

D2 receptors dysfunction related to Synaptic changes in the striatum and globus pallidus in knock-in mouse model of DYT1 dystonia

G. Sancesario



Tor1a^{+/+}: expresses wild type murine TorsinA, control

Tor1a^{+/ Δ gag}: heterozygous knock-in mouse Δ GAG torsin mutation in just one allele

functional rather than degenerative etiology of early onset torsion dystonia

Kevin Rostasy et al., *Neurobiology of Disease* 12 (2003) 11–24

substantia nigra

WT10x

HET 10x



Tor1a^{+/+}wild type

Tor1a^{+/ Δ gag} knock-in mutation

Pathophysiology in early onset dystonia



**Neurobiology
of Disease**

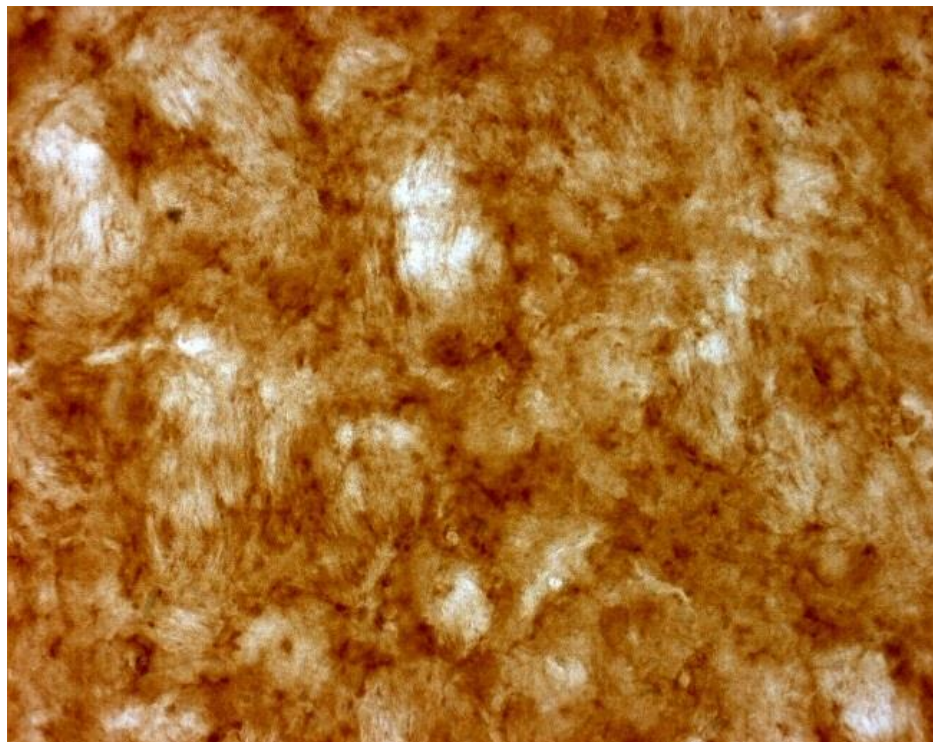
www.elsevier.com/locate/ynbdi
Neurobiology of Disease 24 (2006) 318–325

Altered responses to dopaminergic D2 receptor activation and N-type calcium currents in striatal cholinergic interneurons in a mouse model of DYT1 dystonia

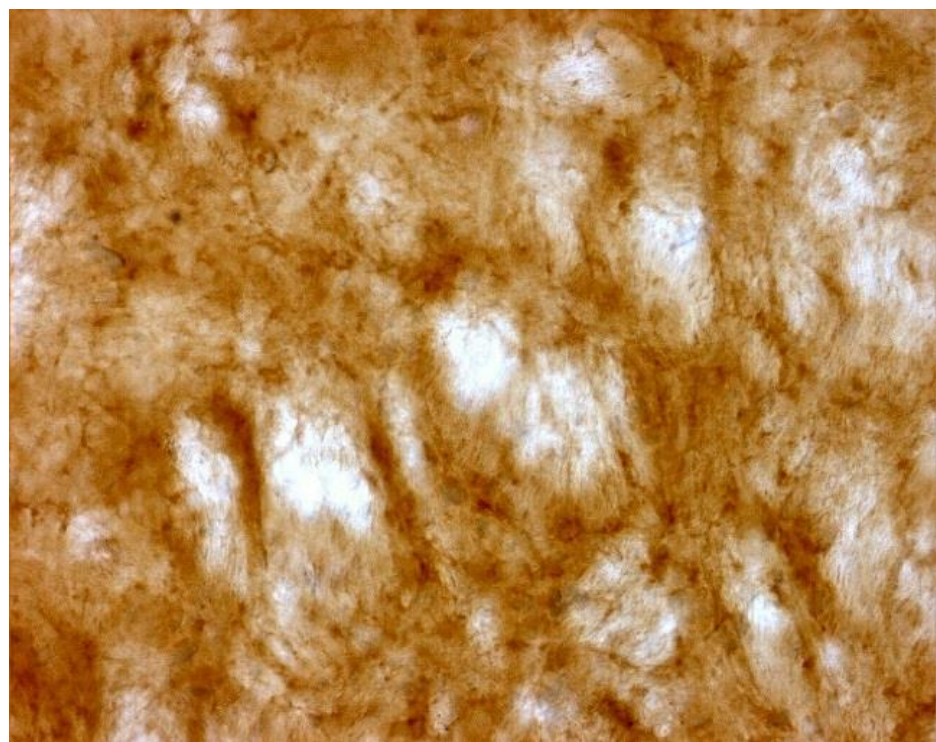
A. Pisani,^{a,b,*} G. Martella,^a A. Tscherter,^a P. Bonsi,^b N. Sharma,^c
G. Bernardi,^{a,b} and D.G. Standaert,^c

D2 receptors immunoreactivity (light microscopy)

globus pallidus



Tor1a^{+/+} wild type

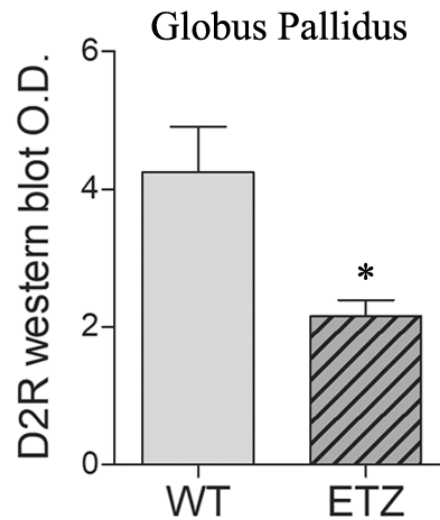
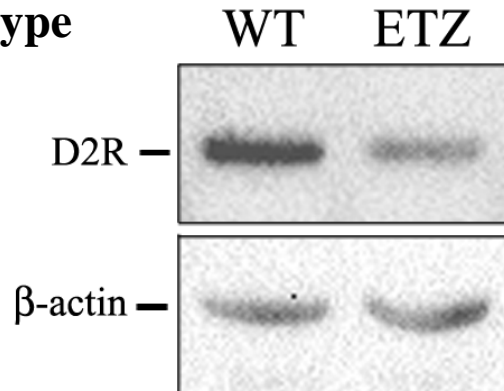


Tor1a^{+/Δgag} knock-in mutation

D2 receptor expression in the globus pallidus

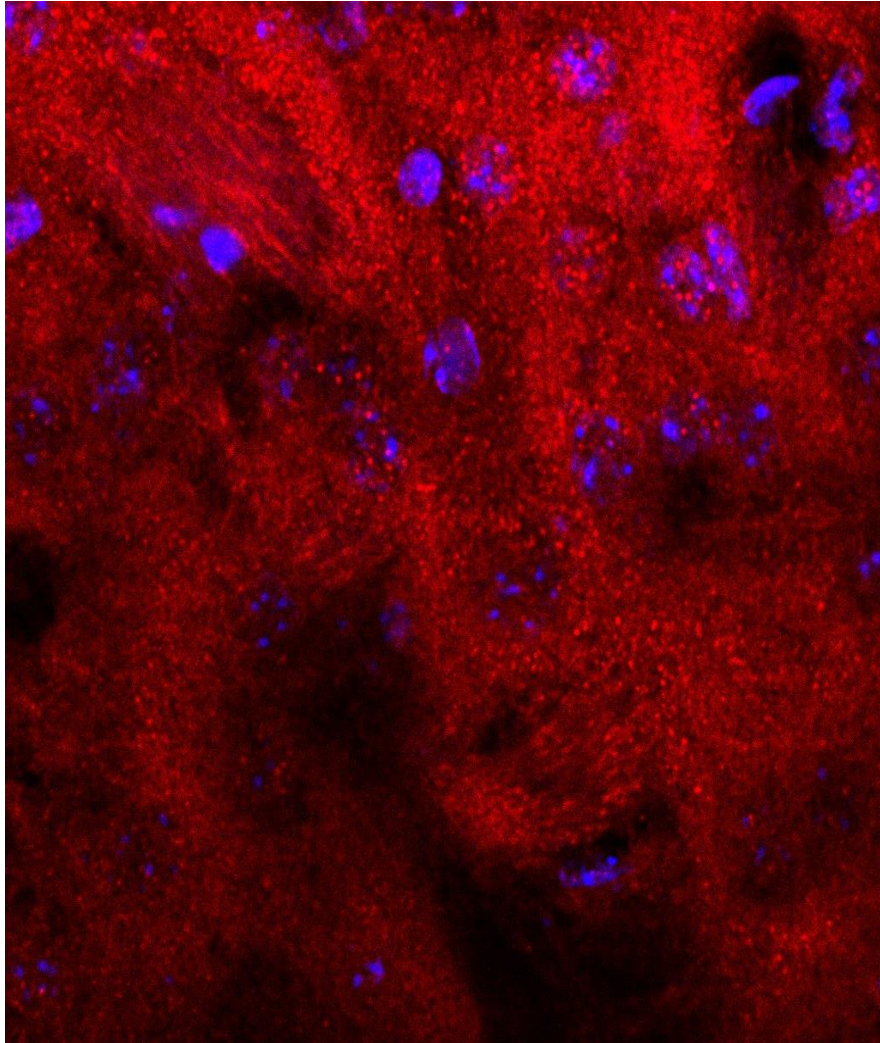
WT = $Tor1a^{+/+}$ wild type

ETZ = $Tor1a^{+/\Delta gag}$ knock-in



D2 receptors immunoreactivity (confocal microscopy)

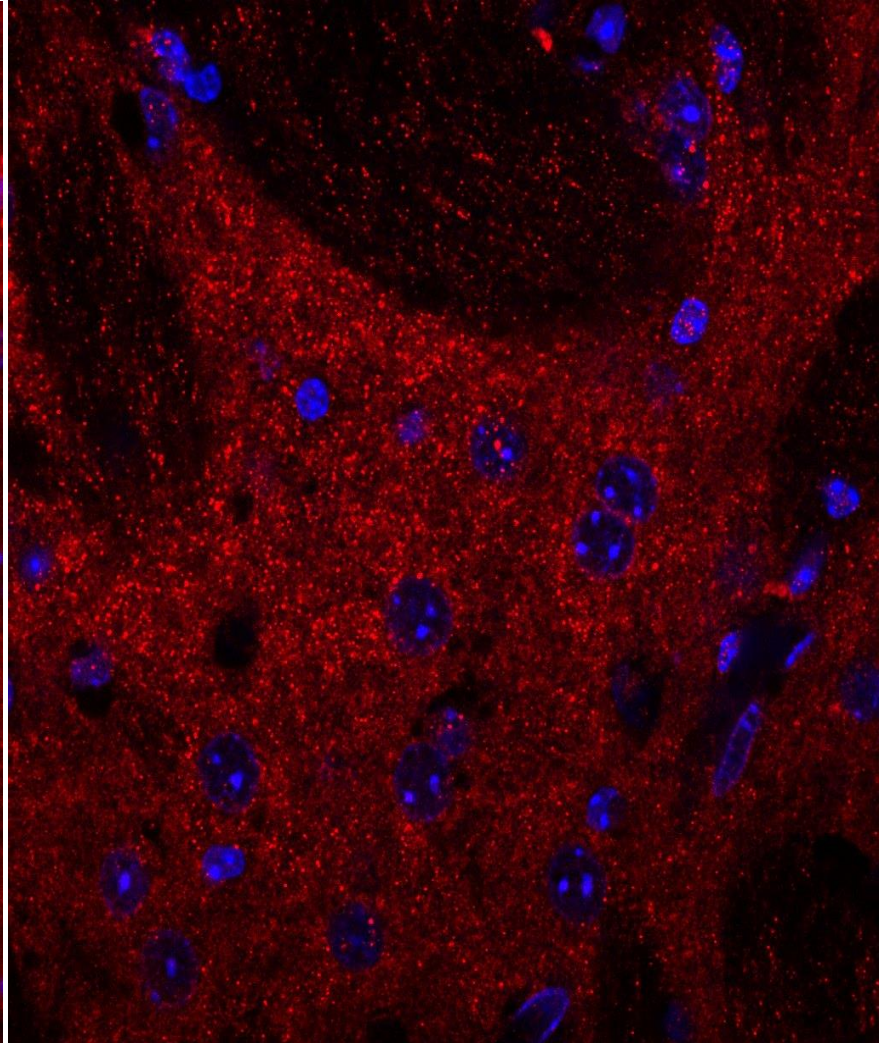
Tor1a^{+/+} wild type



striatum

5 microns

Tor1a^{+/ Δ gag} knock-in mutation

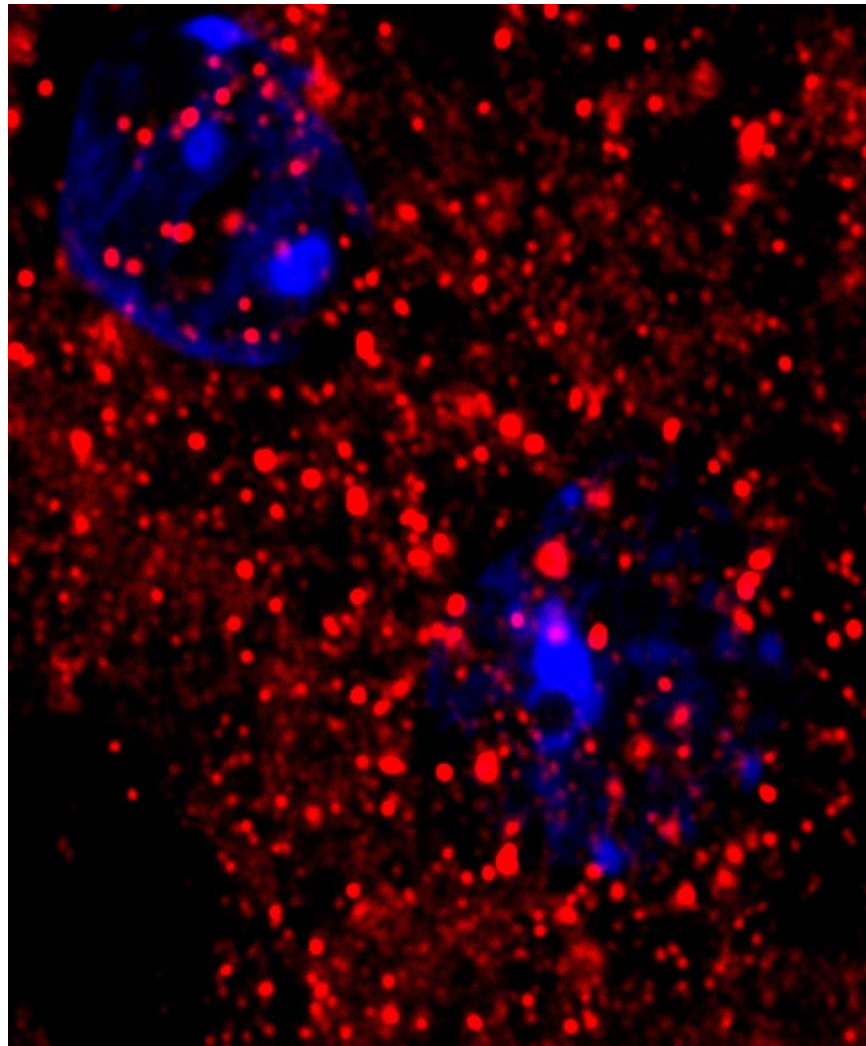


striatum

5 microns

D2 receptors immunoreactivity (confocal microscopy)

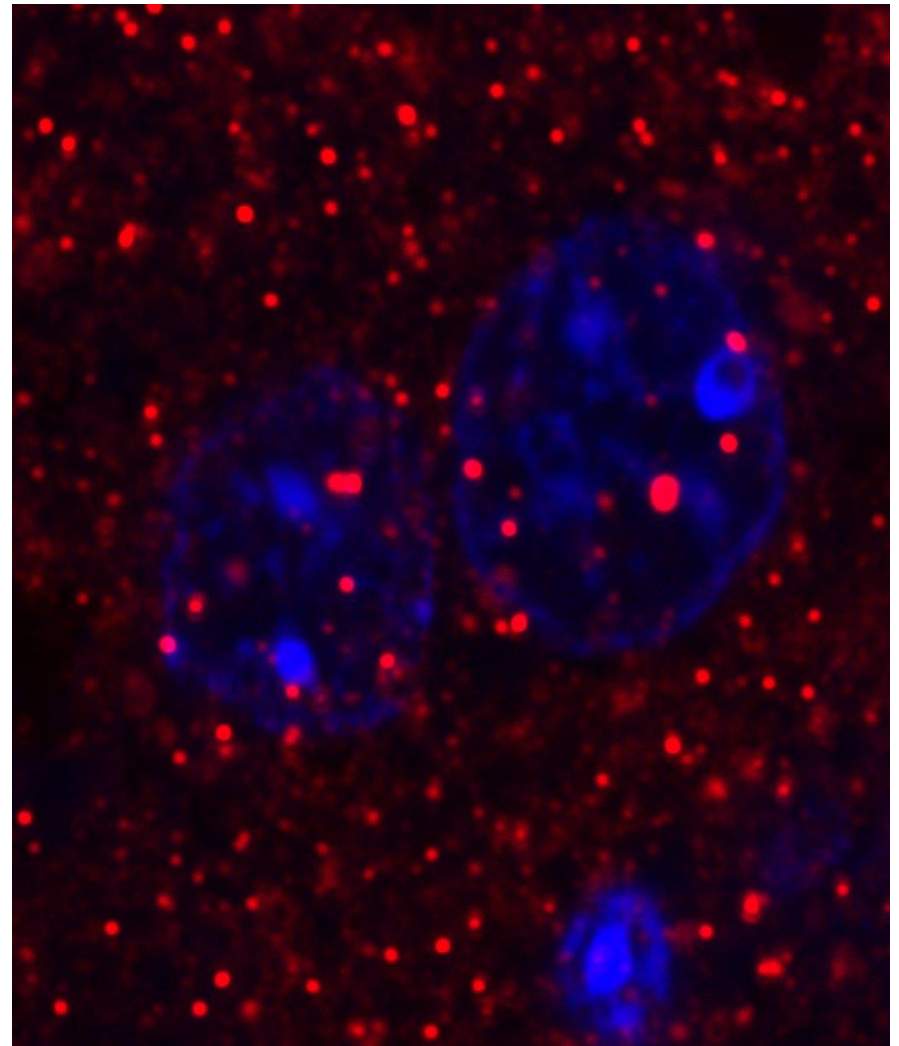
Tor1a^{+/+} wild type



striatum

2 micron

Tor1a^{+/ Δ gag} knock-in mutation



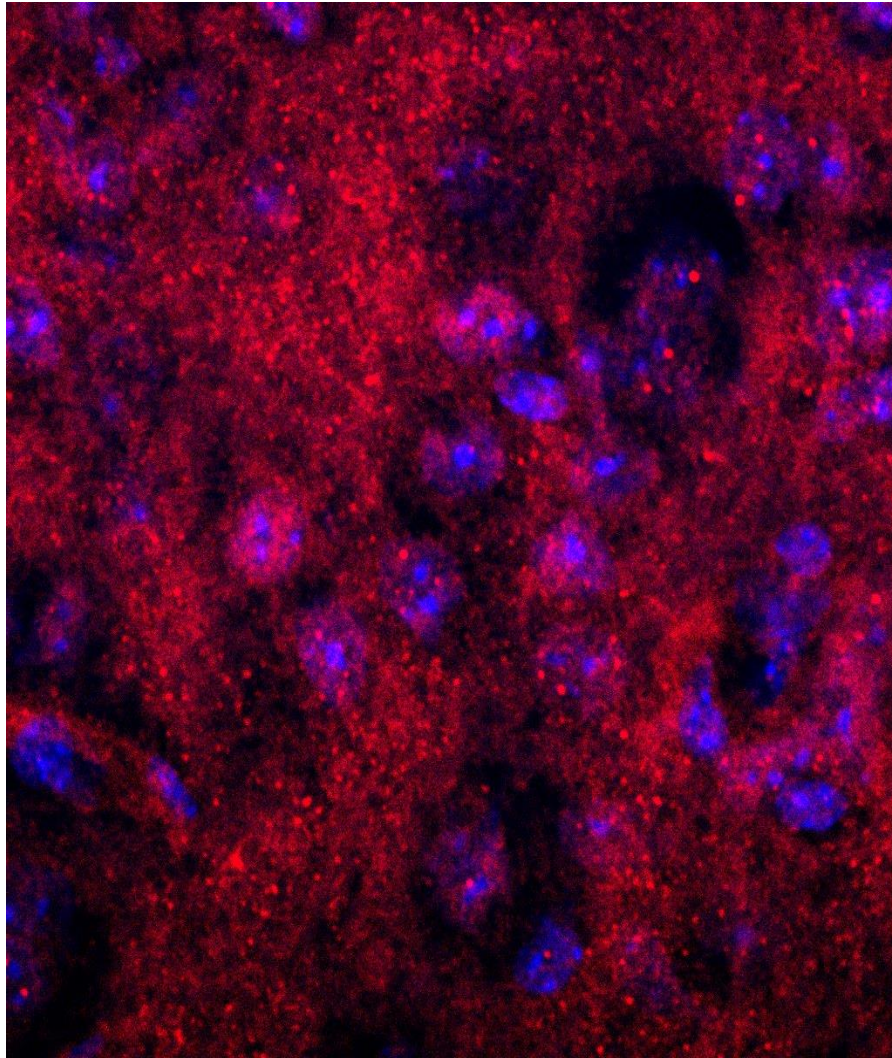
striatum

2 micron

D2 receptors immunoreactivity (confocal microscopy)

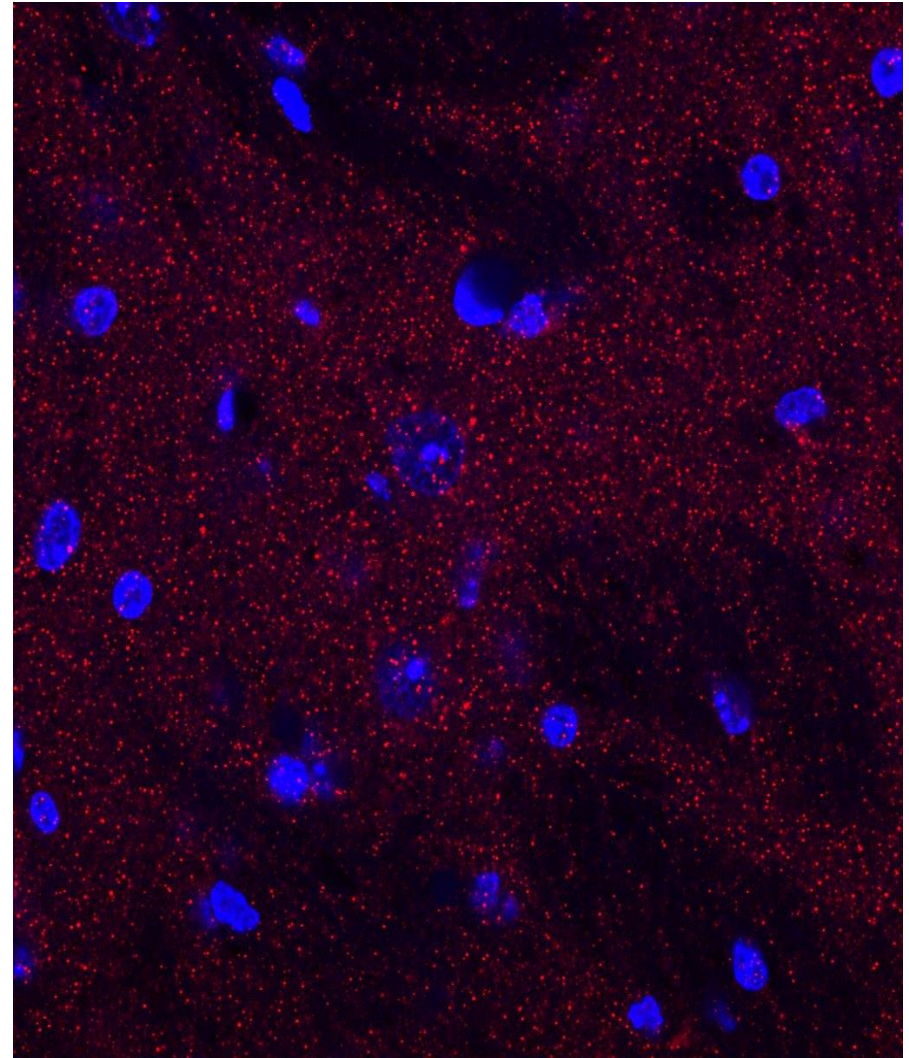
Tor1a^{+/+} wild type

Tor1a^{+/ Δ gag} knock-in mutation



globus pallidus

5 micron



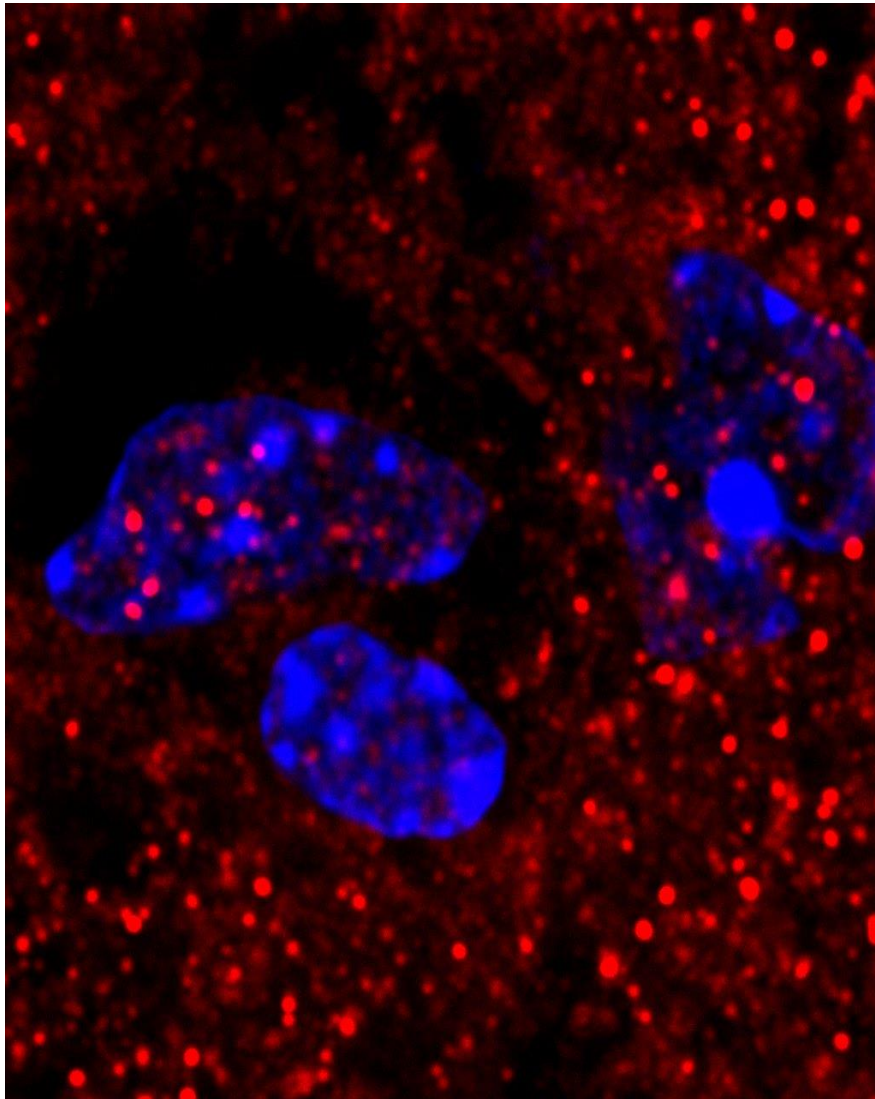
globus pallidus

5 micron

D2 receptors immunoreactivity (confocal microscopy)

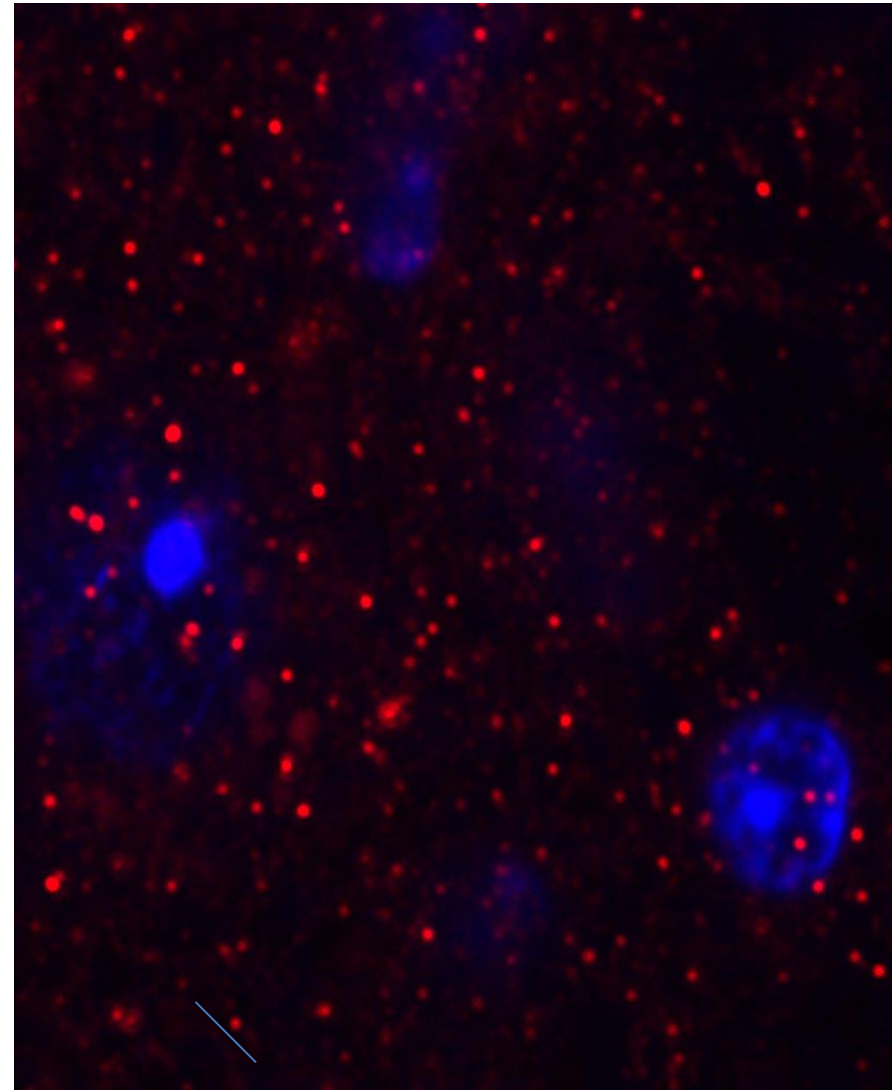
Tor1a^{+/+} wild type

Tor1a^{+/ Δ gag} knock-in mutation



globus pallidus

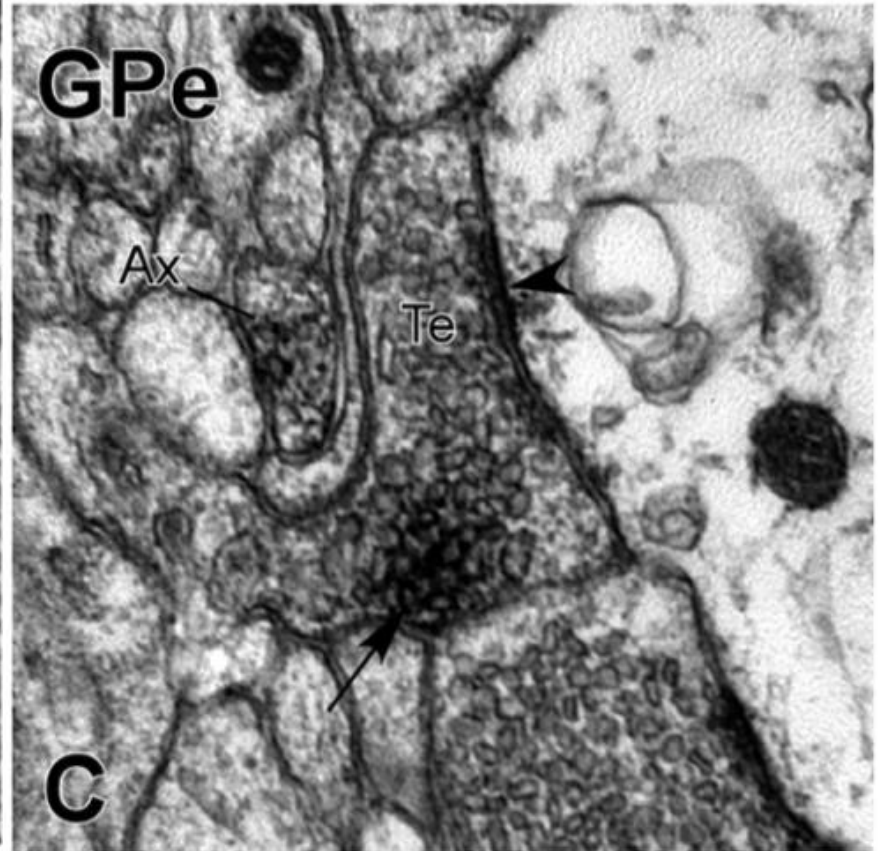
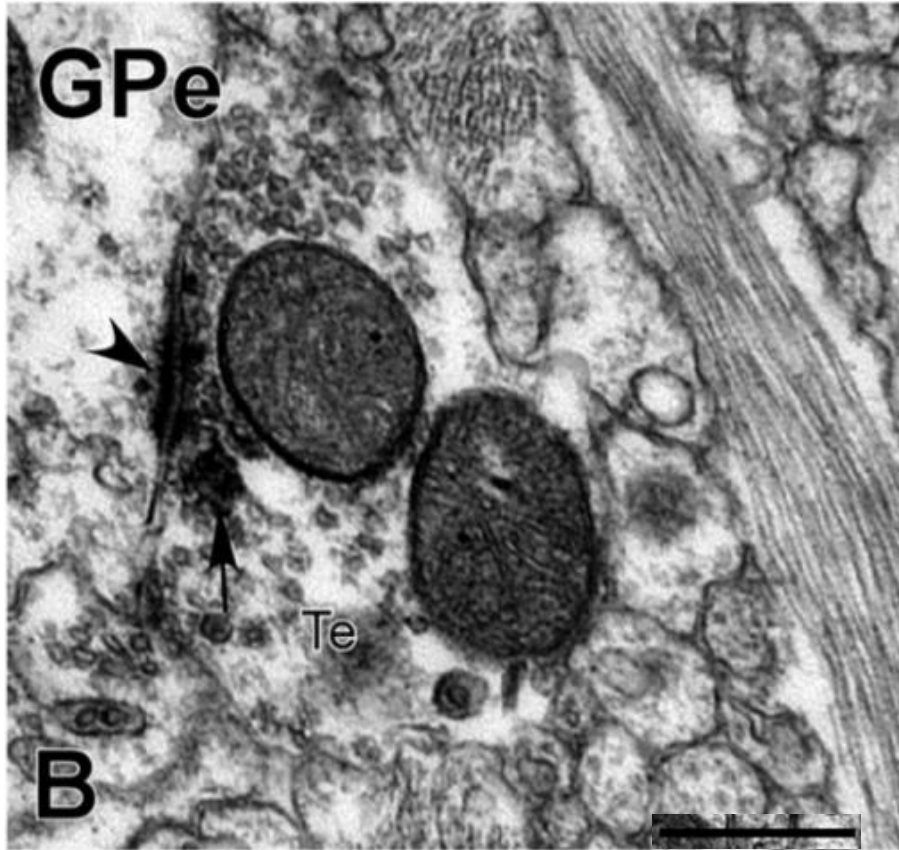
2 micron



globus pallidus

2 micron

D2 receptors in pre-synaptic boutons



bar in B = 0.5 microns

Arash Hadipour-Niktarash et al., *J Neurophysiol* 107: 1500–1512, 2012.

Conclusions

In heterozygote DYT1 knock-in mice, our most striking findings were:

- loss of D2 synaptic boutons in the striatum and in the external globus pallidus**
- Reduced size of surviving D2 synaptic boutons observed in these brain areas**
- D2 synaptic loss and decreased size of D2 synapses suggest that morphological anomalies of both the nigro-striatal and nigro-pallidal pathways are instrumental to dysfunctions of D2 receptors in the pathobiology of DYT1 dystonia.**



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