



# Cross-Indication Profiling of Neurodegenerative Markers in Lysosomal Storage Disease Models

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## Introduction

The close association between lysosomal storage diseases (LSDs) and neurodegenerative diseases has gained increasing attention, both clinically and mechanistically. Several LSDs, including Gaucher disease (GD), Niemann-Pick disease, and Pompe disease, present with pronounced neurological phenotypes, including severe neuronal loss. Increasing evidence points to molecular and mechanistic overlaps between LSDs and neurodegenerative diseases, with multiple shared pathways and protein interactions.

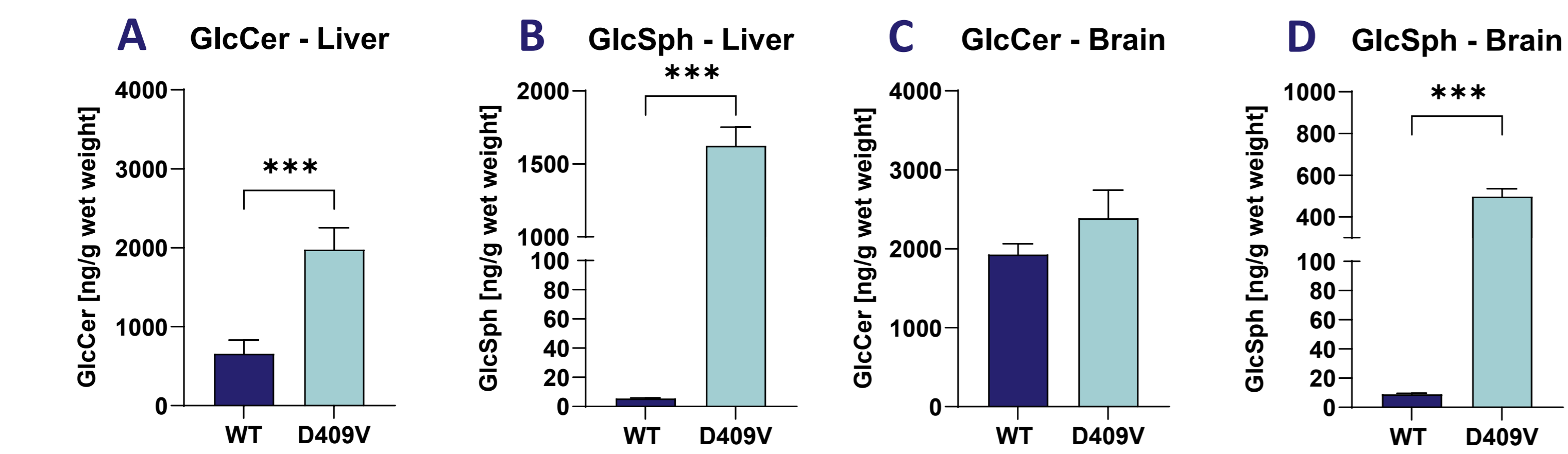
## Methods

In this study, brain tissues from LSD-related preclinical mouse models, including GD (D409V, 4L/PS-NA), Niemann-Pick (NPC1<sup>-/-</sup>), and Pompe disease (6<sup>neo</sup>), were analyzed for neurodegenerative markers such as amyloid- $\beta$  ( $A\beta$ ),  $\alpha$ -synuclein and TDP-43 via Mesoscale Discovery assays or automated western blotting (WES) or immunohistochemical methods. In parallel, LSD-specific biochemical markers, including enzyme activities and substrate accumulation in peripheral tissues and the brain, were assessed to provide a comprehensive molecular profile.

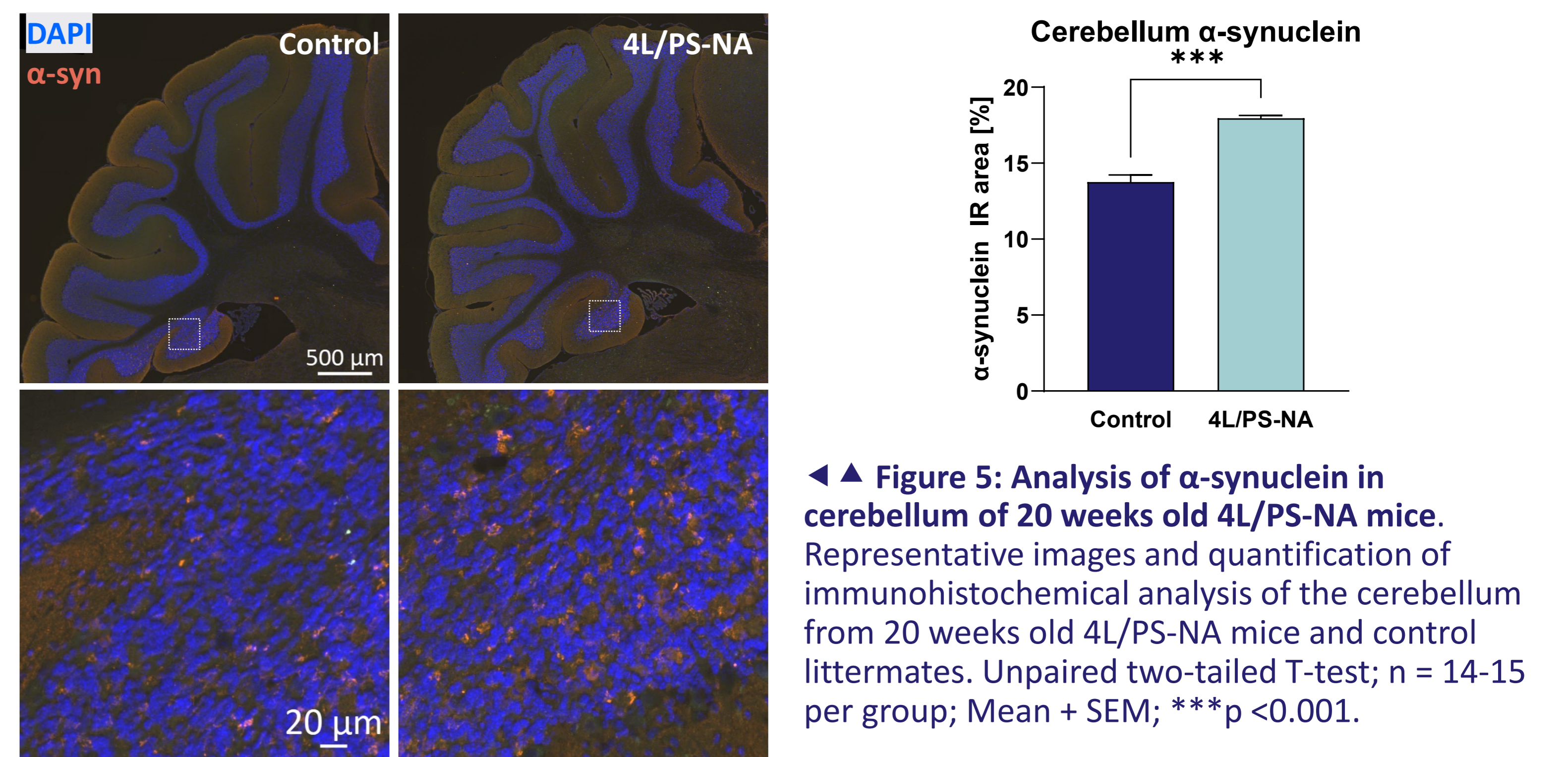
Disease	Mouse model	Deficiency	Substrate accumulation peripheral organs (LIVER or MUSCLE)				Substrate accumulation BRAIN				Cross-Indication		
			Cholesterol	GlcCer	GlcSph	Glycogen	Cholesterol	GlcCer	GlcSph	Glycogen	$\alpha$ -synuclein	$A\beta$	TDP-43
Gaucher	D409V	GBA	no	YES	YES	no	no	no	YES	no	YES	YES	no
Gaucher	4L/PS-NA	GBA/Saposin	no	YES	YES	no	no	no	YES	no	YES	YES	no
Nieman-Pick	NPC1 <sup>-/-</sup>	NPC1	YES	YES	no	no	YES	YES	no	no	no	YES	no
Pompe	6 <sup>neo</sup>	GAA	no	no	no	YES	no	no	no	YES	no	no	YES

## Gaucher Disease – Parkinson's (D409V Mice)

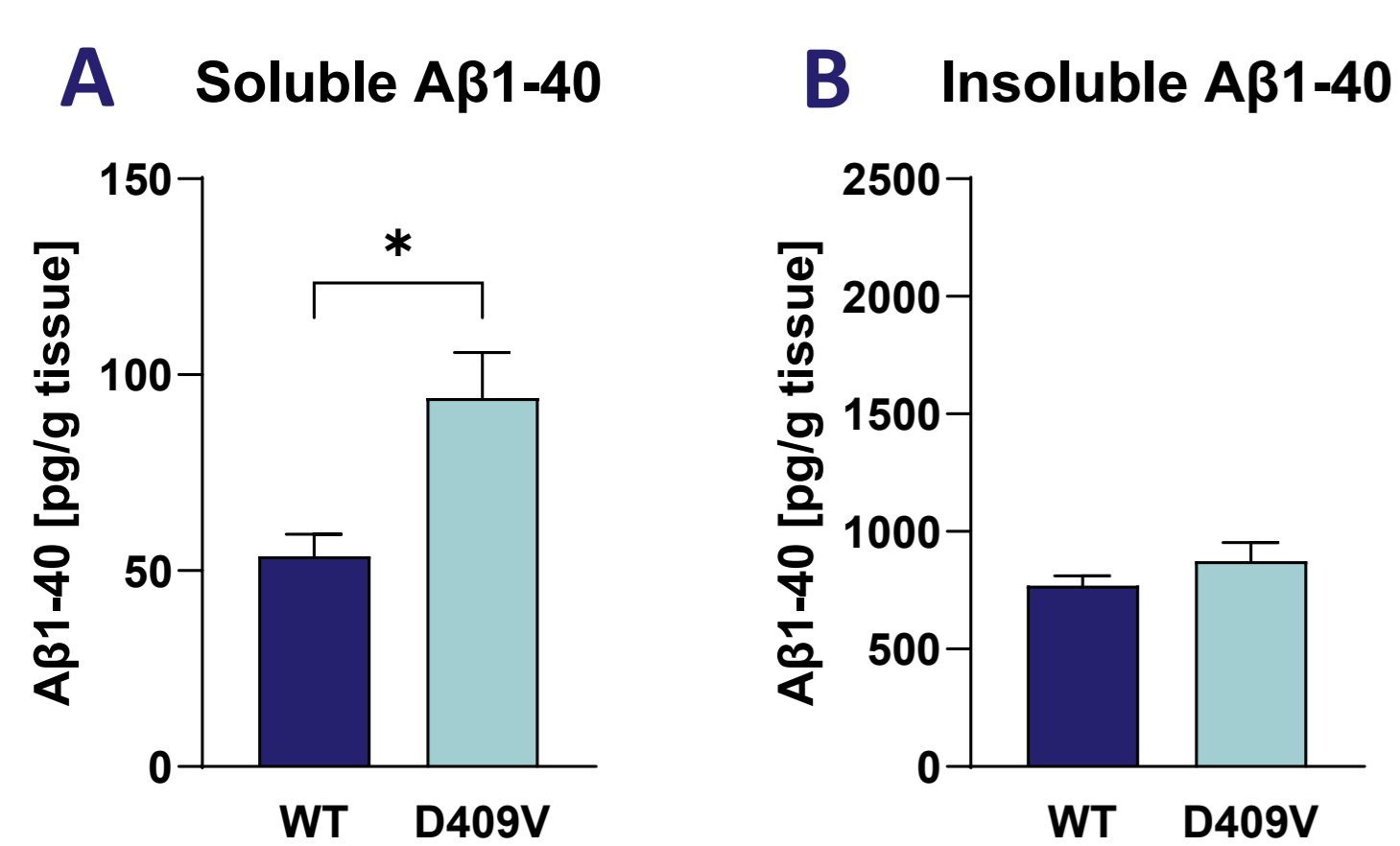
## Gaucher Disease – Parkinson's (4L/PS-NA)



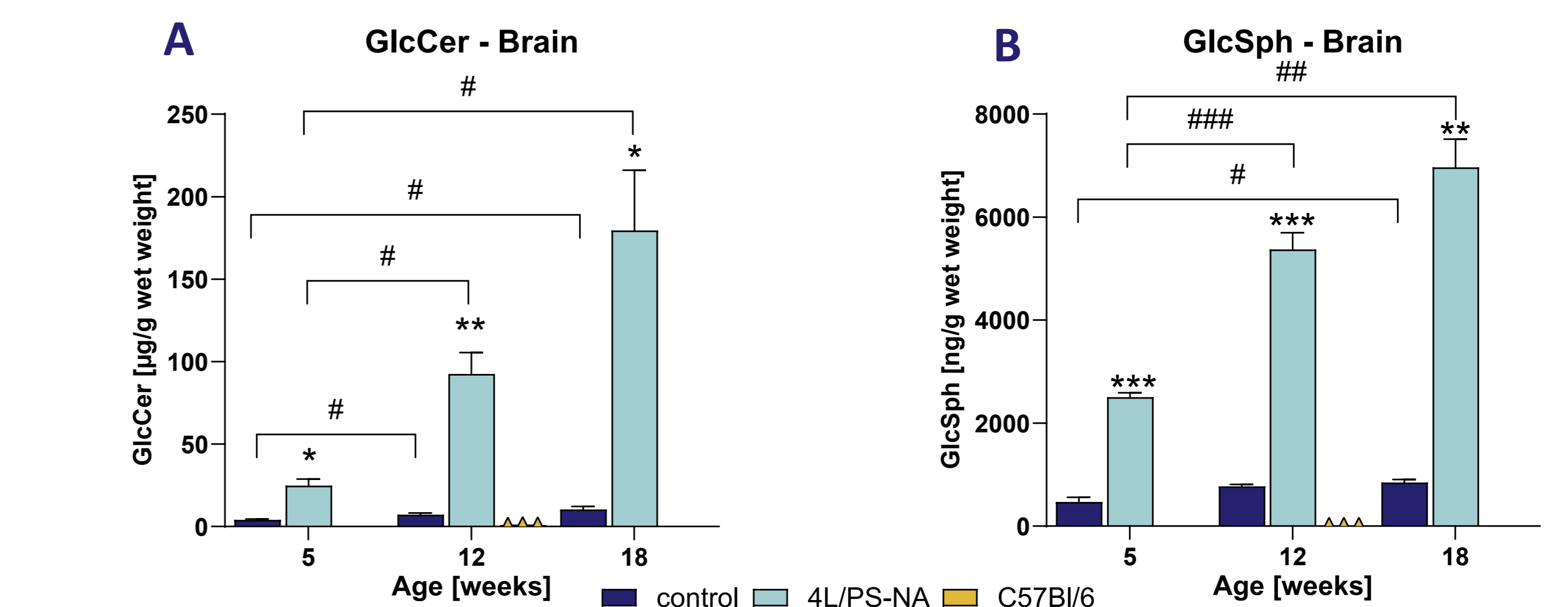
▲ Figure 1: Quantification of glucosylceramide (GlcCer) and glucosylsphingosin (GlcSph) in different tissues of D409V mice. Liver (A, B) or whole brain homogenates (C, D) of D409V homozygous animals wild type littermates (WT) at 6 months of age were analyzed for (A, C) GlcCer and (B, D) GlcSph levels. Unpaired two-tailed T-test; n = 10; Mean + SEM; \*\*\*p < 0.001.



◀ Figure 5: Analysis of  $\alpha$ -synuclein in cerebellum of 20 weeks old 4L/PS-NA mice. Representative images and quantification of immunohistochemical analysis of the cerebellum from 20 weeks old 4L/PS-NA mice and control littermates. Unpaired two-tailed T-test; n = 14-15 per group; Mean + SEM; \*\*\*p < 0.001.



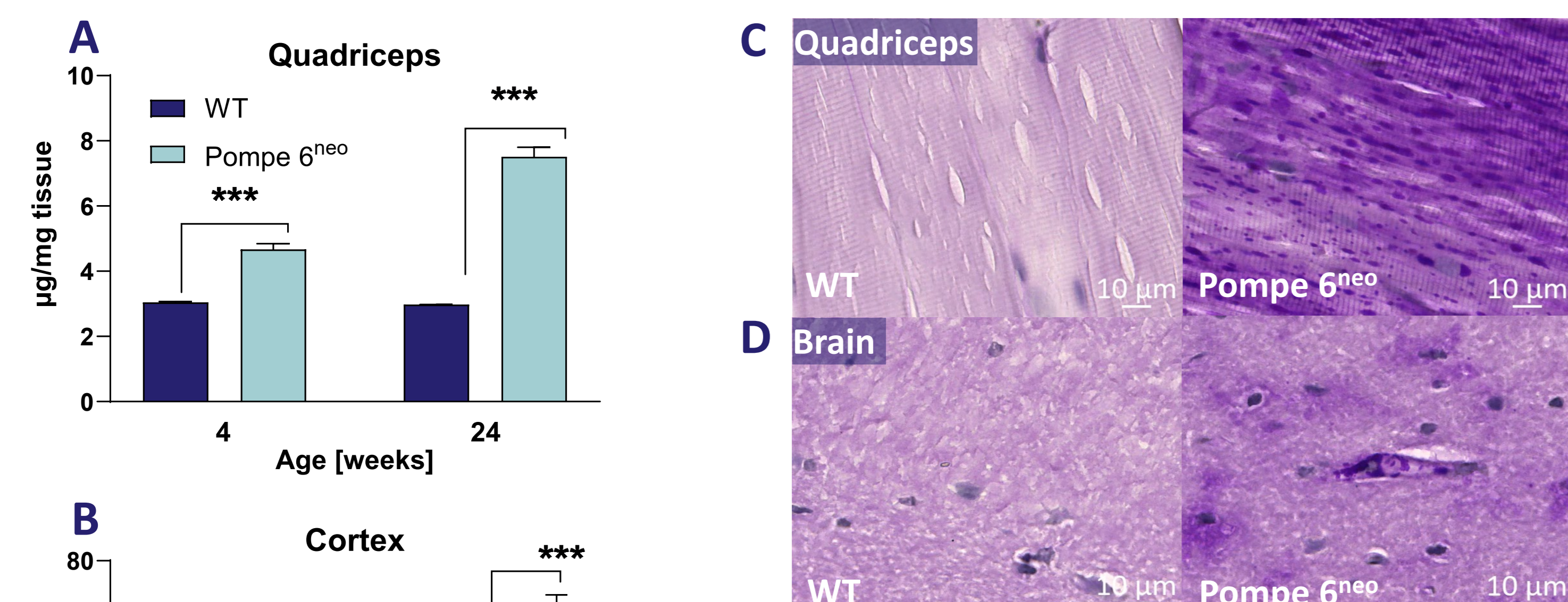
◀ Figure 2: Soluble and insoluble A $\beta$ 1-40 in brain samples of 16 weeks old D409V animals. Murine A $\beta$ 1-40 in soluble (A) and insoluble (B) brain fractions of homozygous (D409V) mice as well as age-matched wild type littermates (WT) at 16 weeks of age. Unpaired t-Test. n = 8; Mean + SEM; \*p < 0.05.



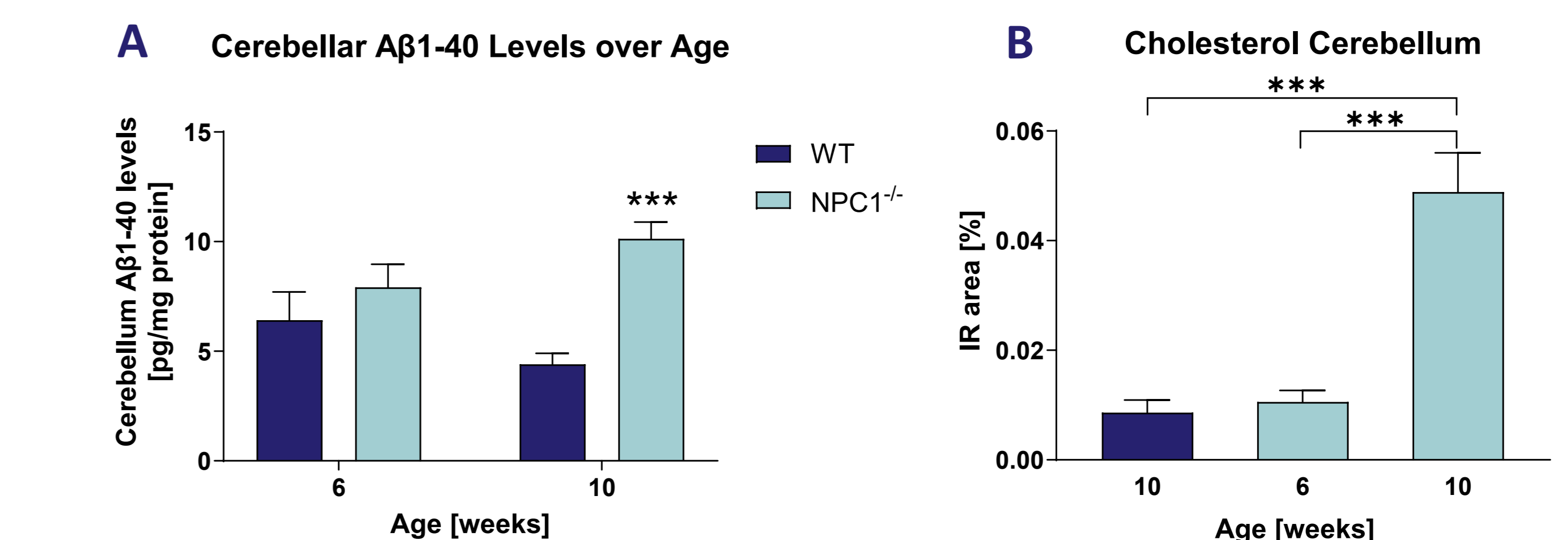
▲ Figure 6: Quantification of glucosylceramide (GlcCer) and glucosylsphingosin (GlcSph) in 4L/PS-NA mice over age. Whole brain homogenates of 5, 12 and 18 weeks old 4L/PS-NA mice, control animals as well as C57Bl/6 mice were analyzed for GlcCer (A) and GlcSph (B) levels per wet weight. Two-way ANOVA with Bonferroni *post hoc* test, n = 5-6; #differences between genotypes; #differences between age groups; Mean + SEM; \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001.

## Pompe Disease – TDP-43 Proteinopathies

## Niemann-Pick Disease – Alzheimer's

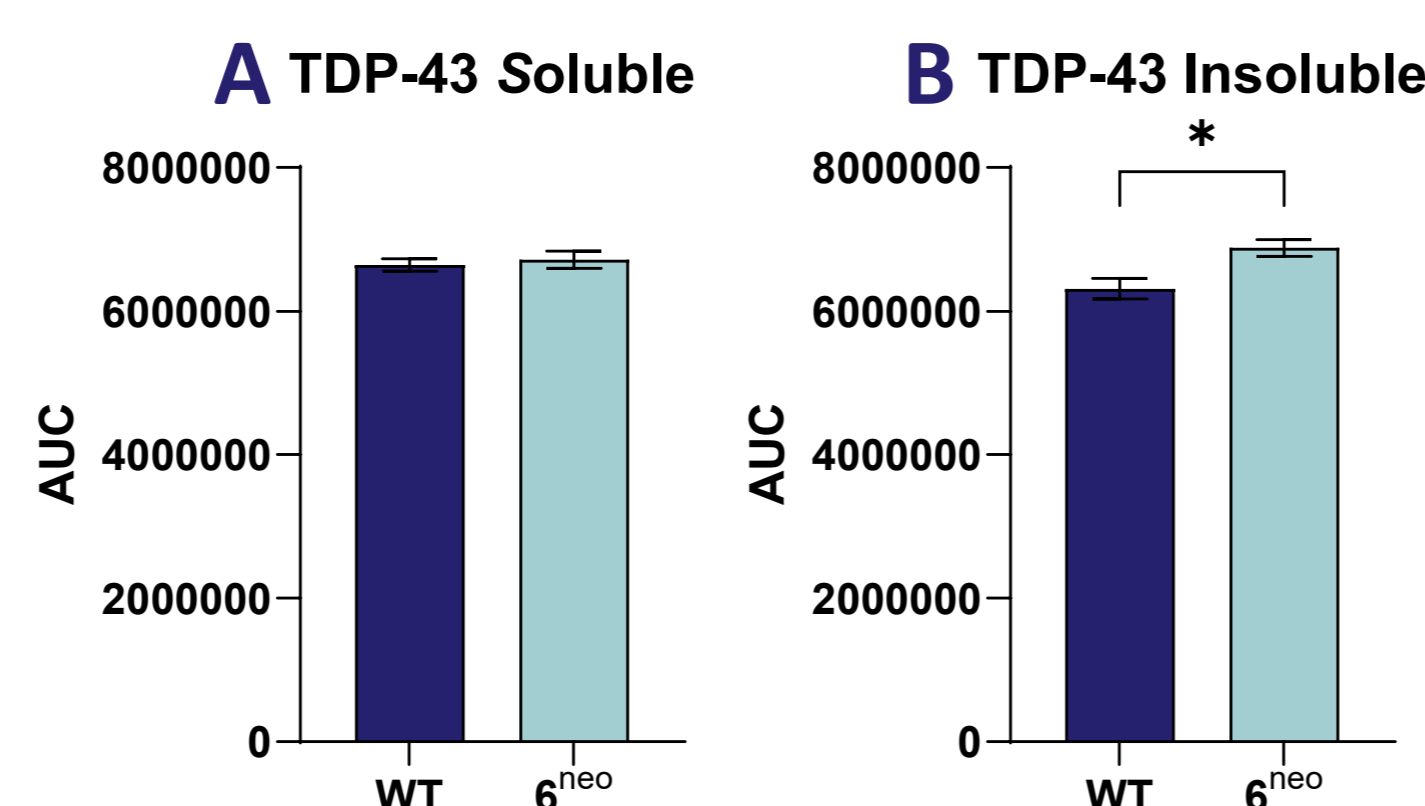


◀ Figure 3: Progressive glycogen accumulation in the quadriceps and cortex of Pompe 6<sup>neo</sup> mice. Glycogen in tissue as  $\mu$ g/mg in quadriceps (A) at ages of 4 & 24 weeks and cortex (B) at the age of 4, 24 & 52 weeks of Pompe 6<sup>neo</sup> and WT littermates. Representative images of PAS staining in quadriceps (C) and brain (D) of WT (left) and Pompe 6<sup>neo</sup> (right) mice. Two-way ANOVA with Šidák's *post hoc* test; n = 16 per group; Mean + SEM; \*\*\*p < 0.001.



▲ Figure 7: Disease progression in ageing NPC1<sup>-/-</sup> mice. Cerebellum of 6 and 10 weeks old NPC1<sup>-/-</sup> and wild type animals was analyzed for A $\beta$ 1-40 or cholesterol. 6 weeks old NPC1<sup>-/-</sup> mice of both sexes were used. Two-way ANOVA (A) or One-way ANOVA with Bonferroni *post hoc* test (B); Mean + SEM n = 6-7. \*\*\*p < 0.001.

► Figure 4: Assessment of soluble and insoluble TDP-43 species in brains of Pompe 6<sup>neo</sup> mice. Hemibrains of 24 weeks old Pompe 6<sup>neo</sup> and WT littermates were processed into soluble (A) and insoluble (B) fraction and analyzed for TDP-43 level via automated western blotting. Unpaired two-tailed T-test; n = 7-8; \*p < 0.05.



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