The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

September 23, 2020

Sex-Dimorphic Microglial Dysfunction in Tauopathy

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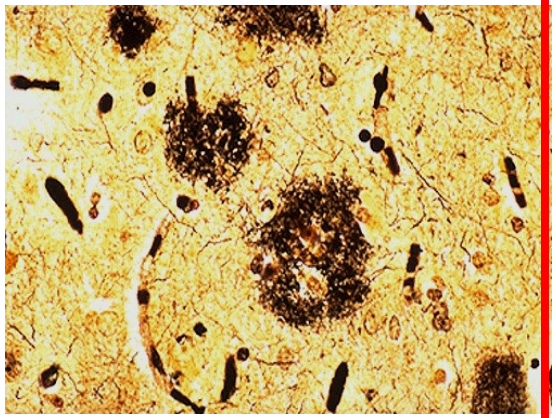
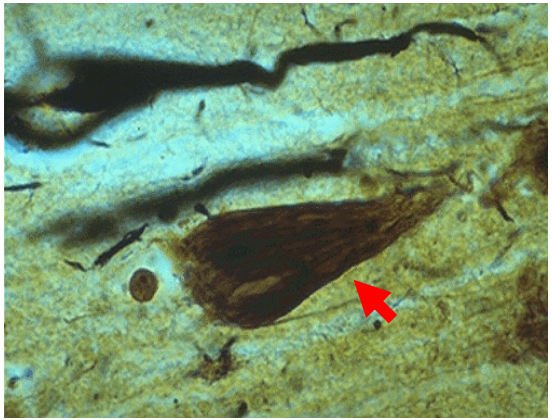
Weill Cornell Medicine

Weill Cornell Medicine

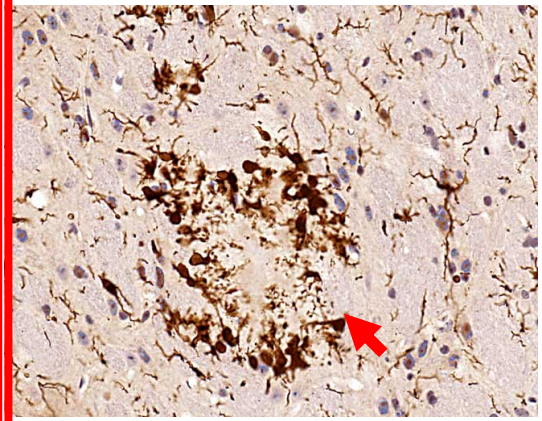
Tau Pathology and Microglia Activation in AD



Amyloid β Plaques

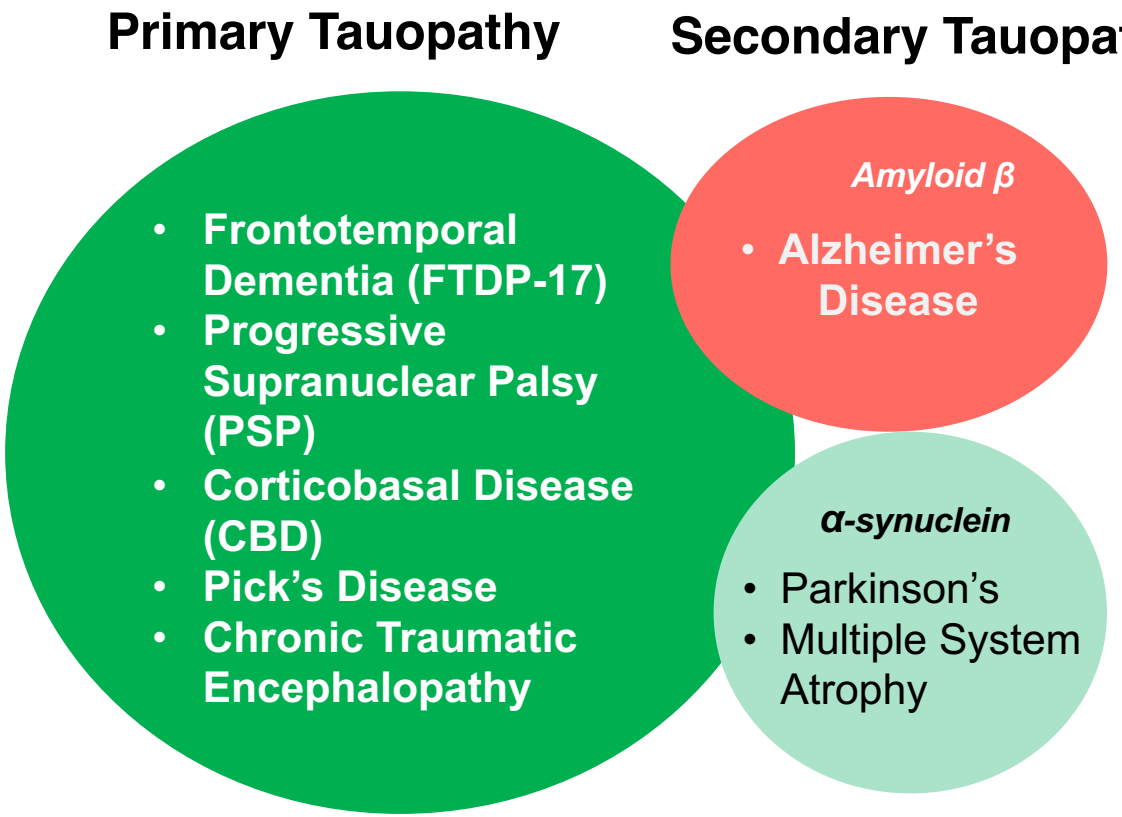


Neurofibrillary Tangles
NFTs
(Tau aggregates)



Inflammatory
Responses
(Microglia)

Tau at the Center of Neurodegeneration

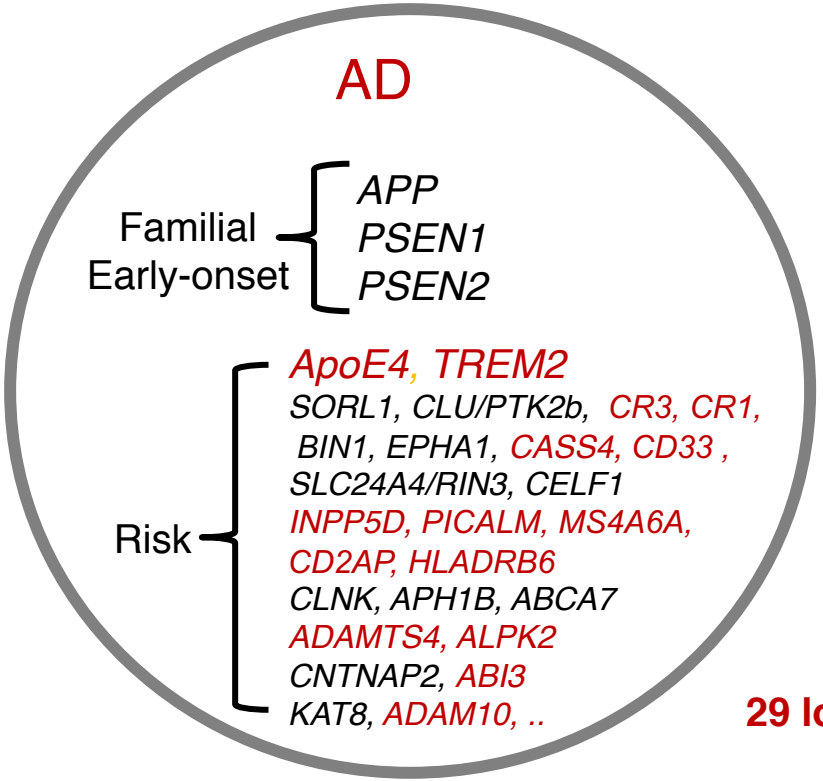


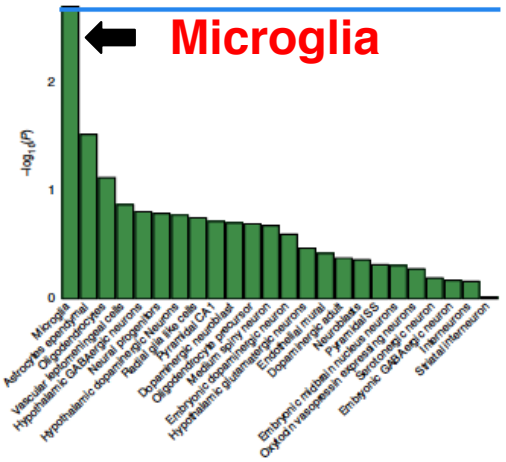
Sex Difference in Tauopathy in AD

- More AD patients are women than men (3.3 million vs.1.9 million (Alvarez-de-la-Rosa et al., 2005).

- Women have more tau tangles than men when controlled for apoE4 and age (Oveisgharan et al., 2018)

Many Risk Genes in AD Are Enriched in Microglia





29 loci implication ~215 genes

Janson et al., Nat. Gene., 2019

Myeloid Cells Exhibit the Strongest Sex Difference Among Immune Cells

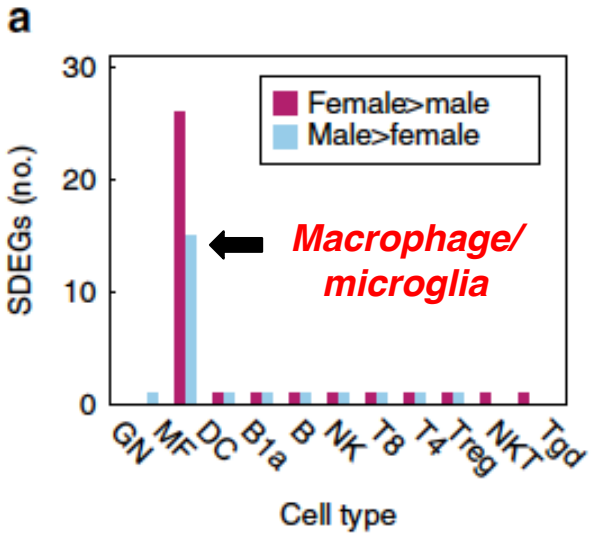
ARTICLE

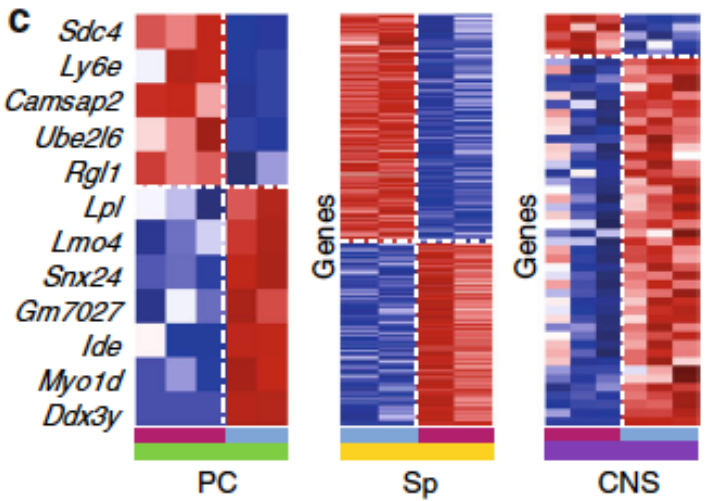
https://doi.org/10.1038/s41467-019-12348-6 OPEN

ImmGen report: sexual dimorphism in the immune system transcriptome

Shani Talia Gal-Oz[1], Barbara Maier[2], Hideyuki Yoshida[3,4], Kumba Seddu[3], Nitzan Elbaz[1], Charles Czysz[5], Or Zuk[6], Barbara E. Stranger[5,7], Hadas Ner-Gaon[1] & Tal Shay[1*]

Female vs. Male macrophage/microglia



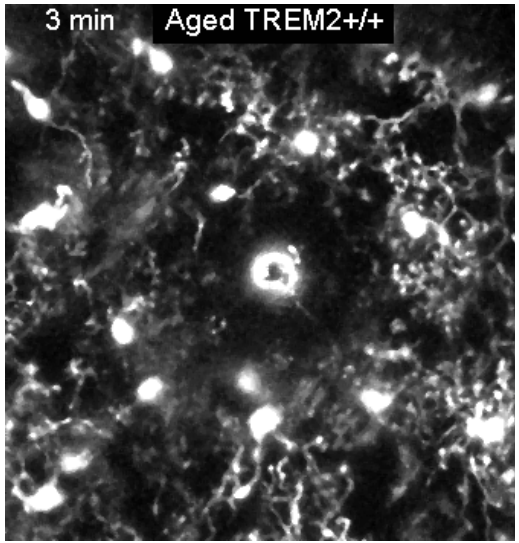


Gal-Oz et al., 2019

Microglia Are Brain's Immune Cells With Complex Personalities

Adaptive

- First responder to injury
- Clearance of aggregates and cell debris
- Tissue repair
- Neurotrophic

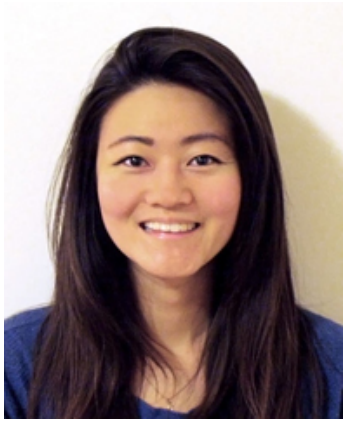


Maladaptive

- Inappropriate responses
- Excessive complement-mediated synaptic pruning
- Excessive cytokines that are neurotoxic

1. How do female vs. male microglia respond to tau pathology differently?

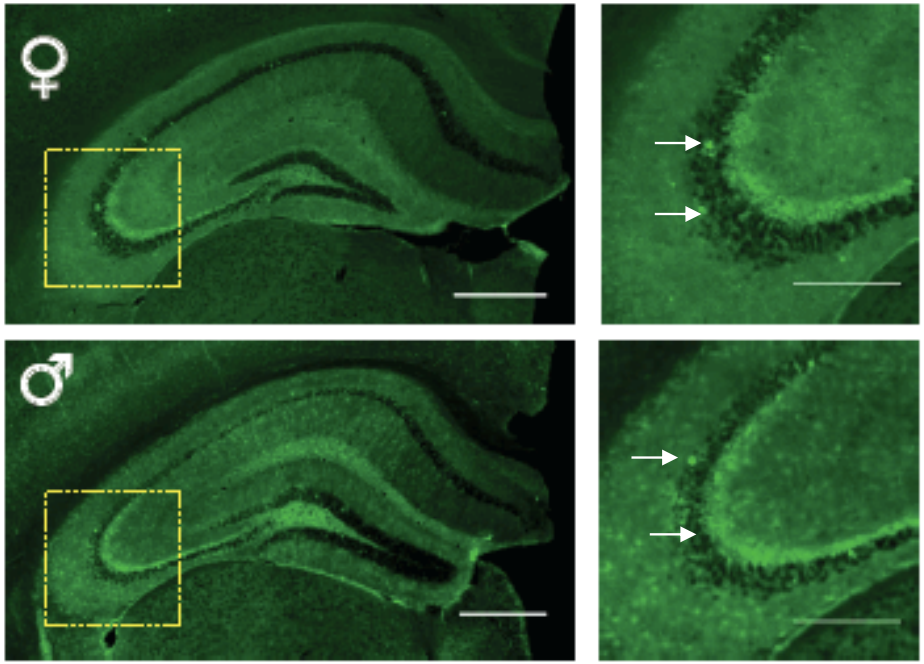
mRNA and miRNA profile



Lay Kodama, Ph.D

Distinct Microglia Response to Tau Pathology in Male and Female Tauopathy Mice

Similar tau pathology

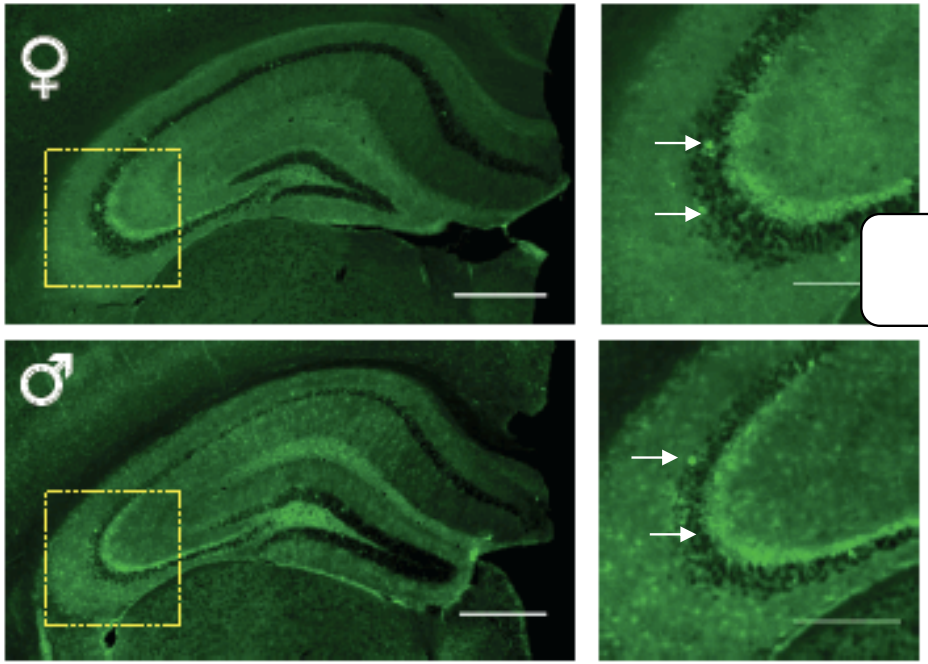


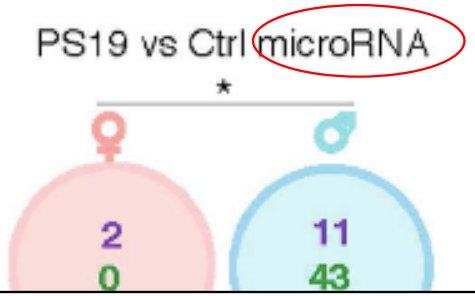
MAPTP301S (PS19)

- Express mutant forms of human tau
- Develop microgliosis and inflammation at 3 months
- Develop spatial memory deficits and inclusions starting at 7 months of age

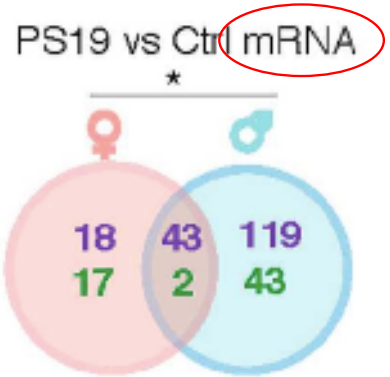
Distinct Microglia Response to Tau Pathology in Male and Female Tauopathy Mice

Similar tau pathology

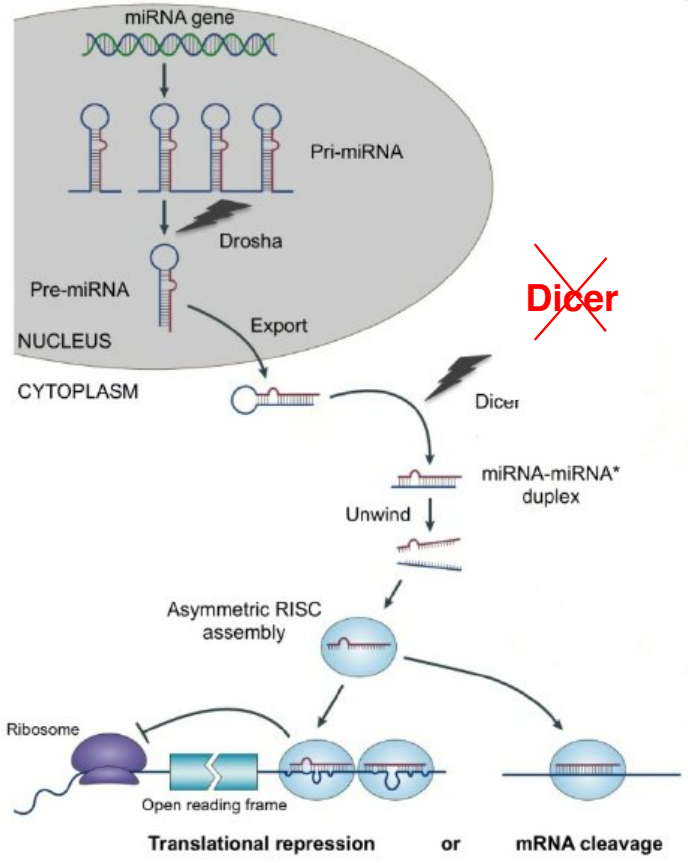




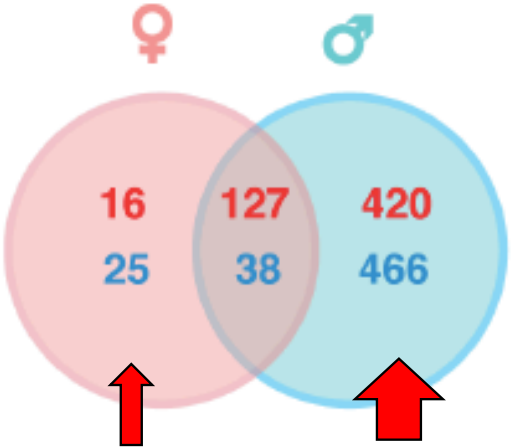
Female MG << Male MG



Sex-specific Response to Selective Removal of Dicer in Male vs. Female Microglia

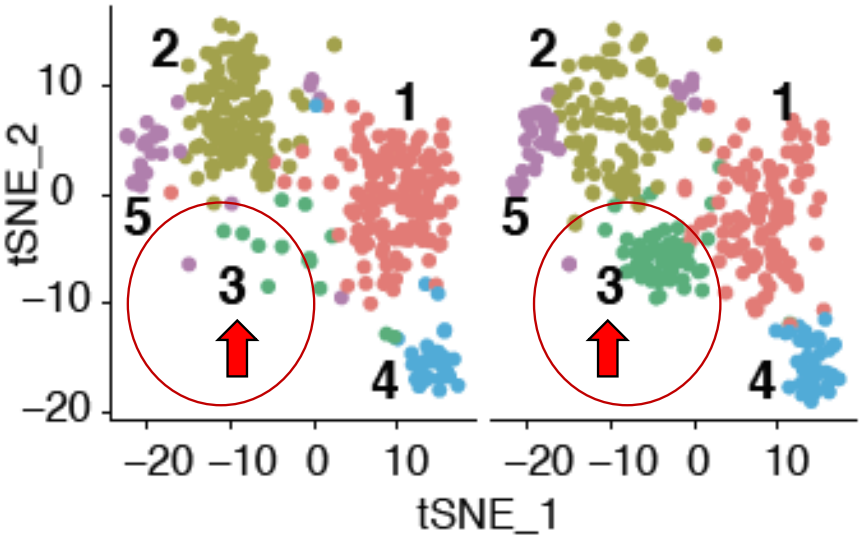


Dicer$^{F/F}$; CX3CR1-cre-ERT



Female MG Transcriptome << **Male MG Transcriptome**

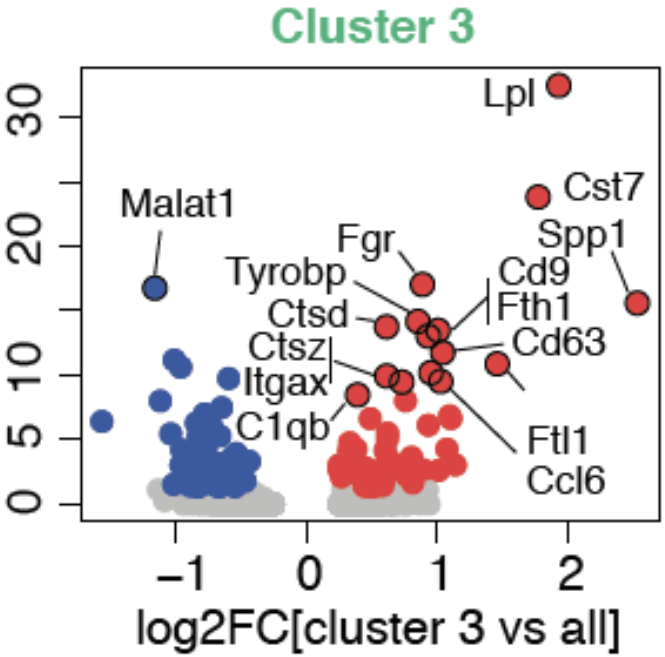
Single Cell RNA-seq of Microglia Tauopathy Mice Lacking Dicer



DicerF/F; CX3Cr1-cre-ERT; P301S (tau)

- Single cell RNA-seq of microglia isolated from mouse hippocampus
- Five microglial subclusters in male and female microglia
- Subcluster 3 is highly expanded in male microglia

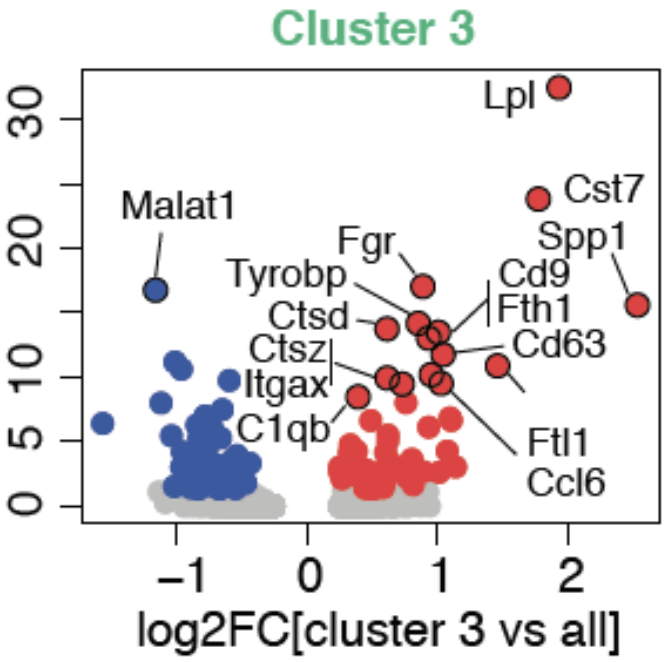
Male-enriched Microglial Cluster Exhibits Elevated Disease-Associated Microglial States (DAMs)

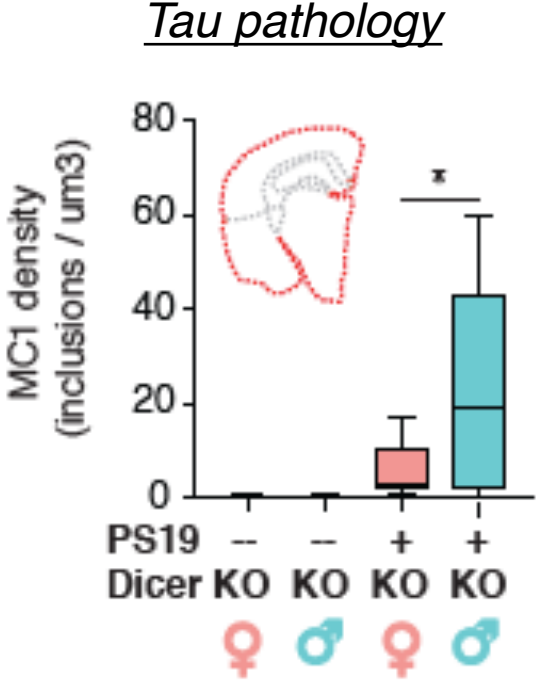


- Associated with neurodegeneration, also called microglial neurodegenerative phenotype (MGnD)
- Downregulation of homeostatic markers
- Upregulation of inflammation and cholesterol metabolism/transport

Krasemann et al., 2017; Keren-Shaul et al., 2017

Ablation of Mature MiRNAs Markedly Exacerbated Tau Pathology in Male Microglia



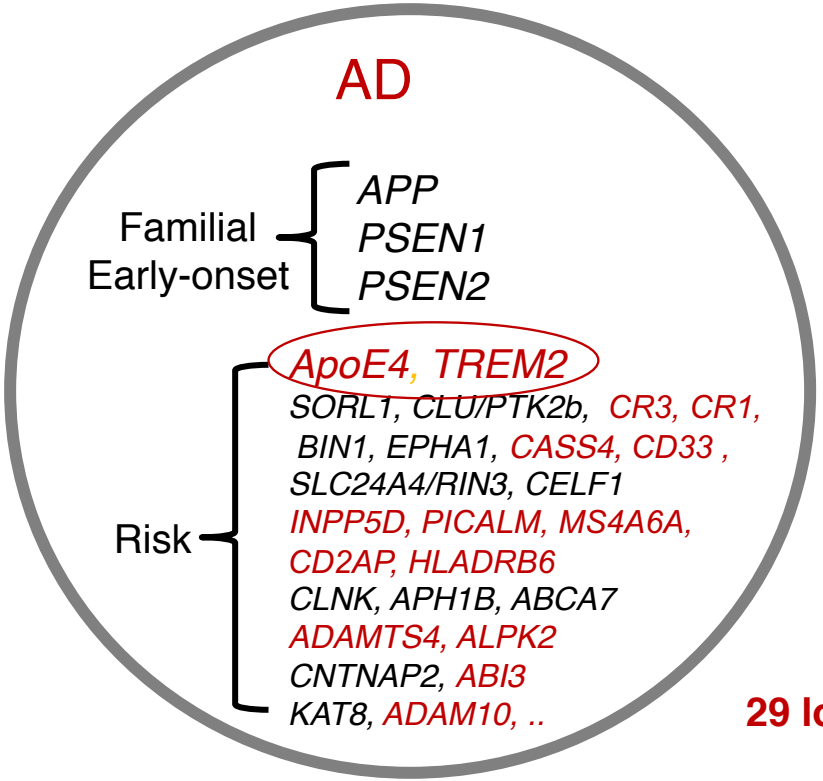


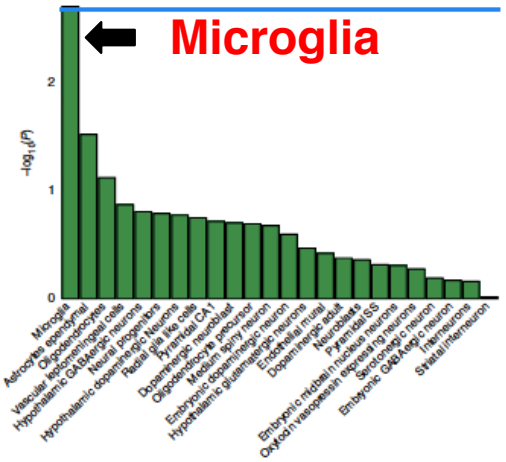
Summary I

- Distinct expression of miRNAs in adult male and female mouse microglia
- Striking sex-dependent response to loss of miRNA in the presence or absence of tau pathology
- Microglial miRNAs influence homeostasis and tau pathogenesis in a sex-specific manner in tauopathy mice

Kodoma et al., *Nat. Neurosci*. 2019

Many Risk Genes in AD Are Enriched in Microglia

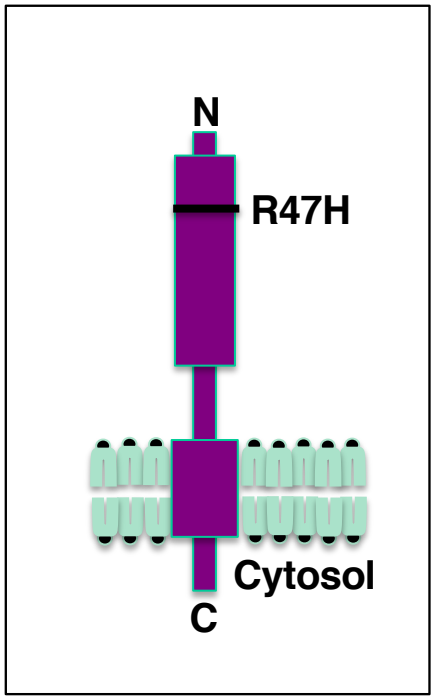




29 loci implication ~215 genes

Janson et al., Nat. Gene., 2019

TREM2 Is the Strongest Immune AD Risk Gene



- In the brain, TREM2 is a microglia-specific gene.
- Mutations leading to complete loss of TREM2 cause Nasu-Hakola Disease with bone cysts and presenile dementia
- Hemizygous R47H-TREM2 variant increases risk for AD & FTD by 2–4.5 fold

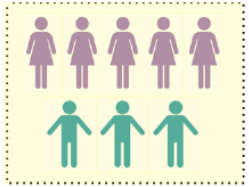
Guerreiro et al. 2013, Jonsson et al. 2013, Yuan et al. 2016; Ulland TK et al., 2017; Wang et al., 2016; Wang et al, 2015; Mazaheri, 2017; Song et al., 2018; Parhizkar et al., 2019

How Does R47H Mutation Affect AD Transcriptomes in Cell Type- and Sex-Specific Manner?

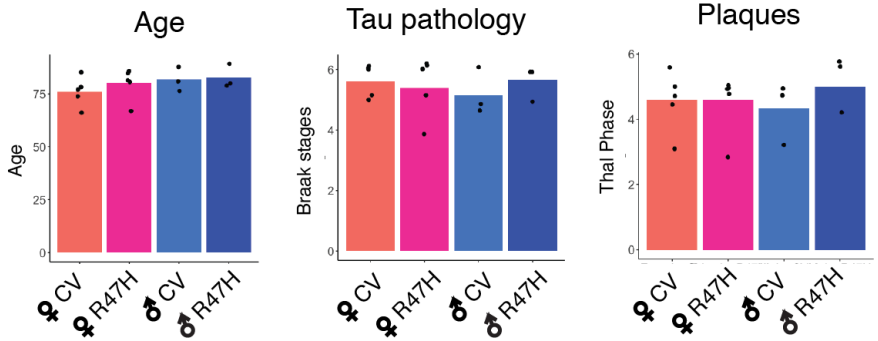
AD; ApoE E3/E4

CV

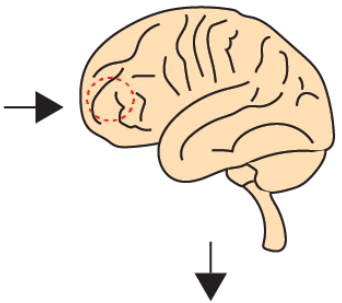
R47H



Matched age, APOE,
Tau and amyloid pathology



Frontal cortex

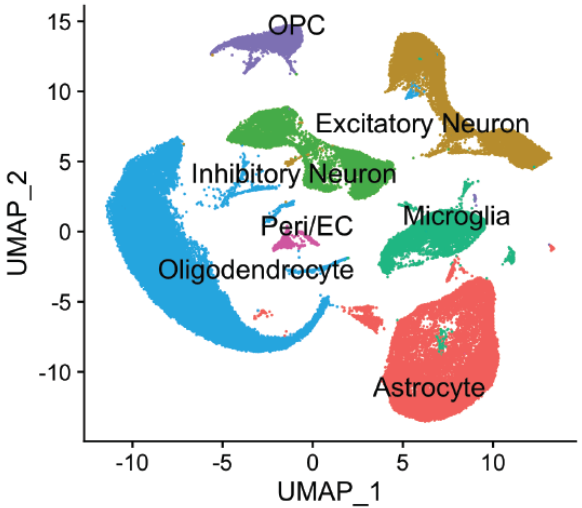


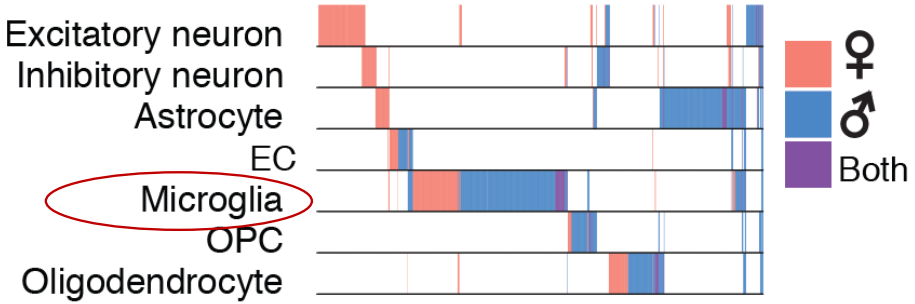
83,051
single-nuclei
analyzed

Dennis Dickson, MD
Mayo Clinic

Lay Kodama, Ph.D
Li Fan, Ph.D

R47H Mutation Exerts Strongest Sex-Specific Effects on Microglial Transcriptomes



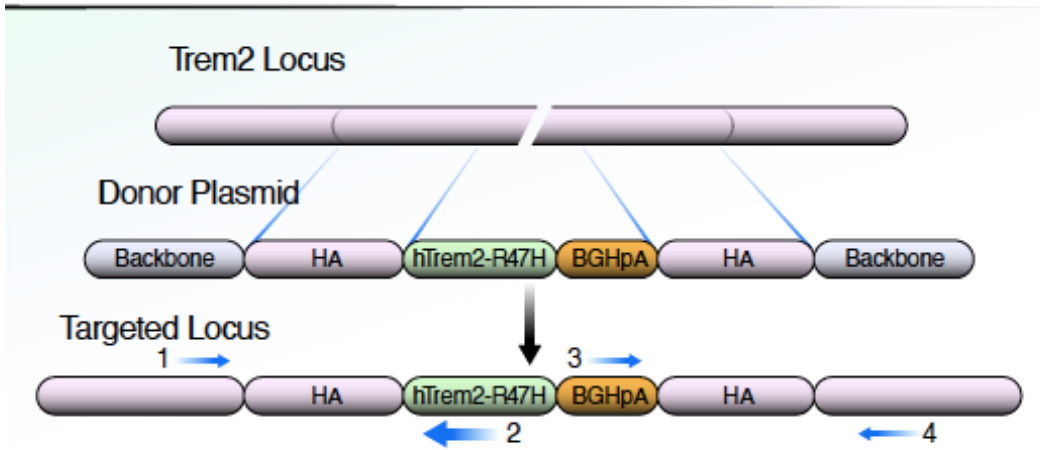


DEGs (889)

Sayed, Kodoma, et al, submitted

Modeling TREM2R47H in Mouse Tauopathy

***TREM2R47H* knockin**



hTREM2WT/+ X TgMAPTP301S

⬇

mTrem2+/+, P301S, P301S/WT/+

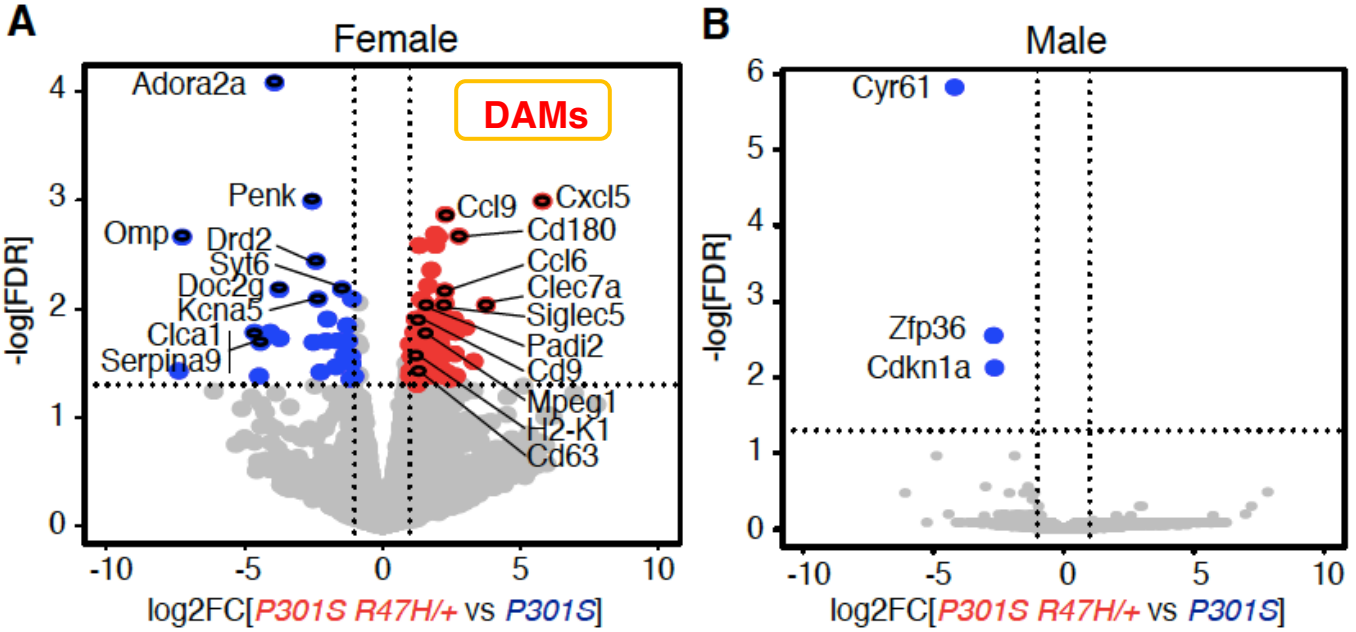
hTREM2R47H/+ X TgMAPTP301S

⬇

mTrem2+/+, P301S, P301S;R47H/+

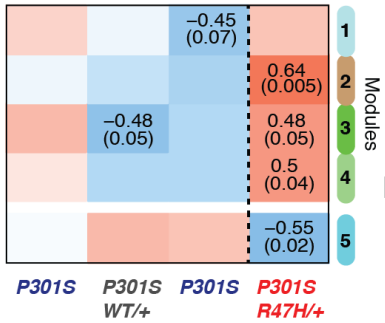
Sayed, Kodoma, et al, submitted

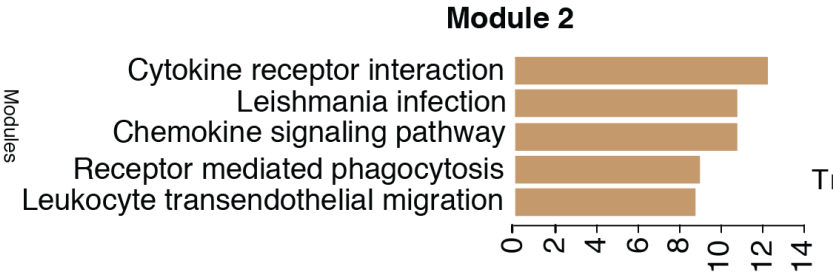
R47H Induces Profound Transcriptome Changes in Female (Not Male) Tauopathy Mice

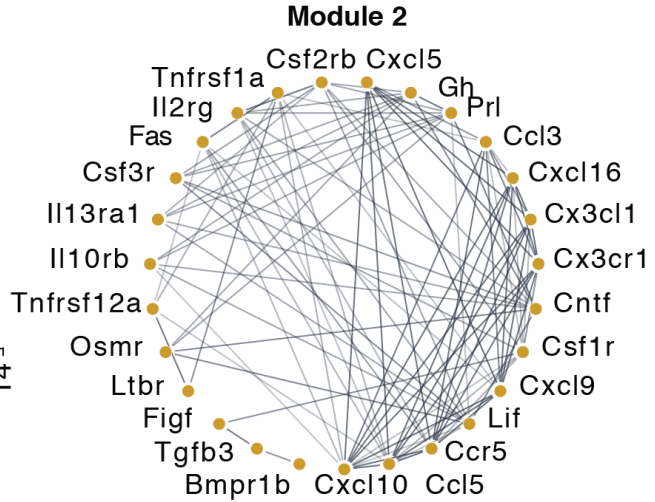


$p < 0.05$ by Benjamini-Hochberg correction and log2FC ≤ -1

R47H Mutation-induced Module Is Enriched With Cytokines/Chemokine Signaling in Female Tauopathy Mice

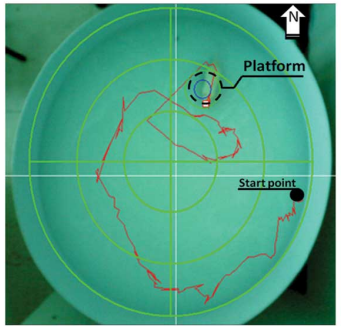






What about tau-mediated functional deficits?

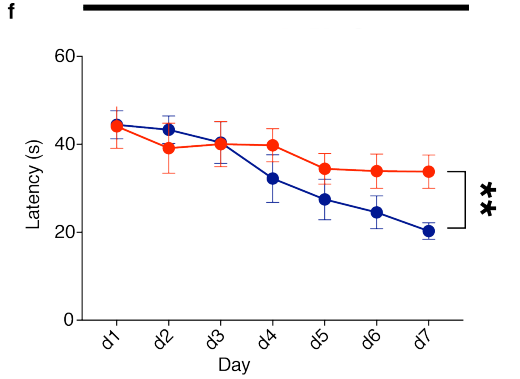
TREM2 R47H Mutation Exacerbates Spatial Learning Memory in Female (Not Male) Tauopathy Mice

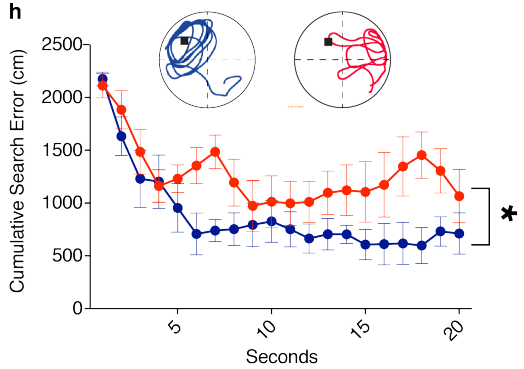


hTREM2 R47H/+; P301S

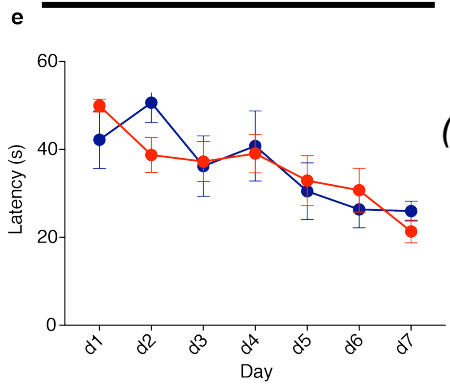
Trem2+/+; P301S

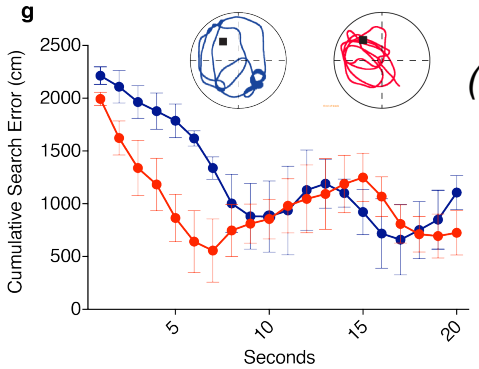
Female





Male





Learning curve (Spatial learning

Probe trial (Spatial memory)

7- to 9-months

Conclusion and Outlook

- Sex strongly modifies the effects of AD risk allele (*TREM2*) on microglial transcriptomes in human AD, and on functional deficits in tauopathy mice.

- Microglial miRNAs influence homeostasis and tau pathogenesis in a sex-specific manner in tauopathy mice.

- Therapeutic implications: Sex disparity in sensitivity to risk alleles, diagnostic biomarkers, immune-targeted therapy; sex-stratified omics in clinical trials

Sayed, Kodama et al., Submitted
Kodama and Gan, Trends in Mol. Med., 2019; Kodama et al., Nat. Neurosci., 2019

Acknowledgements

Weill Cornell Medicine

Collaborators

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Bin Zhang (Mount Sinai)
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Lu Zhou (Stanford/Wash U)
Michael Gill (Gladstone)

Gan Lab

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Shiaoching Gong
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Wenjie Luo
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