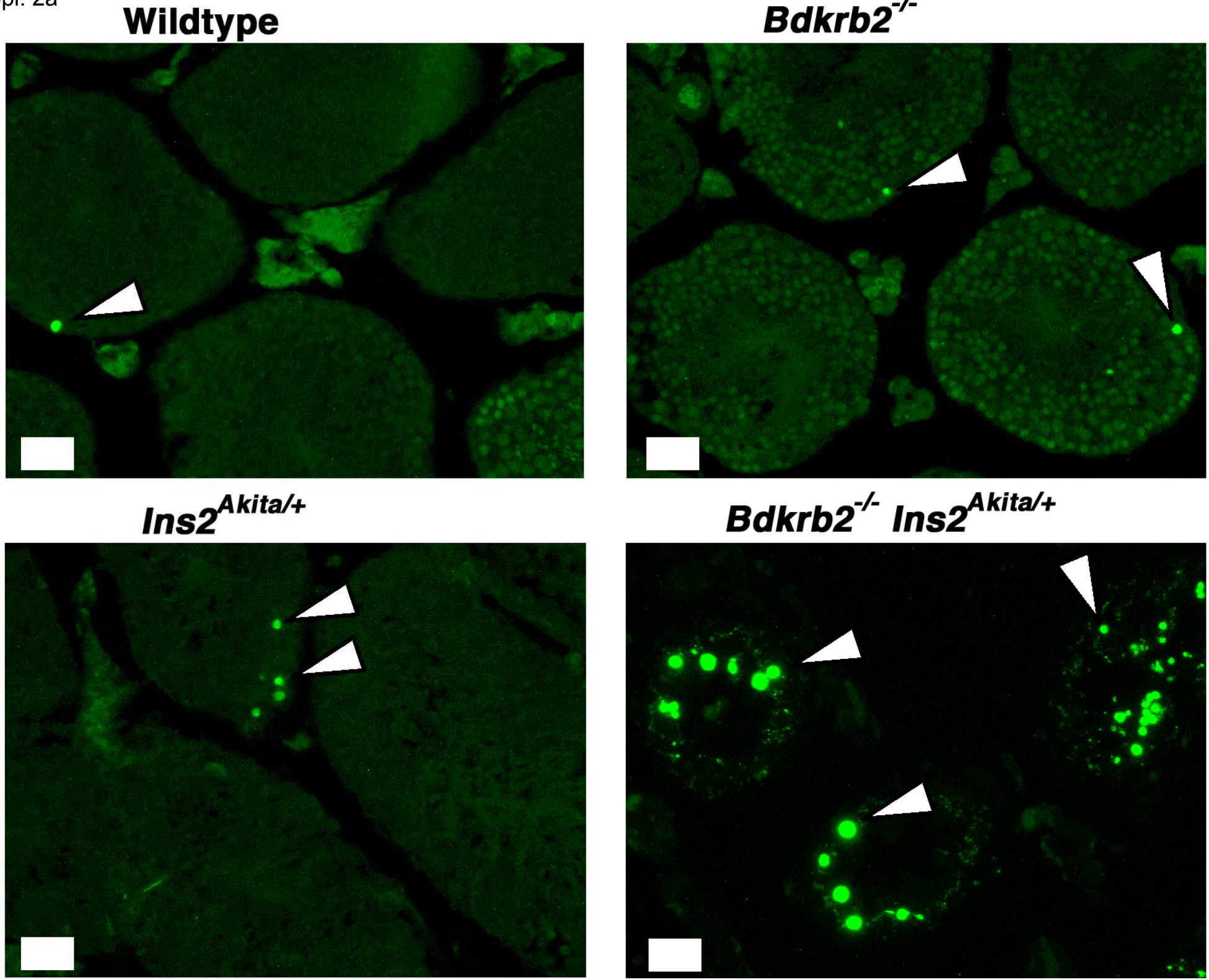
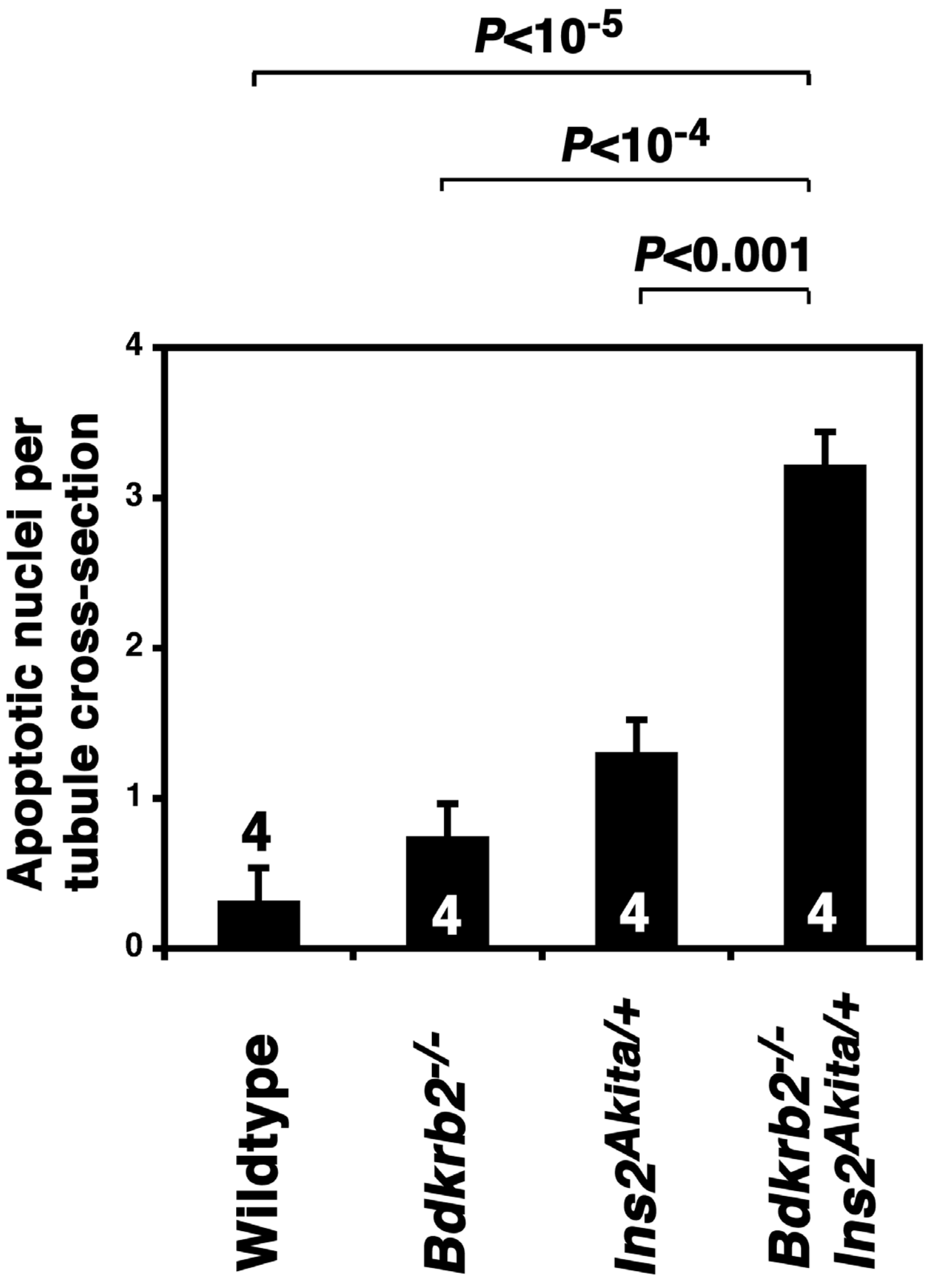
Suppl. 1


1.0
0.8
0.6
0.4
0.2
0
Survival
0
200
400
600
800
1000
Age (days)
Ins2Akita/+
(n=17)
Wildtype (n=10)
Bdkrb2-/-
(n=24)
Bdkrb2-/- Ins2Akita/+
(n=16)

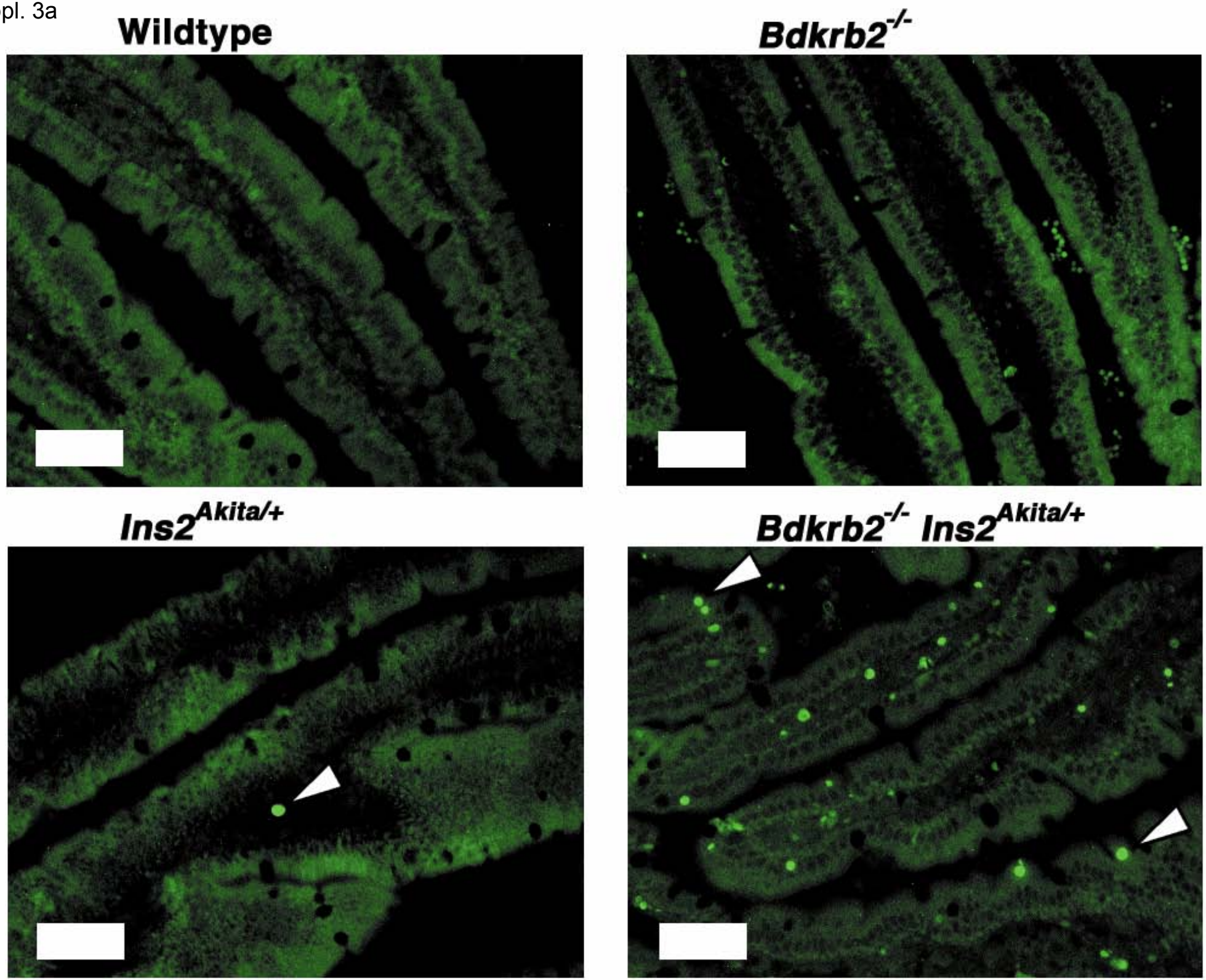
Suppl. 2a



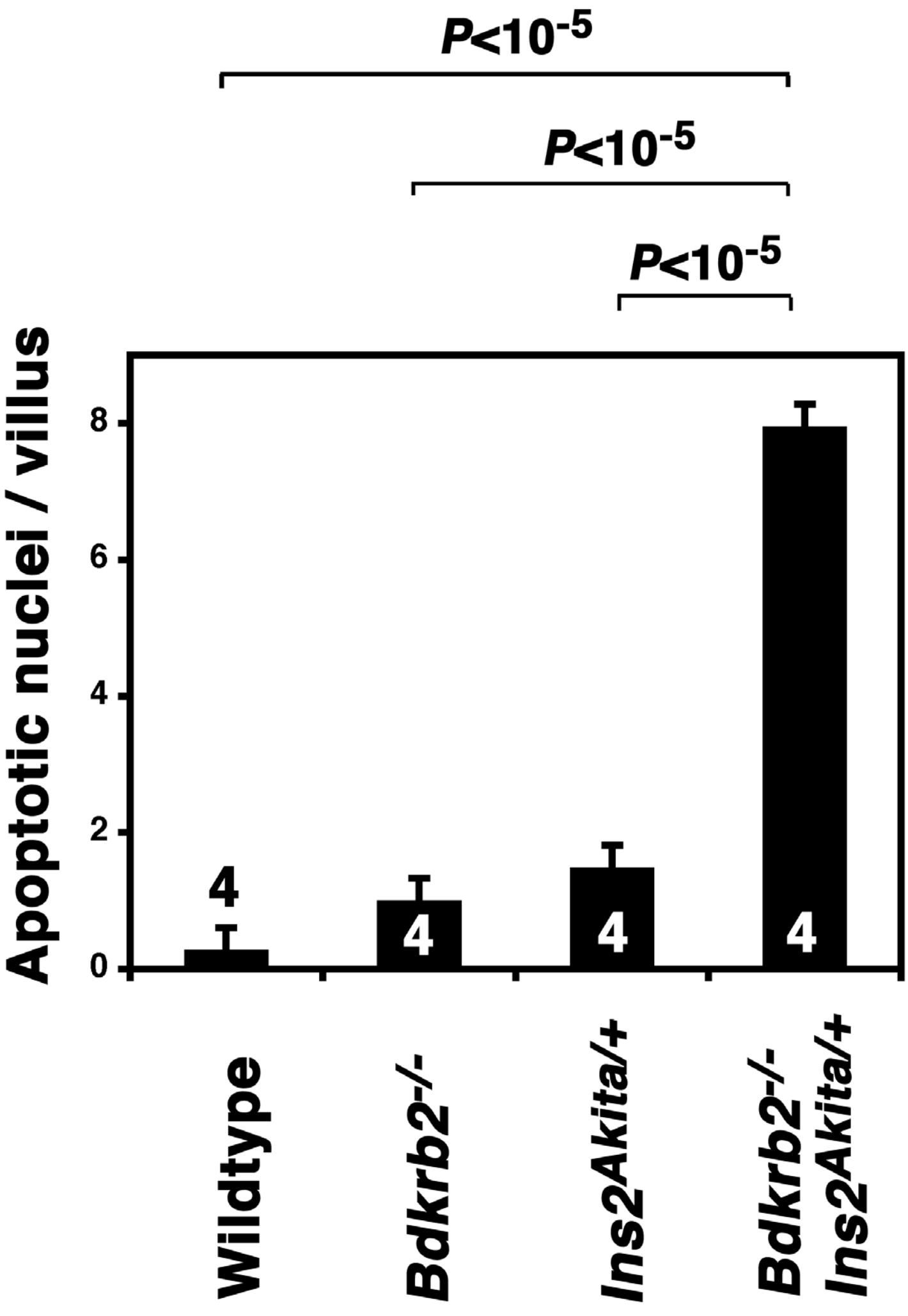
Suppl. 2b


P<10-5
P<10-4
P<0.001
Apoptotic nuclei per tubule cross-section
0
1
2
3
4
4
4
4
4
Wildtype
Bdkrb2-/-
Ins2Akita/+
Bdkrb2-/- Ins2Akita/+

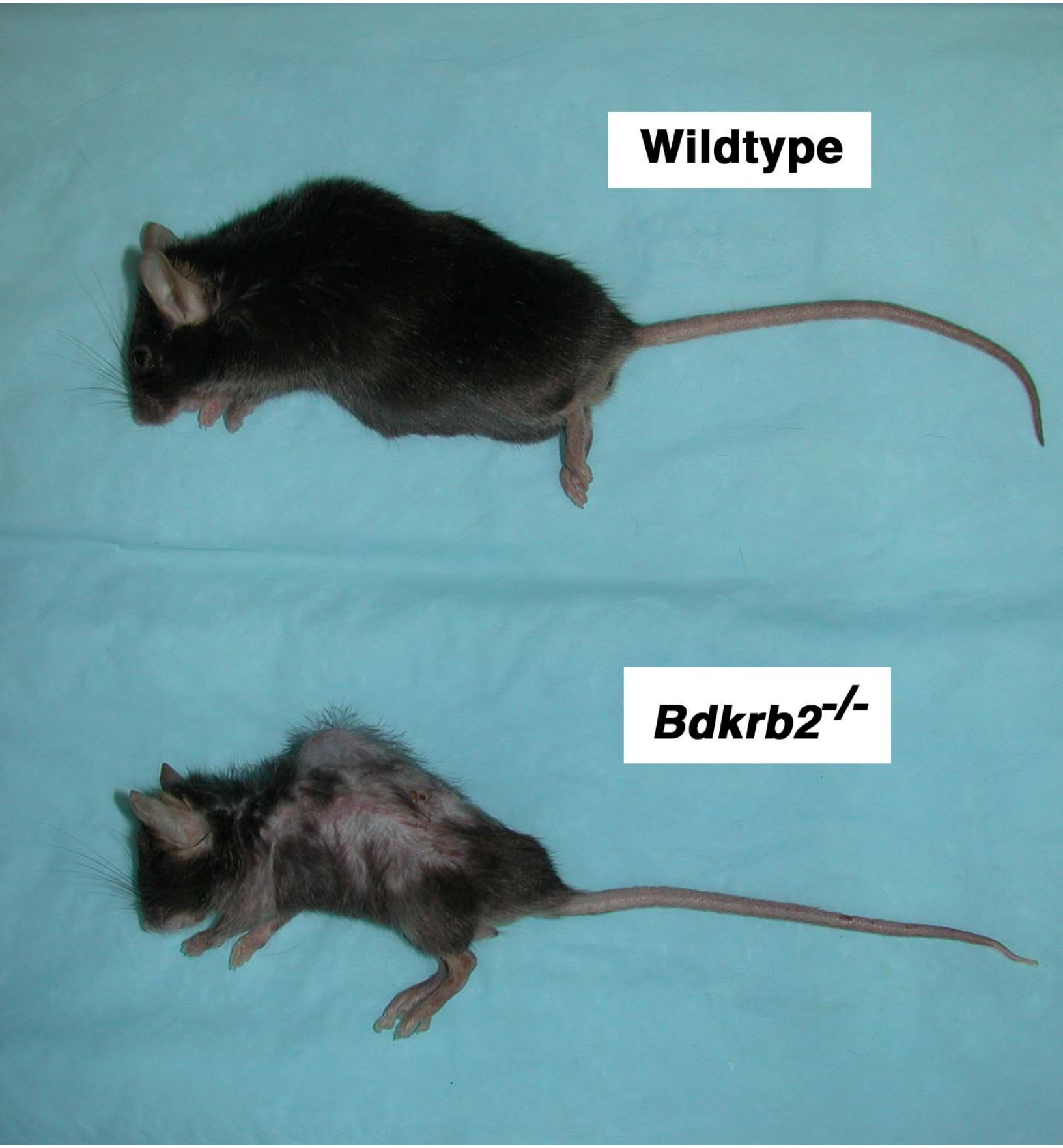
Suppl. 3a



Suppl. 3b


P<10-5
P<10-5
P<10-5
Apoptotic nuclei / villus
0
2
4
6
8
4
4
4
4
Wildtype
Bdkrb2-/-
Ins2Akita/+
Bdkrb2-/- Ins2Akita/+

Suppl. 4



Supplementary Figure 1

Kaplan-Meier analysis of survival in male mice with the four genotypes. P<0.001 in *Bdkrb2*$^{-/-}$ vs. wildtype, P<0.0001 in *Ins2*$^{Akita/+}$ vs. wildtype and in *Bdkrb2*$^{-/-}$*Ins2*$^{Akita/+}$ vs. wildtype, P<0.01 in *Bdkrb2*$^{-/-}$*Ins2*$^{Akita/+}$ vs. *Ins2*$^{Akita/+}$ by log-rank test). The average life span of male wildtype, *Bdkrb2*$^{-/-}$, *Ins2*$^{Akita/+}$, and *Bdkrb2*$^{-/-}$*Ins2*$^{Akita/+}$ mice was 909 ± 45 days, 755 ± 23 days, 373 ± 30 days, and 246 ± 25 days (means ± standard errors), respectively (See Supplementary Table 4 for two-factor ANOVA analysis).

Supplementary Figure 2

(**A**) Apoptotic cells (arrowheads) in the seminiferous tubules of 12-month-old mice with the four genotypes (scale bar = 100 μm). (**B**) Quantification of the apoptotic cells in the seminiferous tubule. The data are means ± standard errors with the numbers of animals shown in white digits (See Supplementary Table 4 for two-factor ANOVA analysis).

Supplementary Figure 3

(**A**) Apoptotic cells (arrowheads) in the duodenum of 12-month-old mice with the four genotypes (scale bar = 100 μm). (**B**) Quantification of the apoptotic cells in the duodenum The data are means ± standard errors with the numbers of animals shown in white digits (See Supplementary Table 4 for two-factor ANOVA analysis).

Supplementary Figure 4

General appearance of 24-month-old male mice with genotypes: wildtype and

homozygous null for the B2 receptor (*Bdkrb2*$^{-/-}$). Kyphosis is moderate in the wildtype mouse; it is severe in the B2 receptor-null animal, which also exhibits marked alopecia. The animals imaged are among the most severely affected of each genotype. The degree of kyphosis and alopecia in severely affected B2 receptor null mice at 24 months of age is essentially indistinguishable from that in severely affected double mutants (Akita diabetic B2 receptor null) at 12 months of age.

Supplementary Table 1. Primers for PCR amplification of mitochondrial cytochrome b gene for detecting point mutations.

(Fwd primer)	5'-CATCGTTGTAATTCAACTACAG-3'
(Rev primer)	5'-CAAGACCAGAGTAATGTTTATAC-3'

Supplementary Table 2. Primers and probes for quantification of the proportion of the D-17 mutant in mitochondrial DNA with quantitative PCR.

Cytochrome b	(Fwd primer)	5'-TCGCTTTCCACTTCATCTTAC-3'
	(Rev primer)	5'-ATCCTGTTTCGTGGAGGAAG-3'
	(Probe)	5'-FAM-CGCGGCCCTAGCAATCGTTCA-Tamra-3'
D-17	(Fwd primer)	5'-TCATGACCAATGAACACTCTG-3'
	(Rev primer)	5'-AGGCTCGCGGACTAGTATAT-3'
	(Probe)	5'-FAM-CCCTAGCCCCCCAACTAATTACC-Tamra-3'

Supplementary Table 3. Primers and probes for quantification of mRNA with quantitative reverse transcription-PCR.

TGF-β1	(Fwd primer)	5'-TGACGTCACTGGAGTTGTACGG-3'
	(Rev primer)	5'-GGTTCATGTCATGGATGGTGC-3'
	(Probe)	5'-FAM-TTCAGCGCTCACGTCTCTTGTGACAG-Tamra-3'
CTGF	(Fwd primer)	5'-AGCCGCCTCTGCATGGTCA-3'
	(Rev primer)	5'-GCGATTTTAGGTGTCCGGAT-3'
	(Probe)	5'-FAM-CCTGCGAAGCTGACCTGGAGGAAA-Tamra-3'
p53	(Fwd primer)	5'-TGCTCCGATGGTGATGGCCT-3'
	(Rev primer)	5'-TGTGGCGAAAAGTCTGCCTG-3'
	(Probe)	5'-FAM-CCCCAGCATCTTATCCGGGTGGA-Tamra-3'
α-synuclein	(Fwd primer)	5'-TACCCACAGGAAGGAATCCT-3'
	(Rev primer)	5'-CTTGGTAGCCTTCCTCTGAA-3'
	(Probe)	5'-FAM-ATGCCTGTGGATCCTGGCAGTGAG-Tamra-3'
FoxO1	(Fwd primer)	5'-TGAAGAGCGTGCCCTACTTC-3'
	(Rev primer)	5'-AGGGACAGATTGTGGCGAAT-3'
	(Probe)	5'-FAM-TCCAGCCCGCCGAGCTGTTGCT-Tamra-3'
β-actin	(Fwd primer)	5'-AAGAGCTATGAGCTGCCTGA-3'
	(Rev primer)	5'-ACGGATGTCAACGTCACACT-3'
	(Probe)	5'-FAM-CACTATTGGCAACGAGCGGTTCCG-Tamra-3'

Supplementary Table 4. P values for 2-factor ANOVA.

	Diabetes mellitus	Absence of B2 recptors	Interaction
TGF-β1 expression	<0.0001	0.0202	0.0575
CTGF expression	<0.0001	0.0588	0.1103
p53 expression	<0.0001	0.0066	0.4666
α-synuclein expression	<0.0001	0.0264	0.2027
FoxO1 expression	<0.0001	0.0119	0.2371
Bone mineral density	<0.0001	0.0030	0.8815
TBARS	<0.0001	<0.0001	0.2133
GSH	<0.0001	0.0010	0.4407
8-OHdG	<0.0001	<0.0001	0.0006
Point mutations	<0.0001	0.0227	0.2067
D-17 deletions	<0.0001	<0.0001	0.0534
Lifespan	<0.0001	<0.0001	0.6541
Apoptosis testis	<0.0001	0.0004	0.0090
Apoptosis duodenum	<0.0001	<0.0001	<0.0001