

Multimodal Characterization of MAPT-GR Mice in MODEL-AD Reveals Tauopathy-Linked Signatures Across Age and Genetic Contexts

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MODEL-AD

Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease



Pitt

ABSTRACT

Tauopathies represent a major subclass of neurodegenerative disorders, including Alzheimer's disease (AD) and frontotemporal dementia (FTD), often driven by mutations in the *MAPT* gene. To better model human-relevant tau pathology in preclinical studies, the MODEL-AD consortium developed and characterized a panel of genetically refined MAPT-GR mice expressing human tau variants (H1 haplotype, P301L, N279K, IVS10+16C>T). We conducted cross-sectional and longitudinal multimodal phenotyping of MAPT-GR mice at 4 and 12 months of age across four major tau mutations. Molecular and cellular profiling included RNA-seq transcriptomics, quantitative proteomics, immunoblotting (WB), and immunohistochemistry (IHC). To assess interactions with inflammatory pathology, a subset of mice were crossed with an amyloid mouse model (hAbSAA). Distinct transcriptomic and proteomic alterations were observed across different ages and mutation types, revealing mutation-specific molecular signatures. Early immune activation pathways were particularly prominent in mice harboring the P301L mutation, while IVS10+16C>T mutation lines exhibited alterations related to RNA splicing mechanisms. These findings indicate that pathogenic processes associated with tauopathy diverge early on depending on the genetic variant, potentially influencing disease onset and progression. IHC and WB analyses provided further validation, demonstrating age-dependent increases in tau accumulation and phosphorylation. This progressive tau pathology was especially evident in N279K mutant mice, reinforcing the connection between specific MAPT mutations and the temporal escalation of tau-related abnormalities in the brain. These MAPT-GR models represent a critical resource for understanding the mutation-specific trajectories of tauopathy and for testing candidate interventions. The integration of tau genetics with inflammatory challenges provides a framework for modeling complex risk profiles in AD and FTD.

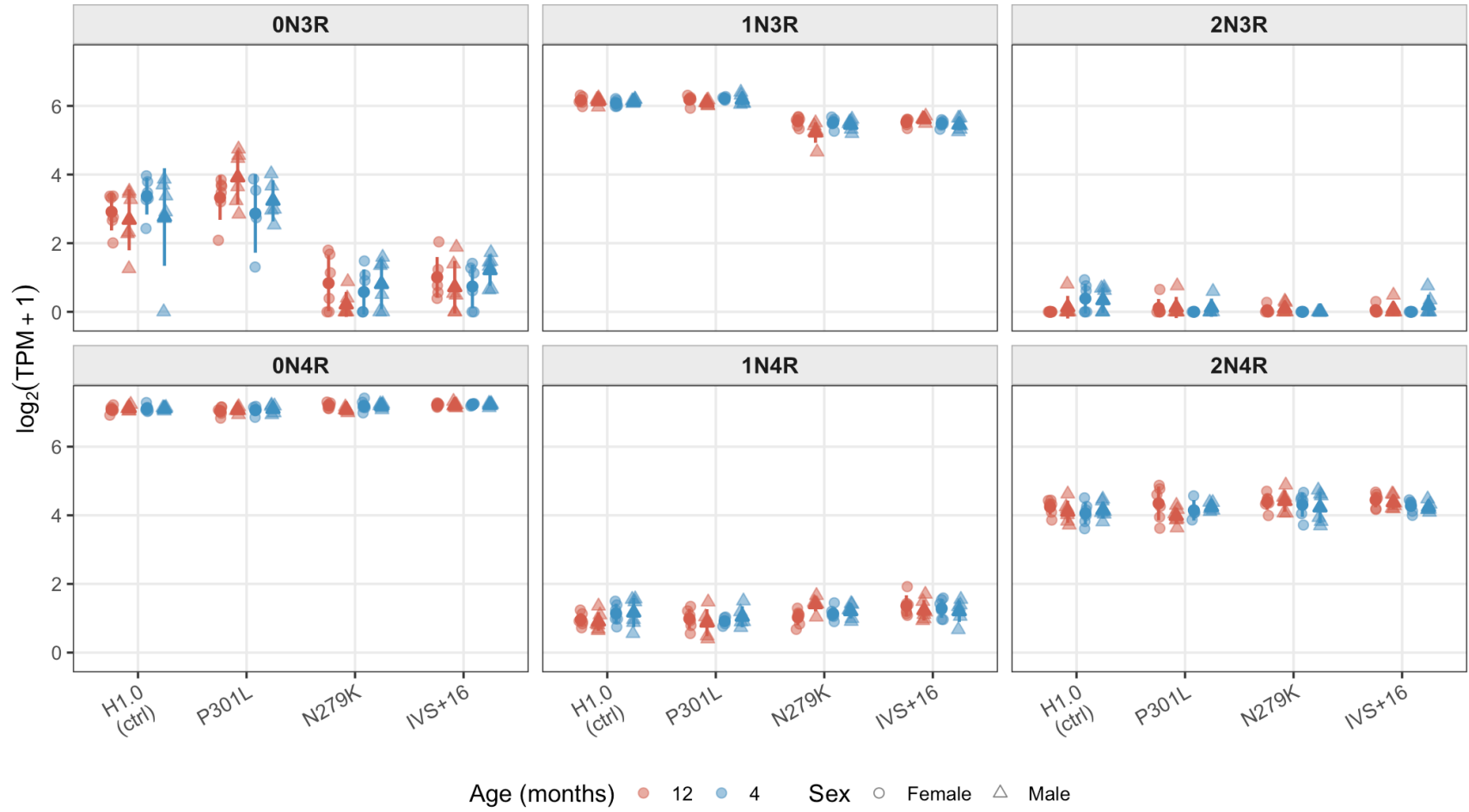
MAPT-KI MODEL DEVELOPMENT

A 190 kb deletion on mouse chromosome 11 (Chr11:104,066,949-104,223,491) stretching from, but not including, Crhr1 to Kansl1 is replaced by a syntenic 190 kb region from human chromosome 17 (HSA17; Chr17:45,838,648-46,029,144). In this transchromosomal (Tc) strain, the mouse Sppl2c (signal peptide peptidase 2C) and Mapt (microtubule-associated protein tau) genes are replaced by human SPPL2C and MAPT (H2 haplotype) genes. The genomic sequences are from human assembly GRCh38.p14 and the mouse assembly [0:00 / 0:03](#) GRCh39. The deletion/insertion was made using C57BL/6N-PRX-B6N embryonic stem cells (ES) and loxN-flanked hygromycin resistance cassette. Correctly targeted ES cells were injected into blastocysts. The resulting chimeric animals were crossed to B6.Cg-Edi3Tg(Sox2-cre)1Amc/J (Stock No. 008454) to remove the hygro cassette and then backcrossed to C57BL/6J for at least 5 generations. The Cre transgene was removed by breeding. Upon arrival, mice were bred to C57BL/6J for at least 1 generation to establish the colony.

MAPT-KI MODELS

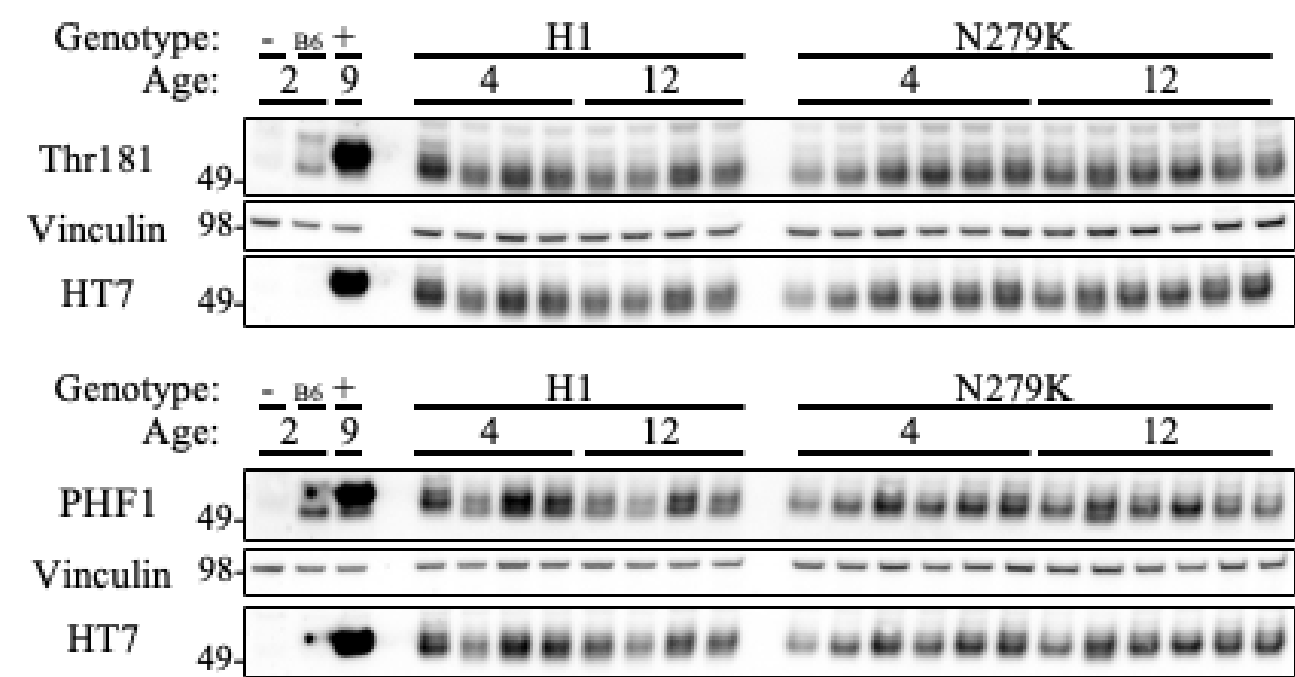
Genotype	Jax #	Ages	Readouts
MAPT-GR(H1)	35398	4MO, 12MO	IF + WB + RNA-seq
MAPT-GR(H1)*IVS10+16	36664	4MO, 12MO	IF + WB + RNA-seq
MAPT-GR(H1)*N279K	35794	4MO, 12MO	IF + WB + RNA-seq
MAPT-GR(H1)*P301L	37420	4MO, 12MO	IF + WB + RNA-seq

Human MAPT Isoform Expression in MAPT(GR) models



Expression analysis of human MAPT isoforms demonstrates robust and stable expression of both 3R (0N3R) and 4R (0N4R) transcripts across GR mouse models. No endogenous murine expression is observed, confirming humanized MAPT expression specificity. Isoform levels are consistent across sex and age, indicating that downstream pathological differences are not driven by gross differences in transcript abundance but rather mutation-specific effects on tau biology.

Thr181 and PHF1 alterations in 4- and 12-month-old animals.

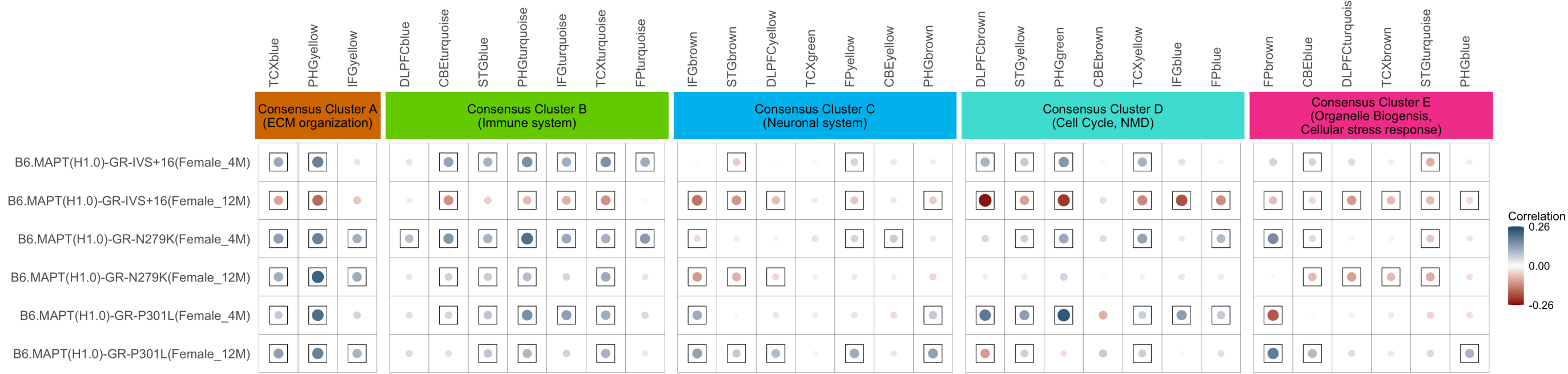


Western blot analysis of Thr181 and PHF1 demonstrates age-dependent increases in tau phosphorylation, with greater accumulation in N279K mice. Higher molecular weight species are enriched in mutant animals, consistent with progressive tau aggregation.

CONCLUSIONS

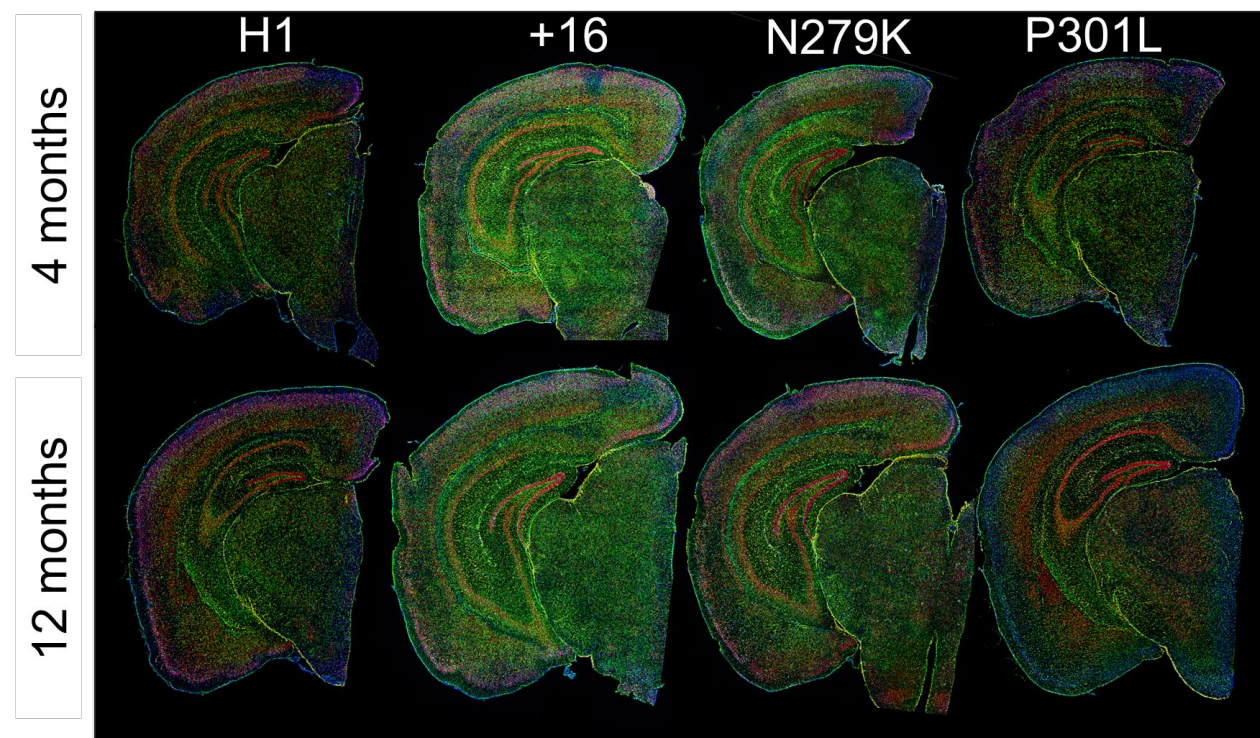
- Humanized MAPT-GR mouse models robustly express both 3R and 4R tau isoforms, enabling physiologically relevant modeling of human tau biology.
- Distinct MAPT mutations drive fundamentally different disease trajectories, rather than converging on a single pathogenic mechanism.
- N279K induces early, large-scale transcriptional activation, with pronounced neuronal and immune pathway engagement at 4 months, consistent with a toxic gain-of-function signaling phenotype.
- P301L promotes progressive tau aggregation and cellular dysfunction, characterized by increased phospho-tau (Thr181, PHF1), accumulation of higher molecular weight tau species, and enrichment of stress and organelle-related pathways at later stages.
- IVS+16 exhibits comparatively modest molecular and cellular disruption, suggesting a more subtle splicing-driven effect on tau biology.
- Transcriptional and proteomic alterations are temporally dynamic, with early pathway activation followed by attenuation, indicating a critical early window for therapeutic intervention.
- Regional and cellular changes align with molecular findings, linking early signaling disruptions to later structural and pathological outcomes.

Distinct MAPT mutations drive divergent pathway-level responses, with N279K promoting early transcriptional activation and P301L associated with later cellular stress and dysfunction



Consensus pathway analysis reveals mutation-specific biological signatures, with early neuronal and immune activation in N279K mice and late stress-related pathway engagement in P301L mice.

Parahippocampal Quantification Reveal Age- and Mutation-Dependent Neuroanatomical and Cellular Colocalization Changes in MAPT Models



These data demonstrate that MAPT mutations drive distinct trajectories of neurobiological change, with early alterations in N279K mice and more progressive, age-dependent changes in P301L animals.

The alignment of these structural and cellular changes with:

- early transcriptional disruption (N279K)
- late aggregation and stress responses (P301L)

supports a model in which different tau mutations engage distinct temporal and mechanistic pathways of disease progression.

Acknowledgements

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