Animal Models for Neurological Diseases

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阿茲海默氏病 (Alzheimer's disease)
基因轉殖動物模式

類澱粉前驅蛋白 (Amyloid Precursor Protein, APP)基因轉殖動物 (Nature 373:523-527, 1995; Nature 395:755-756, 1998)探討神經退化機制

LETTERS TO NATURE

Alzheimer-type neuropathology in transgenic mice overexpressing V717F β-amyloid precursor protein

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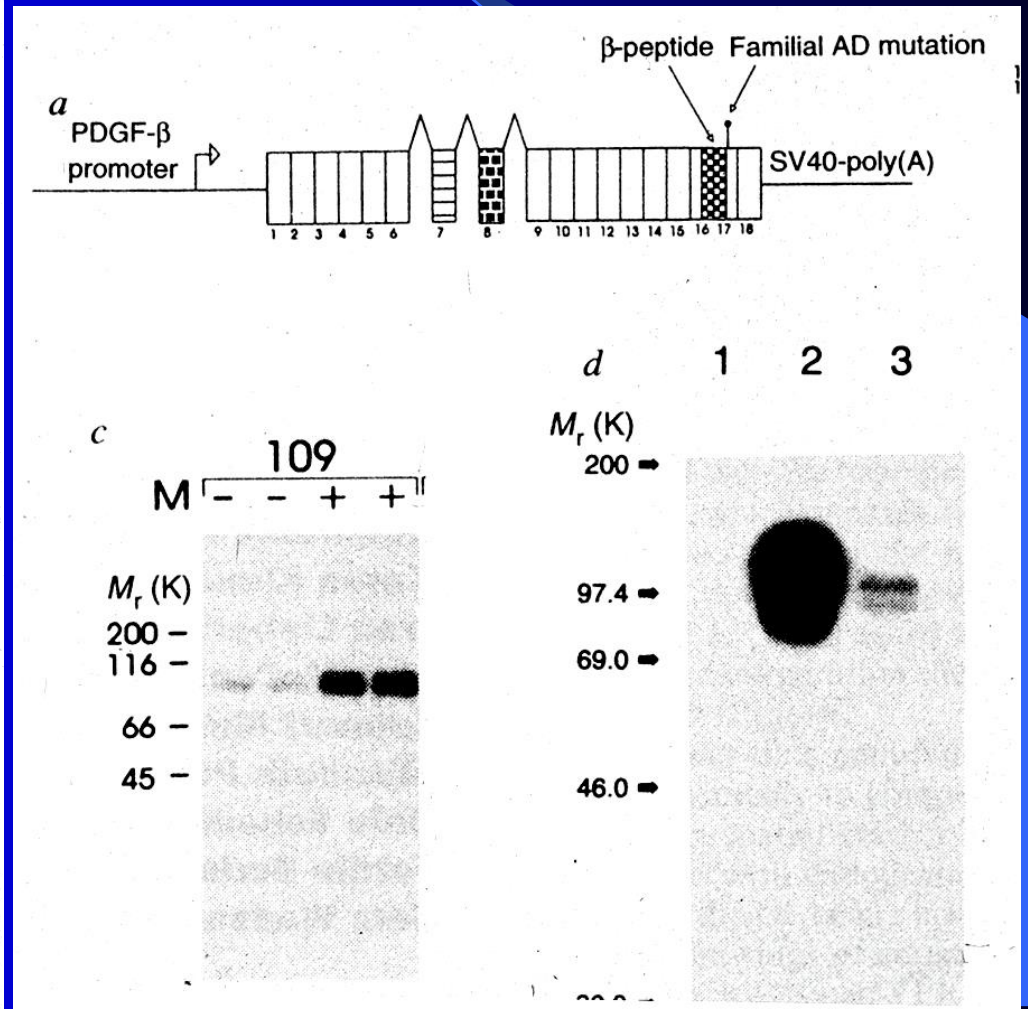
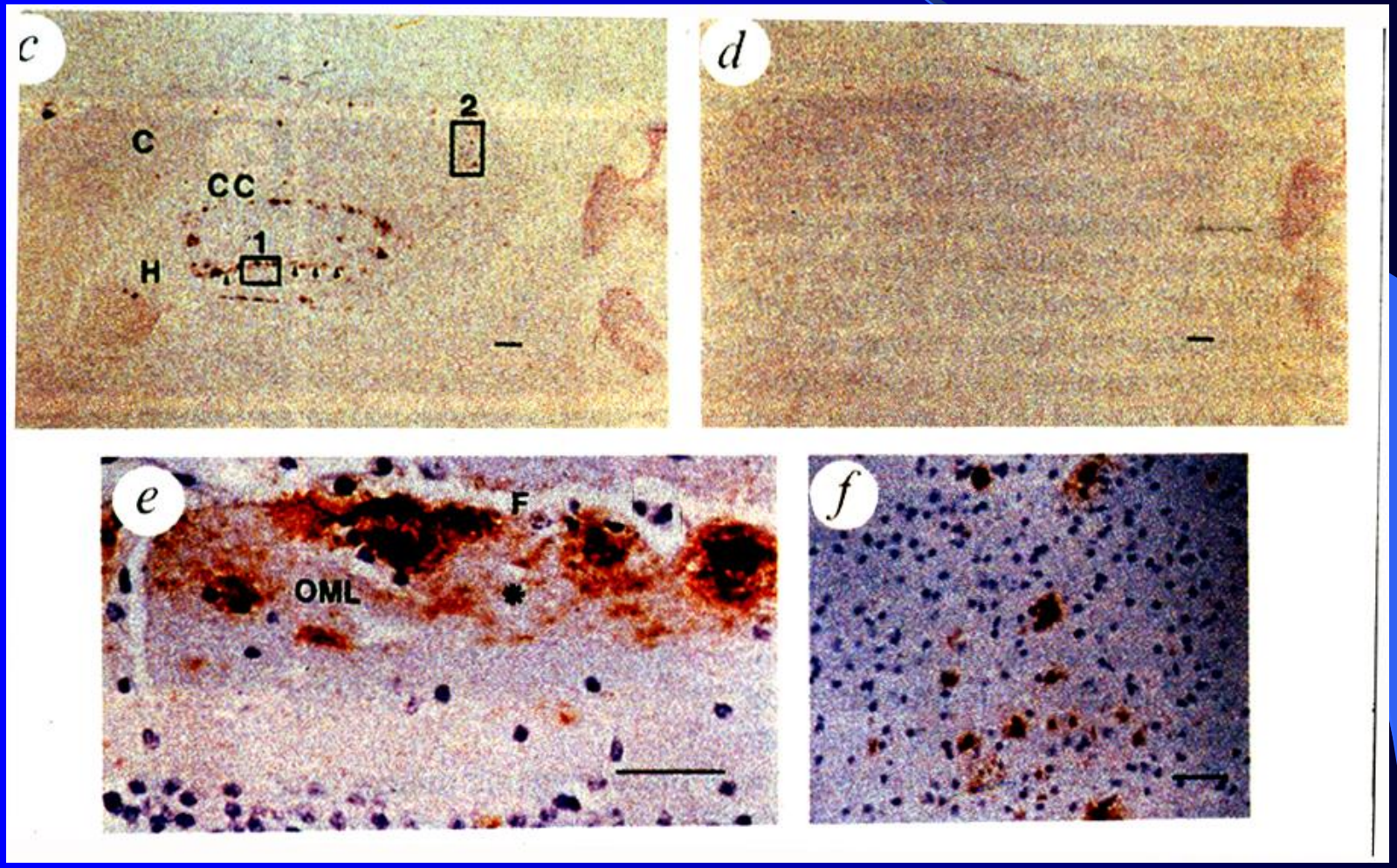
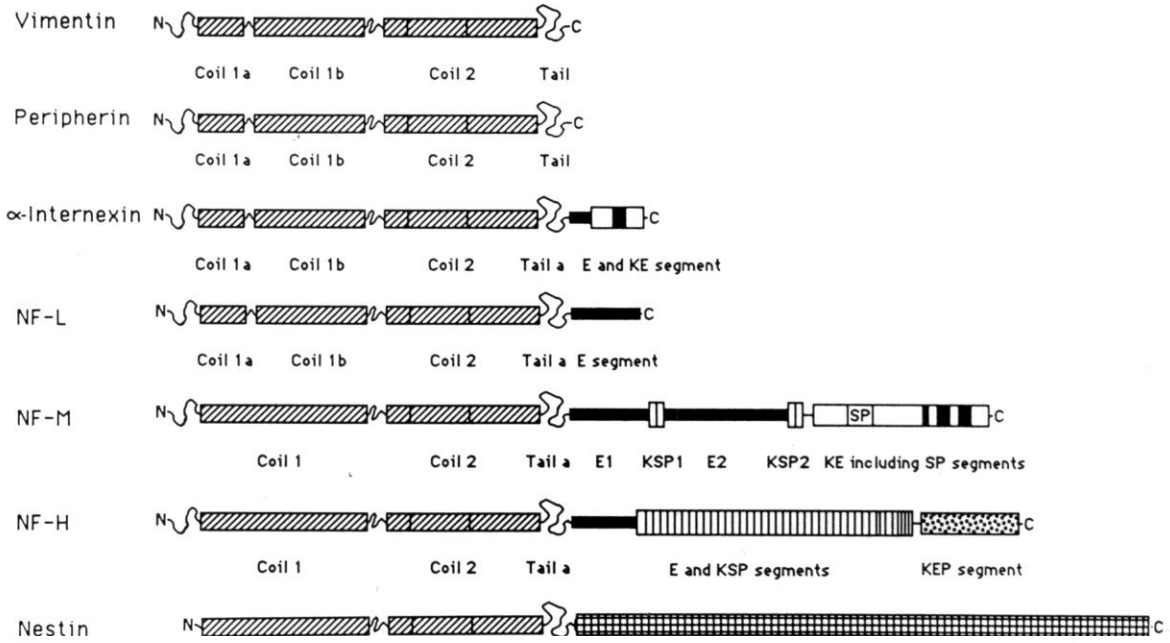
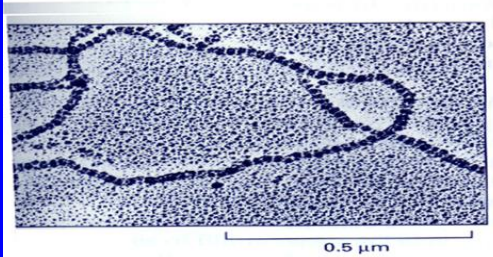
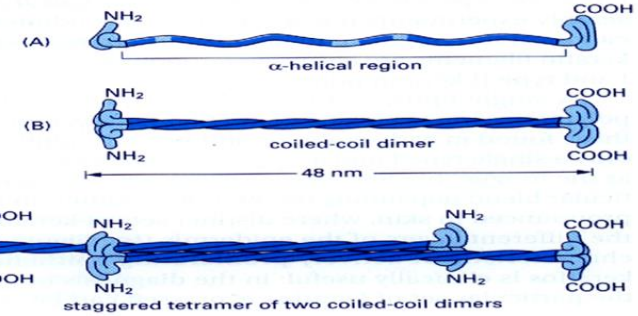


基因轉殖鼠腦中具有與
阿滋海默症一樣的老年斑(Senile plaques)

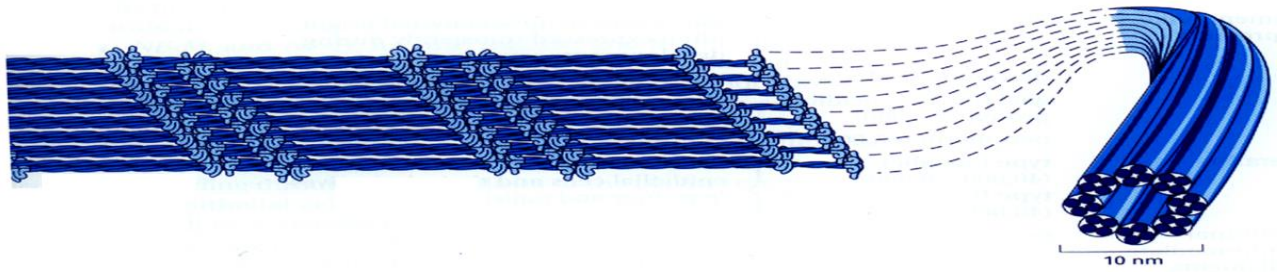



Vimentin
N
C
Coil 1a
Coil 1b
Coil 2
Tail
Peripherin
N
C
Coil 1a
Coil 1b
Coil 2
Tail
∝-Internexin
N
C
Coil 1a
Coil 1b
Coil 2
Tail a
E and KE segment
NF-L
N
C
Coil 1a
Coil 1b
Coil 2
Tail a
E segment
NF-M
N
SP
C
Coil 1
Coil 2
Tail a
E1
KSP1
E2
KSP2
KE including SP segments
NF-H
N
C
Coil 1
Coil 2
Tail a
E and KSP segments
KEP segment
Nestin
N
C


0.5 μm

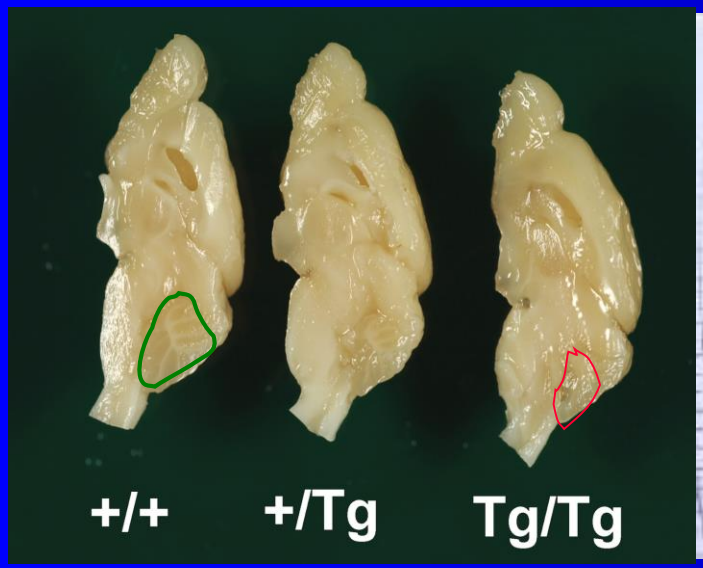

(A)
NH2
COOH
α-helical region
(B)
NH2
COOH
coiled-coil dimer
NH2
COOH
48 nm
(C)
COOH
NH2
NH2
COOH
COOH
NH2
NH2
COOH
staggered tetramer of two coiled-coil dimers


(D)
two tetramers packed together

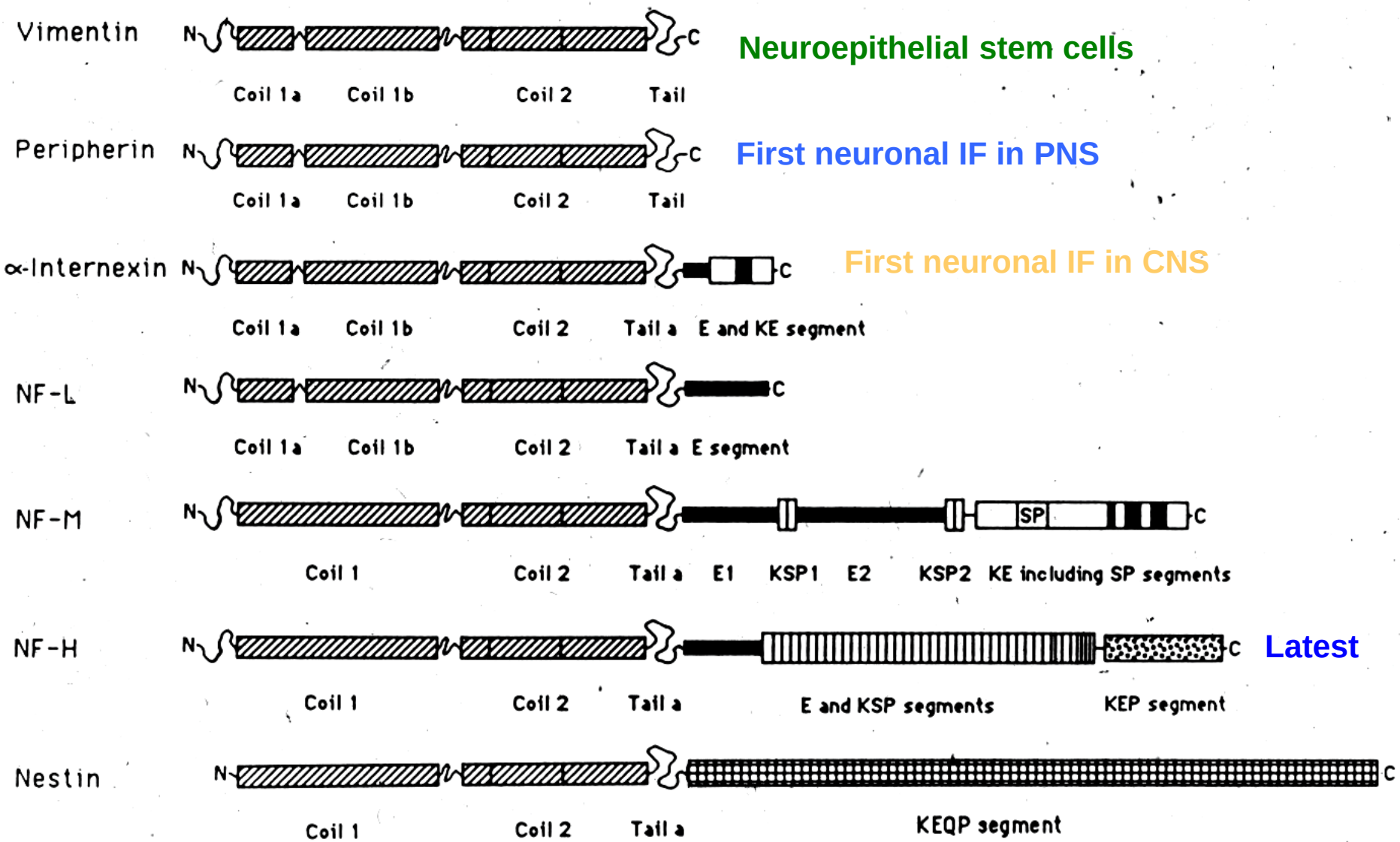

10 nm

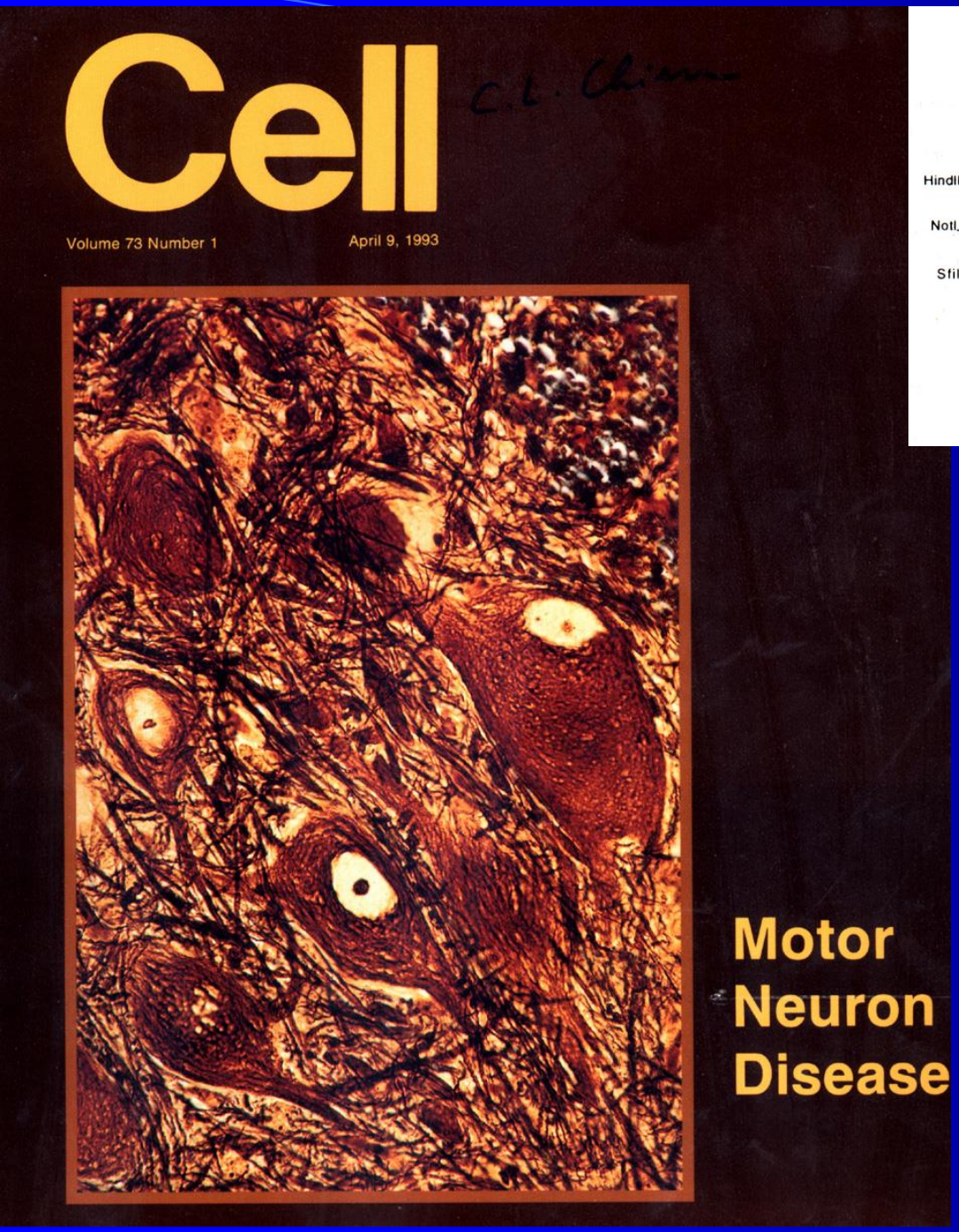
1. A transgenic mouse over expressed the neuronal intermediate filament α-internexin gene that represent a model for the cerebellar atrophy.

2. A nature mutant dystonia musculorum (*dt*) mouse that showed a recessive hereditary sensory neuropathy.



Seven Intermediate Filament Proteins in Neural Differentiation

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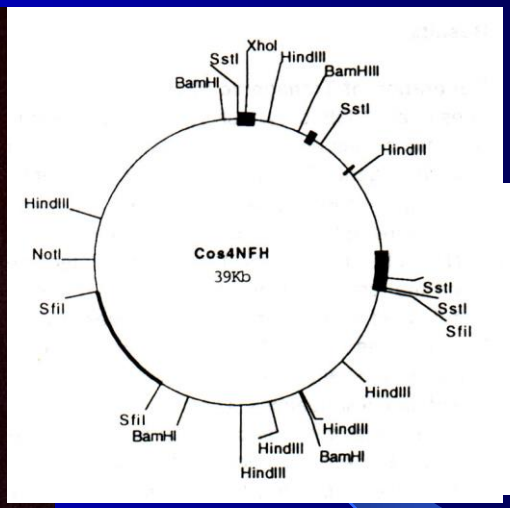
Volume 73 Number 1
April 9, 1993
Motor
Neuron
Disease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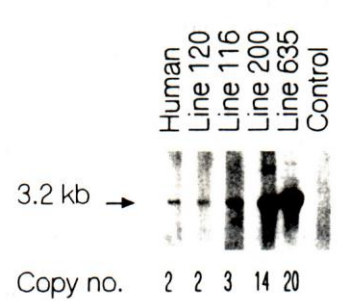
39Kb
XhoI
HindIII
BamHI
SstI
NotI
SfiI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Line 116
Line 200
Line 635
Control
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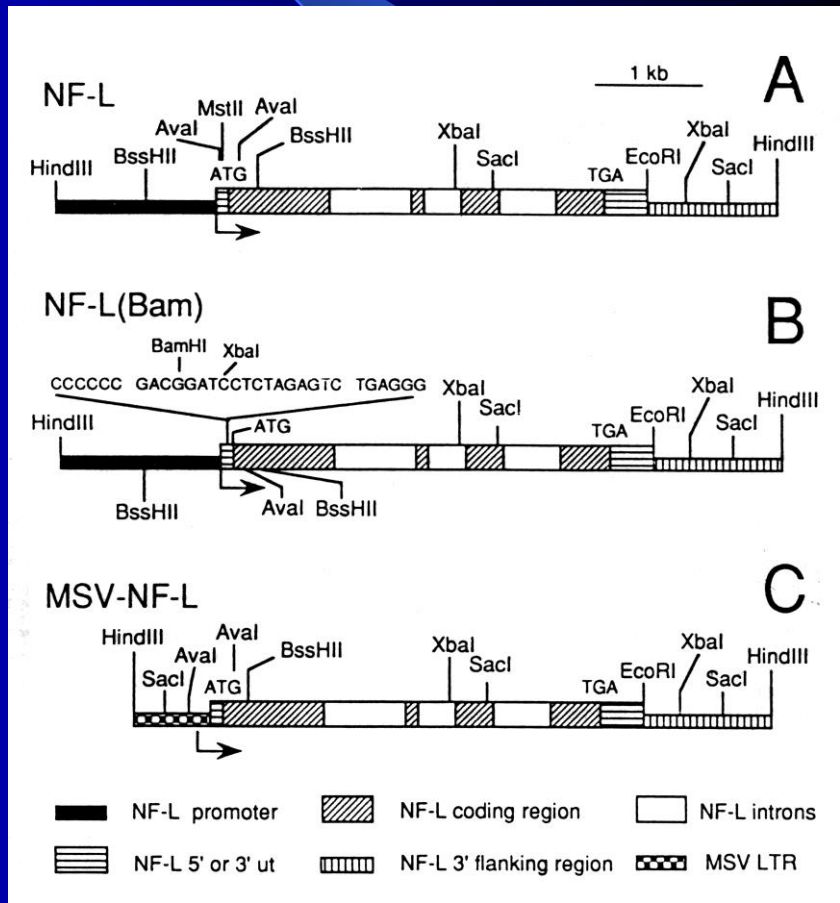
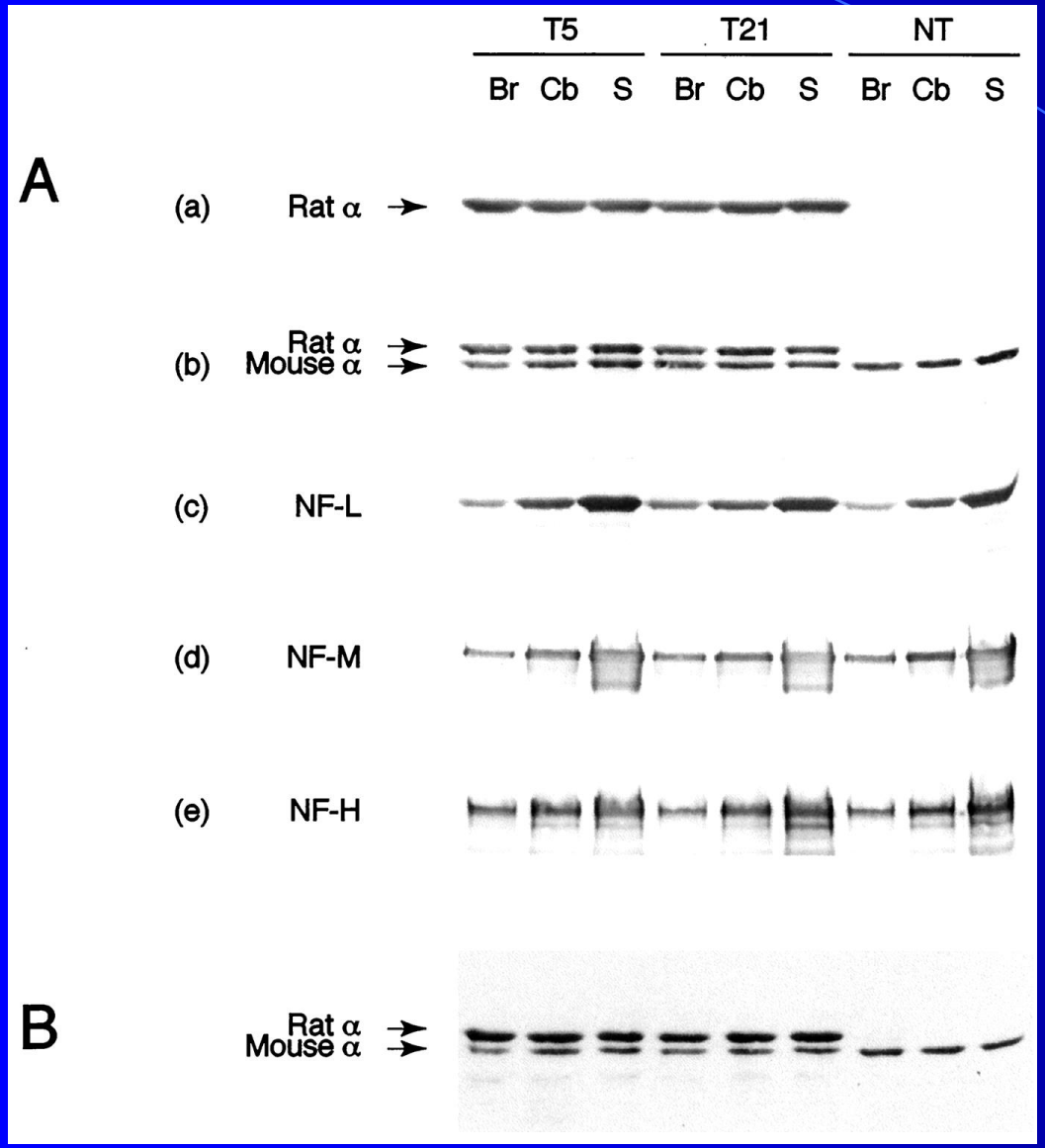
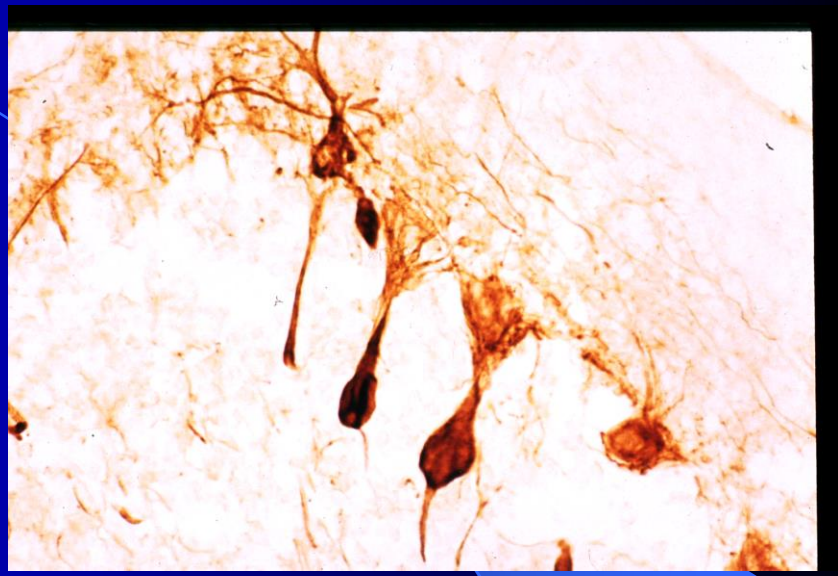
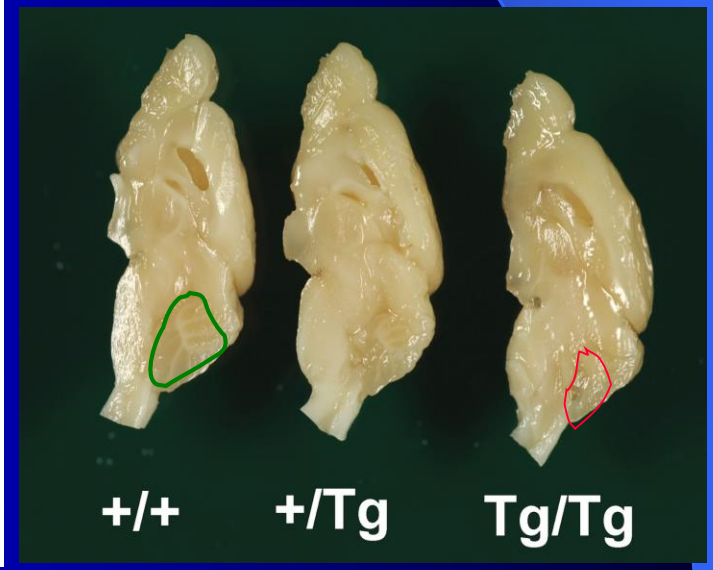
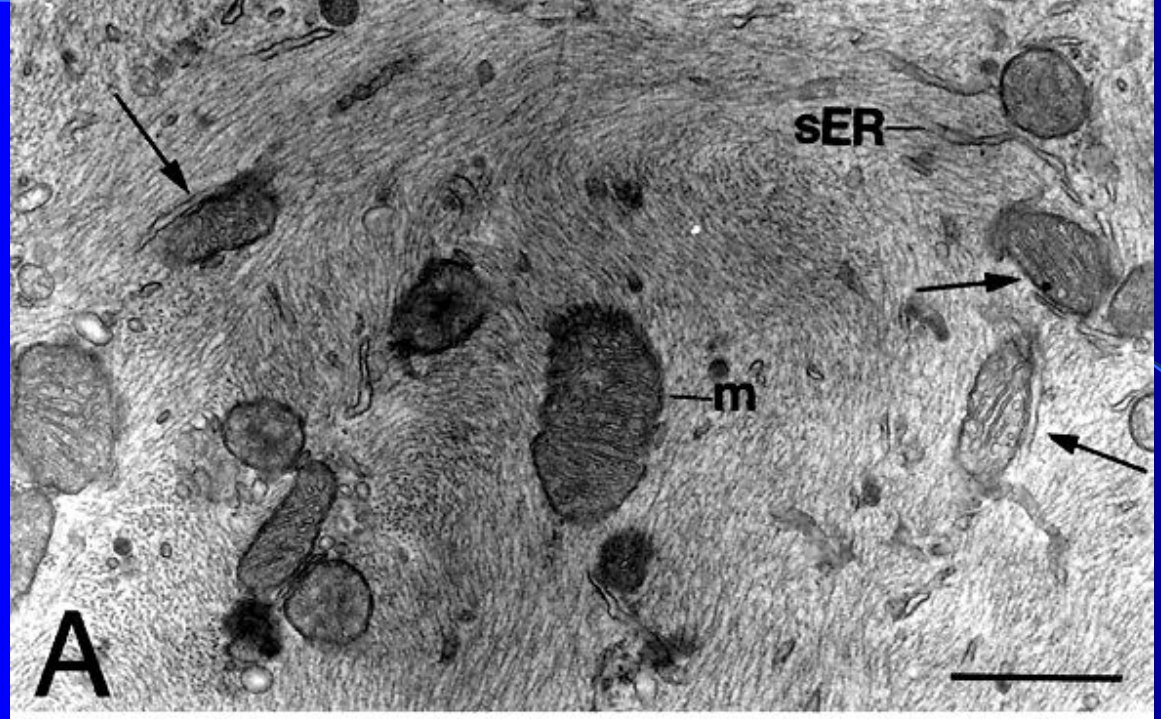

NF-L
1 kb
A
MstII
AvaI
BssHII
XbaI
SacI
EcoRI
HindIII
ATG
TGA
NF-L(Bam)
B
BamHI
CCCCCC GACGGATCCTCTAGAGTC TGAGGG
MSV-NF-L
C
NF-L promoter
NF-L coding region
NF-L introns
NF-L 5' or 3' ut
NF-L 3' flanking region
MSV LTR

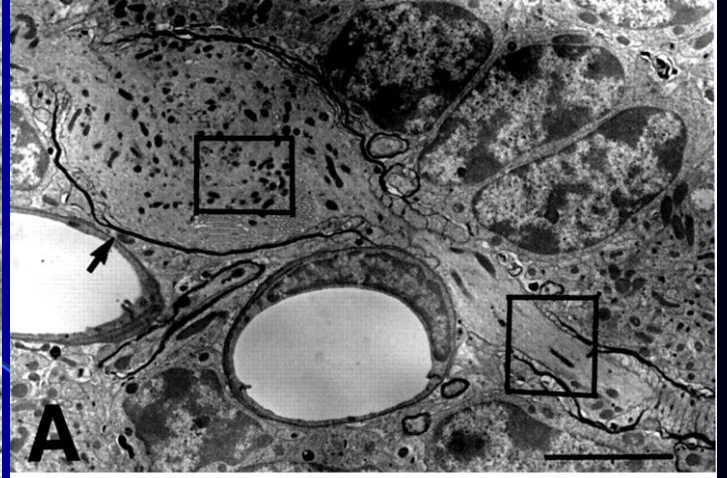
Animal model for cerebellar atrophy (J. Neurosci. 19:2974-2986, 1999)








sER
m
A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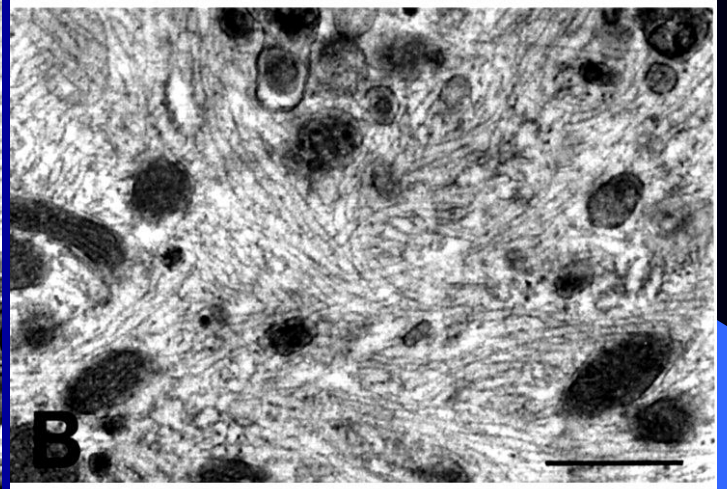
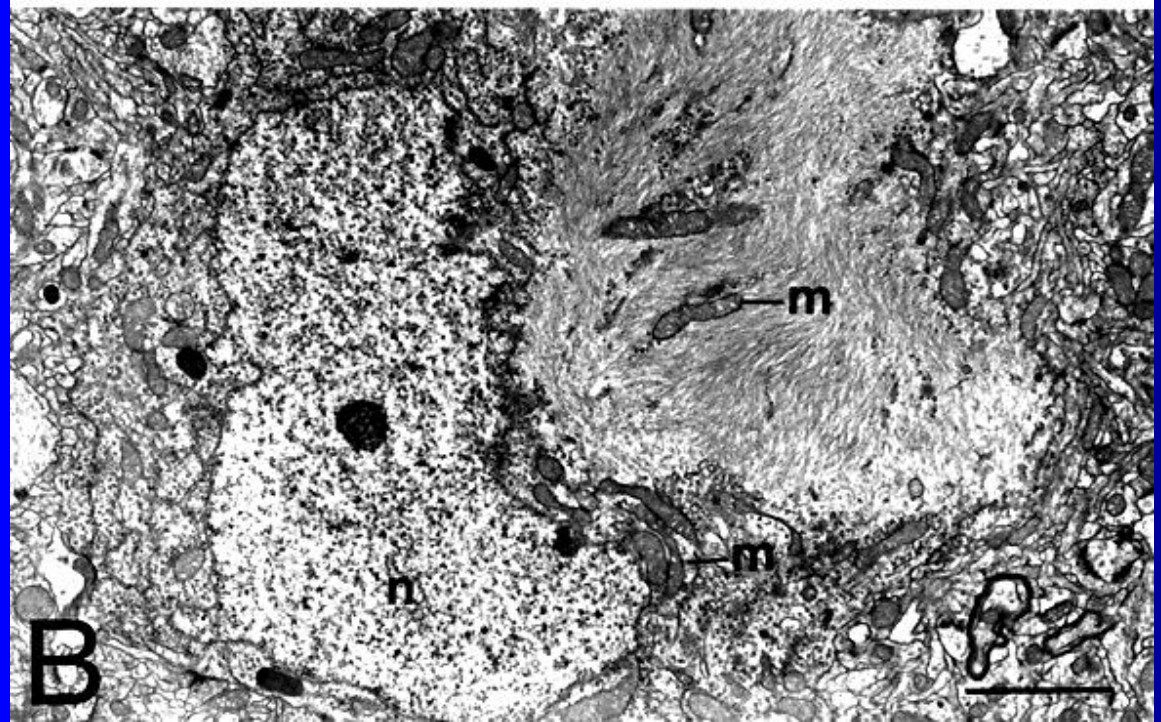

B


m
m
n
B


C

12 m cerebella

18 m cerebella

18 m thalamus

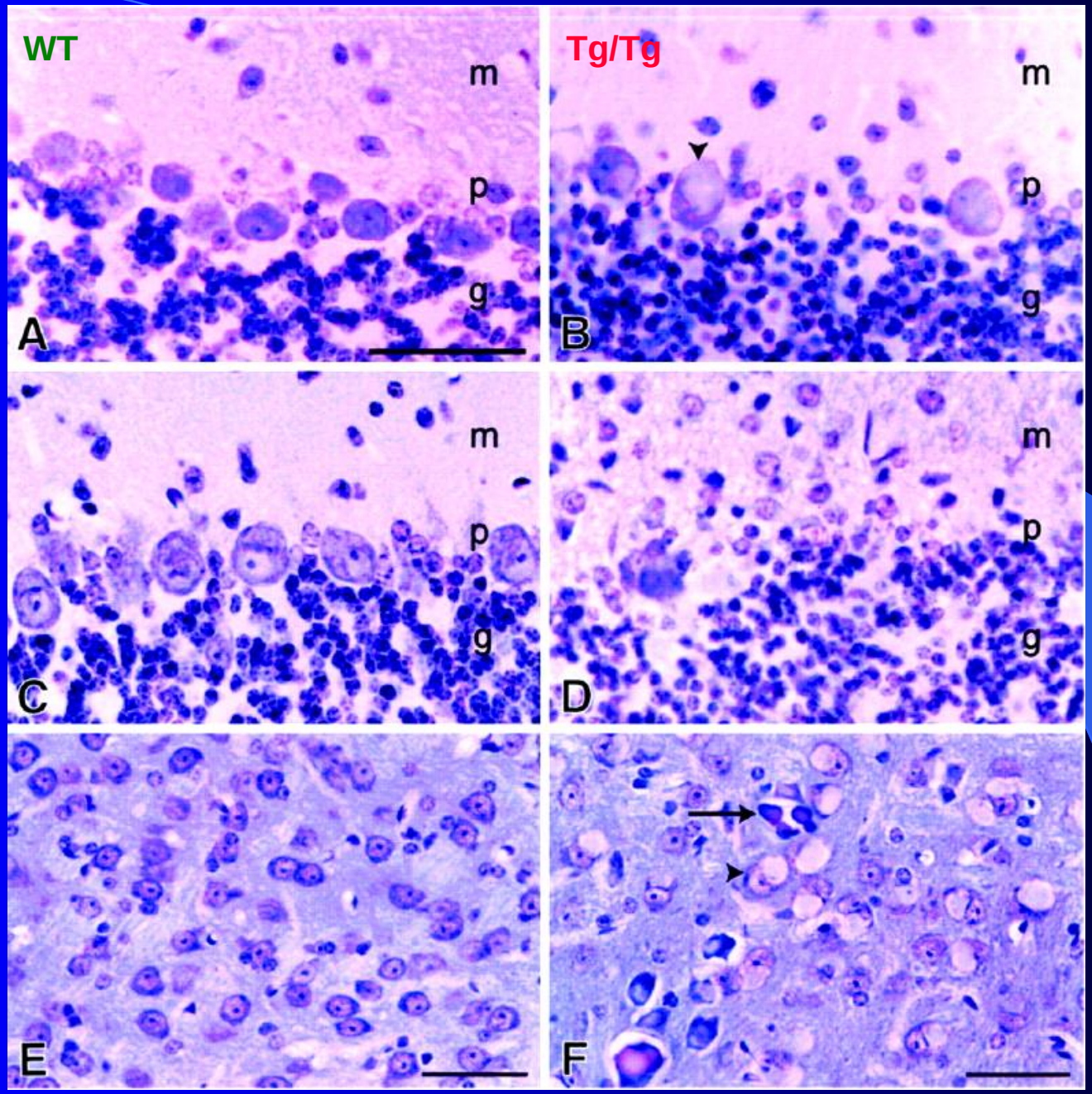


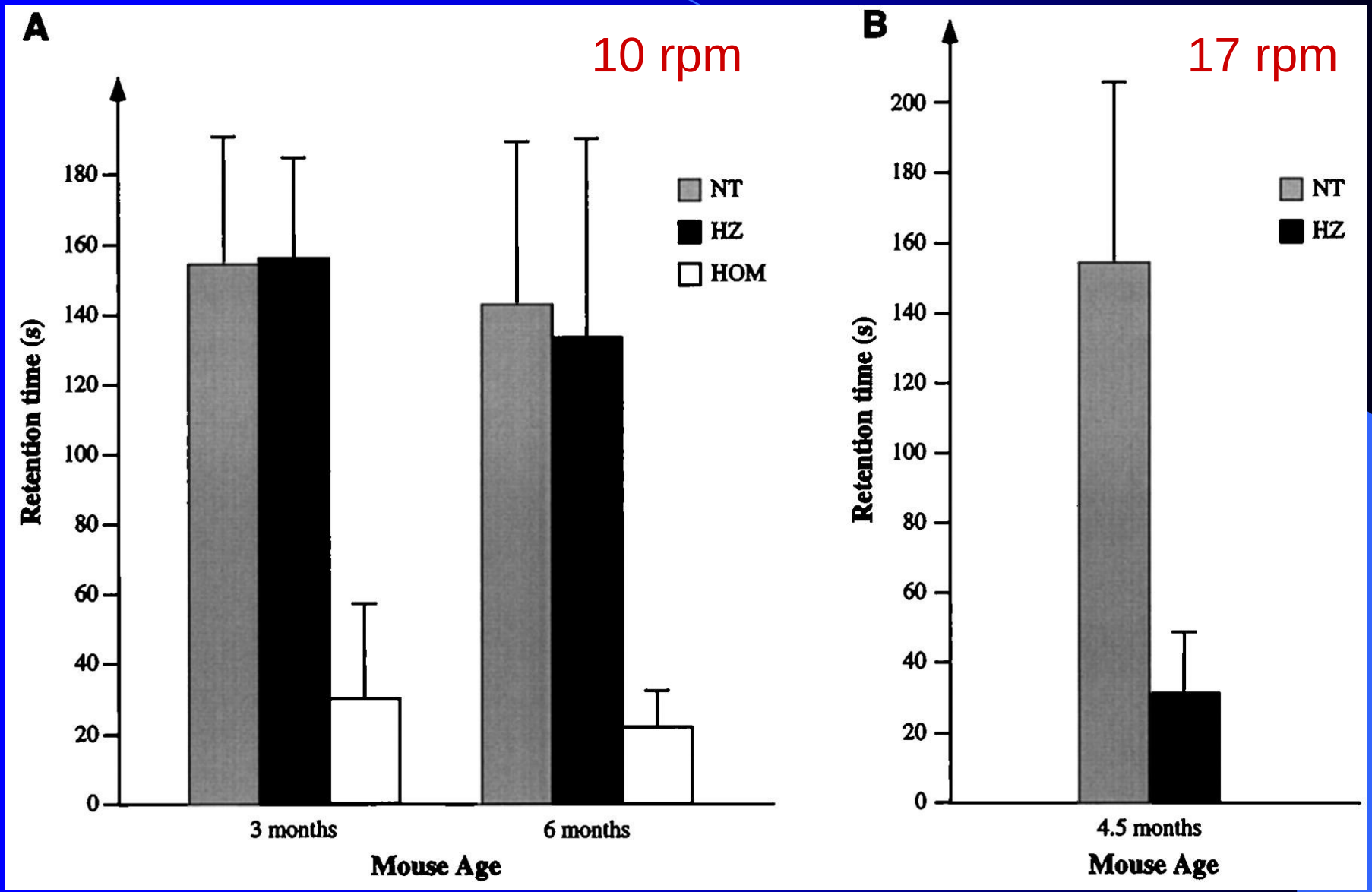
Table 2. Quantitation of Purkinje cell numbers in transgenic mice overexpressing α -internexin

Genotype	Age (months)	Number of Purkinje cells present (%)*
Hemizygous	12	83.4 ± 2.1
	18	39.4 ± 4.4
Homozygous	12	62.6 ± 3.7
	18	28.5 ± 5.1

*Numbers of Purkinje cells present in the transgenic mice are expressed as percentages of those in the nontransgenic littermates.

Values given are means ± SD (from quantitation of three or four pairs of transgenic/nontransgenic mice in each group).

Comparison of performance in the rotorod test



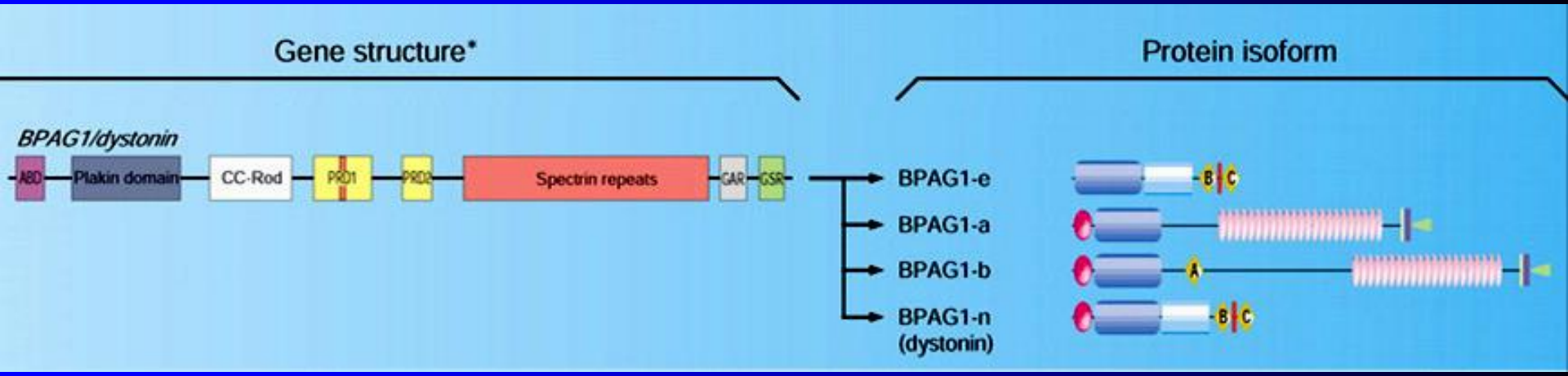
Summary

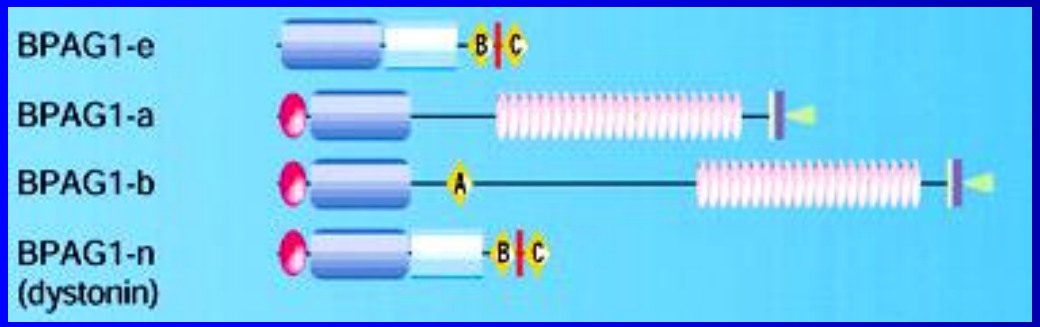
1. high levels of misaccumulated neuronal intermediate filaments lead to neuronal dysfunction, progressive neurodegeneration, and ultimate loss of neurons.

2. the degrees of neuronal dysfunction and degeneration are proportional to the levels of misaccumulated neuronal intermediate filaments.

- *Dystonia musculorum (dt)* mouse is a recessive hereditary sensory neuropathy of the mutant mouse, which is defective in *BPAG1* gene.
- It is a very interesting neurological mutant, first discovered as a spontaneously occurring, autosomal recessive variant (Duchen et al., 1963).
- Mice affected with *dt* are seemingly normal at birth, but by 10–12 days they begin twitching, writhing, and exhibiting uncoordinated movements.

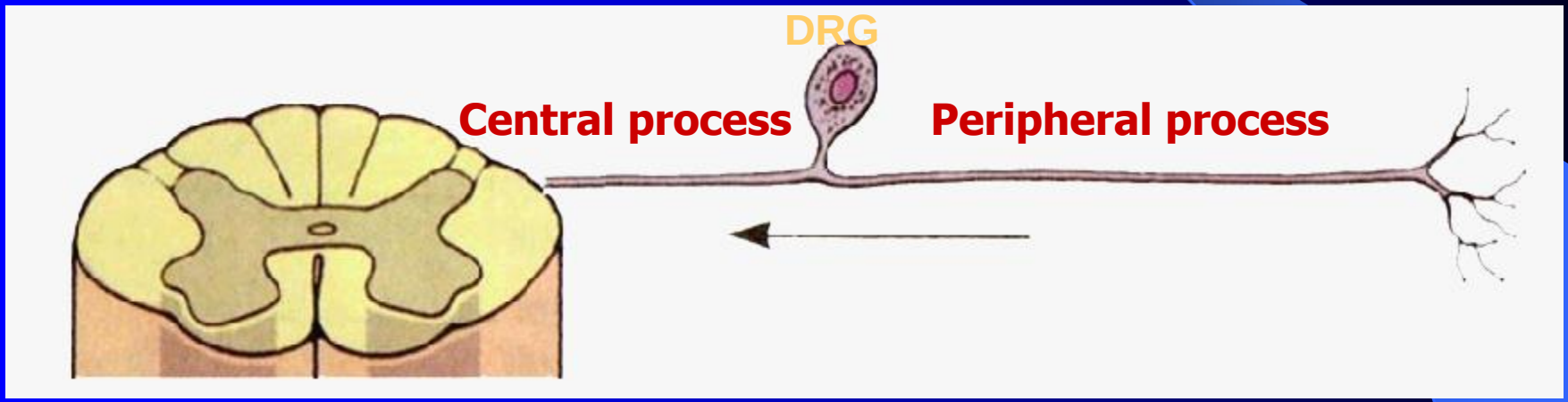
- Dystonin, a neural isoform of BPAG1, contains actin-binding domain (ABD) at N-terminus, and is a cytoskeletal crosslinker protein.

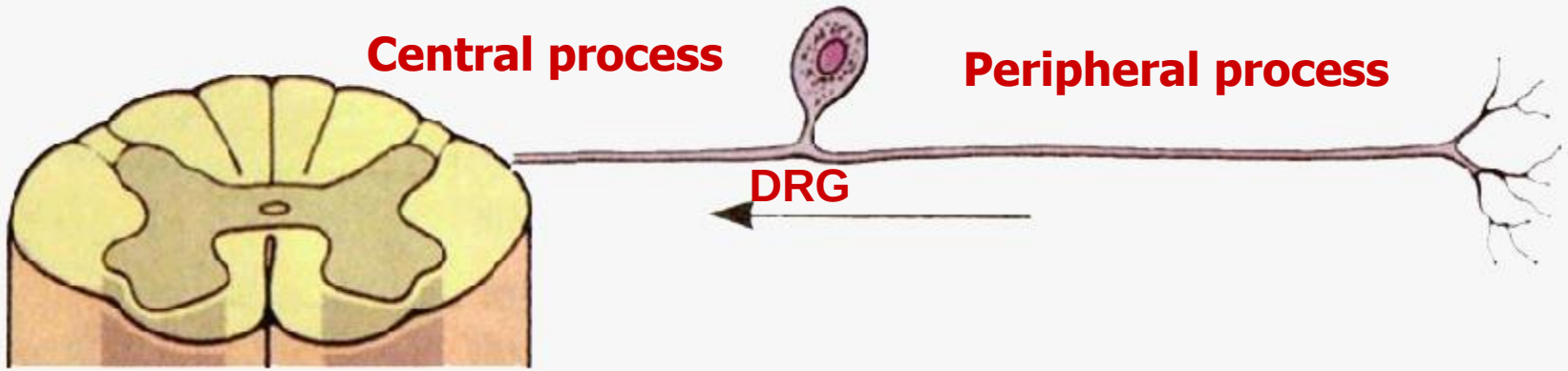




BPAG1: bullous pemphigoid antigen 1

To study the neural dysfunction and degeneration of primary sensory neurons in dorsal root ganglia and motor neurons in ventral horn of spinal cord in *dt* mice.



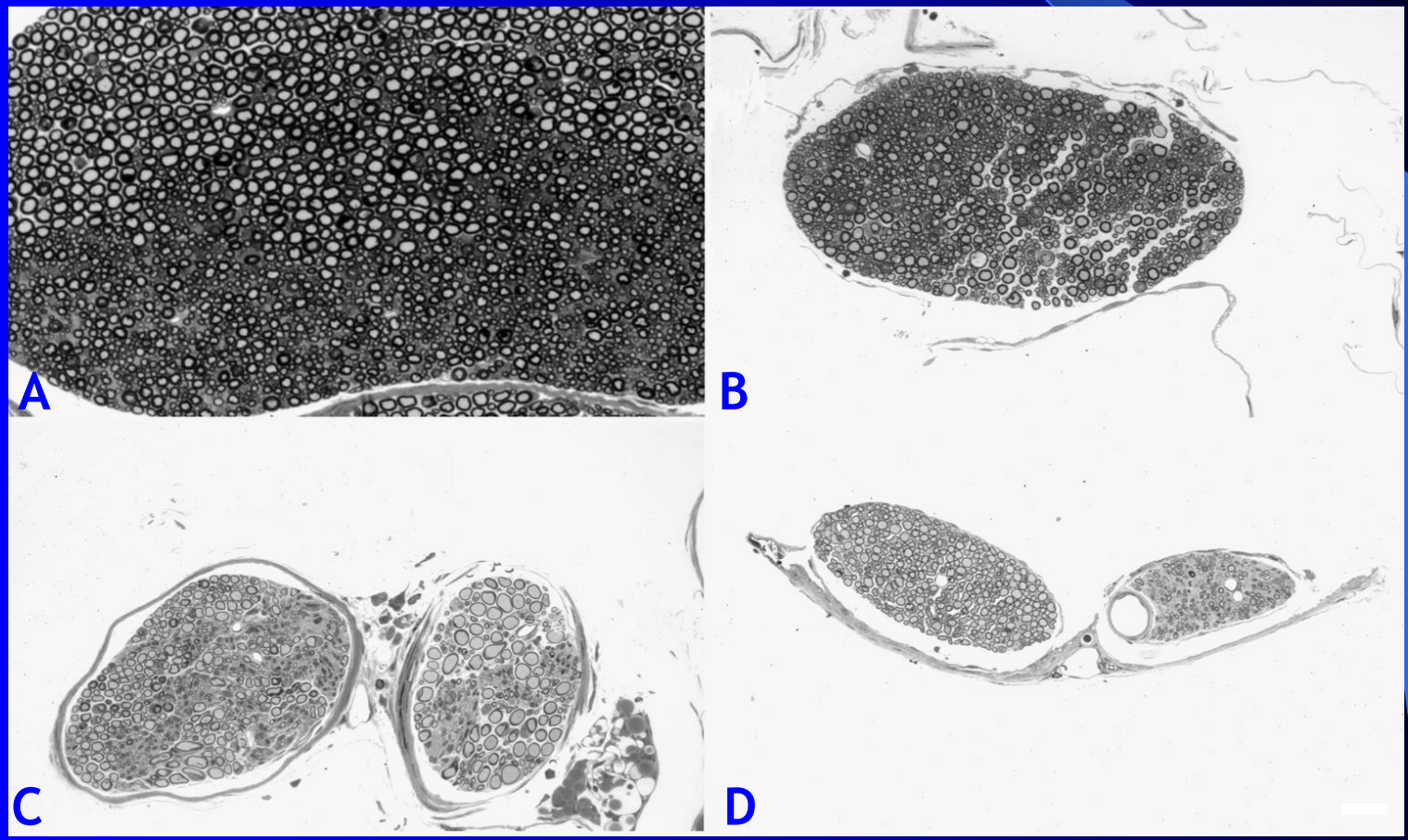


Peripheral process

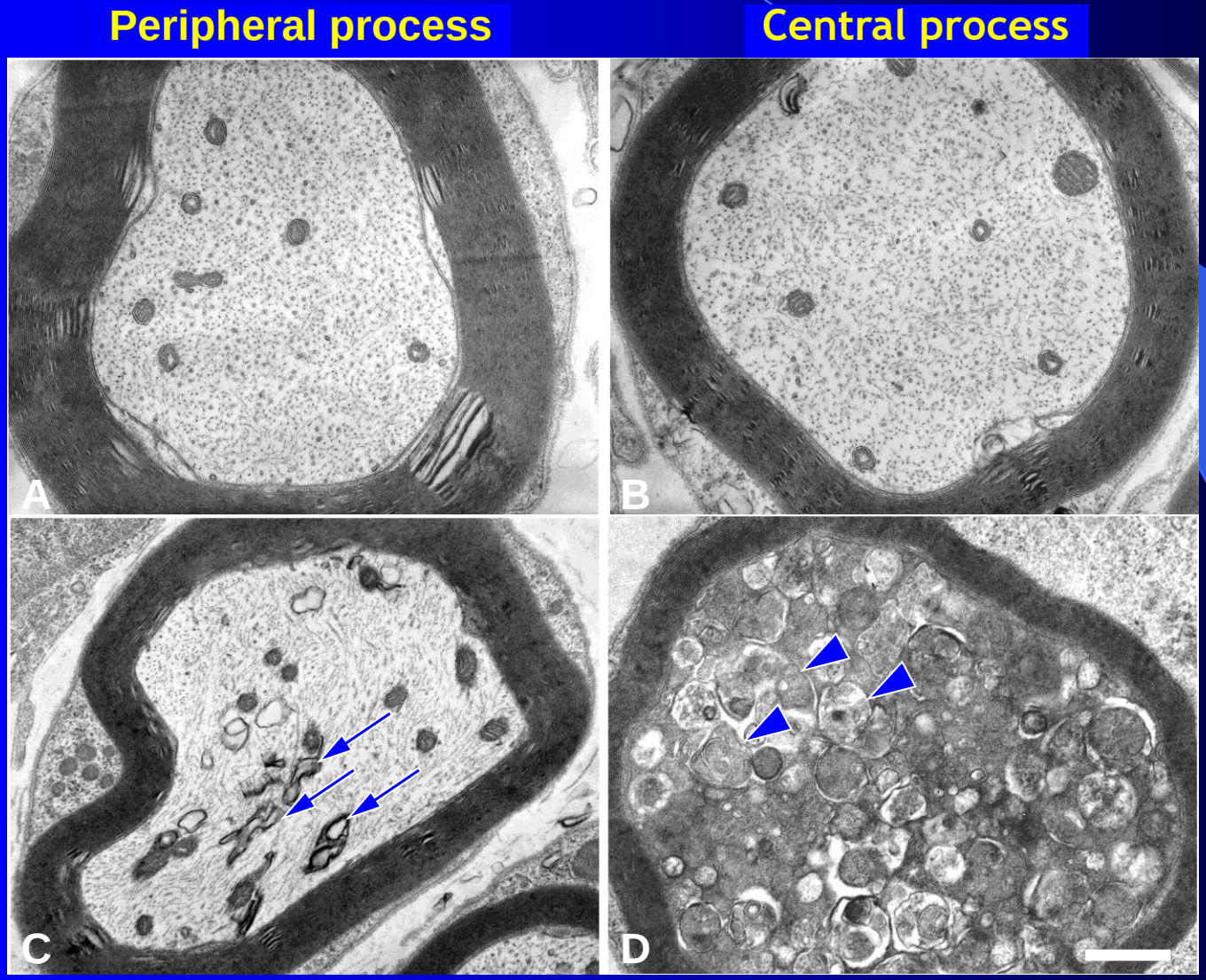
Central process

WT

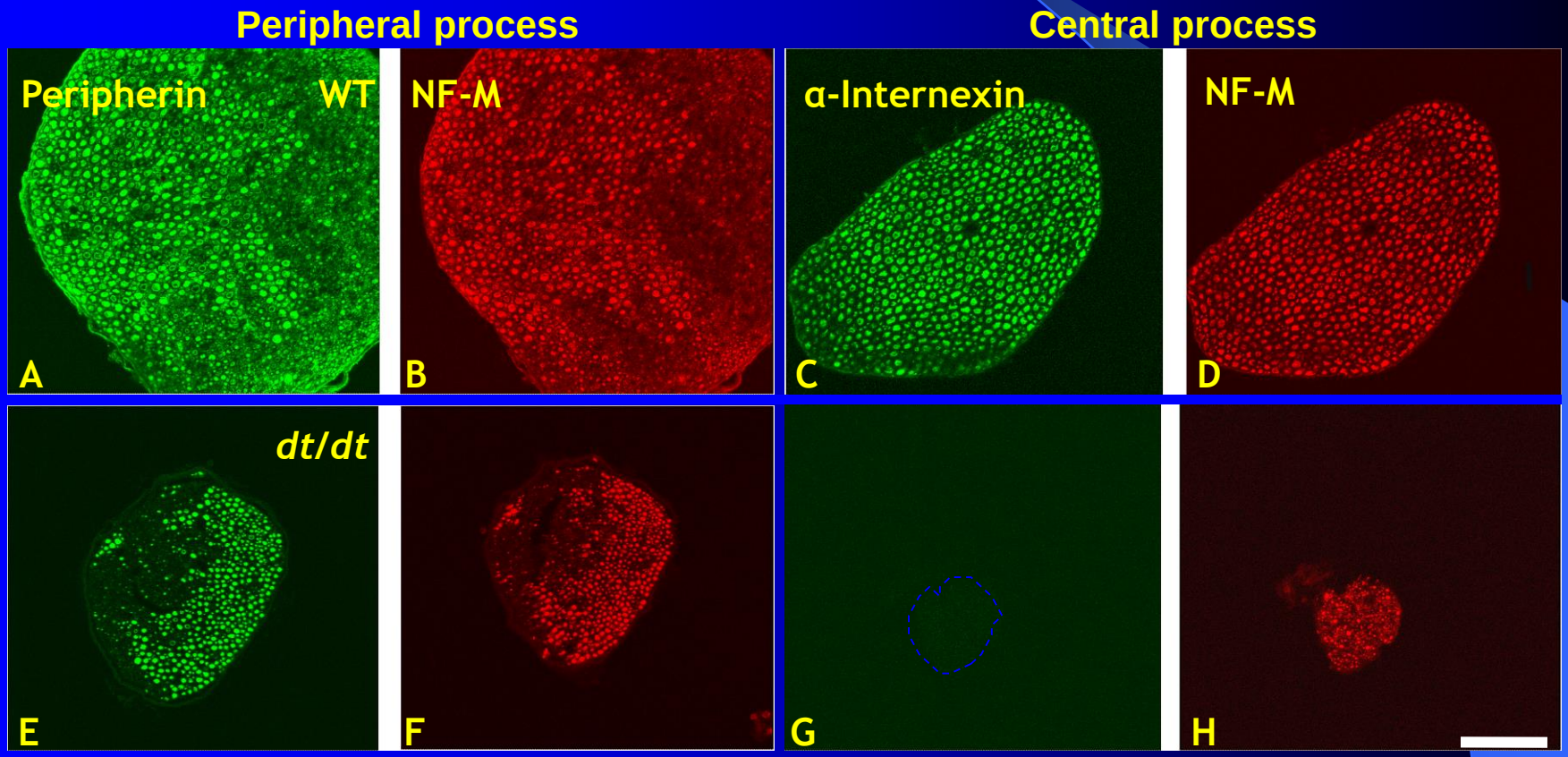
dt/dt



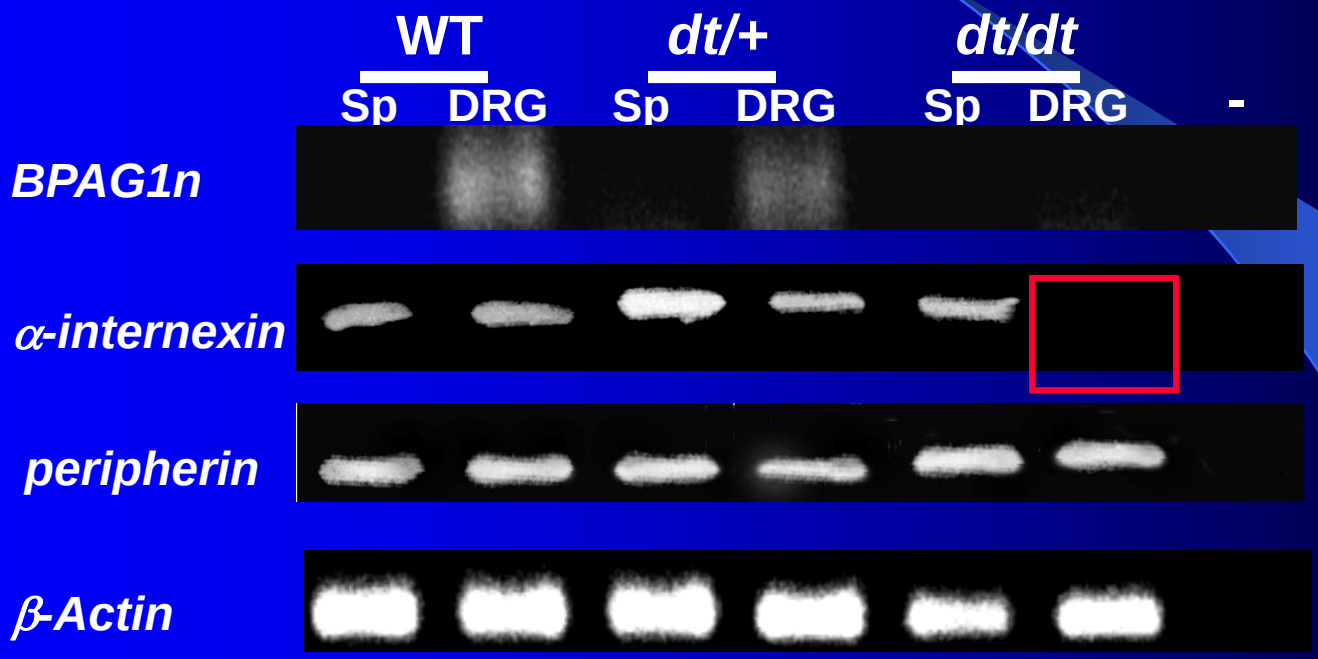
Ultrastructures of peripheral and central process from WT and *dt/dt* mice



Expression of neurofilaments in WT and *dt/dt* mice

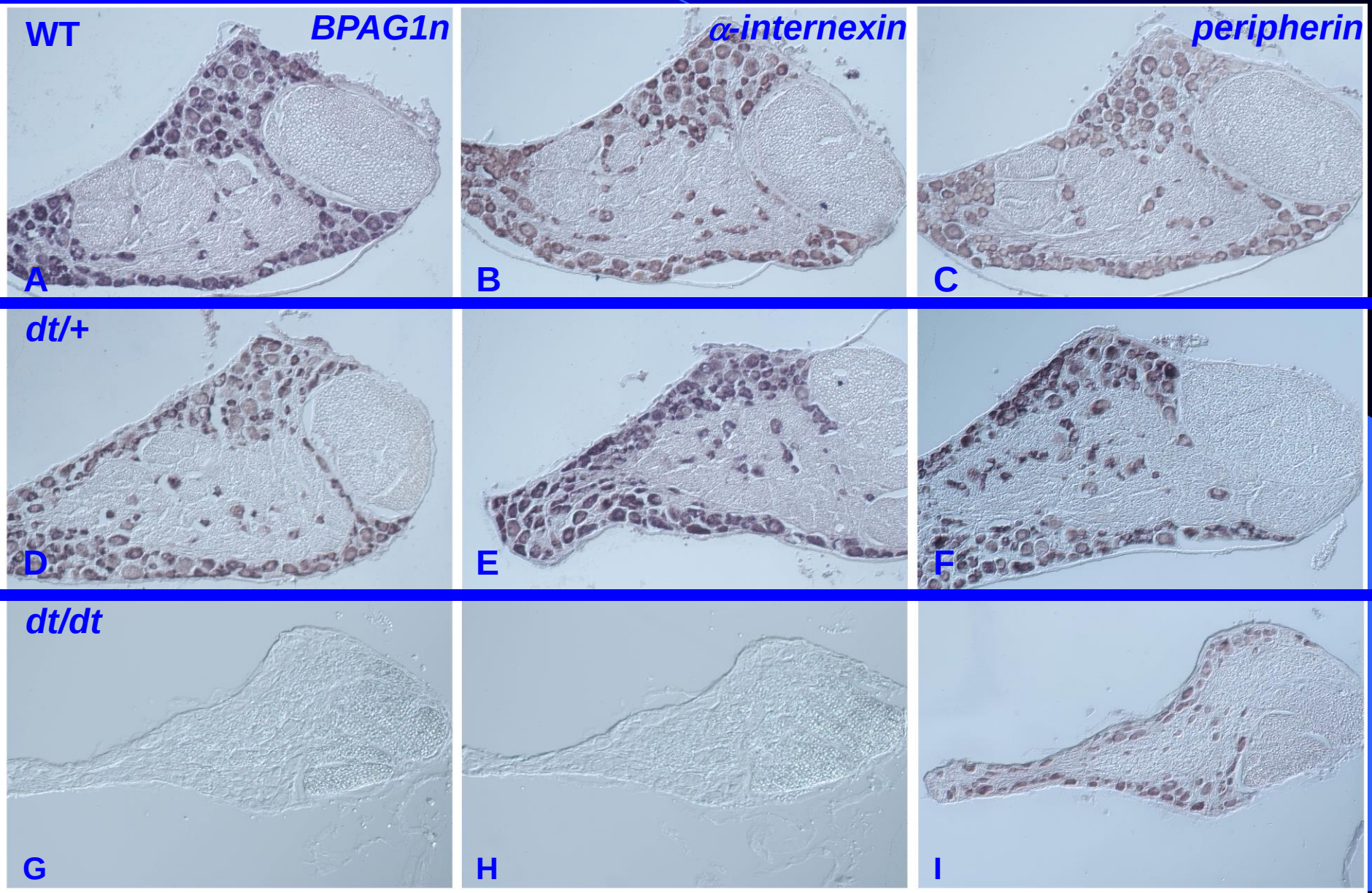


RT-PCR analysis

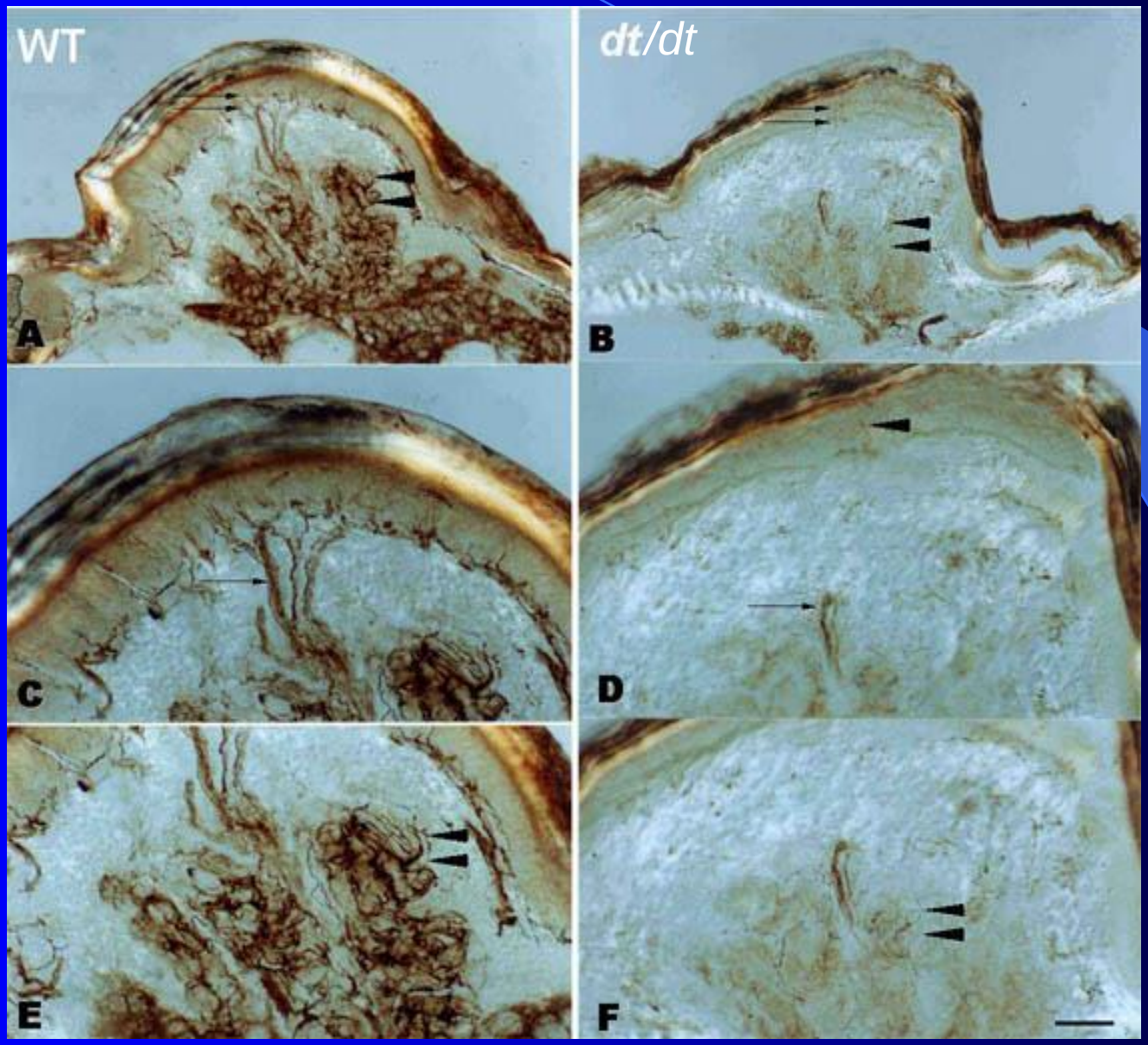


Why ***α-internexin*** disappeared in the DRG of *dt/dt* mutant?

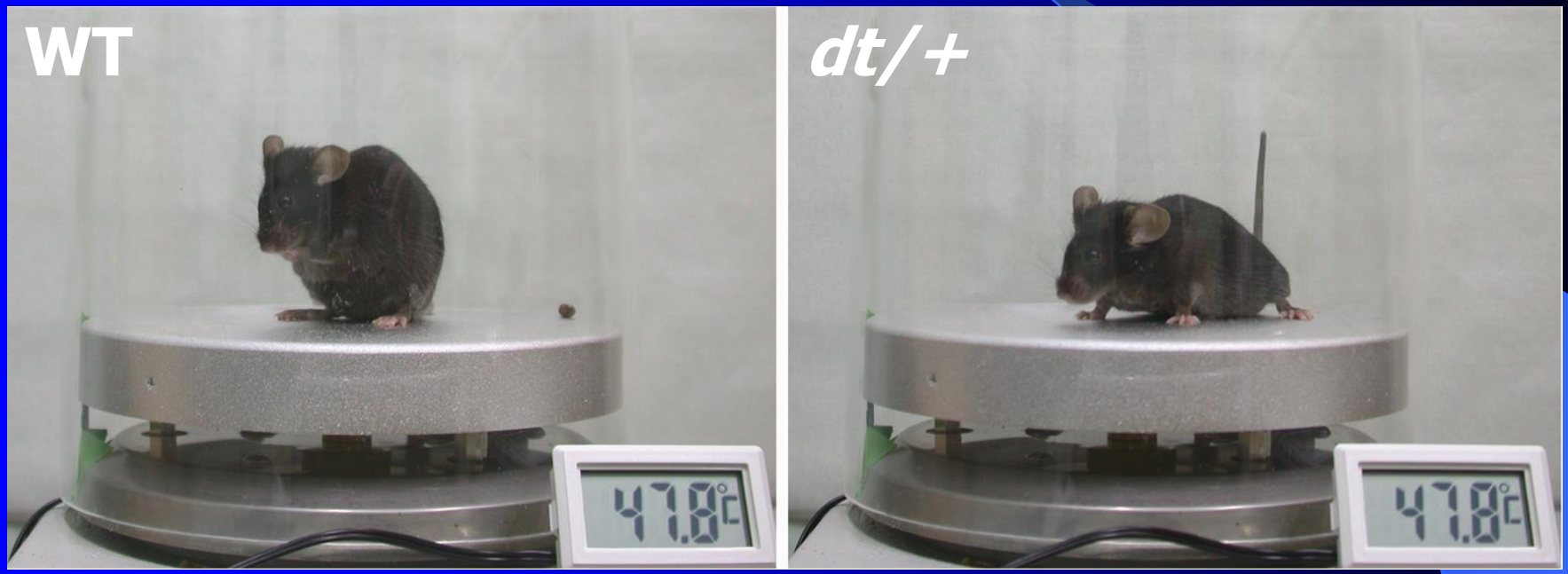
In situ hybridization analysis the *BPAG1n*, *α-internexin* and *peripherin*



Sensory and autonomic nerves in the skin

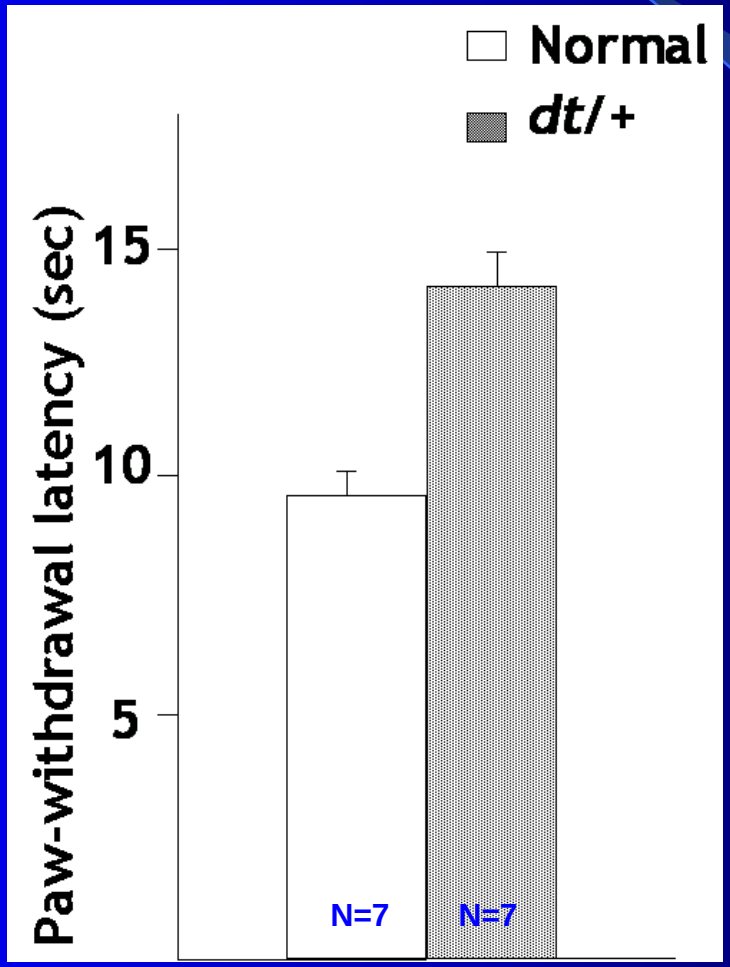


Different performances of *dt*/+ and WT mice in the hot plate test

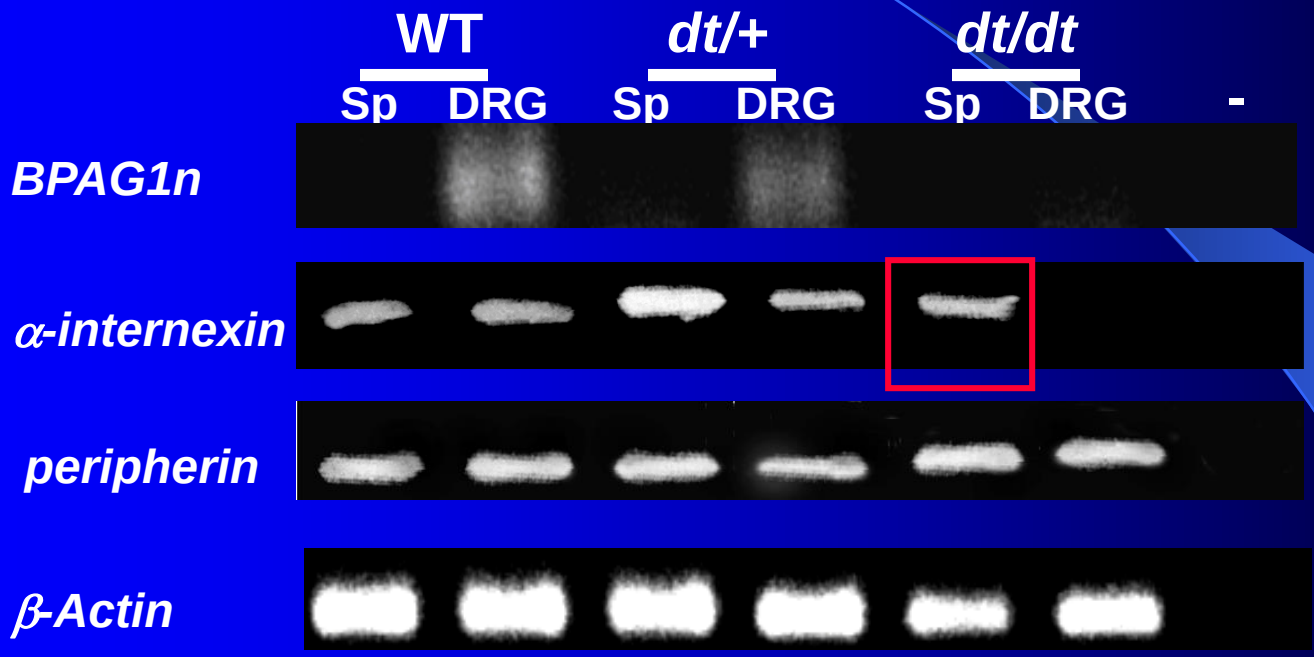


Hot-plate test was used to measure the mouse response latencies

dt/+ mice showed the longer paw-withdrawal latency

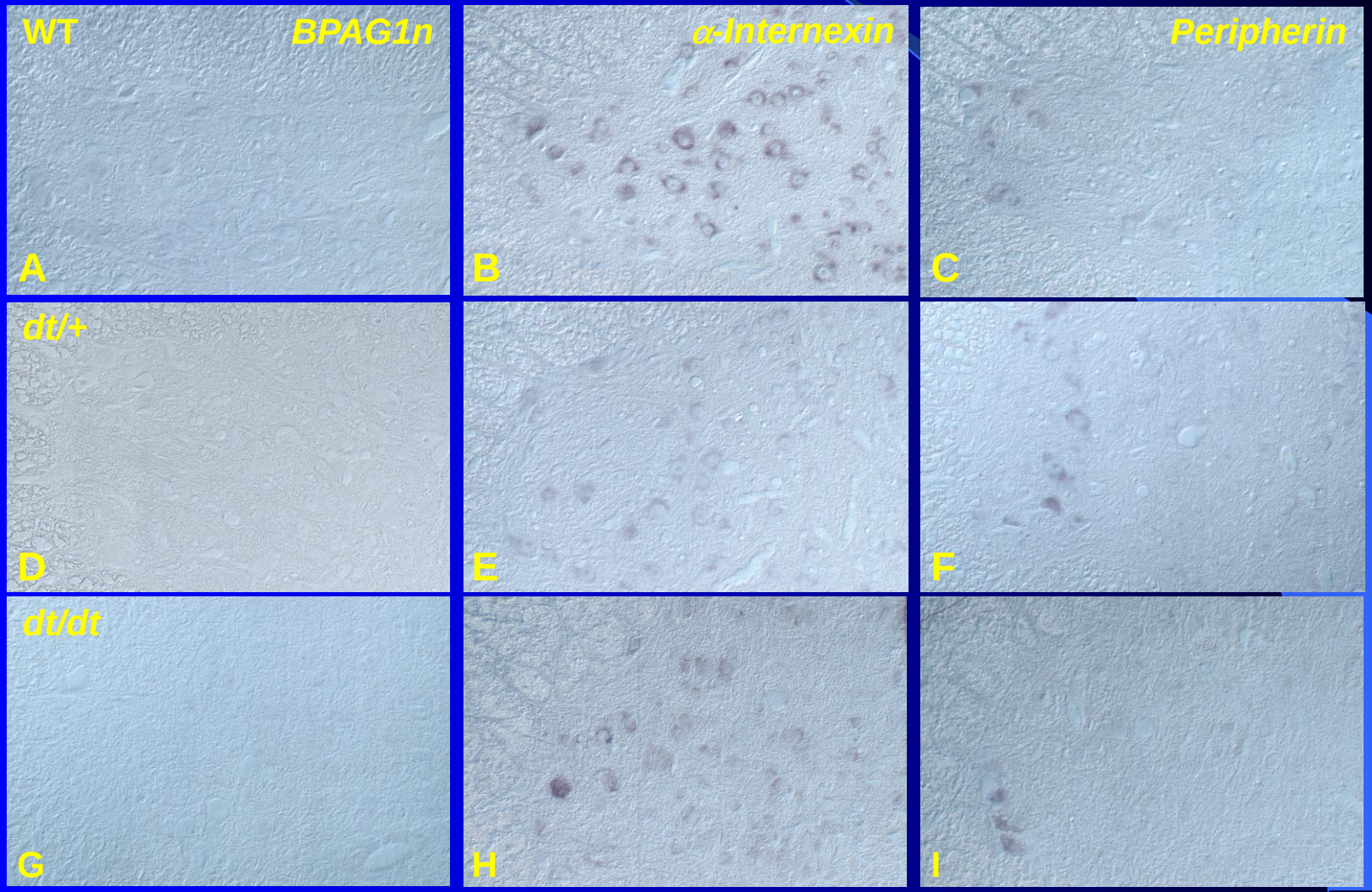


RT-PCR analysis

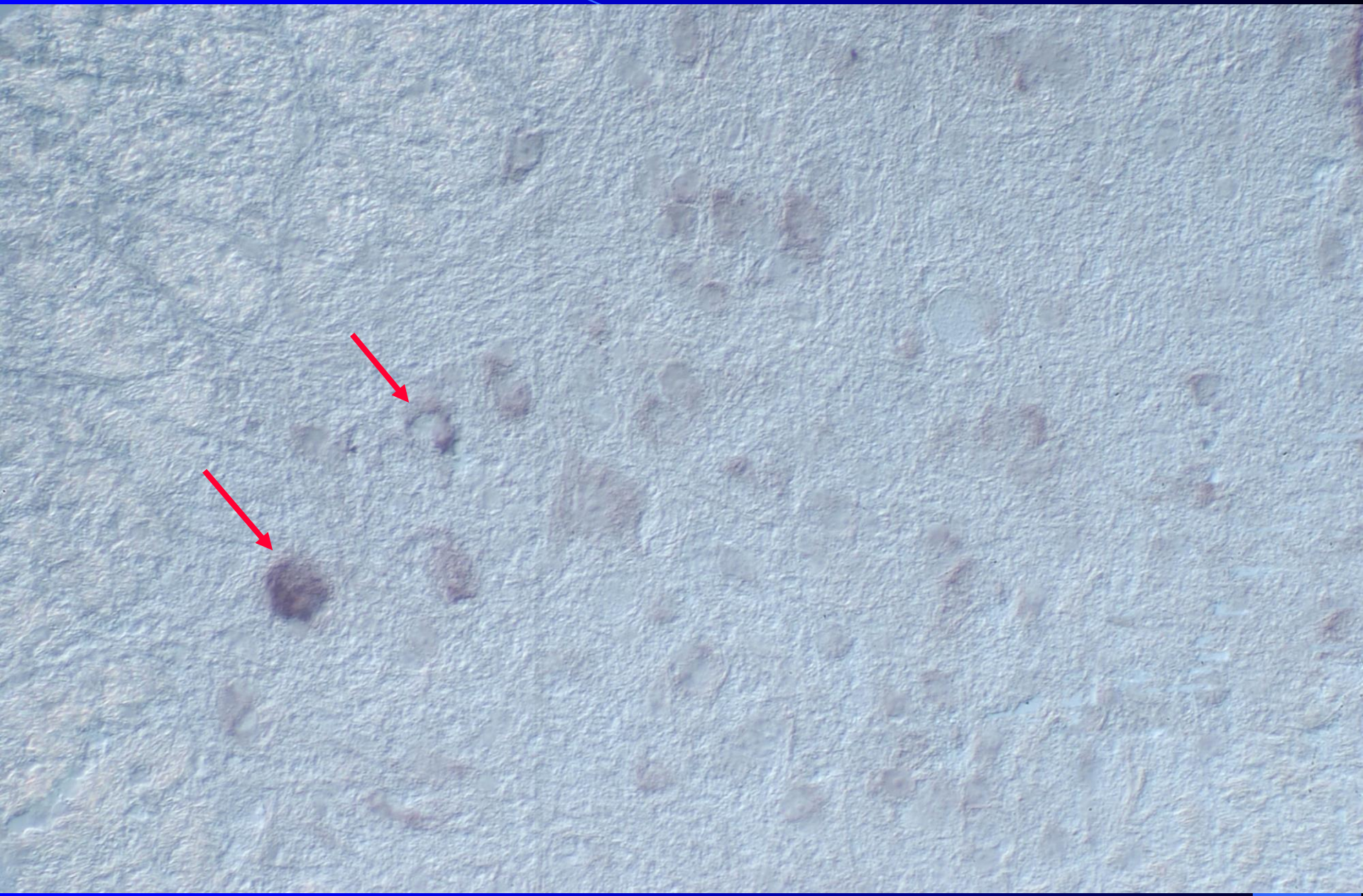


α-internexin **plays what kind of role in the spinal cord of dt/dt mutant?**

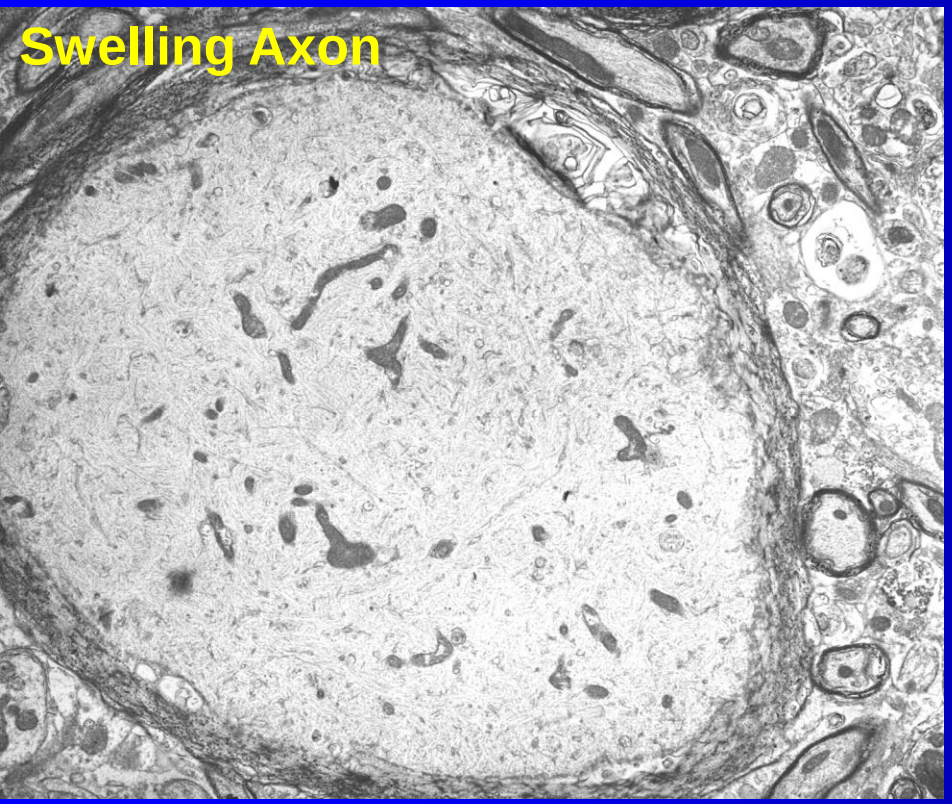
In situ hybridization analysis the *BPAG1n*, *α-internexin* and *peripherin* mRNA in the ventral horn of spinal cord

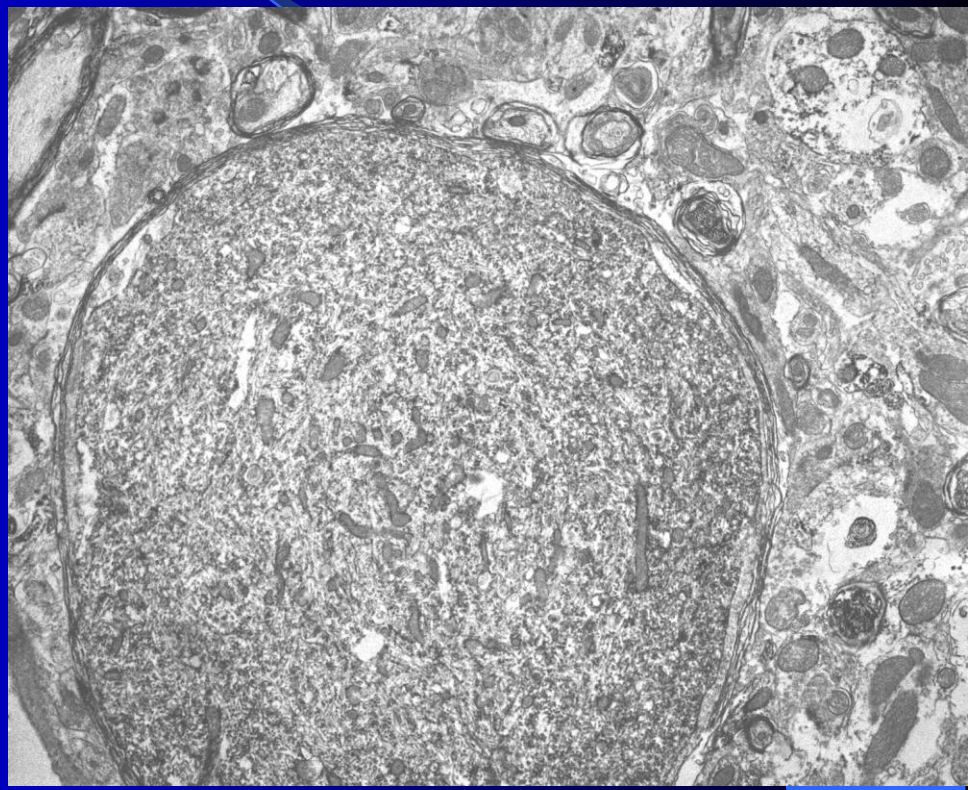


In situ hybridization analysis the α *-internexin* mRNA in the ventral horn of *dt/dt* spinal cord

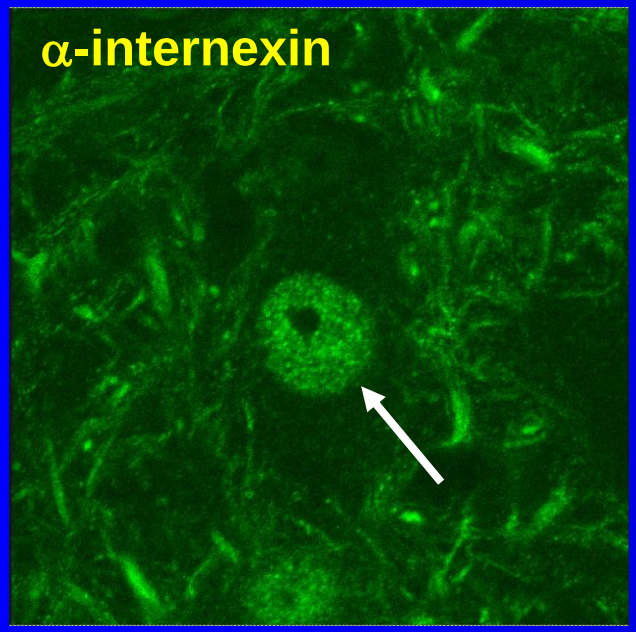


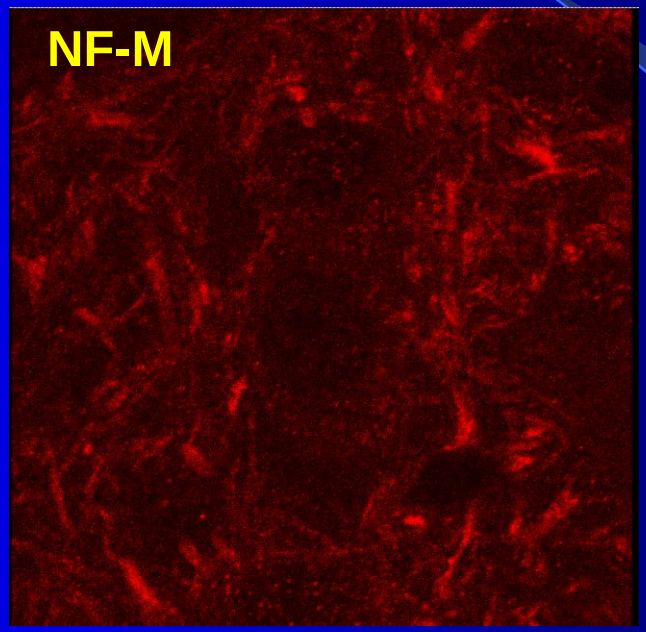
Immunostaining of α-internexin in Swelling Axon of Motor Neuron

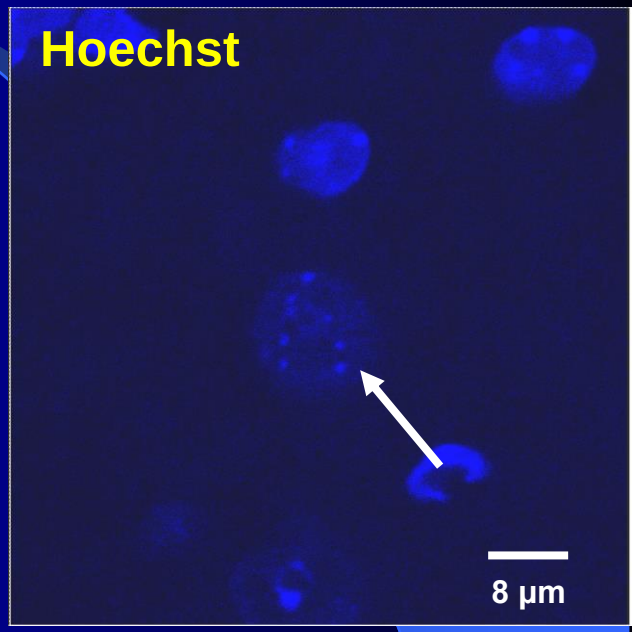




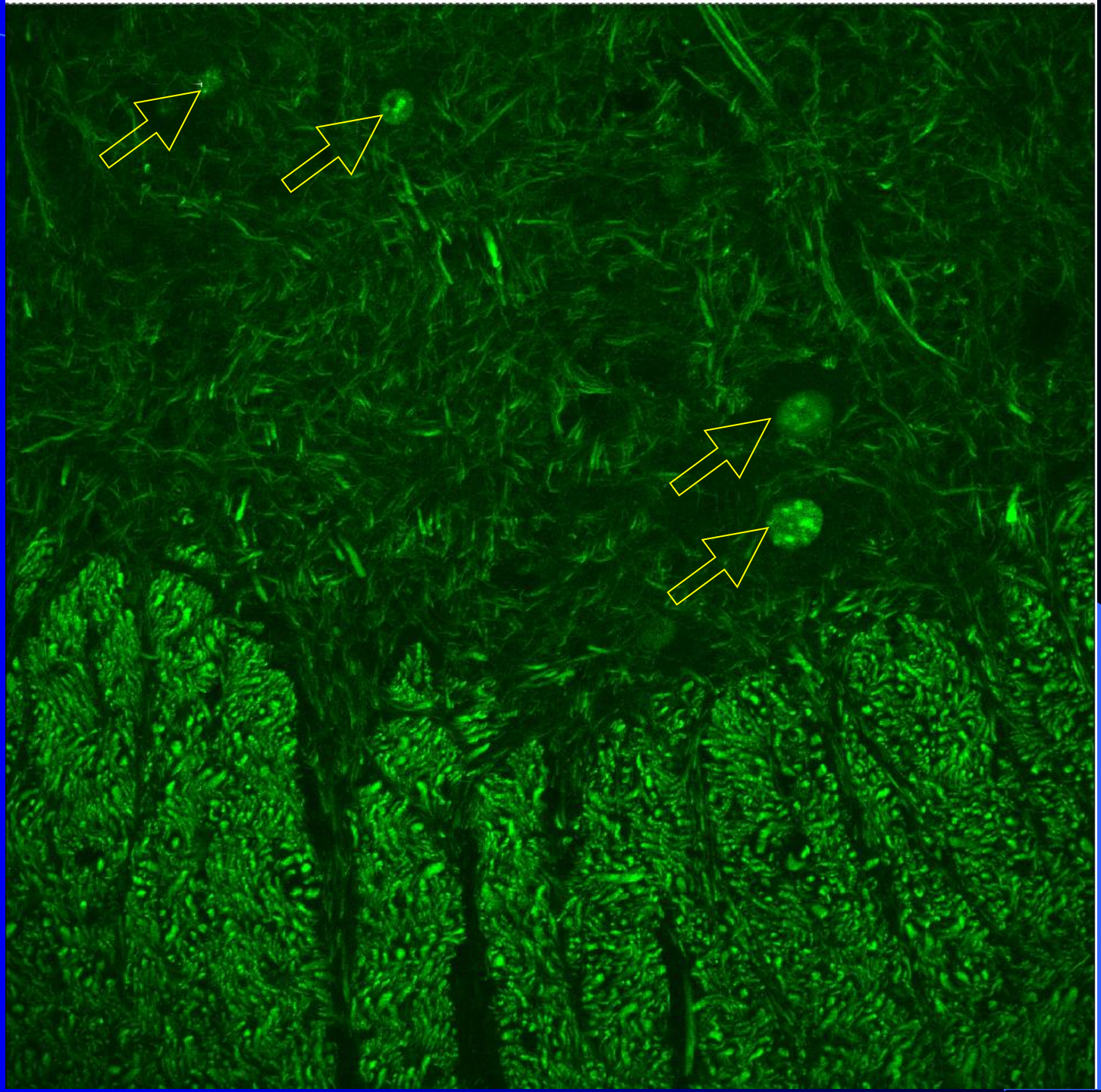
α -internexin translocated into cell nucleus of motor neuron in the *dt* spinal cord



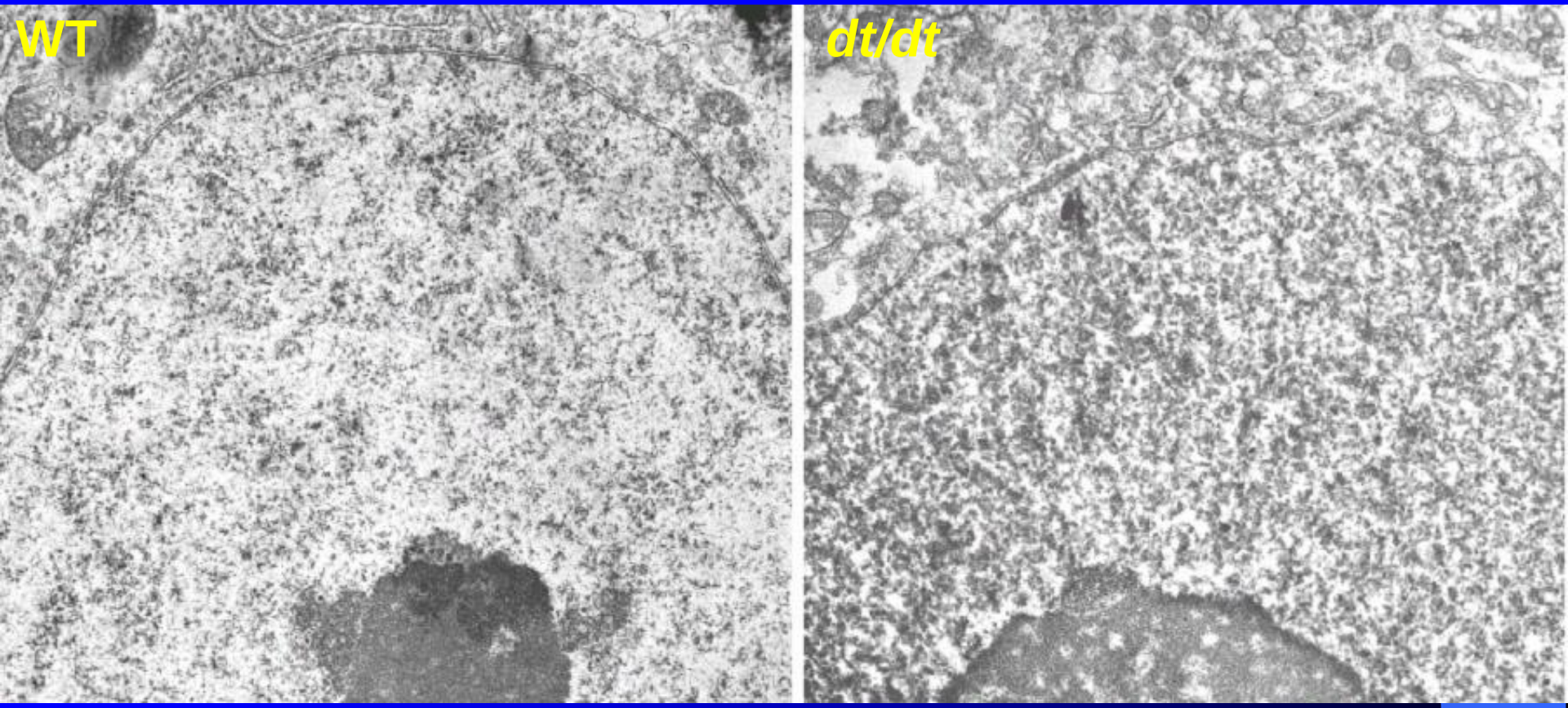


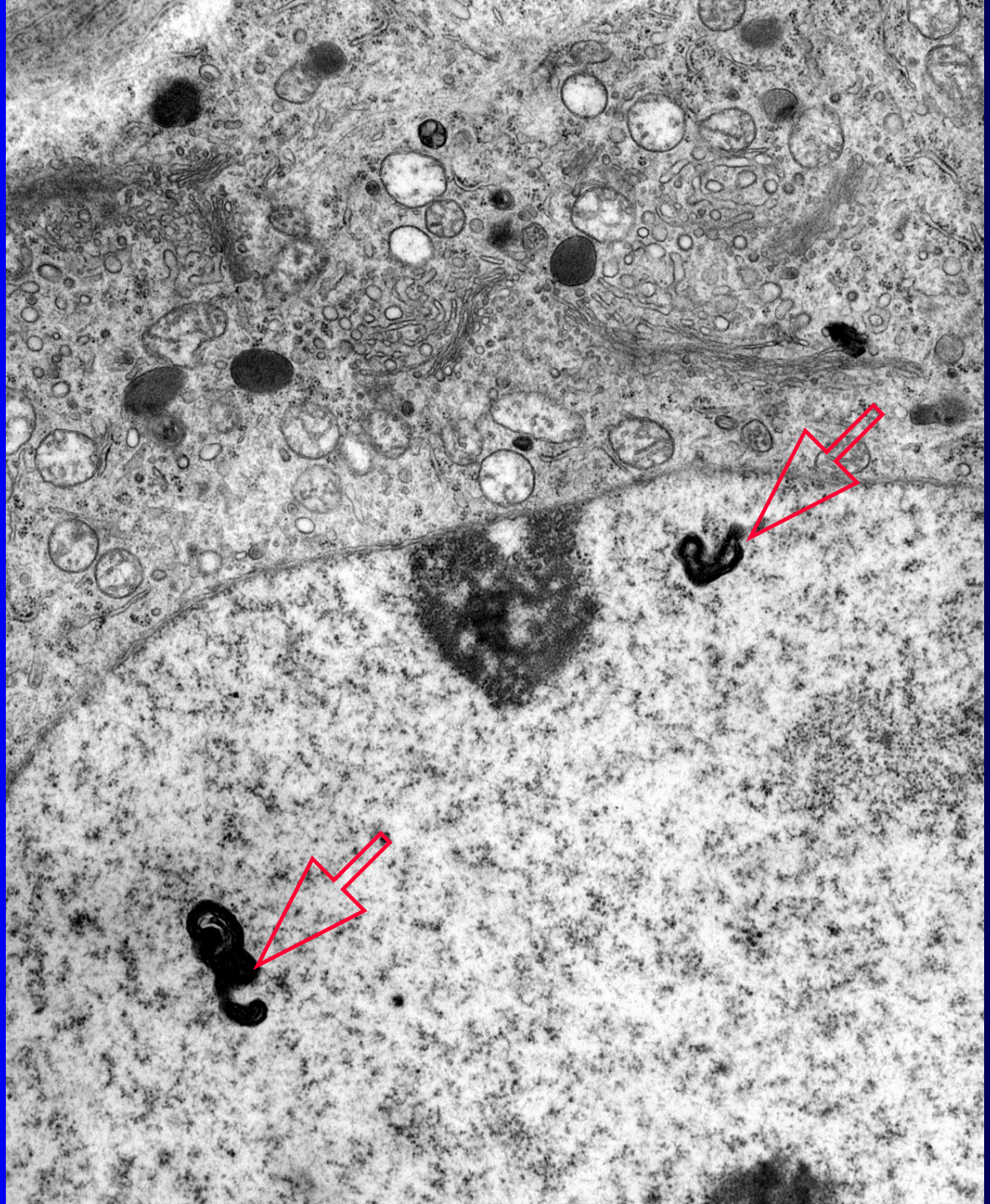


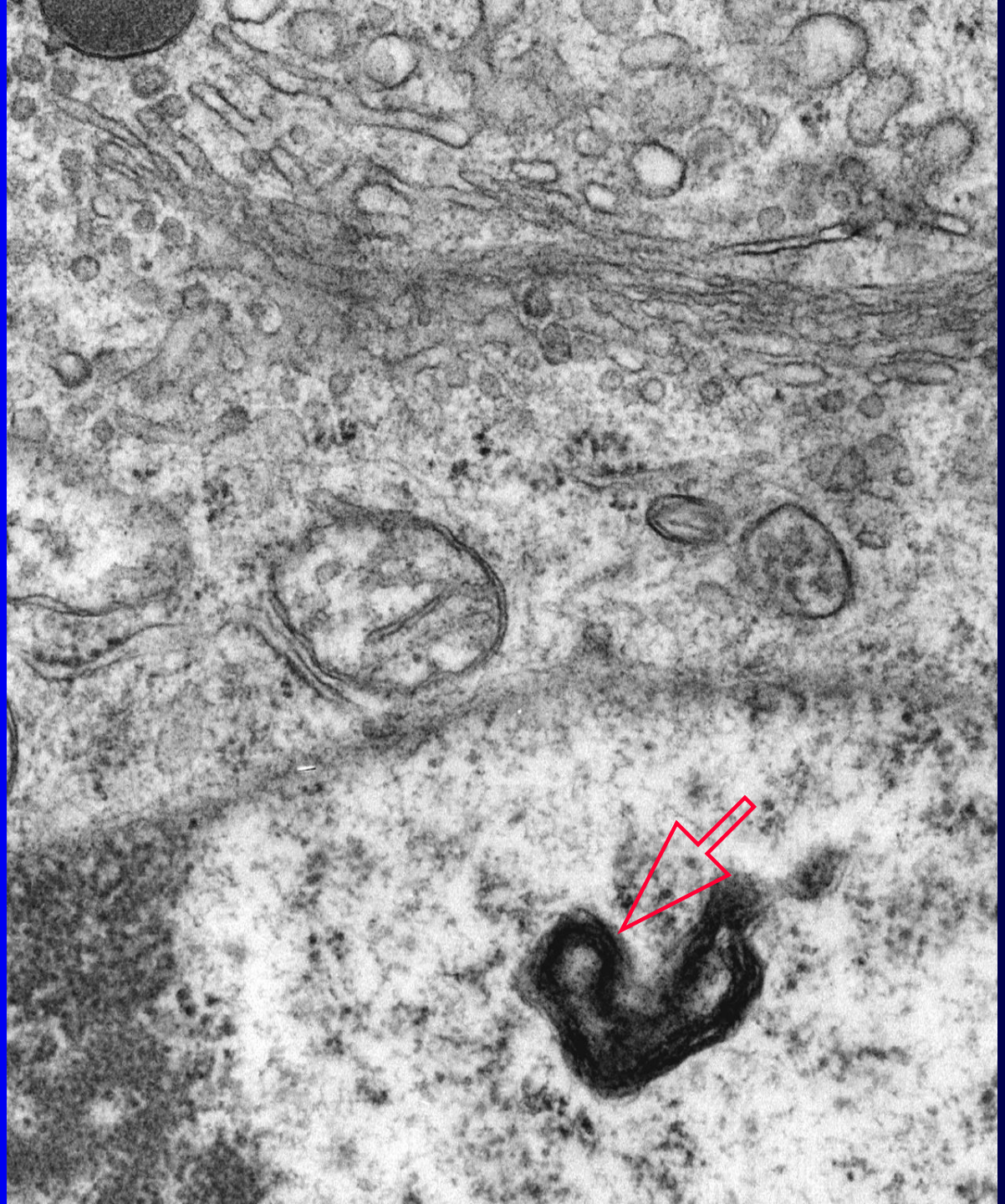
α -internexin translocated into cell nucleus of motor neuron in the *dt* spinal cord



Immunoreactivity of α-internexin in Nucleus of Motor neuron







Summary

1. We demonstrated that α-internexin is localized in DRN and its mRNA is expressed in DRG neurons of wild type mice, but not in that of *dt* mice.

2. The absence of α-internexin in DRN of *dt* mice suggests that sensory nerve fibers in DRN and peripheral nerve may degenerate by different mechanisms.

Questions:

- **Why *α-internexin* disappeared in the DRG of *dt/dt* mutant?**
- **Why α -internexin translocated into cell nucleus of motor neuron in the *dt/dt* spinal cord ?**
- **What kind of relationship between *α-internexin* and *BPAG1n?***

Acknowledgments

Dr. Ronald Liem
Dr. Gee Ching
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