Mitochondrial DNA Quantity and Quality in Aging and AD

Hans-Ulrich Klein PhD

Assistant Professor

Center for Translational & Computational Neuroimmunology

Columbia University Medical Center

ADRC Spring Meeting

May 13, 2022

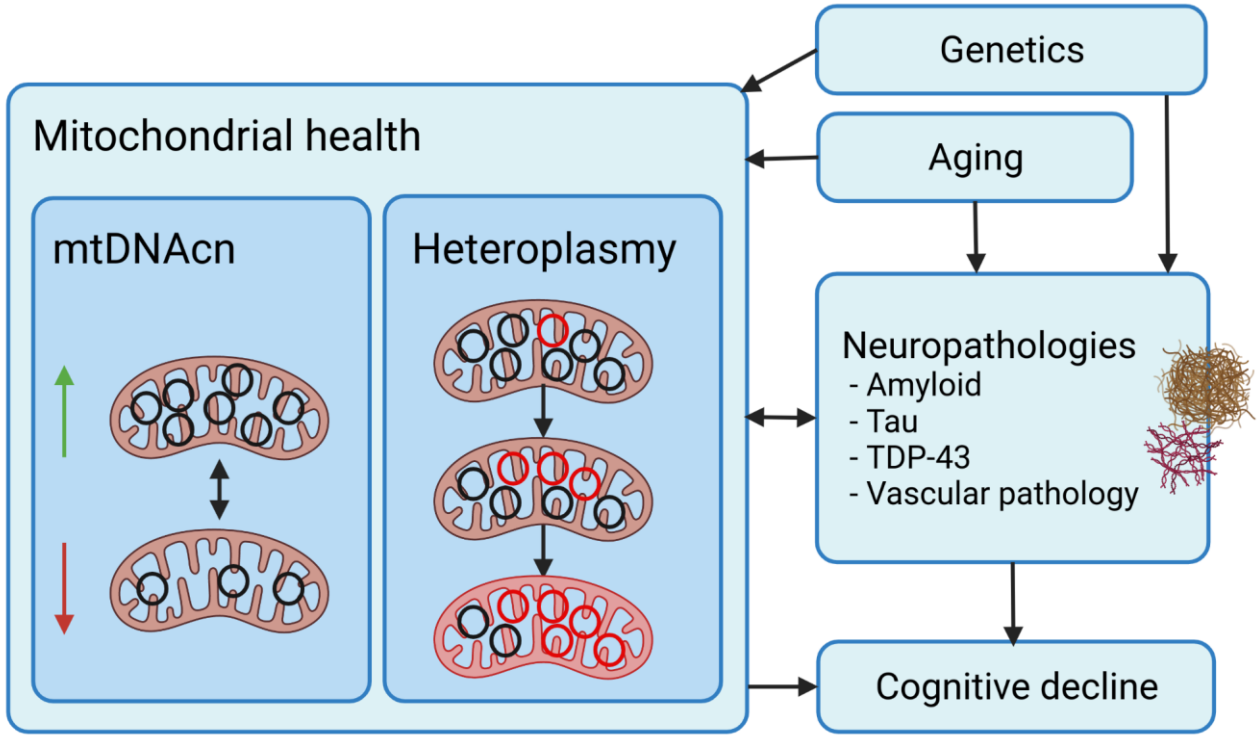
CTCN

THE CENTER FOR TRANSLATIONAL & COMPUTATIONAL NEUROIMMUNOLOGY

COLUMBIA UNIVERSITY MEDICAL CENTER

Mitochondrial dysfunction in neurodegeneration

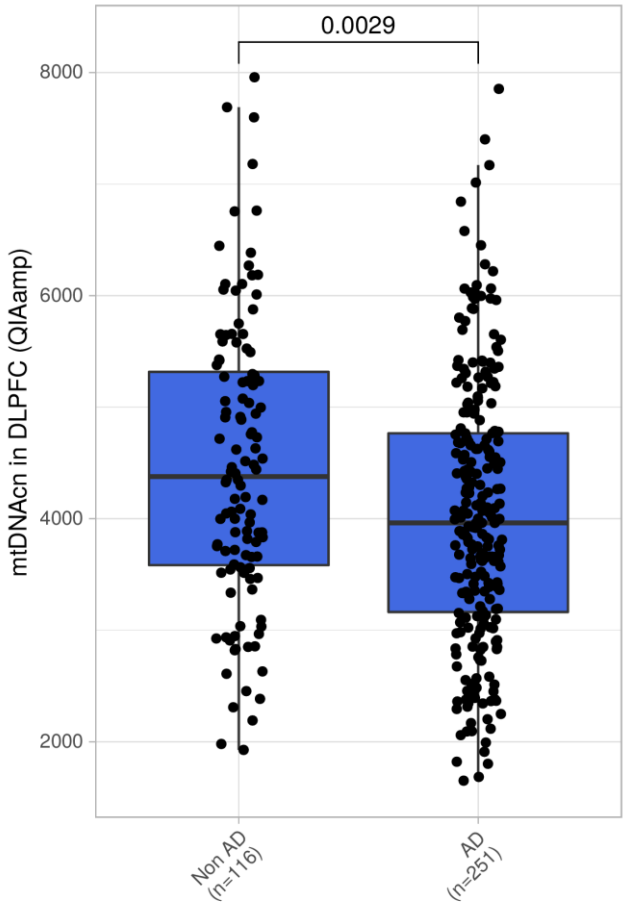
- Mitochondrial dysfunction is a common feature of neurodegenerative diseases
- Aim: Identify robust associations of Mt markers with brain pathologies, cognitive function and aging in different brain regions
- Potential markers of mitochondrial health from WGS data:
  - mtDNAcn
  - mtDNA heteroplasmy
- WGS data from ROSMAP
  (3 brain regions, 762 samples) and
  Mayo and MSBB
  (1 brain region each, 262 + 337 samples)



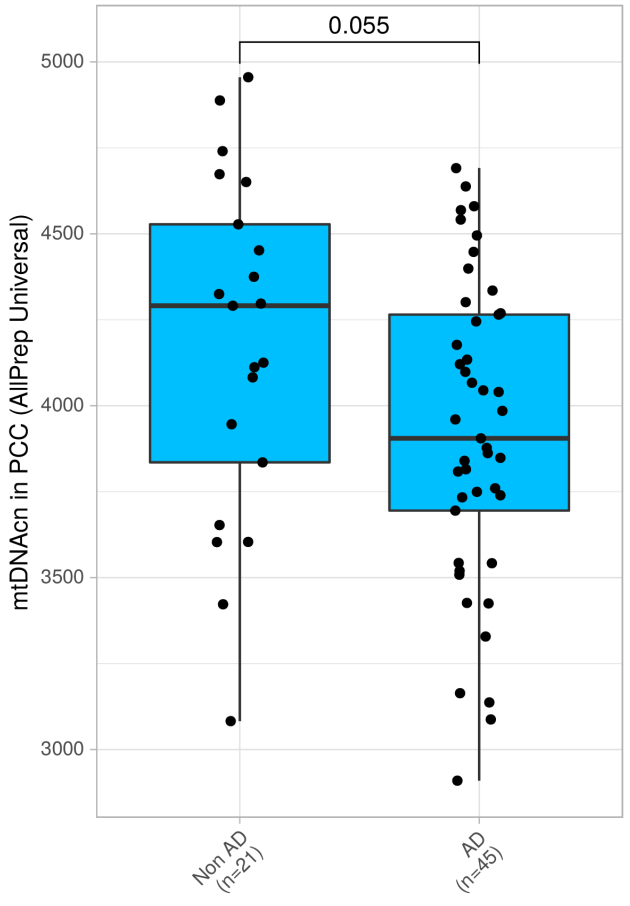
$$mtDNAcn = 2 \times \frac{MT\ coverage}{autosomal\ coverage}$$

Reduced mtDNAcn in the AD cortex

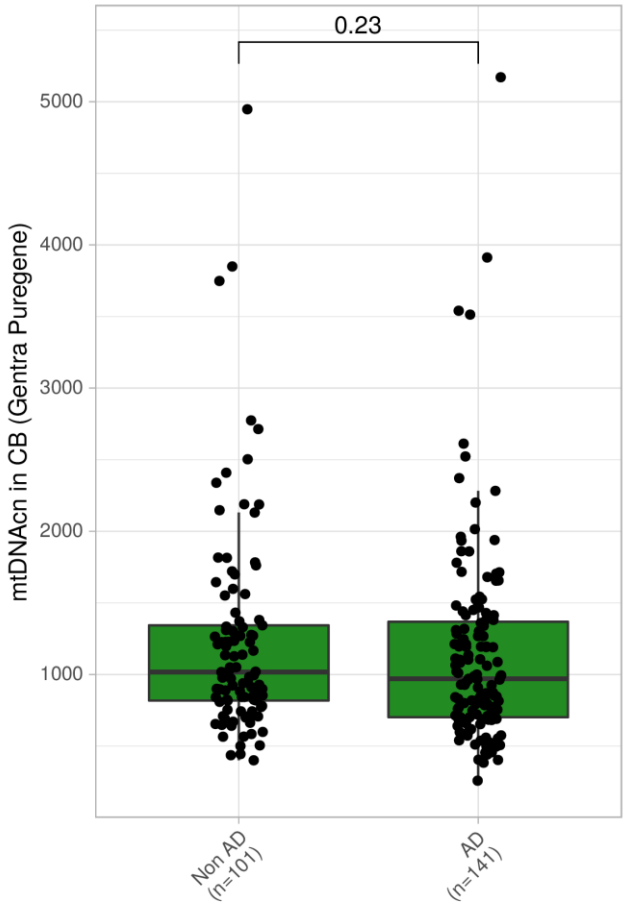
Dorsolateral prefrontal cortex (DLPFC)



Posterior cingulate cortex (PCC)

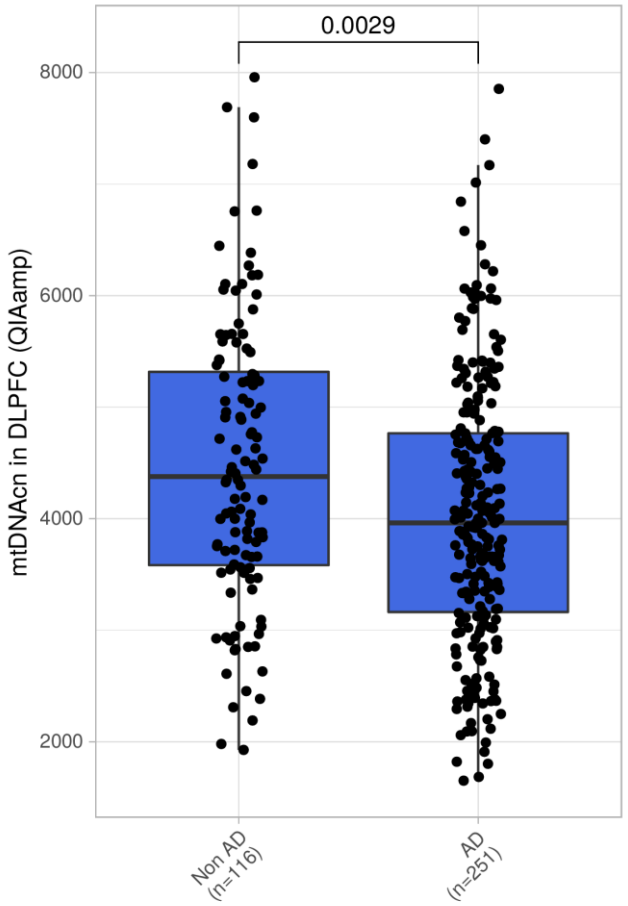


Cerebellum (CB)

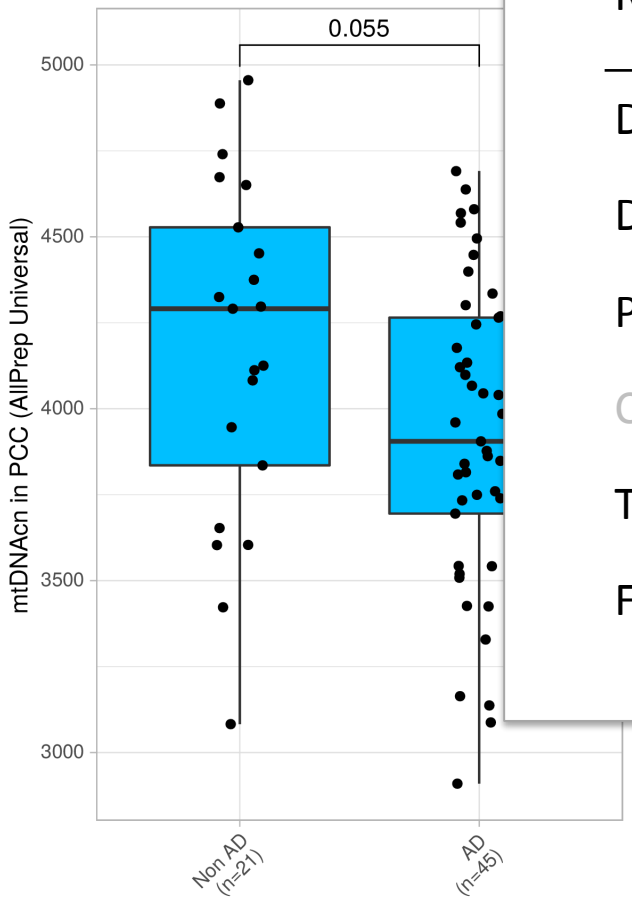


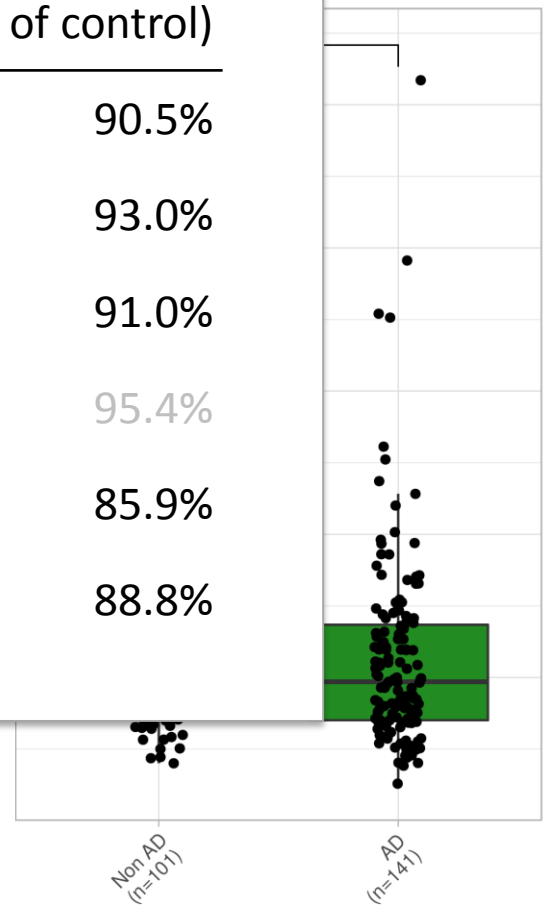
Reduced mtDNAcn in the AD cortex

Dorsolateral prefrontal cortex (DLPFC)



Posterior cingulate c (PCC)

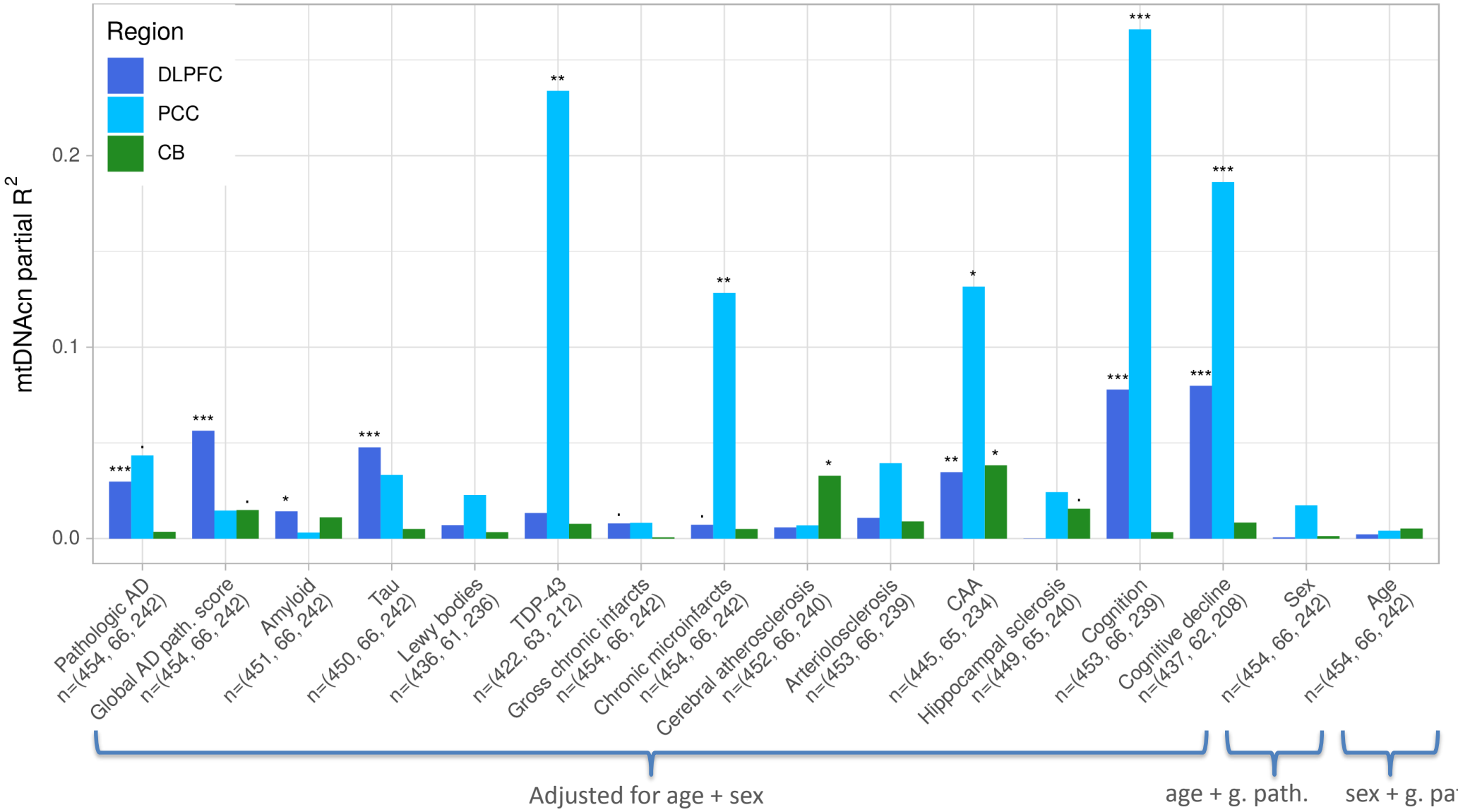




um

Region	mtDNAcn in AD (% of control)
DLPFC	90.5%
DLPFC	93.0%
PCC	91.0%
CB	95.4%
TCX	85.9%
FP	88.8%

Association with pathologies (univariate)

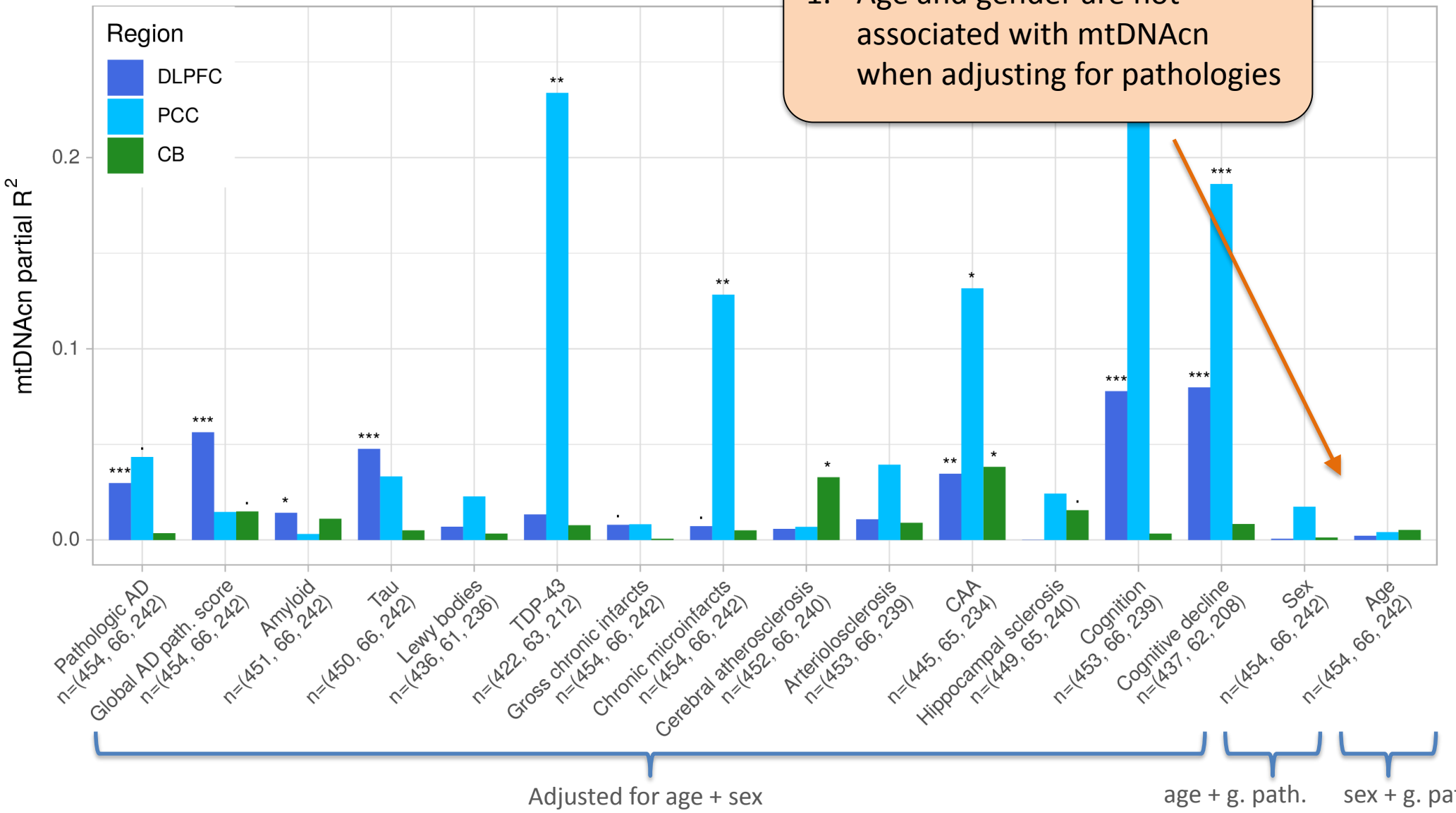


***	$p \leq 0.001$
**	$p \leq 0.01$
*	$p \leq 0.05$
·	$p \leq 0.1$

All significant associations with pathologies are inverse: pathology ↑, mtDNAcn ↓

Association with pathologies (univariate)

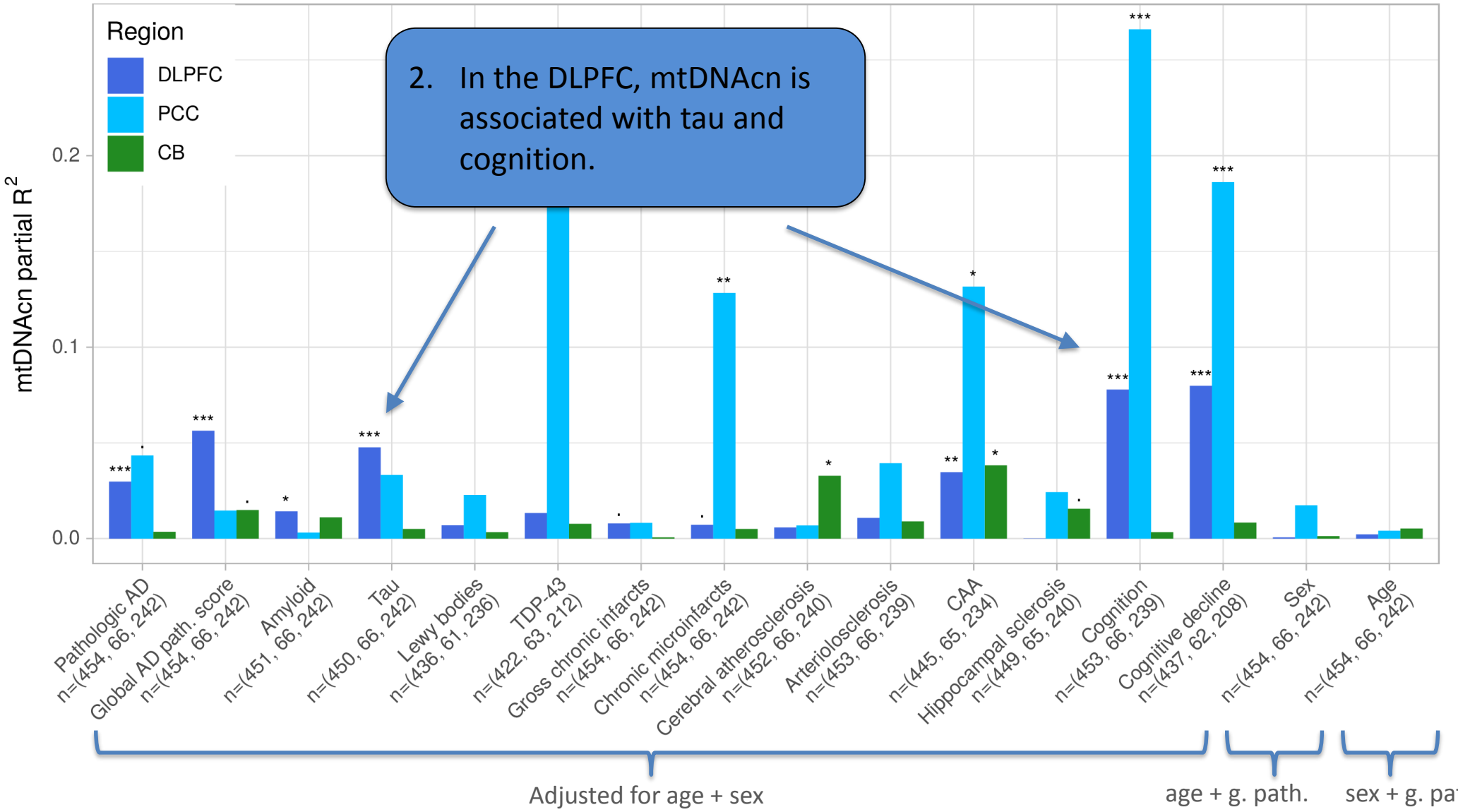
1. Age and gender are not associated with mtDNAcn when adjusting for pathologies



***	$p \leq 0.001$
**	$p \leq 0.01$
*	$p \leq 0.05$
·	$p \leq 0.1$

All significant associations with pathologies are inverse: pathology ↑, mtDNAcn ↓

Association with pathologies (univariate)

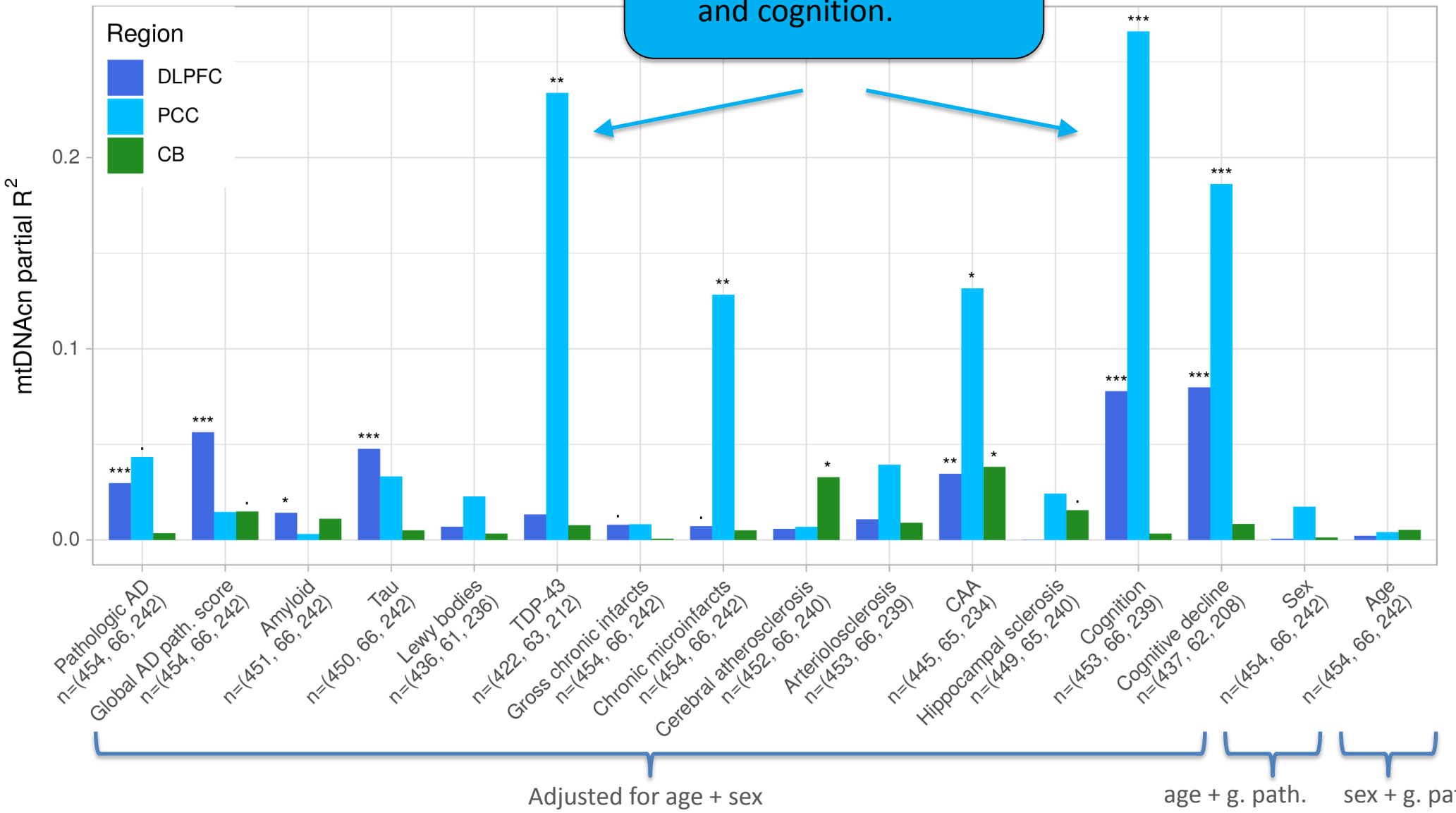


***	$p \leq 0.001$
**	$p \leq 0.01$
*	$p \leq 0.05$
·	$p \leq 0.1$

All significant associations with pathologies are inverse: pathology ↑, mtDNAcn ↓

Association with p univariate)

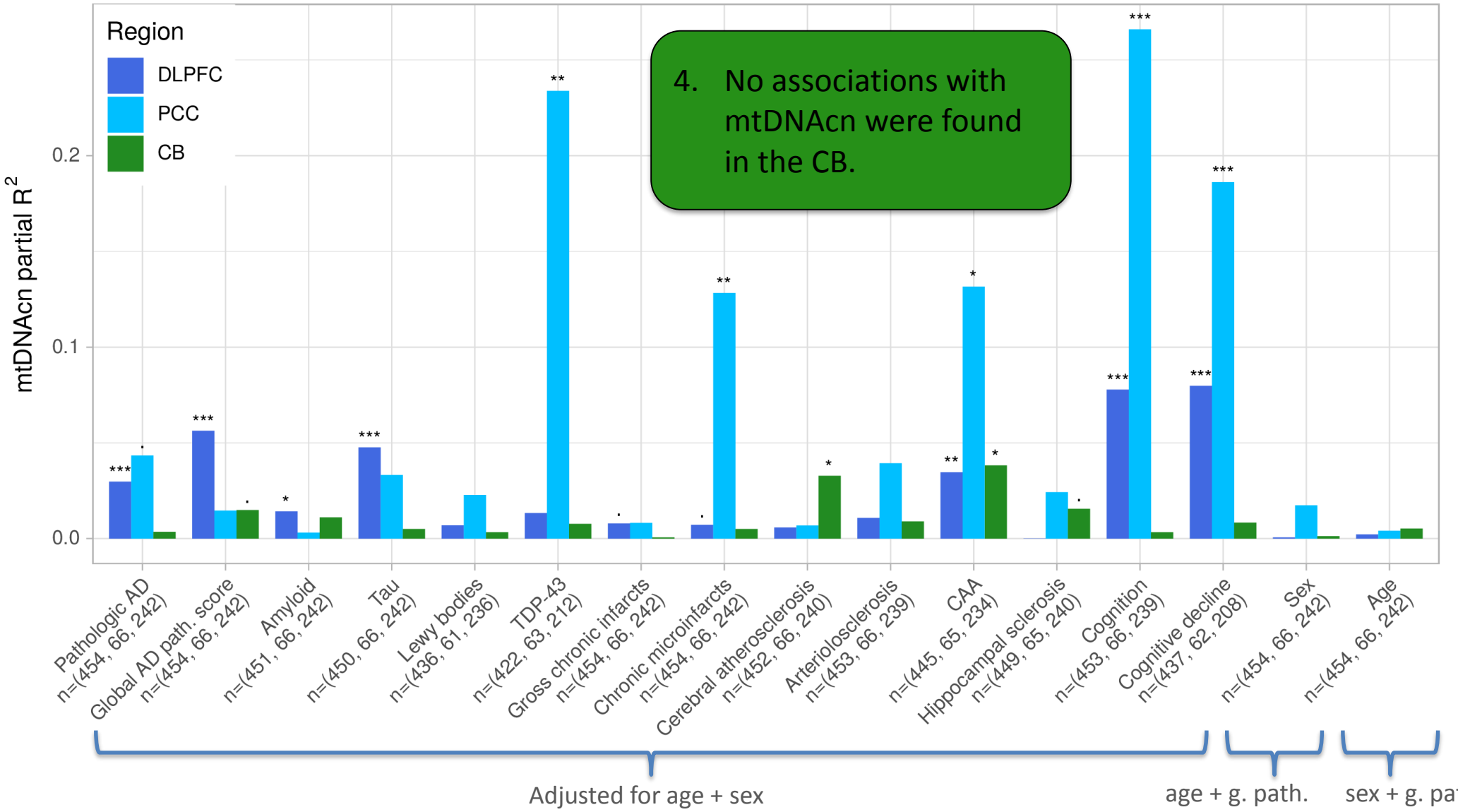
3. In the PCC, mtDNAcn is associated with TDP-43 and cognition.



***	$p \leq 0.001$
**	$p \leq 0.01$
*	$p \leq 0.05$
·	$p \leq 0.1$

All significant associations with pathologies are inverse: pathology ↑, mtDNAcn ↓

Association with pathologies (univariate)

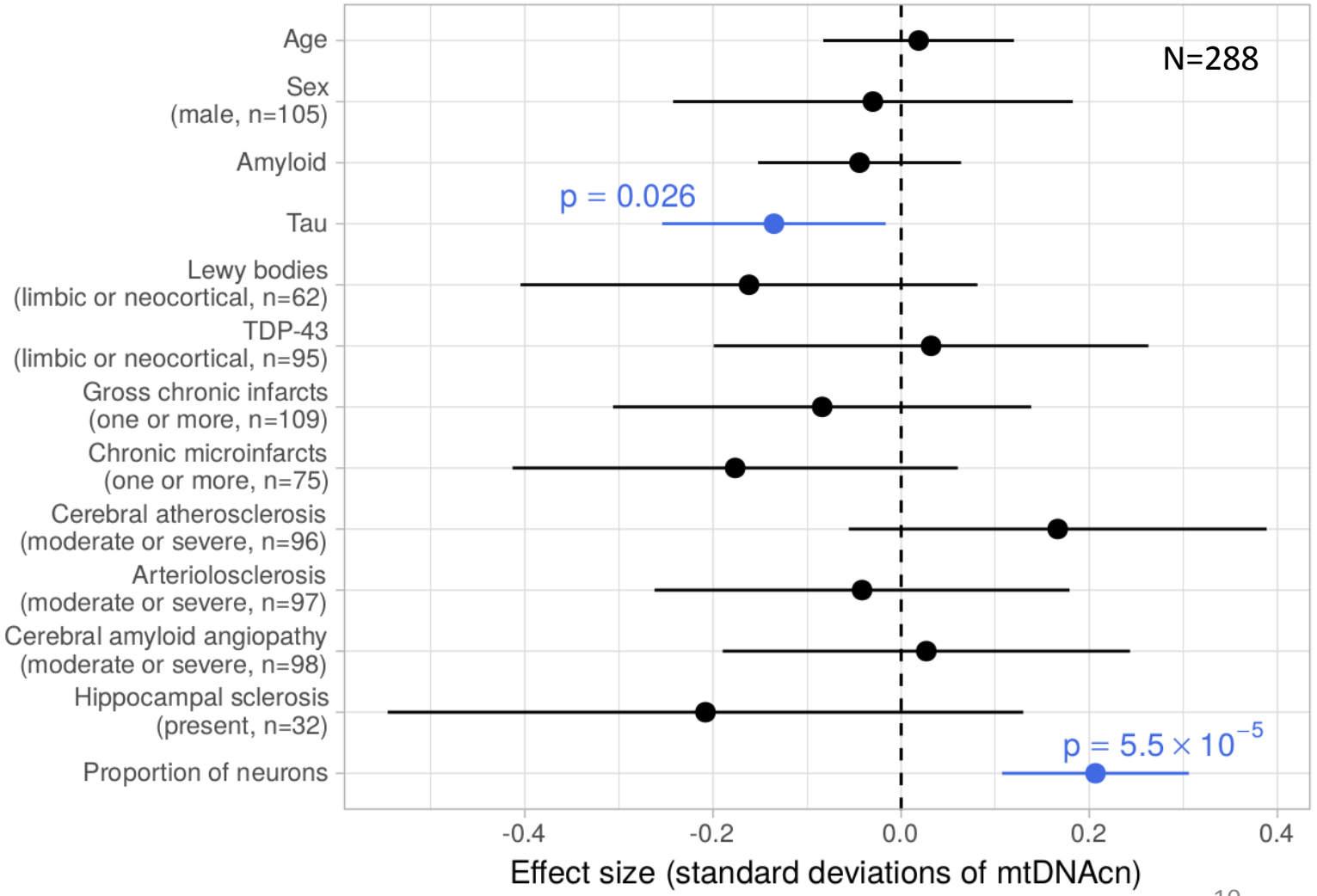


***	$p \leq 0.001$
**	$p \leq 0.01$
*	$p \leq 0.05$
·	$p \leq 0.1$

All significant associations with pathologies are inverse: pathology ↑, mtDNAcn ↓

mtDNAcn in the DLPFC is associated with Tau

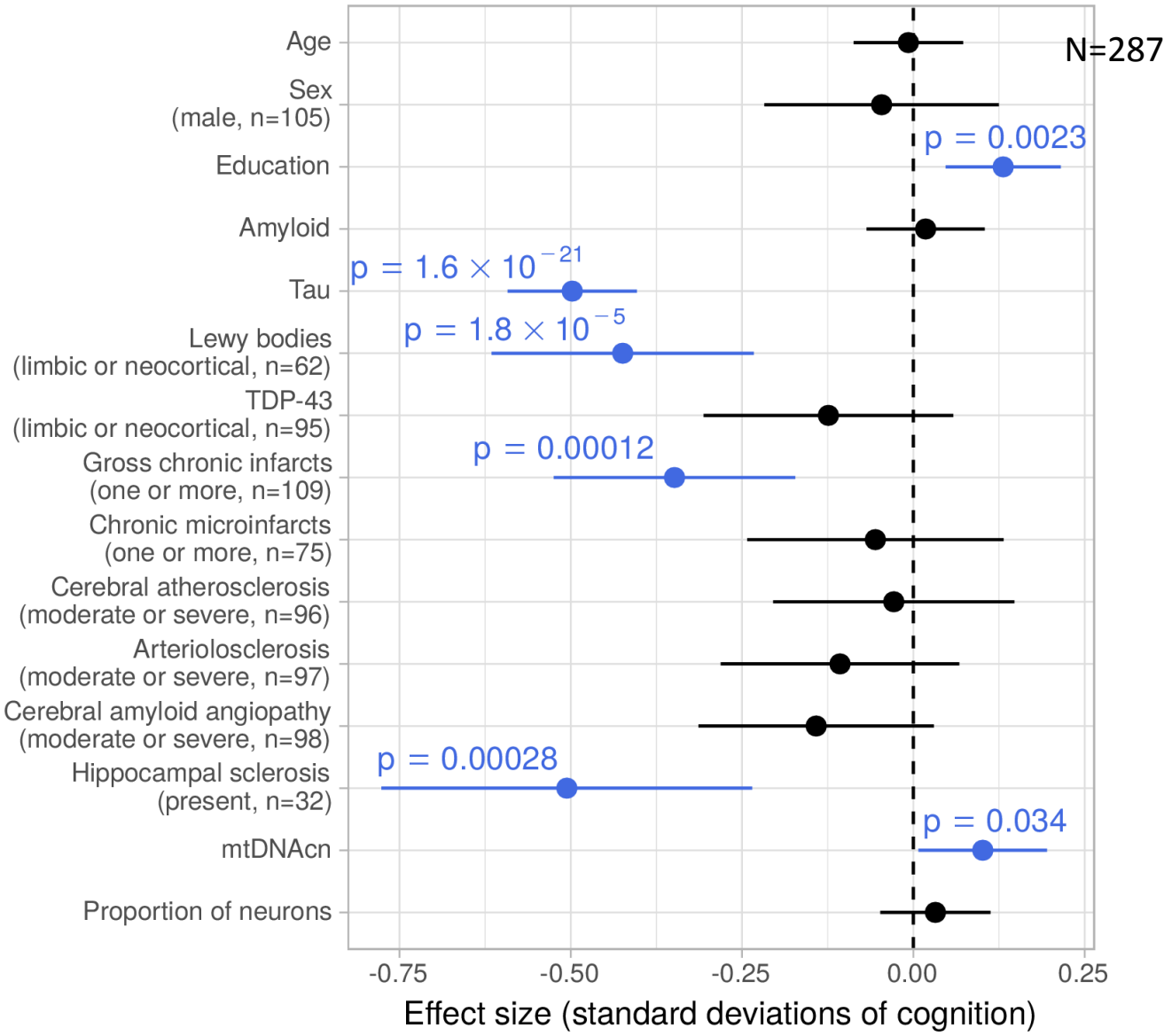
- Multivariable regression, outcome: mtDNAcn in DLPFC
- Proportion of neurons estimated from RNA-seq data (327 out of 454 DLPFC samples) is associated with mtDNAcn
- Tau remains significantly associated with mtDNAcn
  → association not completely mediated by neuronal loss



mtDNAcn in the DLPFC is associated with cognition

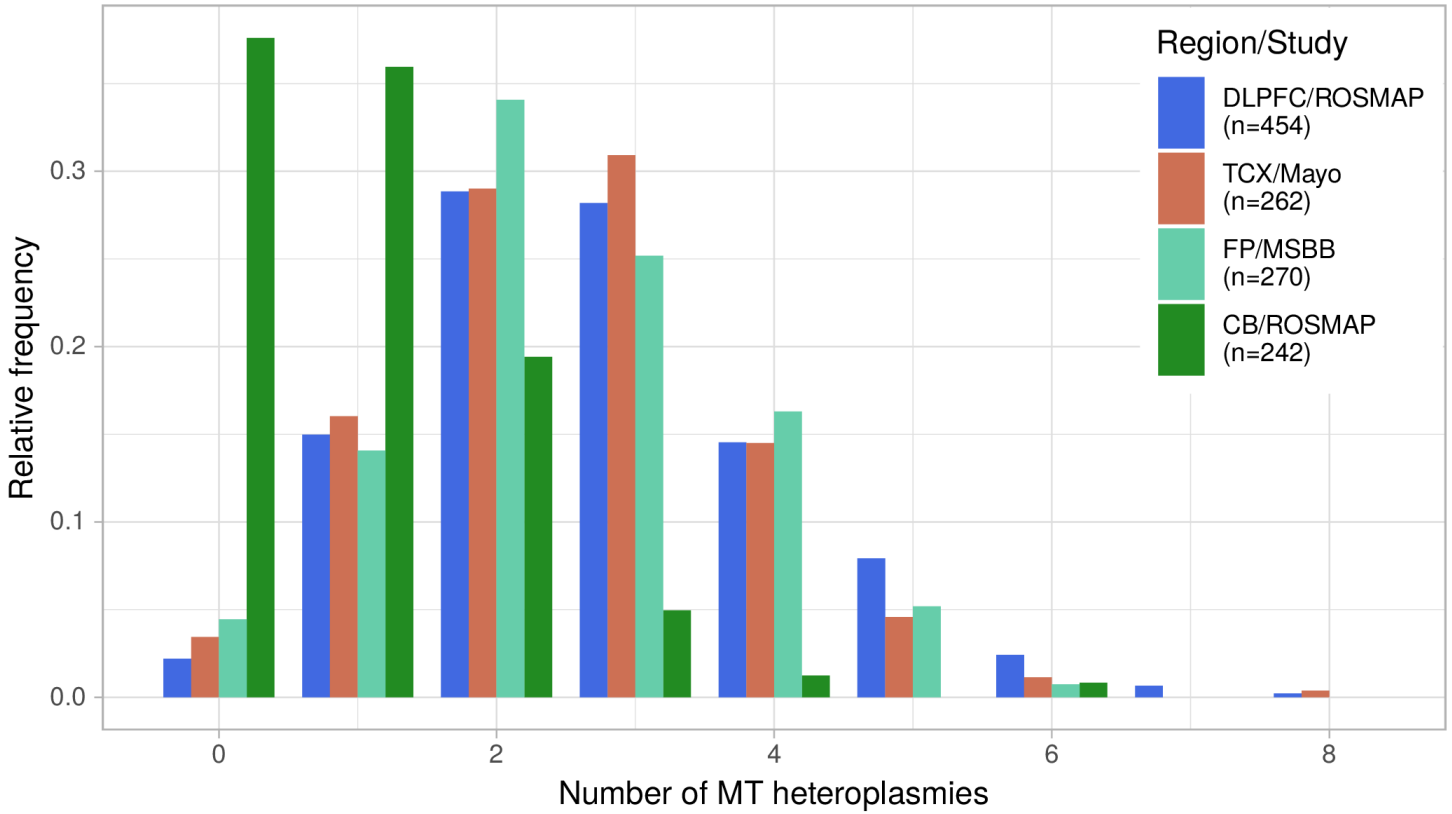
- Multivariable regression, outcome: cognition proximal to death

- mtDNAcn and pathologies remain significantly associated with cognition
  → association between mtDNAcn and cognition is partly independent of pathologies



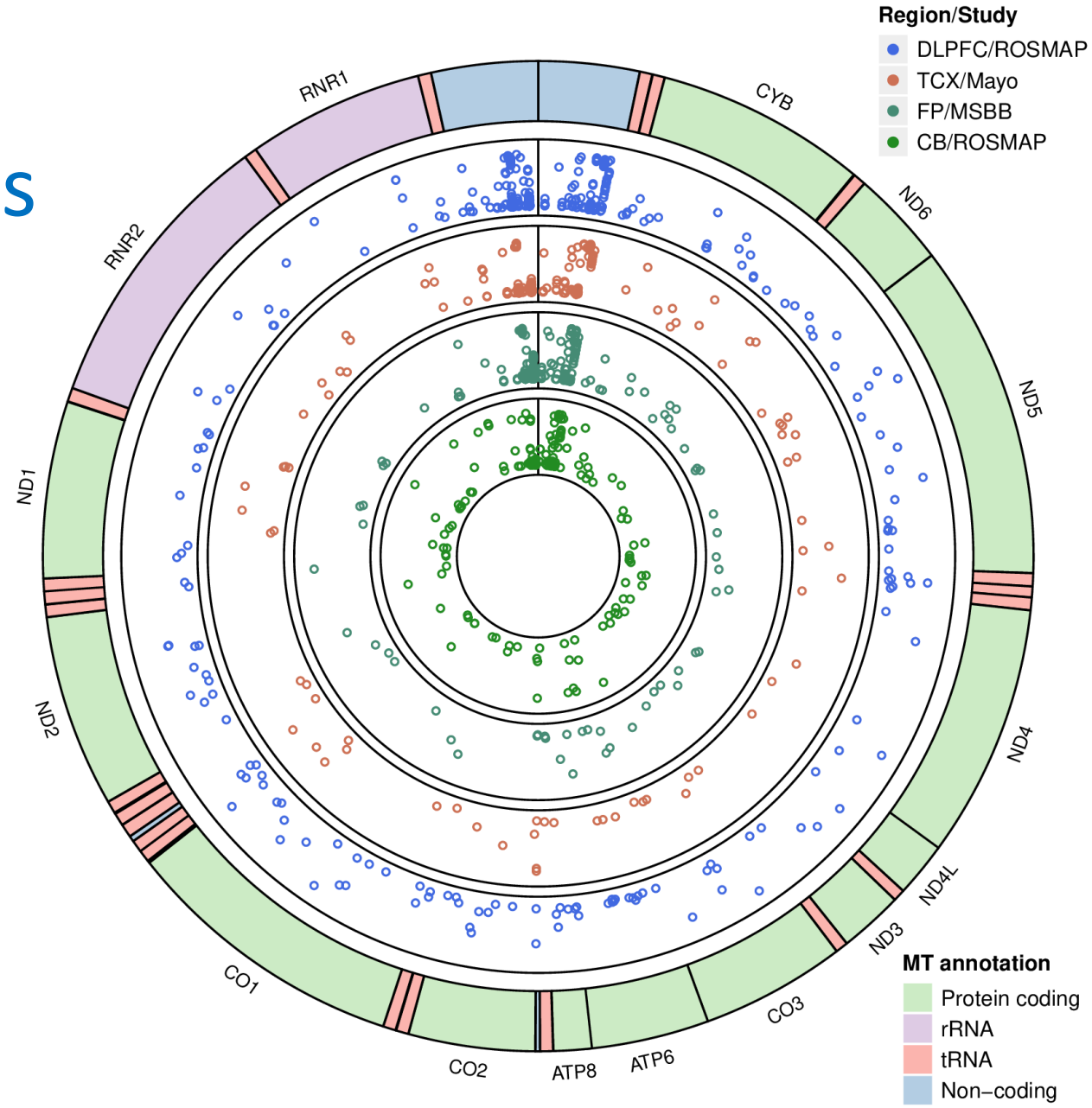
mtDNA heteroplasmy levels

- Variants with relative frequencies between 0.03 and 0.9
- Can be caused by intra- or intercellular heterogeneity of mtDNA
- Less heteroplasmic mutations in the CB than in cortical regions



Distribution of mtDNA heteroplasmic mutations

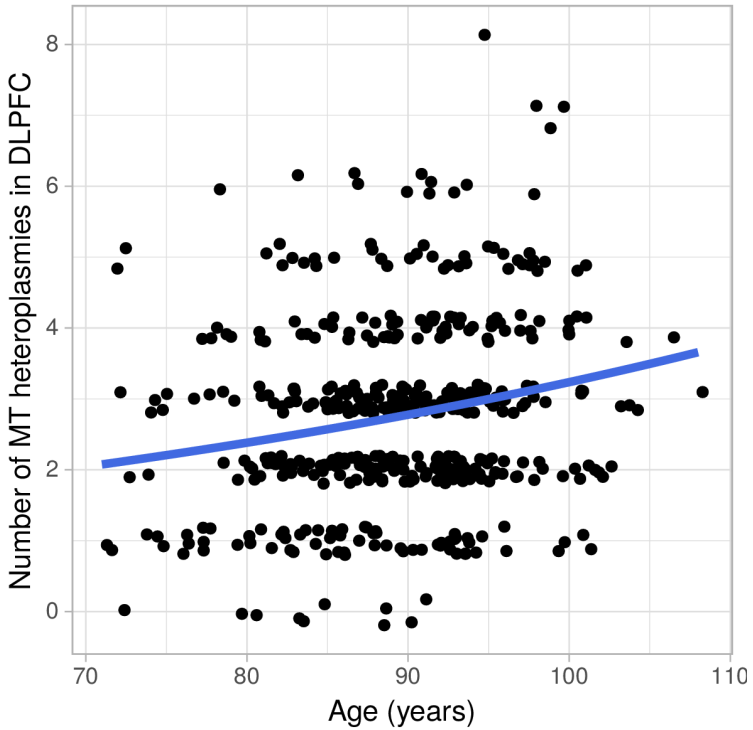
- Most heteroplasmic mutations are in the non-coding highly-variable region (87% - 91% in the cortical regions, 65% in CB)
- No enrichment of heteroplasmic mutations in Mt genes
- Majority of heteroplasmic mutations (71%) have low relative frequency (<0.1)

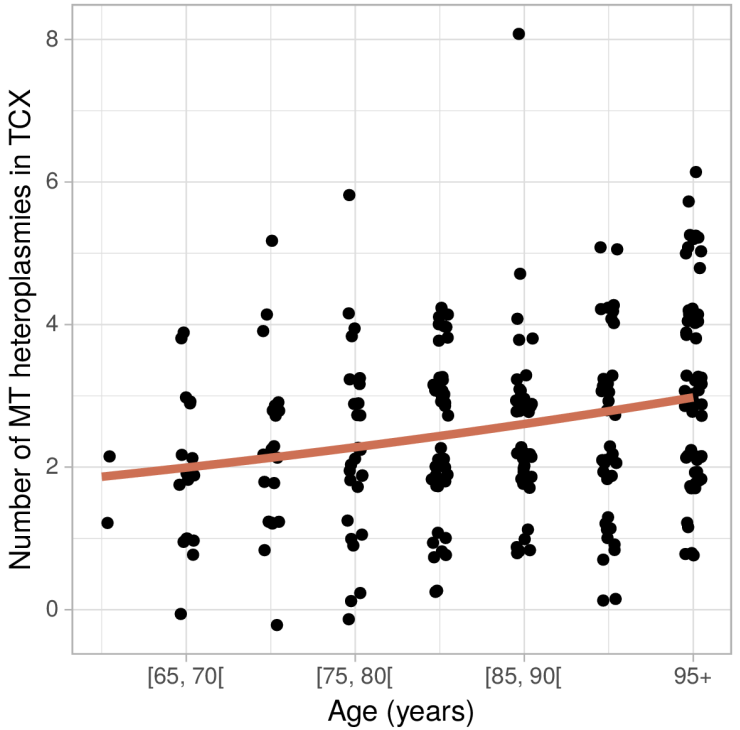


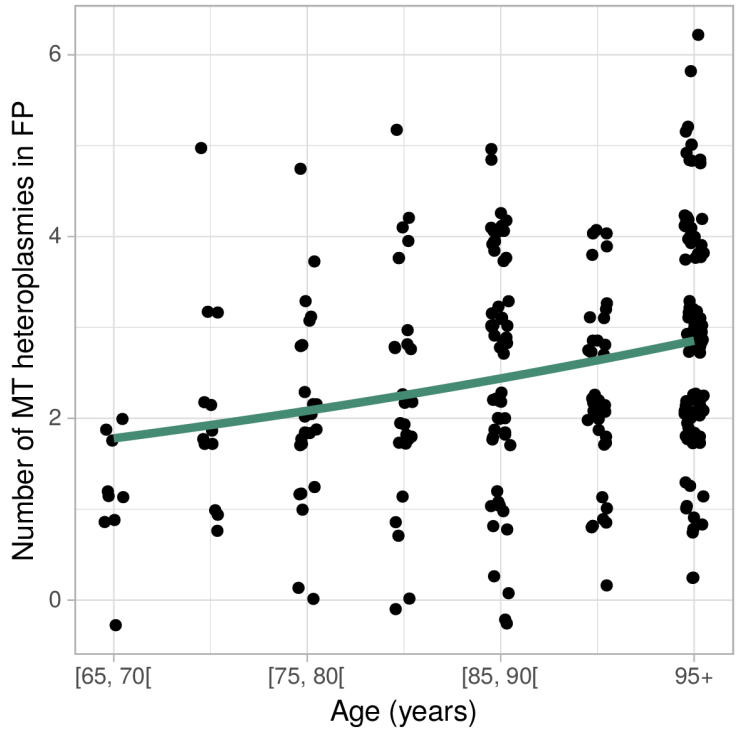
mtDNA heteroplasmy level is associated with age

- mtDNA heteroplasmy level not associated with AD pathologies or cognition in ROSMAP when adjusted for age and sex
- Increased mtDNA heteroplasmy levels in the cortical regions but not in the cerebellum with age

Region/Study	Effect size (% increase per year)	P value
DLPFC/ROSMAP	1.5% [0.8%; 2.2%]	2.8×10^{-5}
TCX/Mayo	1.6% [0.9%; 2.4%]	5.9×10^{-5}
FP/MSBB	1.6% [0.8%; 2.4%]	1.0×10^{-4}
CB/ROSMAP	-0.8% [-2.8%; 1.3%]	0.46

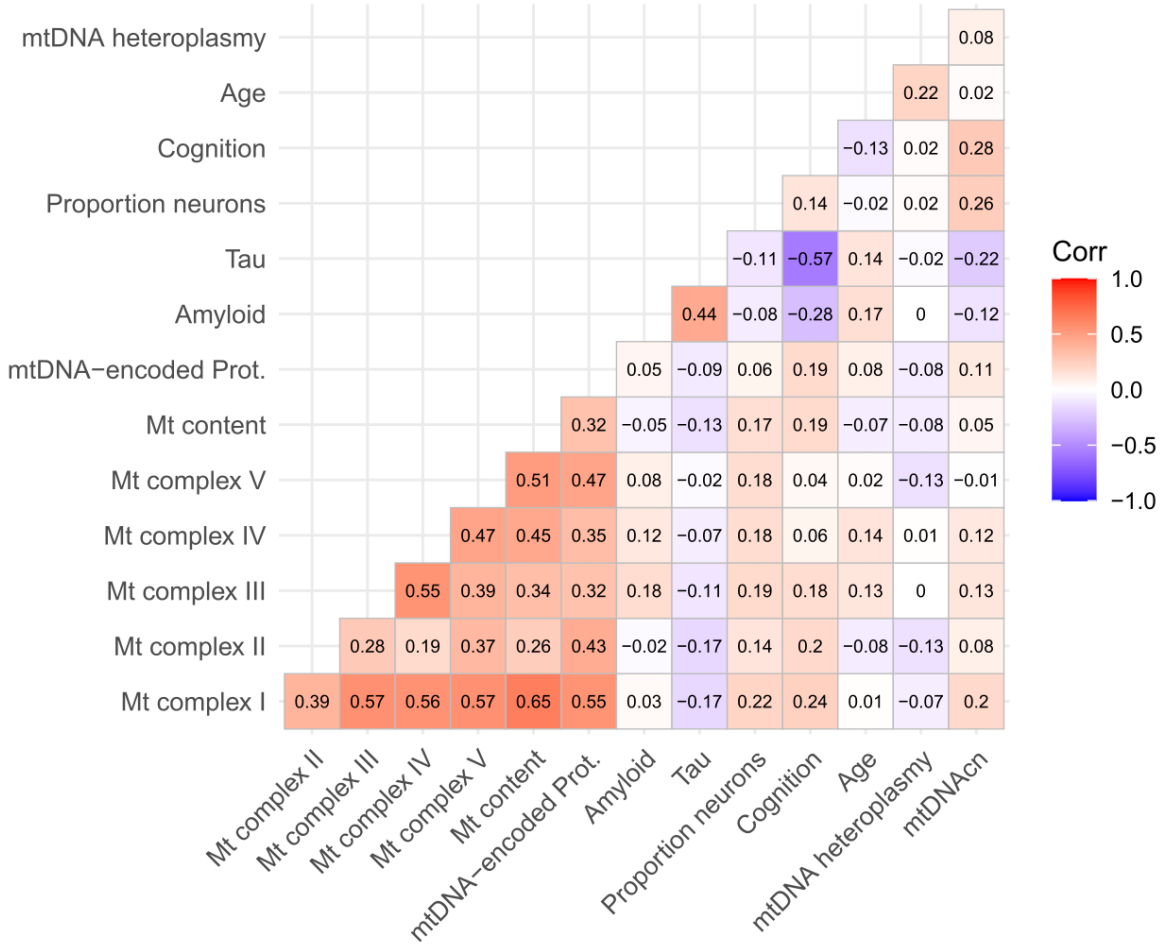




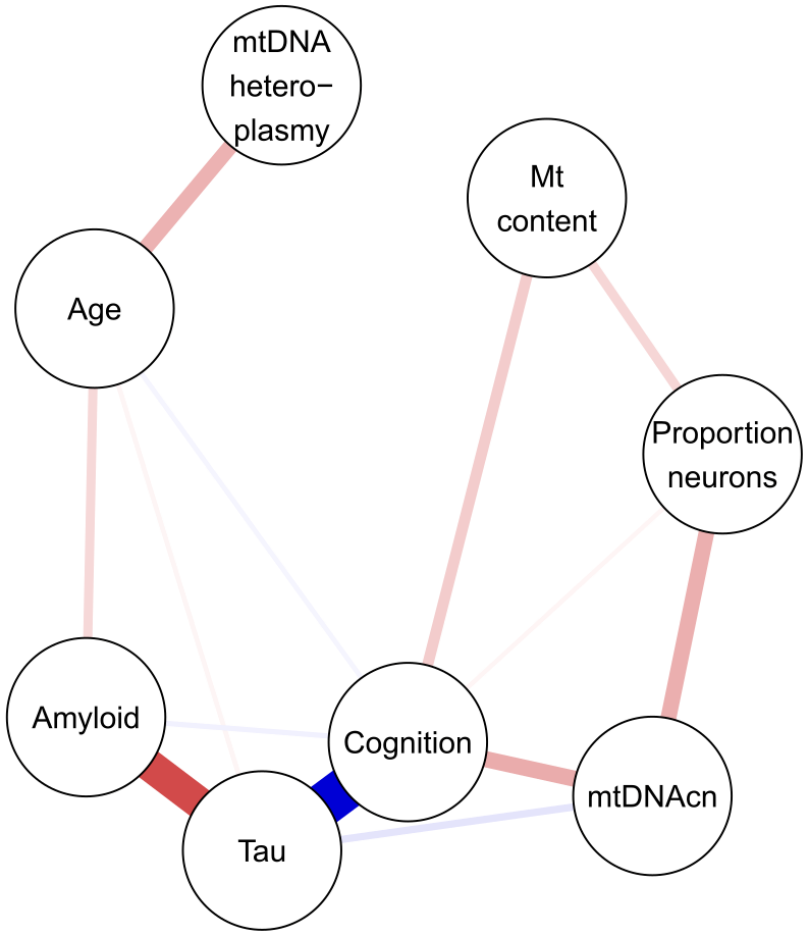


mtDNAcn and Mt content are uncoupled

- mtDNAcn alone is difficult to interpret
- Mt content estimated from abundances of 10 Mt proteins measured by mass spec



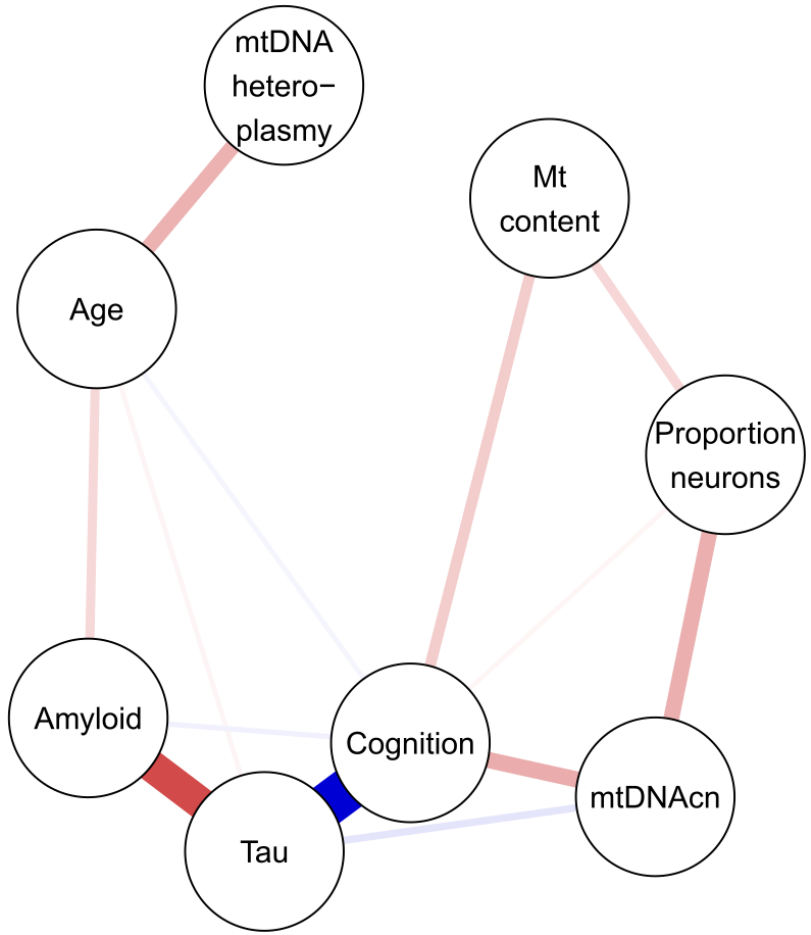
Graph shows sparse partial correlation structure between the different variables in the DLPFC



Summary

- Lower mtDNAcn in brain regions affected by pathology
- mtDNA heteroplasmy levels increase with age but are not related to neurodegenerative processes
- DLPFC: tau is the primary driver of lower mtDNAcn. mtDNAcn has an independent effect on cognition.
- PCC: TDP-43 pathology is associated with lower mtDNAcn
- Complex relationship between mtDNAcn and Mt content: mtDNAcn captures only part of mitochondrial health

Graph shows sparse partial correlation structure between the different variables in the DLPFC

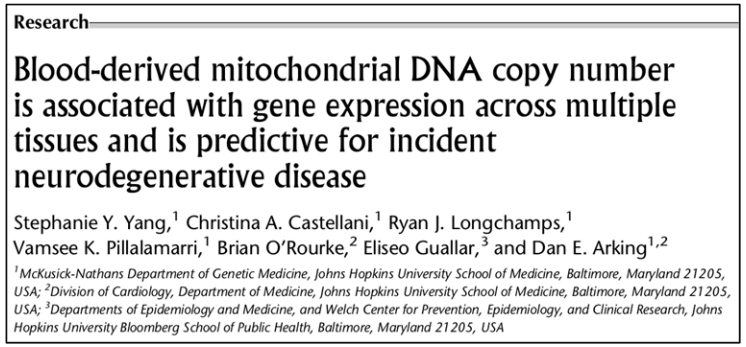


Summary

- Lower mtDNAcn in brain regions affected by pathology
- mtDNA heteroplasmy levels increase with age but are not related to neurodegenerative processes
- DLPFC: tau is the primary driver of lower mtDNAcn. mtDNAcn has an independent effect on cognition.
- PCC: TDP-43 pathology is associated with lower mtDNAcn
- Complex relationship between mtDNAcn and Mt content: mtDNAcn captures only part of mitochondrial health

Limitations/challenges

- Which cell (sub)types are driving the observed associations? Are certain neurons particularly vulnerable to mitochondrial dysfunction?
- Are large heteroplasmic mtDNA deletions and insertions implicated in AD?
- Does the loss of mtDNAcn reflect bioenergetic dysfunction?
- Could mtDNAcn measured in blood be used as biomarker?


Research

Blood-derived mitochondrial DNA copy number is associated with gene expression across multiple tissues and is predictive for incident neurodegenerative disease

Stephanie Y. Yang,[1] Christina A. Castellani,[1] Ryan J. Longchamps,[1] Vamsee K. Pillalamarri,[1] Brian O'Rourke,[2] Eliseo Guallar,[3] and Dan E. Arking[1,2]

[1]McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA; [2]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA; [3]Departments of Epidemiology and Medicine, and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland 21205, USA

Acknowledgements

COLUMBIA UNIVERSITY MEDICAL CENTER

Philip De Jager
Martin Picard
Caroline Trumpff
Annie Lee

RUSH UNIVERSITY MEDICAL CENTER

David Bennett

BWH BRIGHAM AND WOMEN'S HOSPITAL

Hyun-Sik Yang

Thank you for your attention!

Manuscript: Klein et al. (2021), Molecular Neurodegeneration, 16(1):75

CTCN
THE CENTER FOR TRANSLATIONAL & COMPUTATIONAL NEUROIMMUNOLOGY