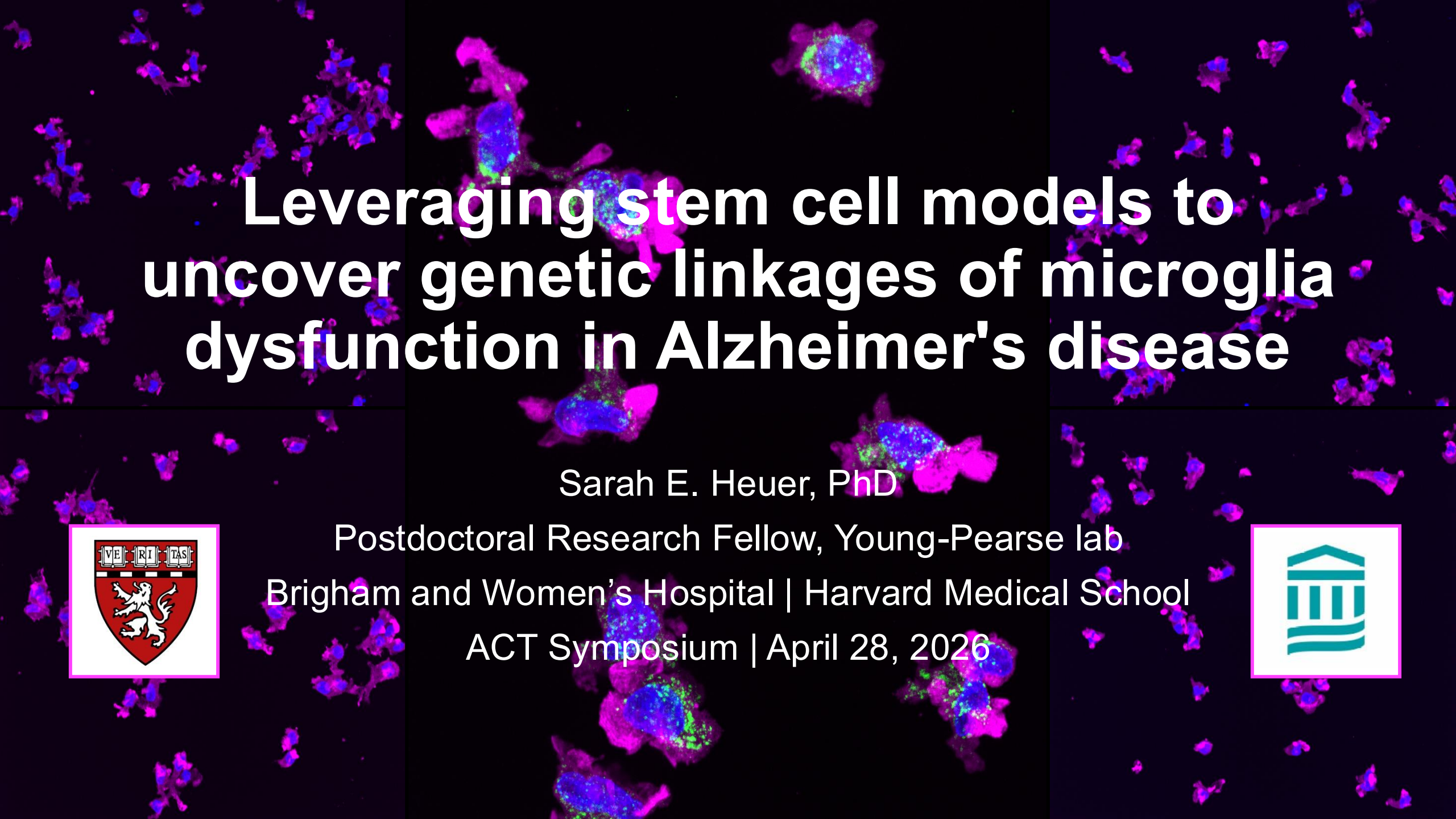


Leveraging stem cell models to uncover genetic linkages of microglia dysfunction in Alzheimer's disease

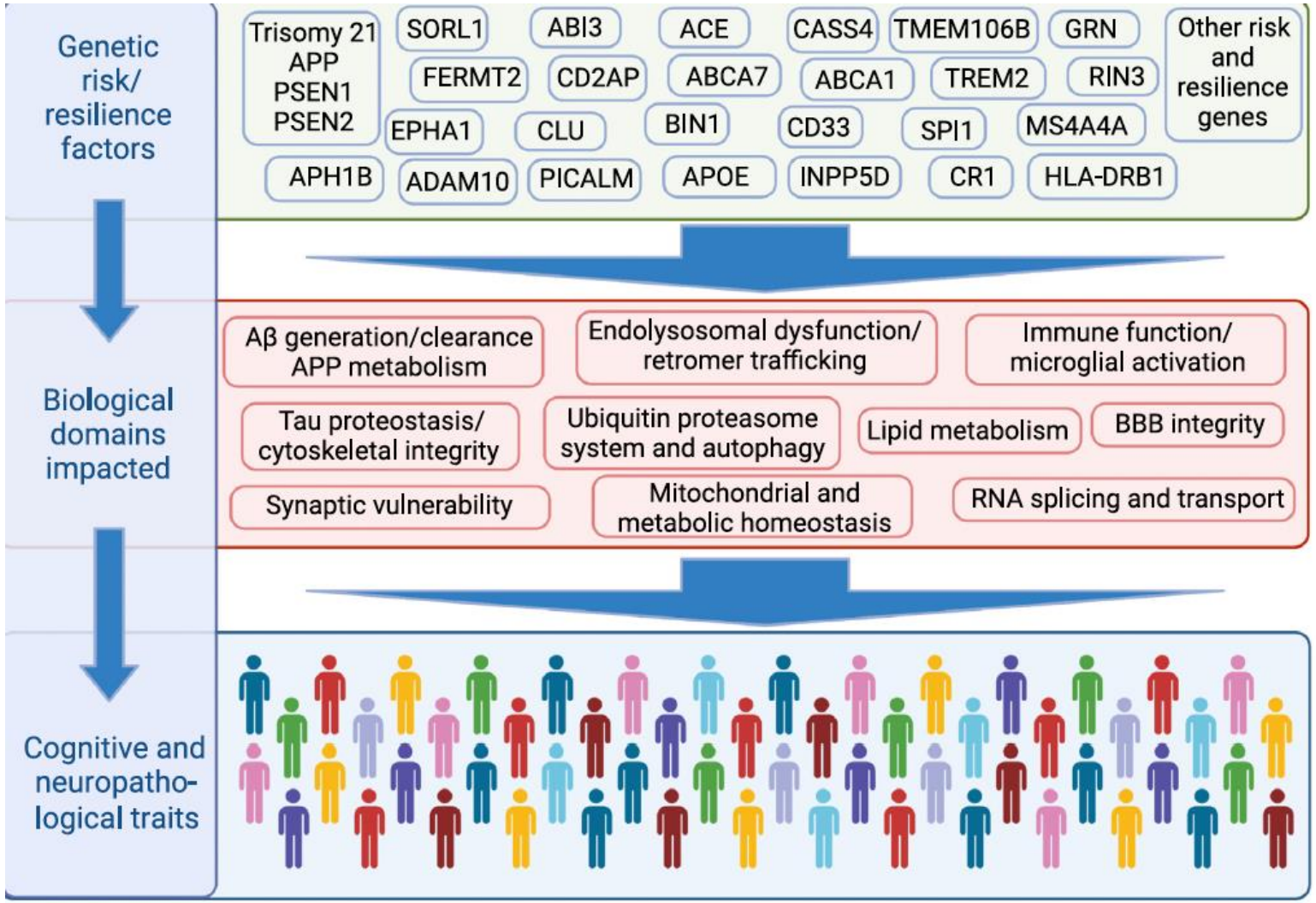
Sarah E. Heuer, PhD

Postdoctoral Research Fellow, Young-Pearse lab

Brigham and Women’s Hospital | Harvard Medical School

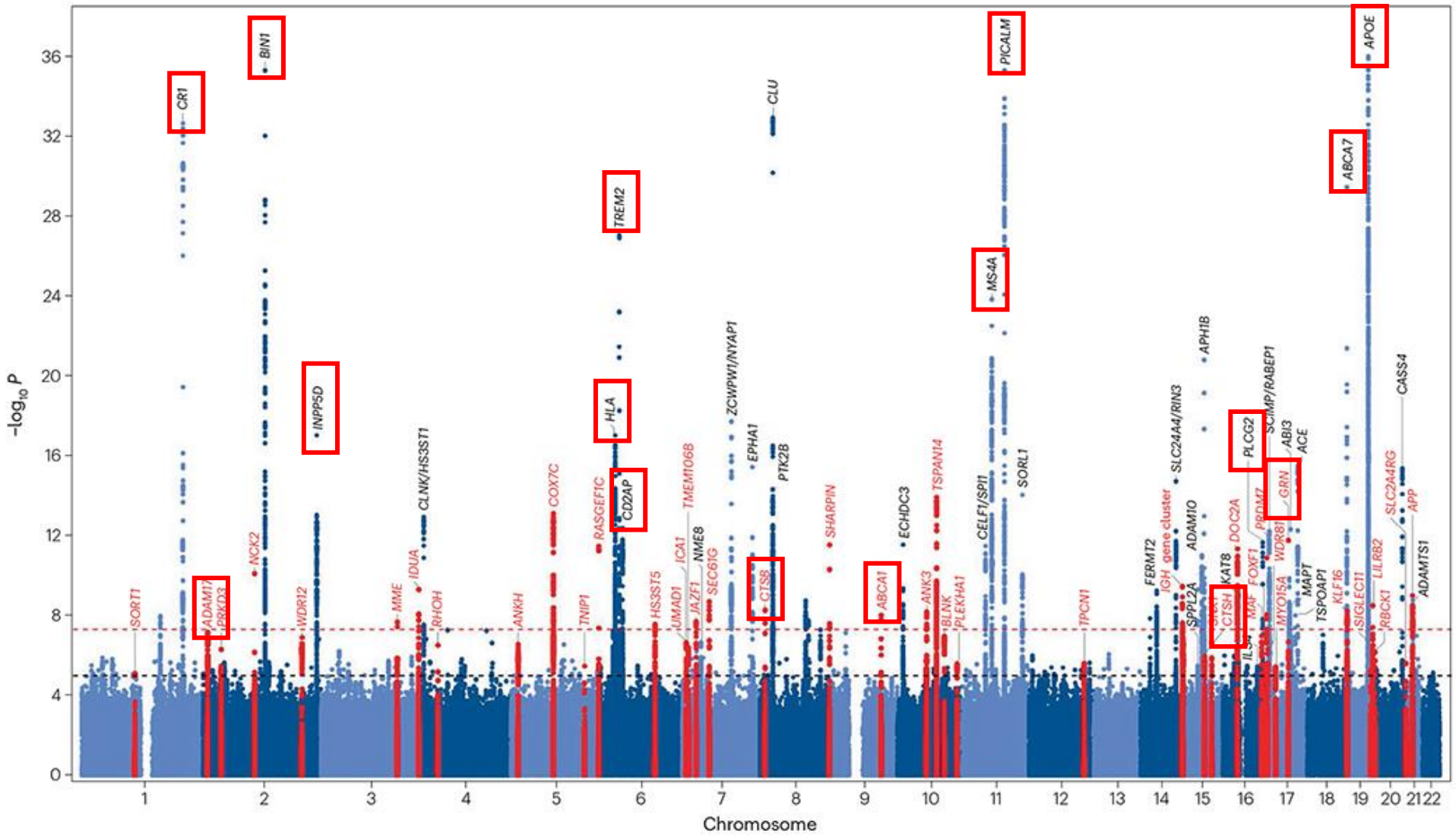
ACT Symposium | April 28, 2026

Both familial and sporadic Alzheimer's Disease (AD) have a strong genetic etiology that is thought to influence inter-individual disease outcomes



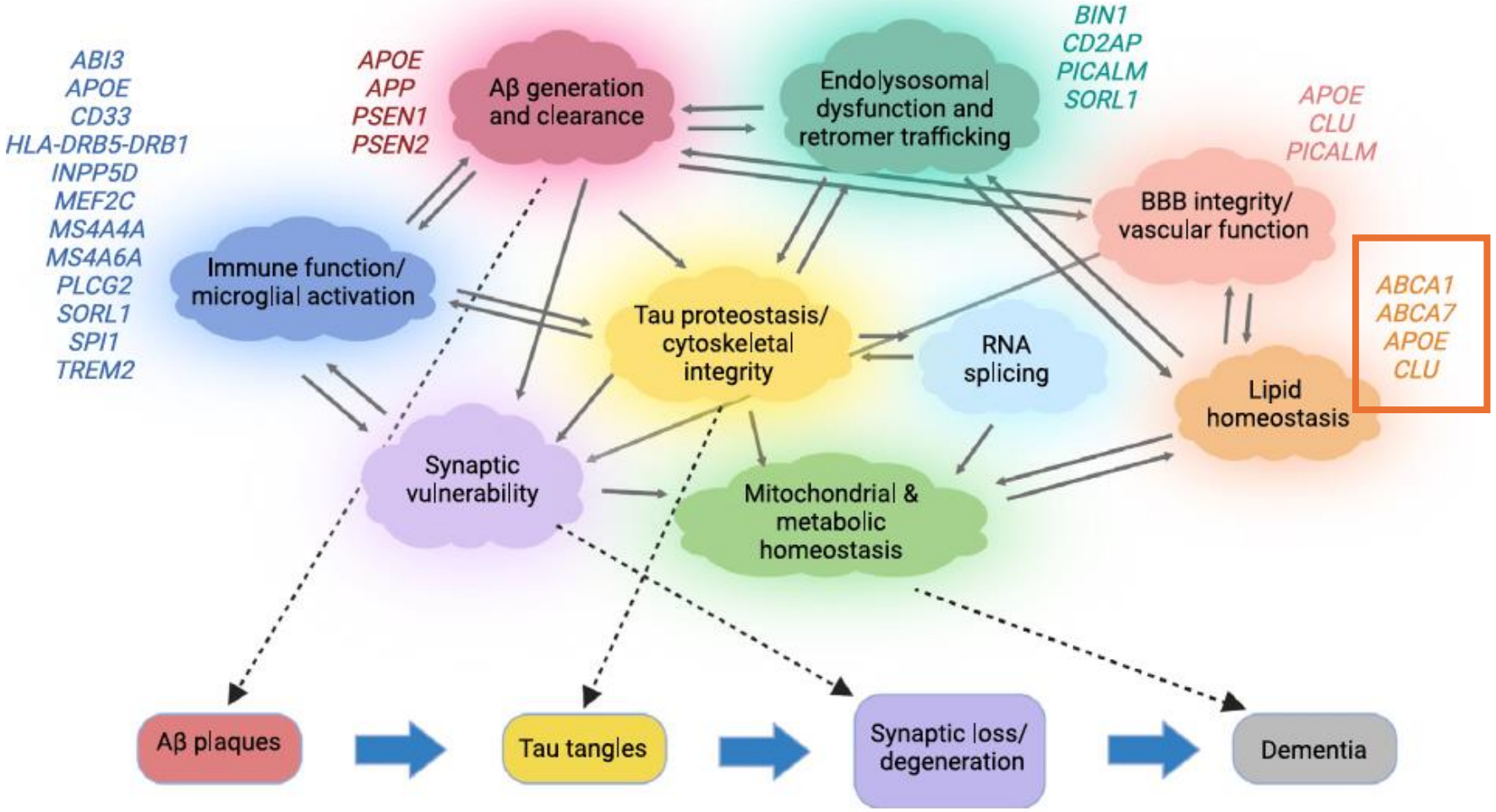
Young-Pearse et al, *Trends in Neuroscience*, 2023

Human genetic studies have implicated microglia in driving AD complexity and severity



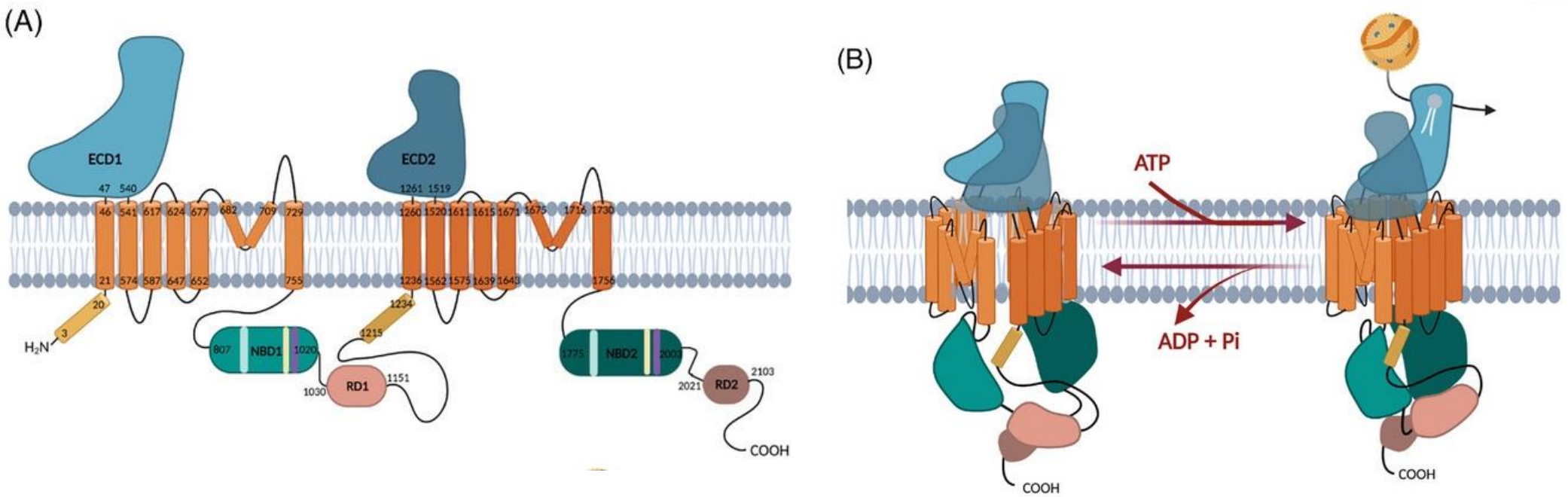
Bellenguez et al, *Nat Gen*, 2022

Understanding how AD genetic risk factors work in isolation as well as in epistasis will better inform patient outcomes and treatments



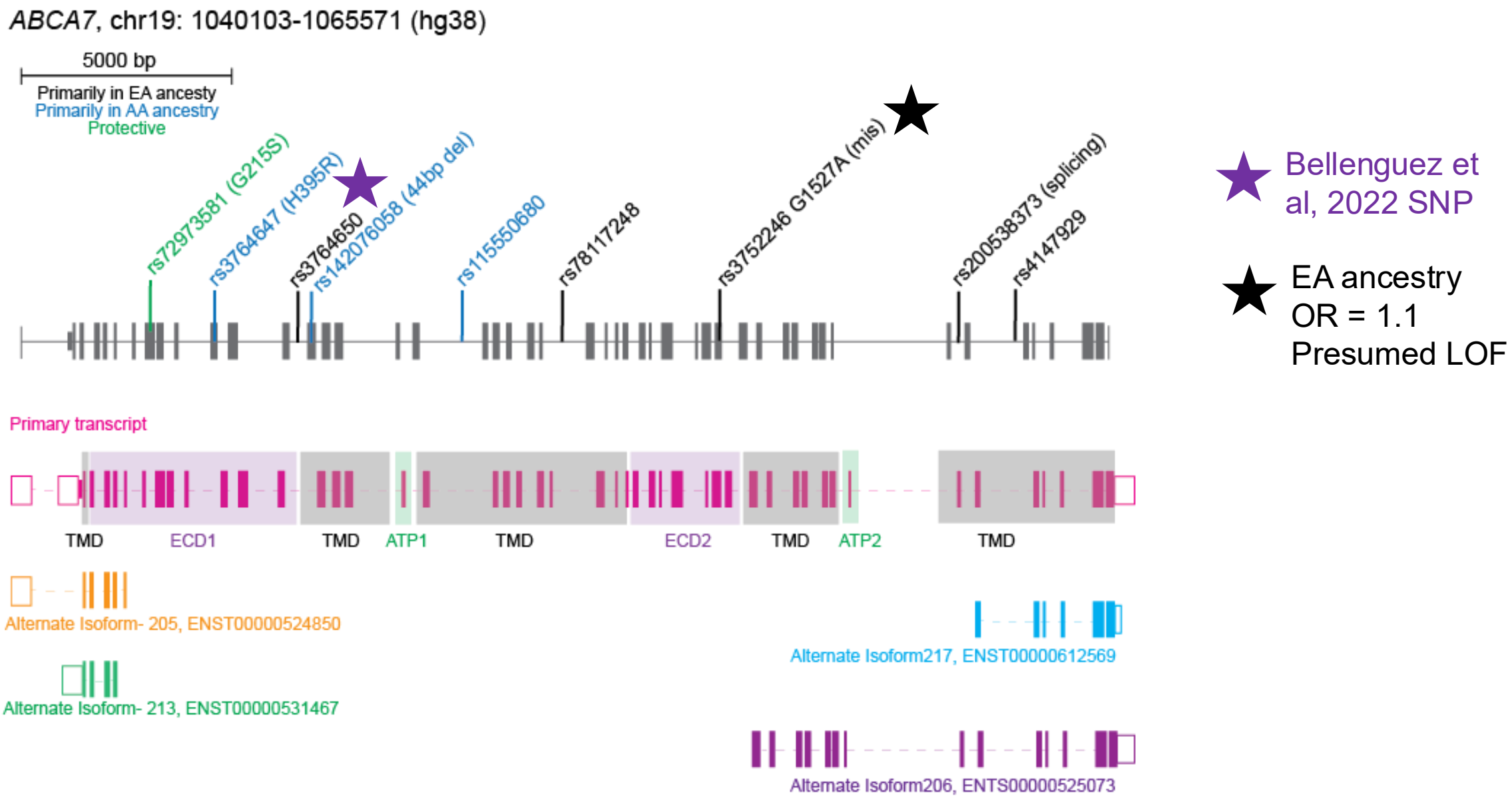
Young-Pearse et al, *Trends in Neuroscience*, 2023

ABCA7 is a transmembrane protein involved in the efflux of intracellular lipids



Duchateau et al, *Alz & Dementia*, 2024

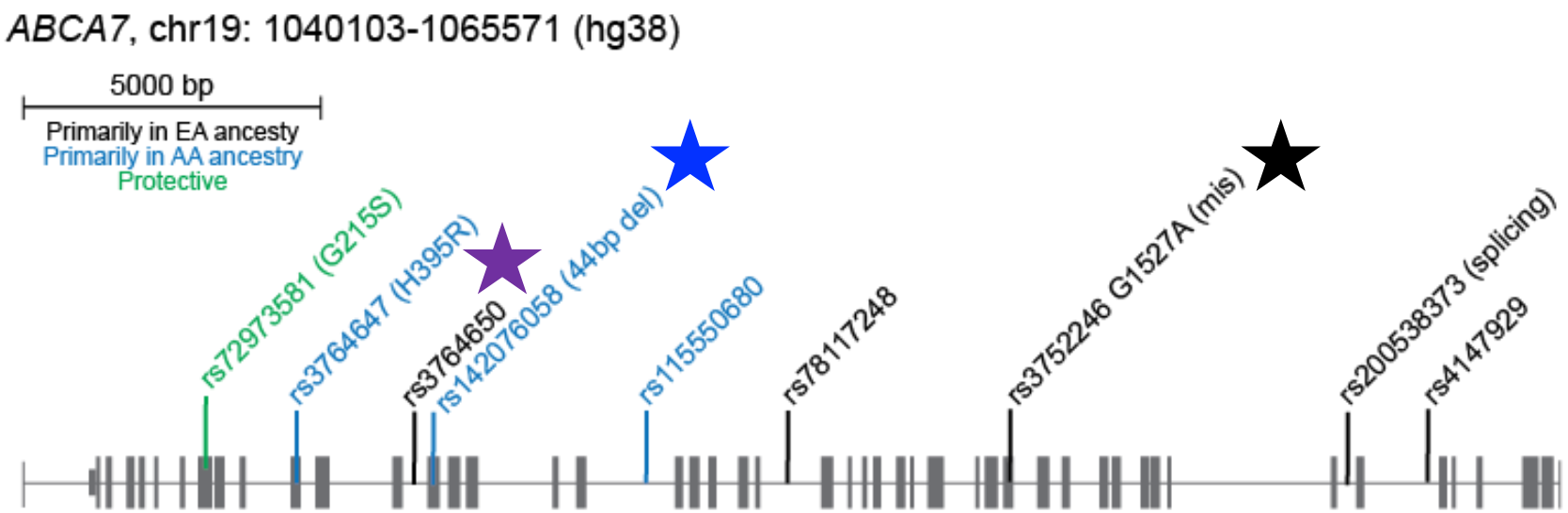
ABCA7 carries variants conferring AD risk across multiple genetic contexts



★ Bellenguez et al, 2022 SNP

★ EA ancestry
OR = 1.1
Presumed LOF

ABCA7 carries variants conferring AD risk across multiple genetic contexts



★ Bellenguez et al, 2022 SNP

★ EA ancestry
OR = 1.1
Presumed LOF

★ **AFR ancestry**
OR = 1.8
Presumed LOF

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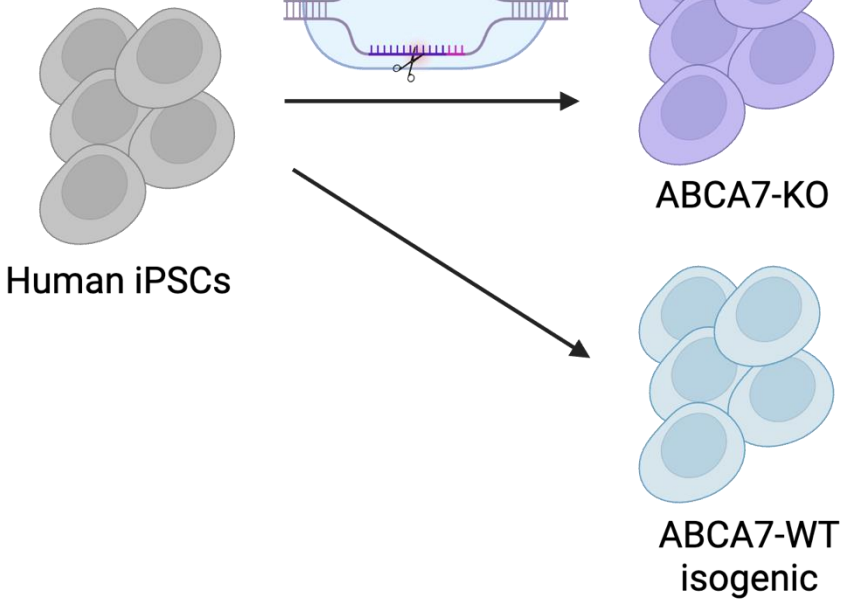
ARTICLES | May 17, 2016 |

Check for updates

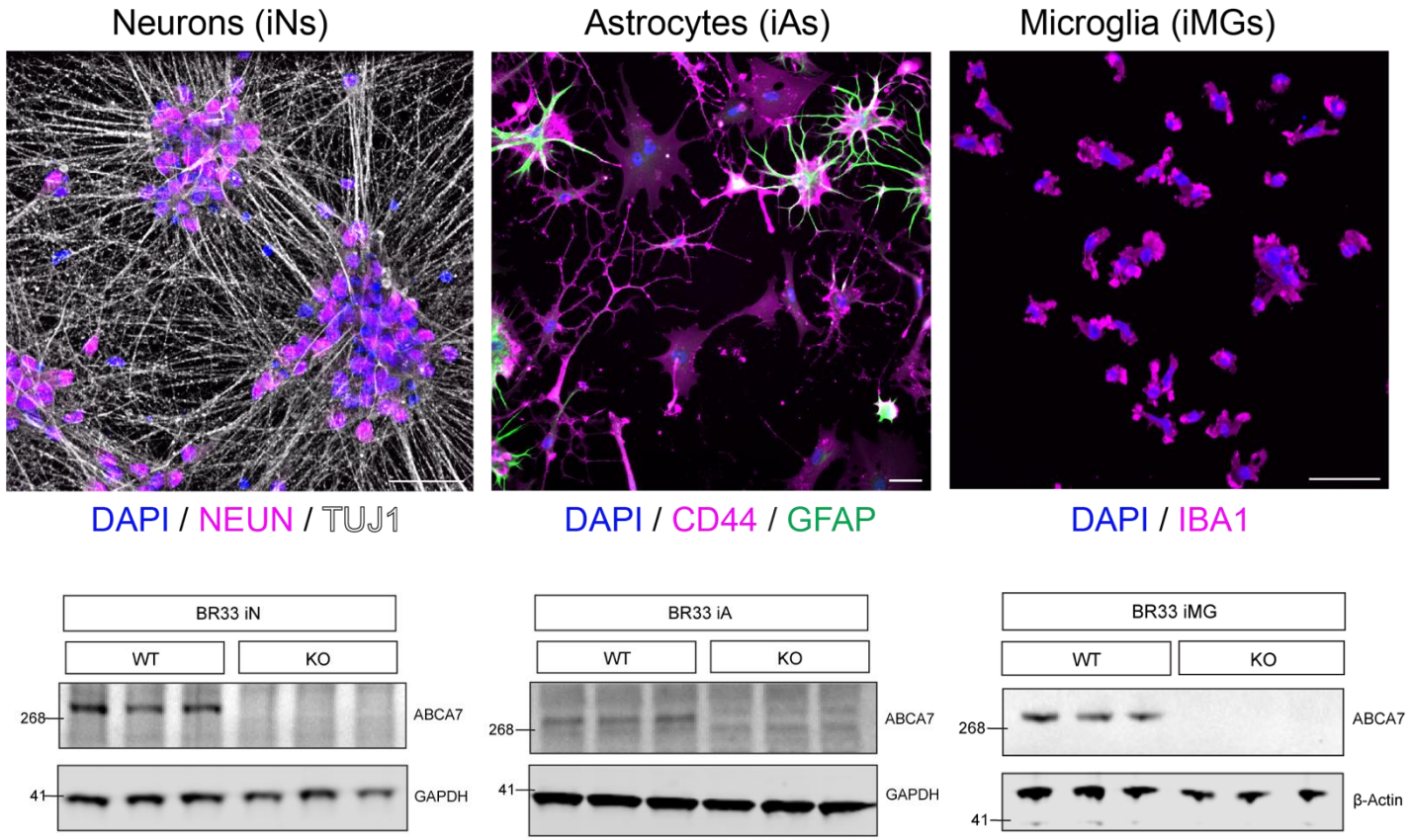
ABCA7 frameshift deletion associated with Alzheimer disease in African Americans

Holly N. Cukier, PhD, Brian W. Kunkle, PhD, MPH, Badri N. Vardarajan, PhD, Sophie Rolati, MS, Kara L. Hamilton-Nelson, MPH, Martin A. Kohli, PhD, Patrice L. Whitehead, BS, ... SHOW ALL ... For the Alzheimer's Disease Genetics Consortium | AUTHORS INFO & AFFILIATIONS

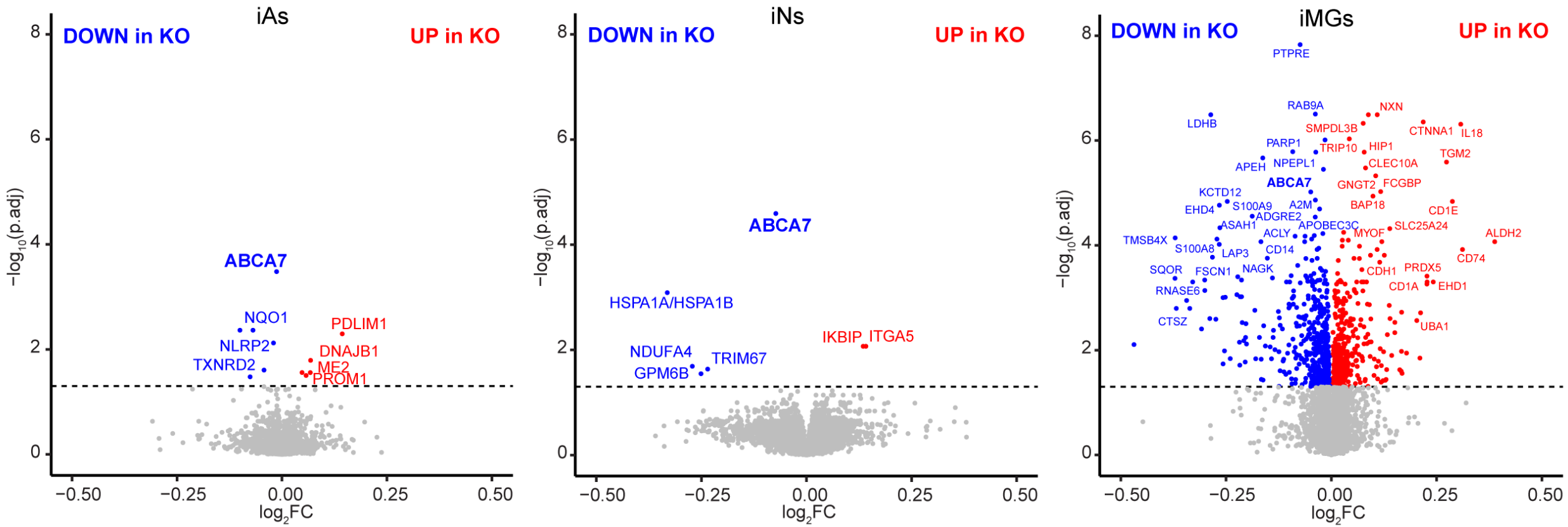
Human induced pluripotent stem cells (iPSCs) as a powerful tool to understand functional impacts of AD genetic risk factors like ABCA7



"Living human brain cells"

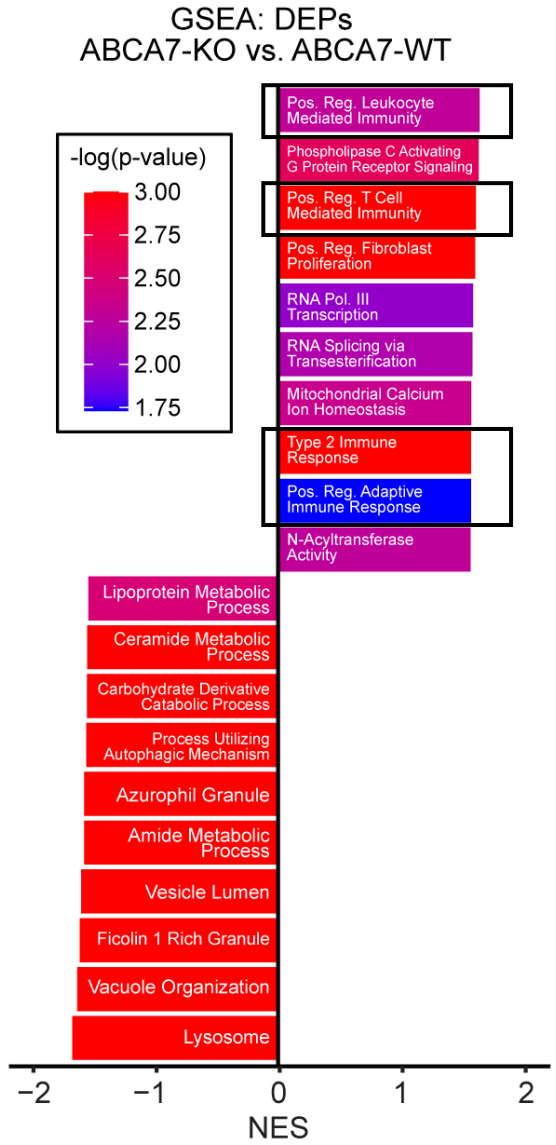


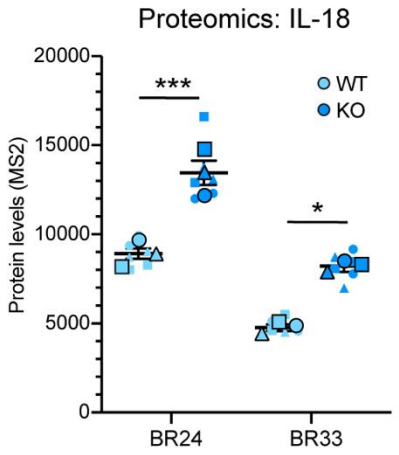
Human microglia show the greatest ABCA7-dependent proteomic changes compared to neurons and astrocytes

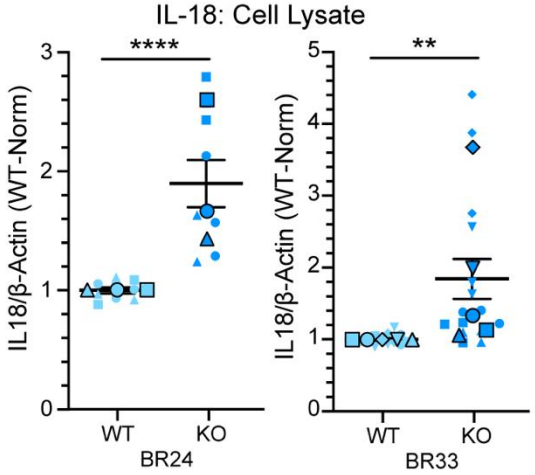


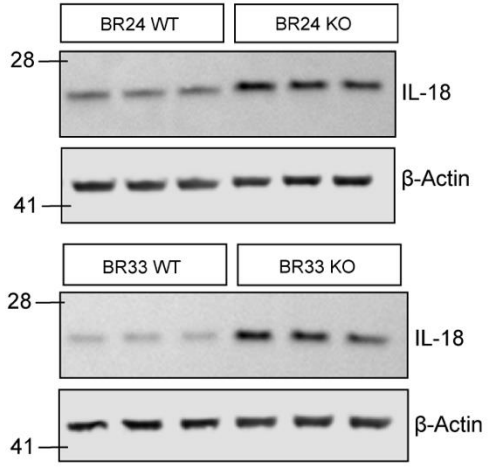
Heuer *et al*, *under review*

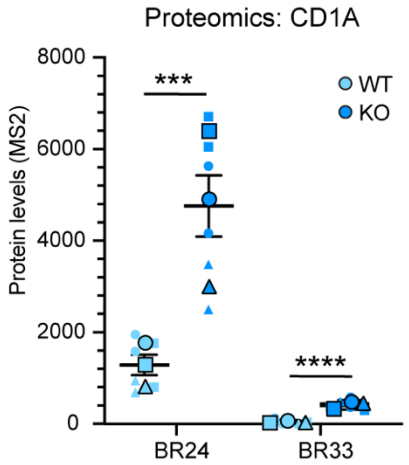
ABCA7-KO microglia exhibit robust changes in immunoregulatory, lysosomal and lipid metabolism proteins

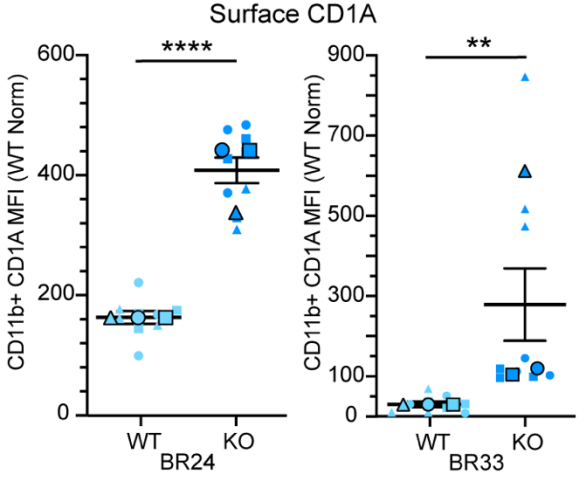


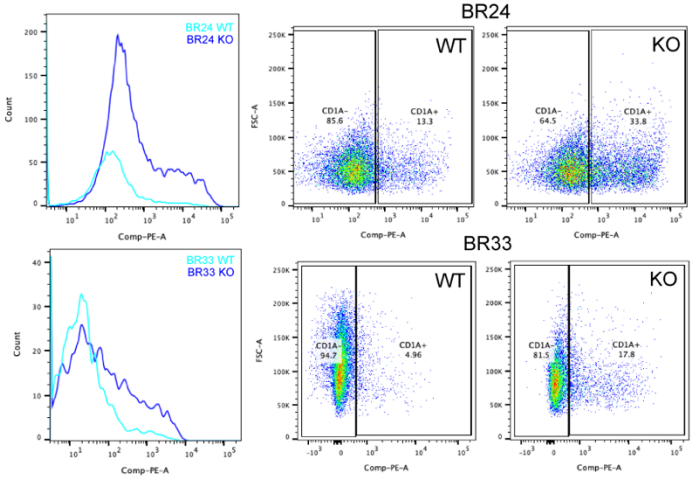






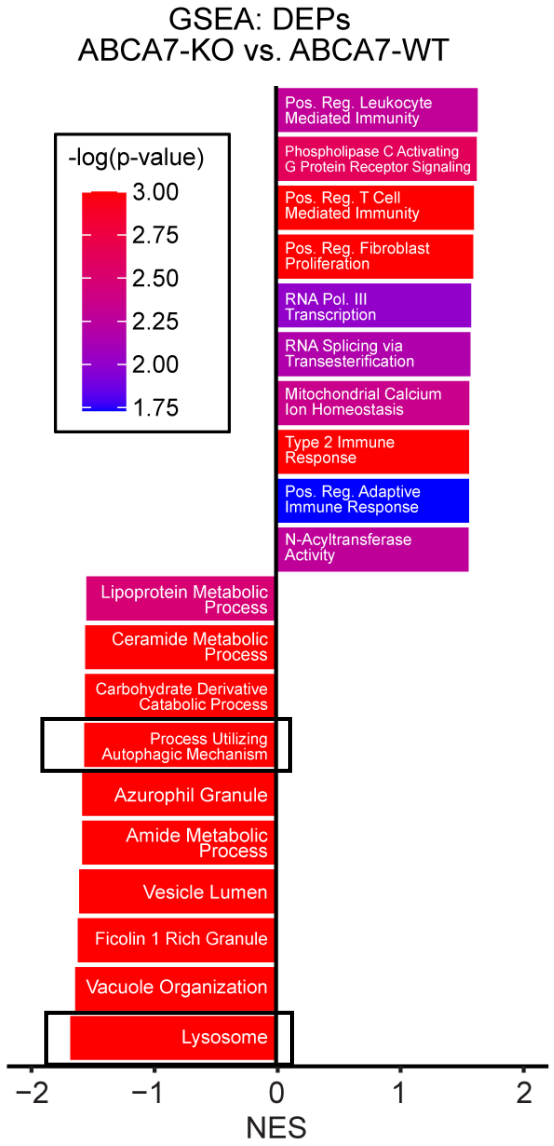


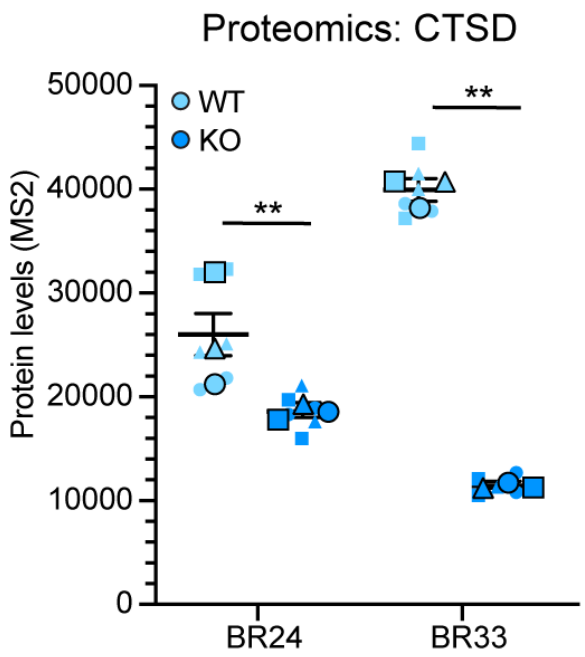


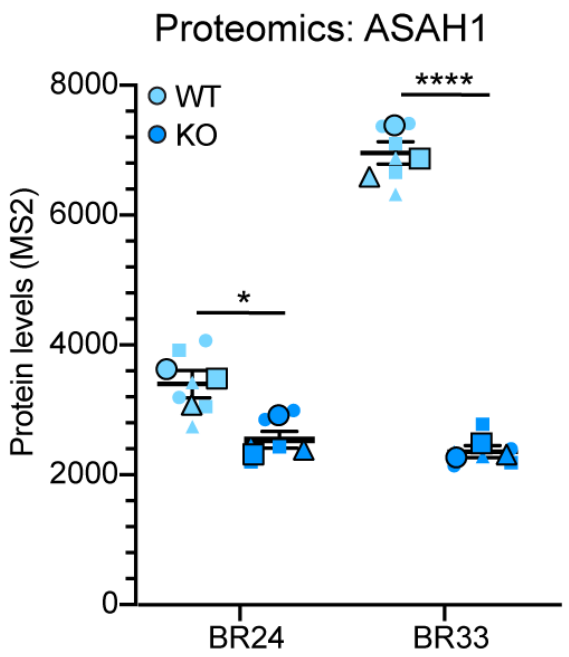


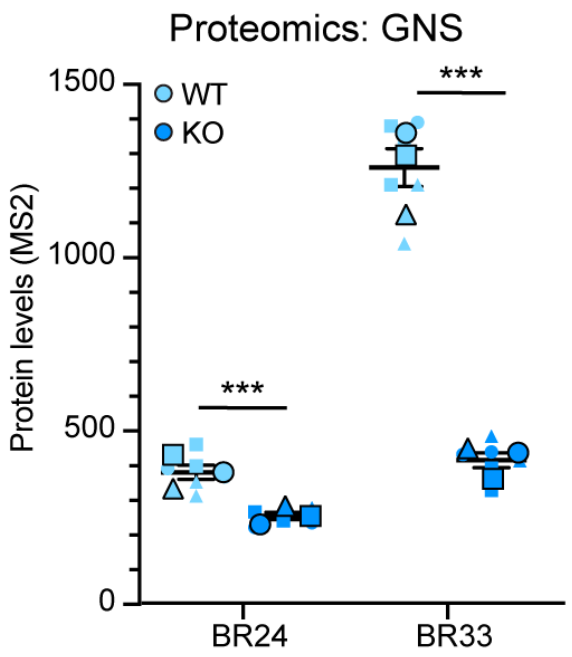
Heuer *et al*, *under review*

ABCA7-KO microglia exhibit robust changes in immunoregulatory, lysosomal and lipid metabolism proteins



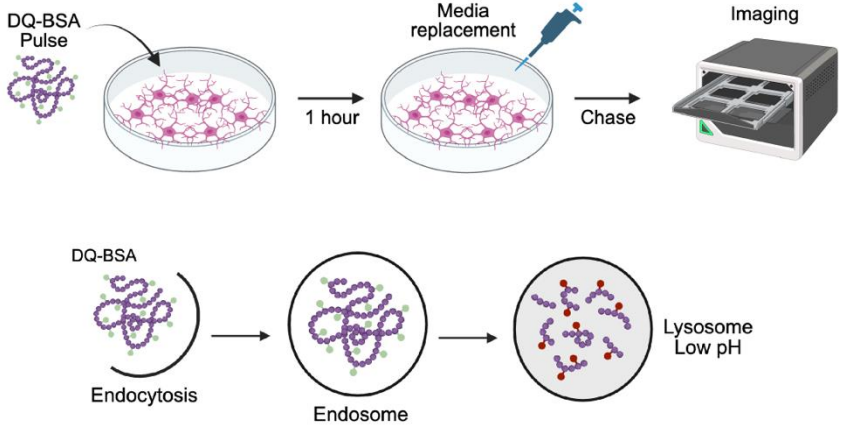


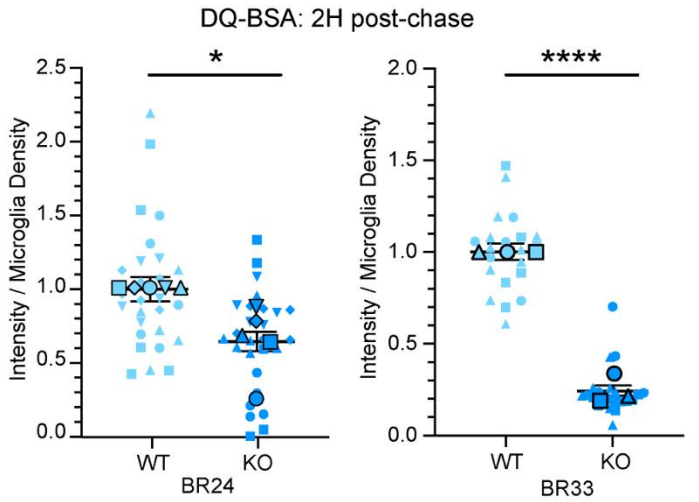


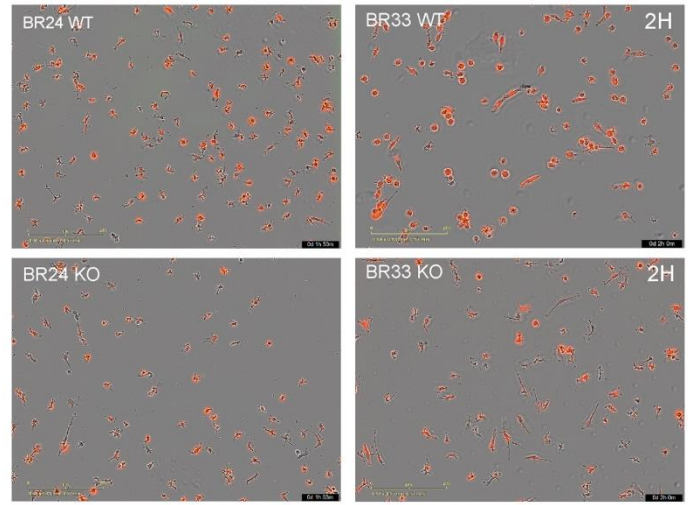


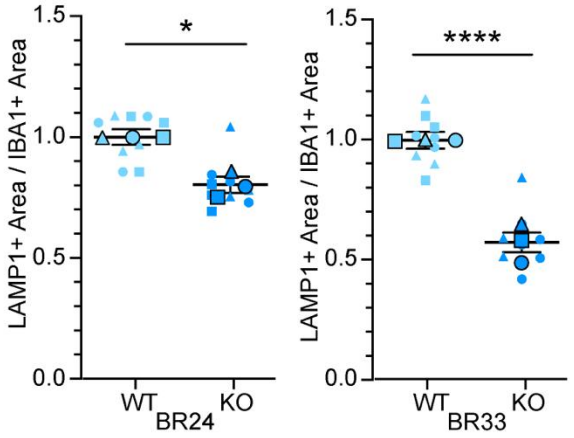
Heuer *et al*, *under review*

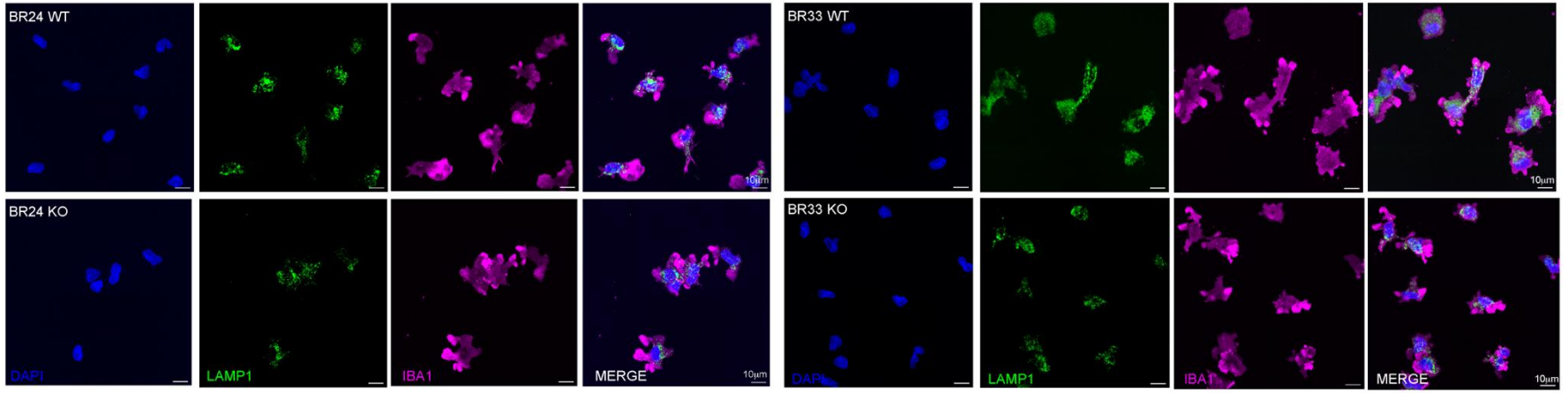
Loss of lysosomal proteins corresponds to impairments in lysosomal homeostasis in ABCA7-KO microglia





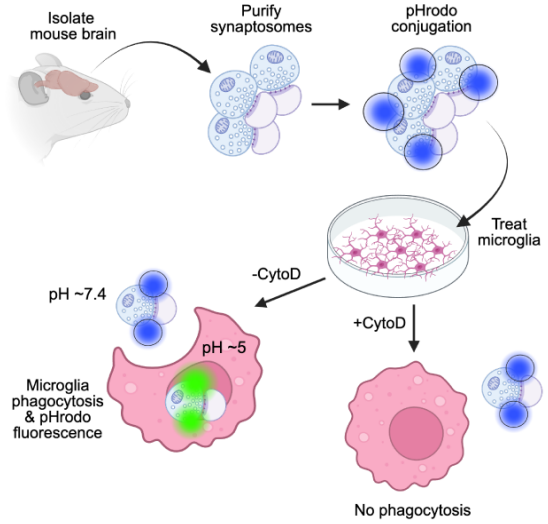


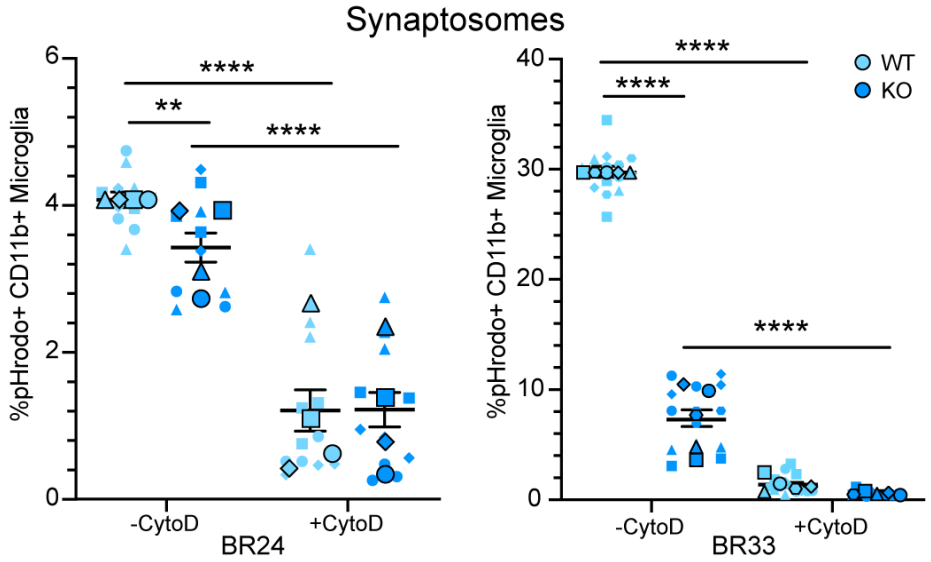


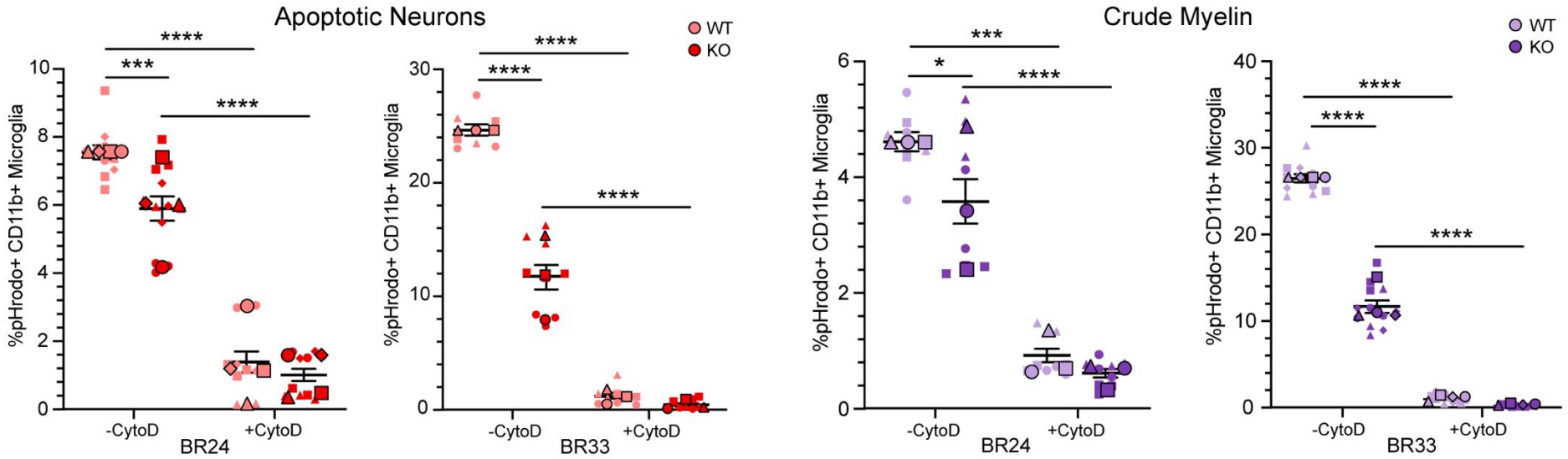


Heuer *et al*, *under review*

ABCA7-KO microglia are unable to ingest extracellular debris, regardless of source

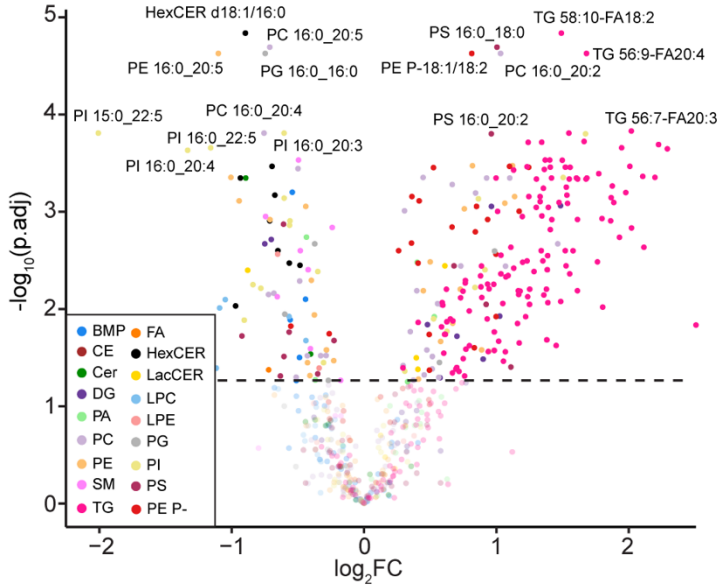


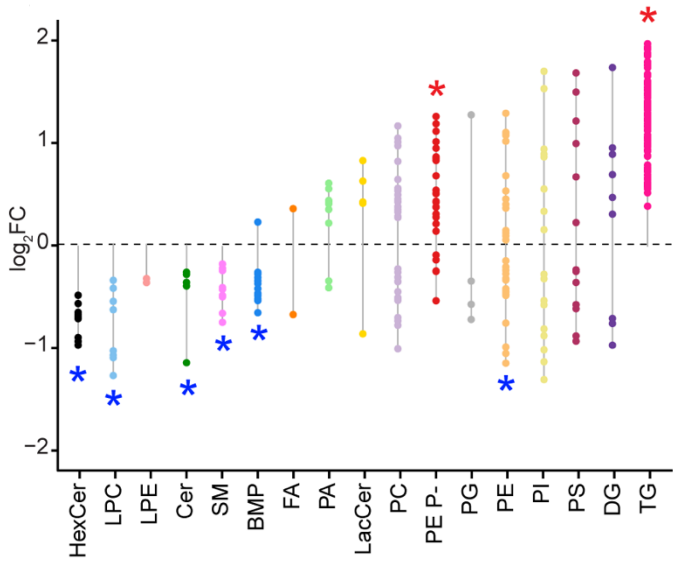


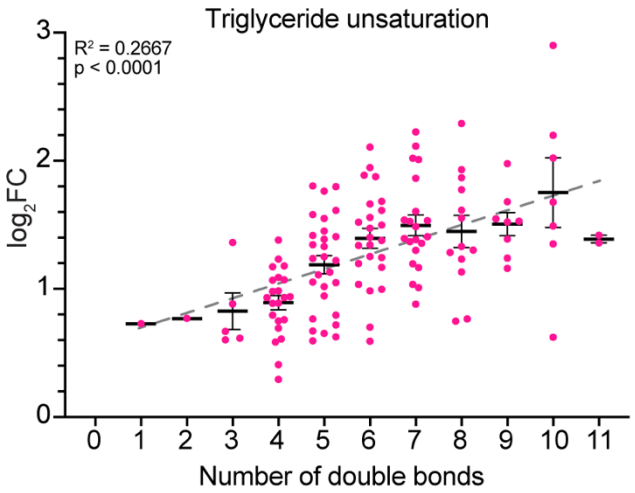


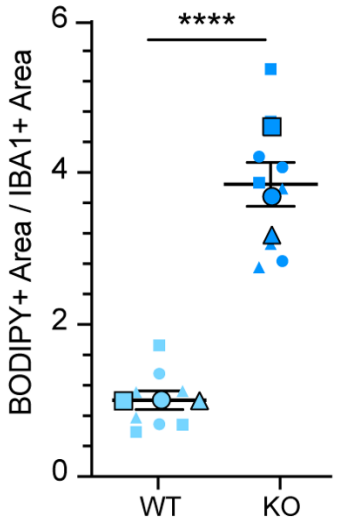
Heuer *et al*, *under review*

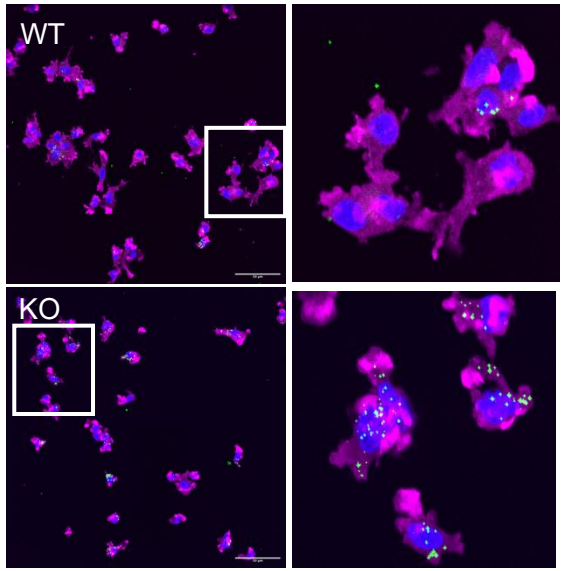
Microglia lacking ABCA7 have deficits in lipolysis, measured via unbiased lipidomics and intracellular lipid droplet accumulation





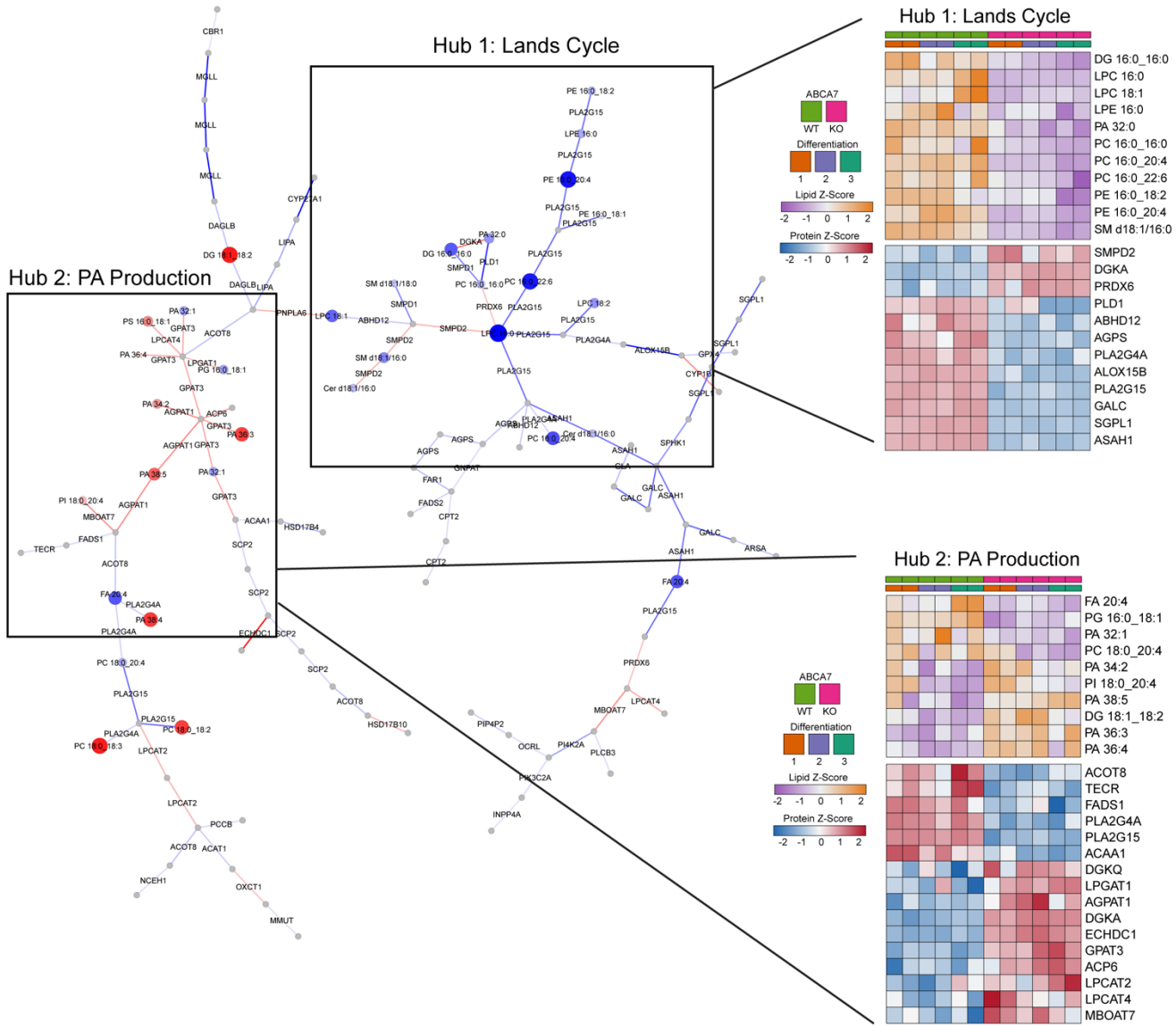


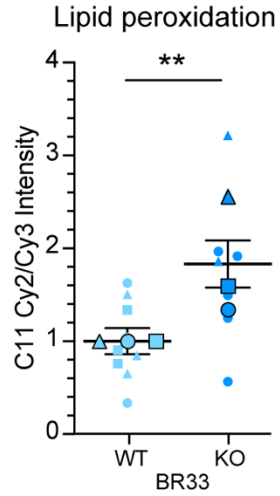


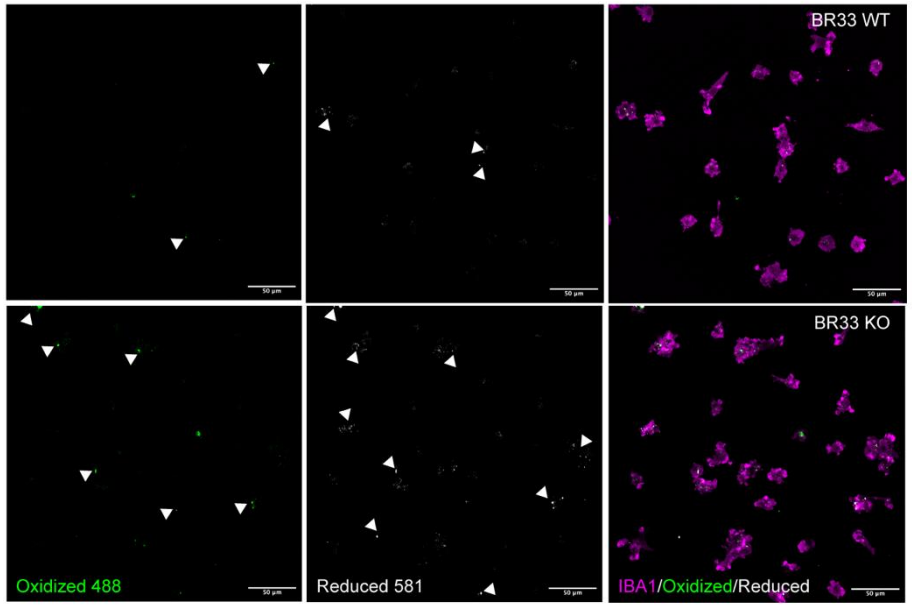


Heuer *et al*, *under review*

Multi-omic lipid-protein integration identifies two key hubs of ABCA7-dependent intracellular dysfunction including increased oxidative stress



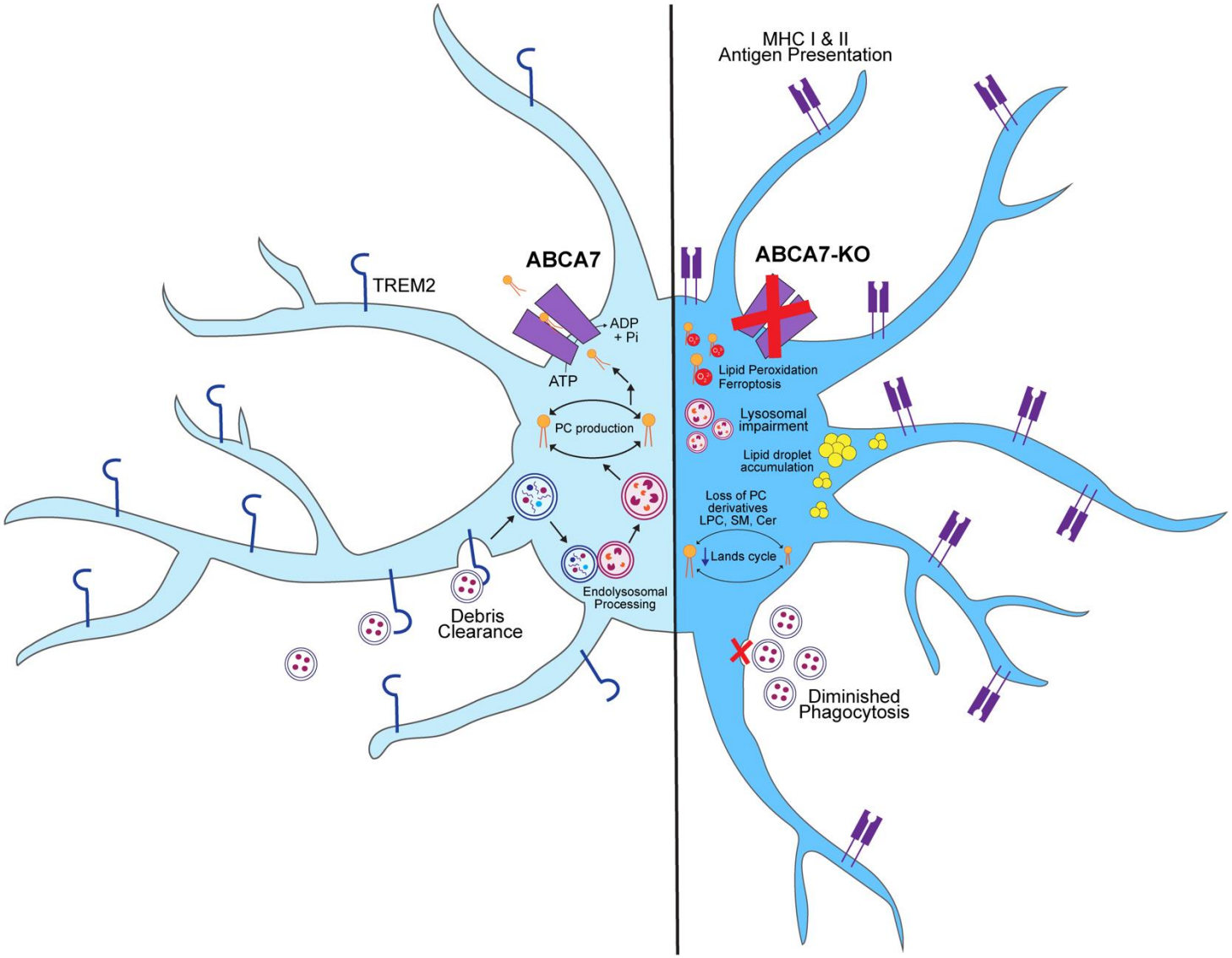




Heuer *et al*, *under review*

Building a model to understand how loss of ABCA7 affects microglia molecular and cellular function

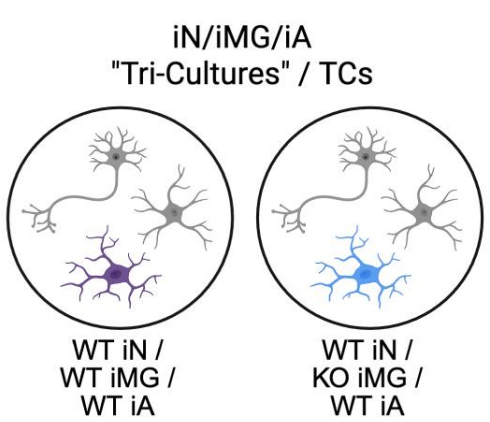
ABCA7 present:
- Microglia recognize and take up debris
- Debris are digested and processed through endo-lysosomal system
- Lipid bi-products are leveraged for cellular energy & maintenance
- Toxic lipids are exported out of the cell appropriately

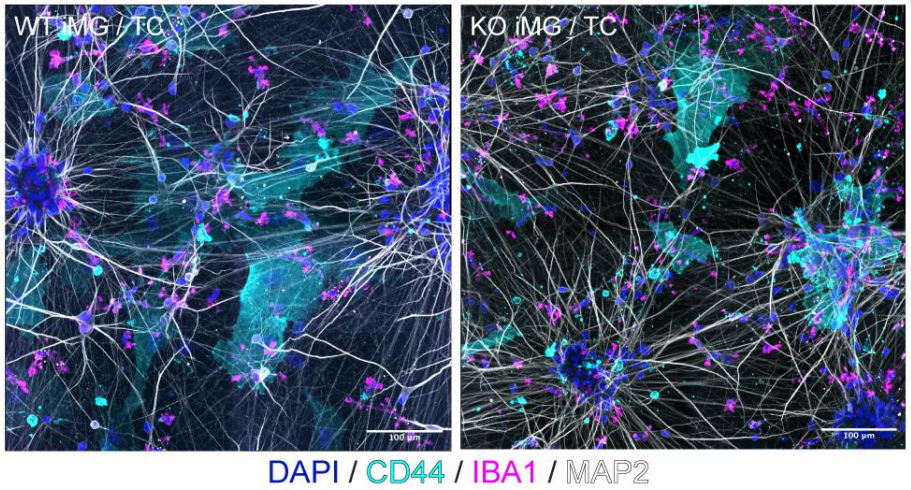


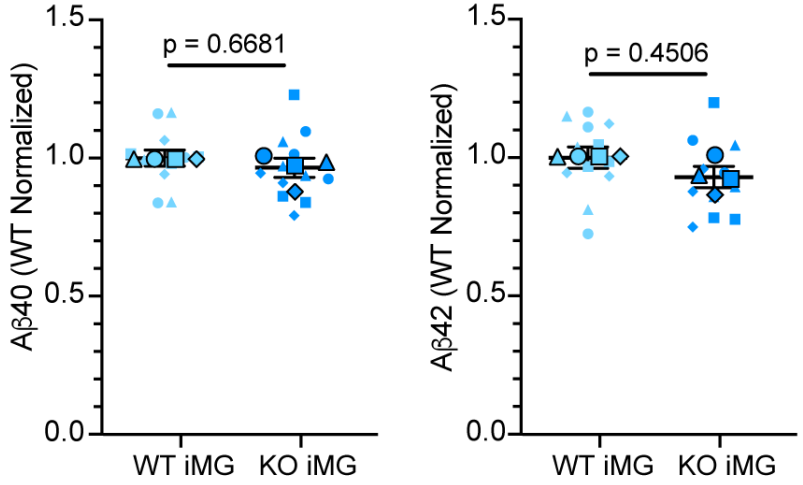
ABCA7 absent:
- Toxic lipids cannot be exported out of the cell
- Toxic lipid buildup triggers inflammatory intracellular events such as ferroptosis
- Excessive lipids are stored in lipid droplets
- Lysosomal catabolism shuts down
- Microglia do not bring in additional debris-lose phagocytic capacity

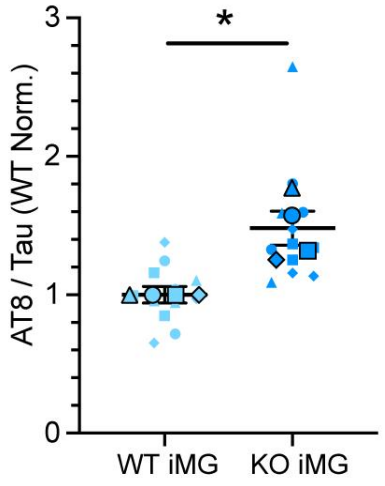
Heuer *et al*, *under review*

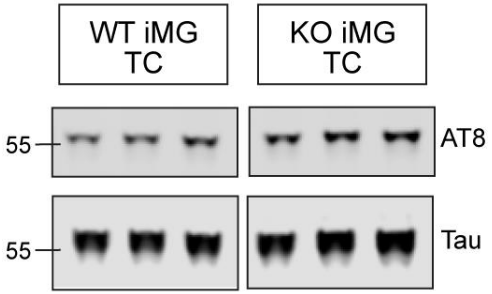
How do ABCA7-deficient microglia affect surrounding cells?

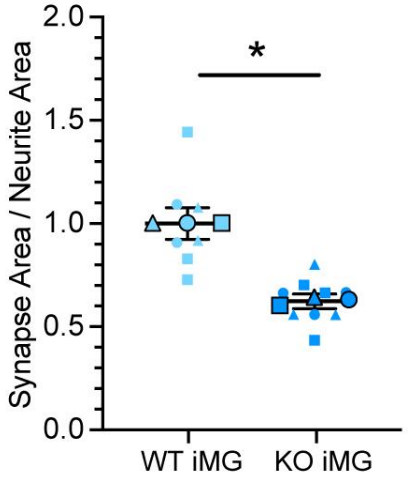


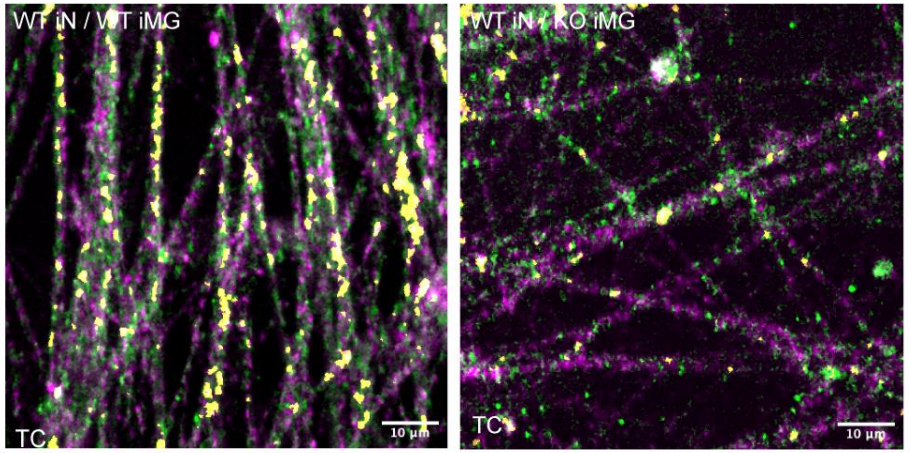






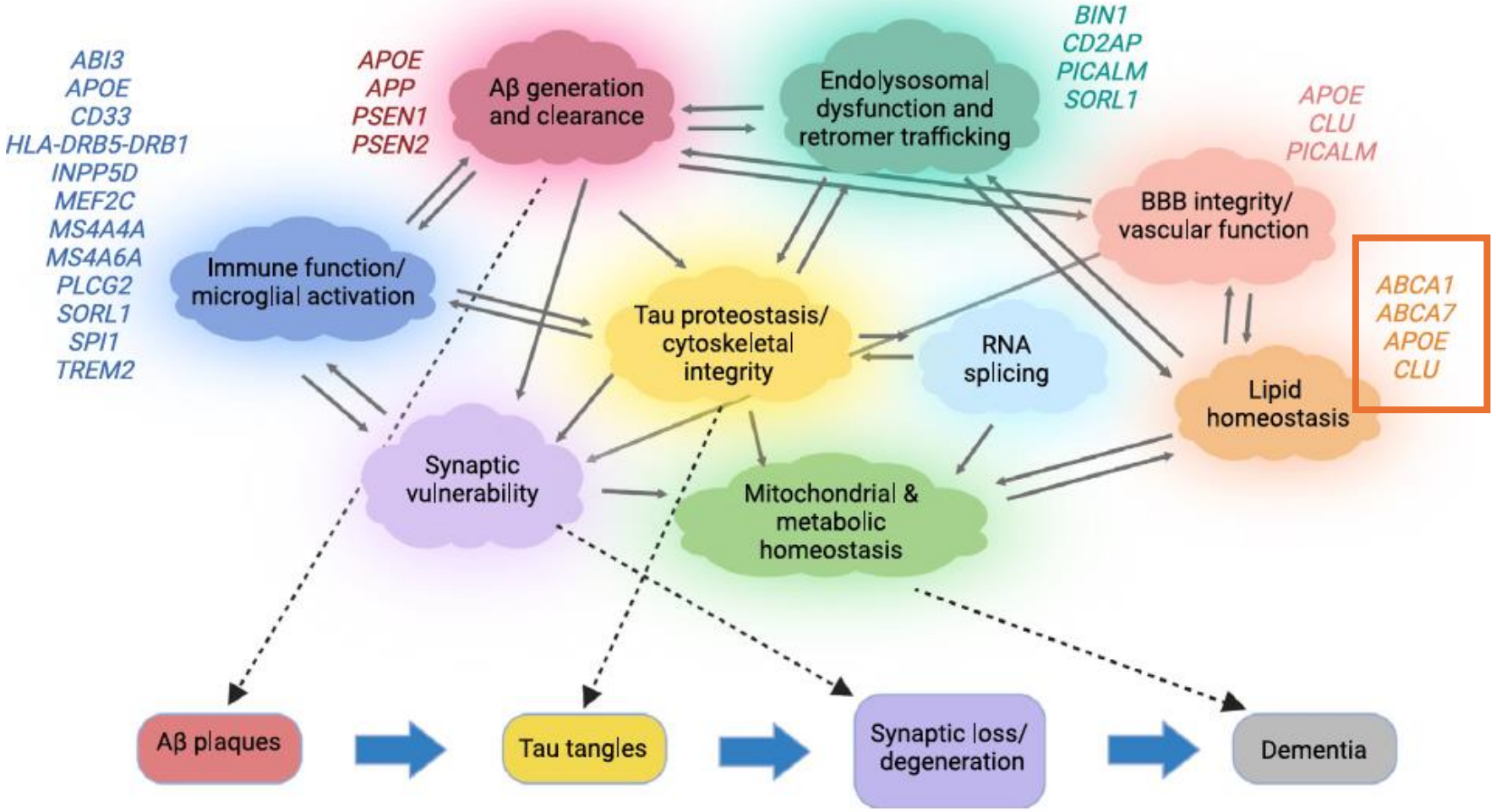






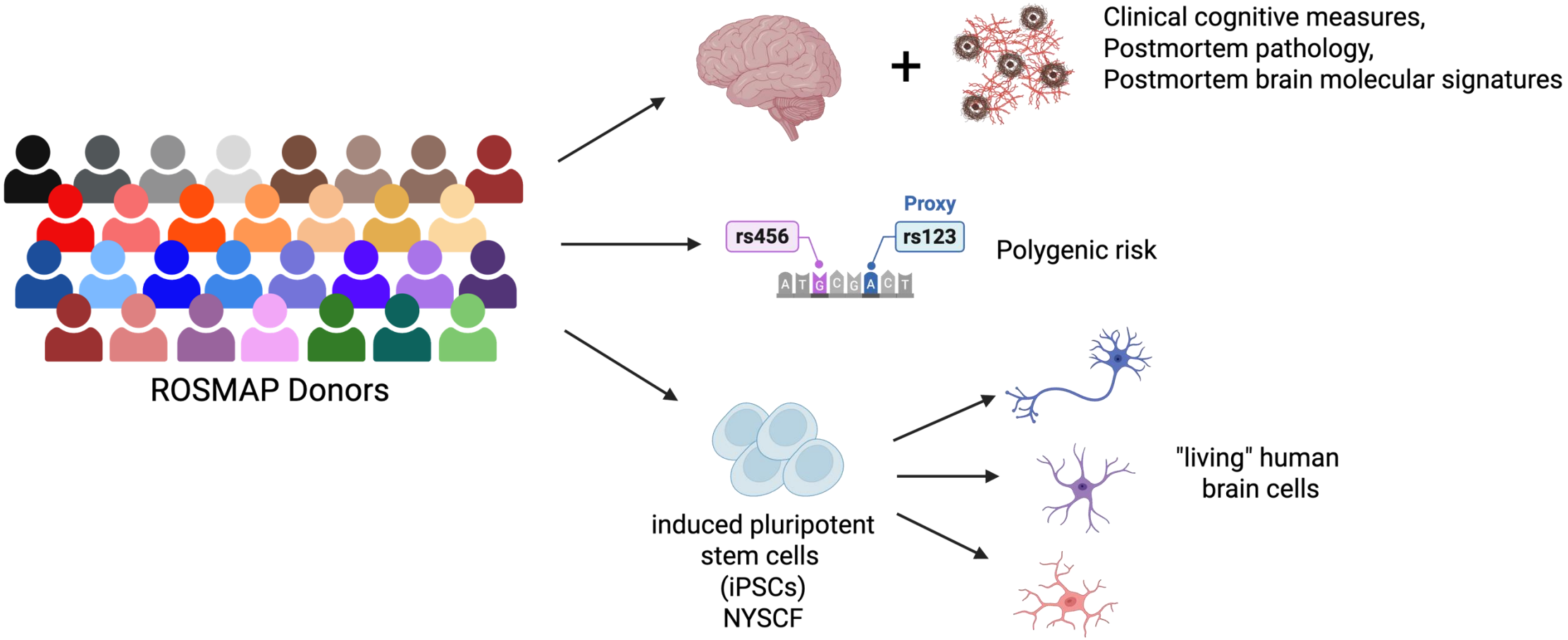
Heuer *et al*, *under review*

How can we use stem cell models to uncover polygenic influences of AD risk?

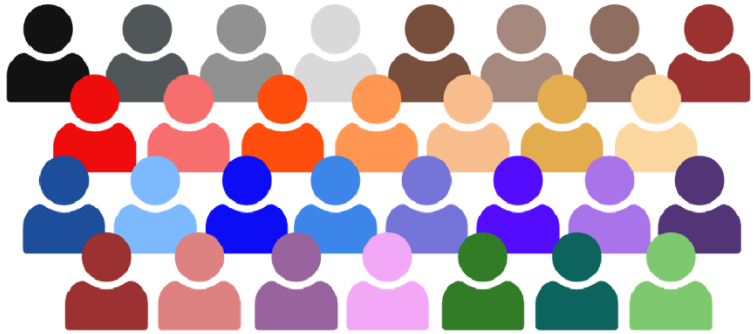


Young-Pearse et al, *Trends in Neuroscience*, 2023

Studying molecular and cellular underpinnings of Alzheimer's disease genetic risk using ROSMAP donor iPSCs

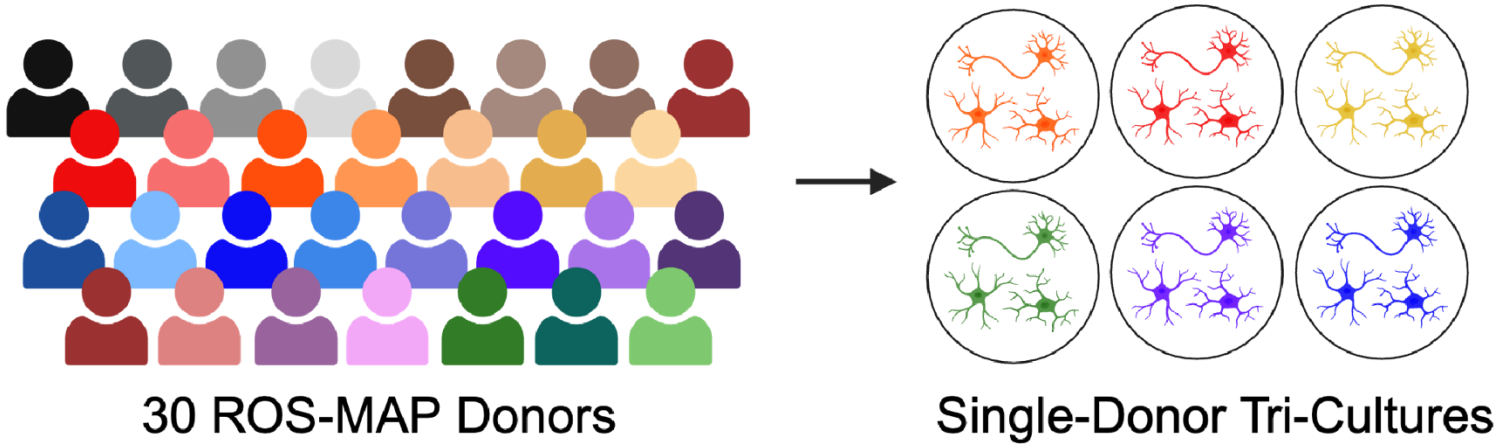


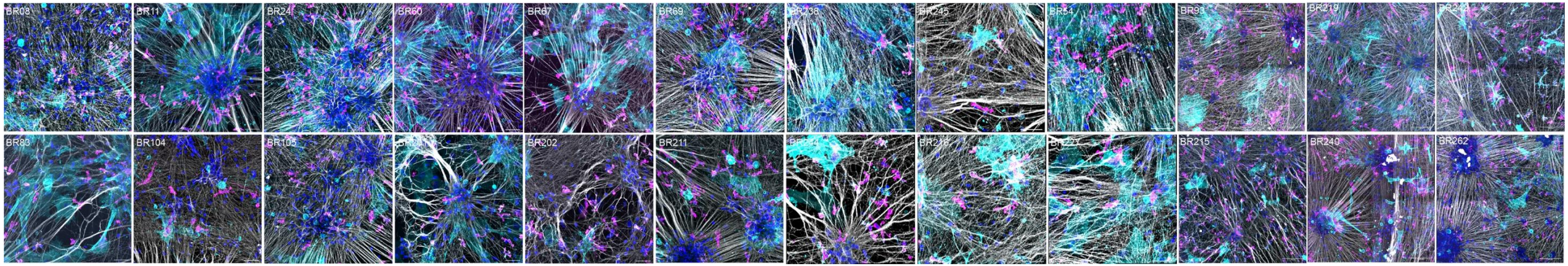
Experimental design: Define how polygenic risk affects parenchymal cellular states by leveraging co-culture models



30 ROS-MAP Donors

Experimental design: Define how polygenic risk affects parenchymal cellular states by leveraging co-culture models





DAPI / CD44 / IBA1 / TUJ1

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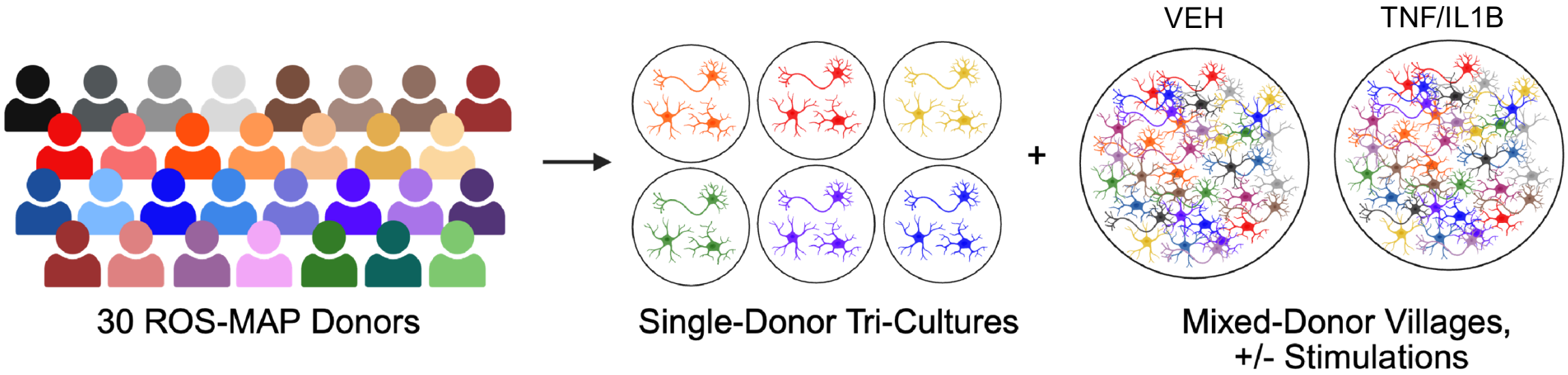

Mixed-donor Villages: Advantageous for in vitro environmental control to delineate genetically-driven cellular & molecular responses

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A village in a dish model system for population-scale hiPSC studies

Drew R. Neavin, Angela M. Steinmann, Nona Farbehi, Han Sheng Chiu, Maciej S. Daniszewski, Himanshi Arora, Yasmin Bermudez, Cátia Moutinho, Chia-Ling Chan, Monique Bax, Mubarika Tyebally, Vikkitharan Gnanasambandapillai, Chuan E. Lam, Uyen Nguyen, Damián Hernández, Grace E. Lidgerwood, Robert M. Graham, Alex W. Hewitt, Alice Pébay, Nathan J. Palpant & Joseph E. Powell

Article | Published: 26 June 2024

Brain Chimeroids reveal individual susceptibility to neurotoxic triggers

Noelia Antón-Bolaños, Irene Faravelli, Tyler Faits, Sophia Andreadis, Rahel Kastli, Sebastiano Trattaro, Xian Adiconis, Anqi Wei, Abhishek Sampath Kumar, Daniela J. Di Bella, Matthew Tegtmeyer, Ralda Nehme, Joshua Z. Levin, Aviv Regev & Paola Arlotta

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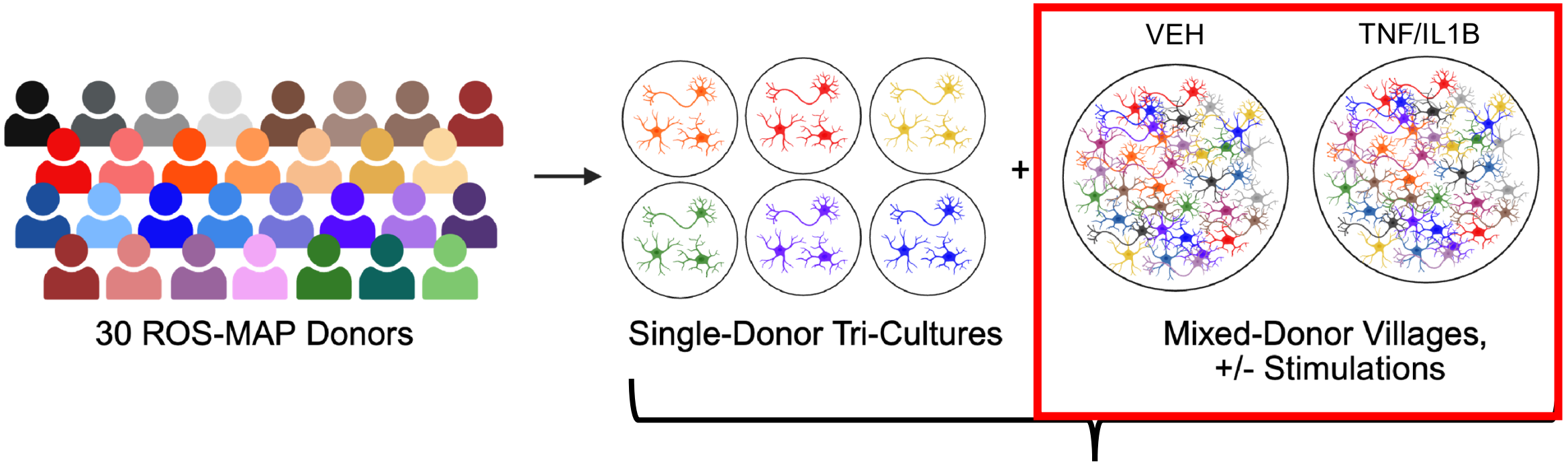
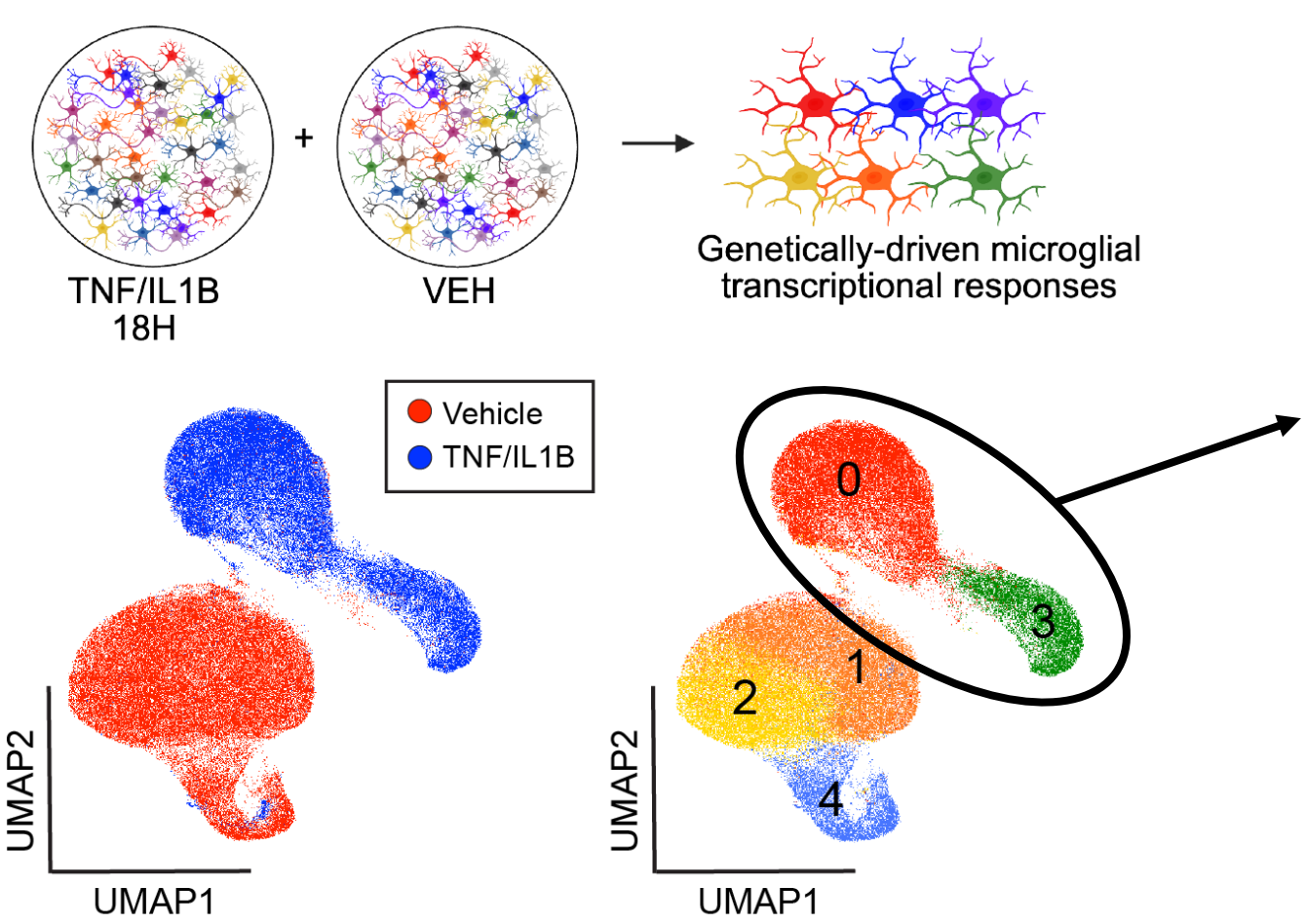
Experimental design: Define how polygenic risk affects parenchymal cellular states by leveraging co-culture models

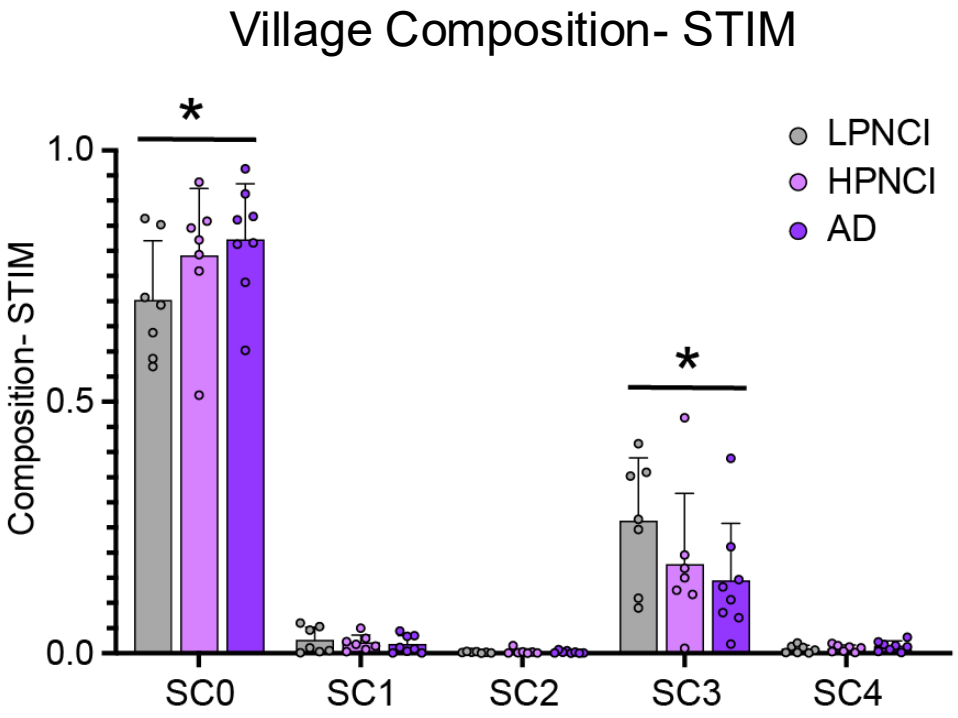


Single cell RNA sequencing:

- Genetic demultiplexing
- Cell-type-specific disease-relevant transcriptional signatures
- Disease-related cellular states

Inflammatory-challenged microglia states correspond to AD diagnosis in mixed-donor villages

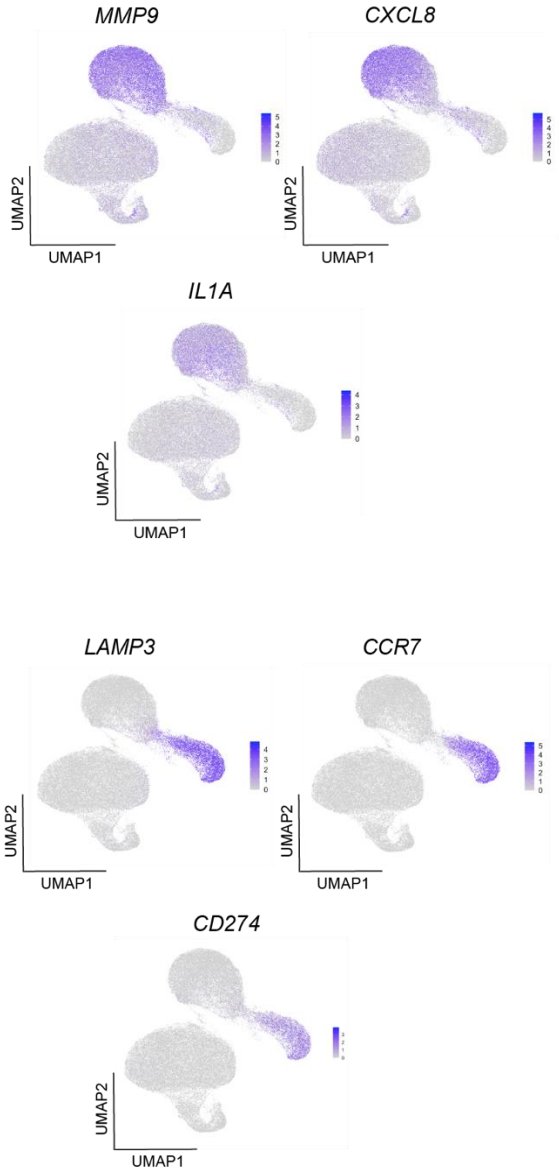


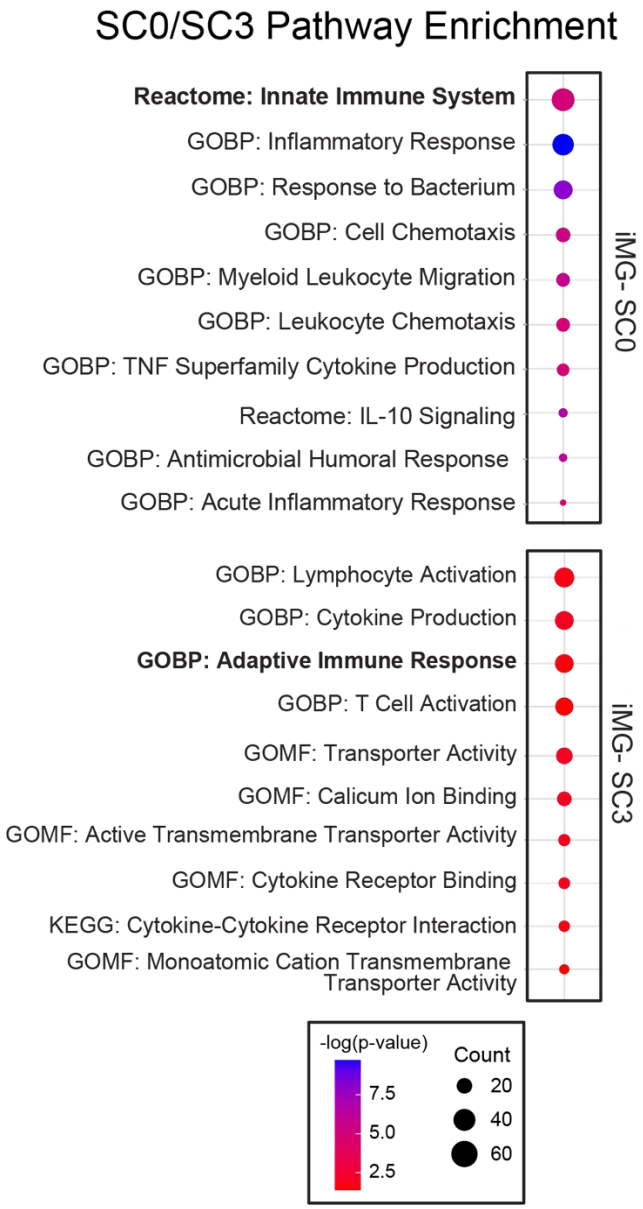


SC0 and SC3 reflect two microglial response “flavors” influenced by genetics

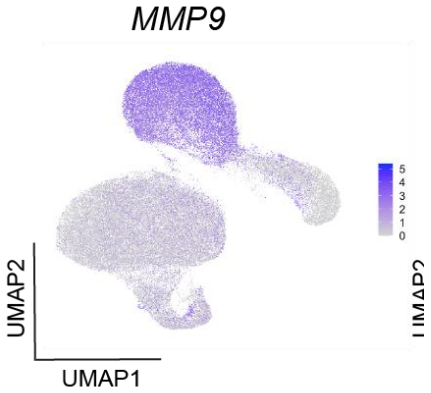
SC0: UP in AD
Innate, immediate response

SC3: DOWN in AD
Adaptive, secondary response

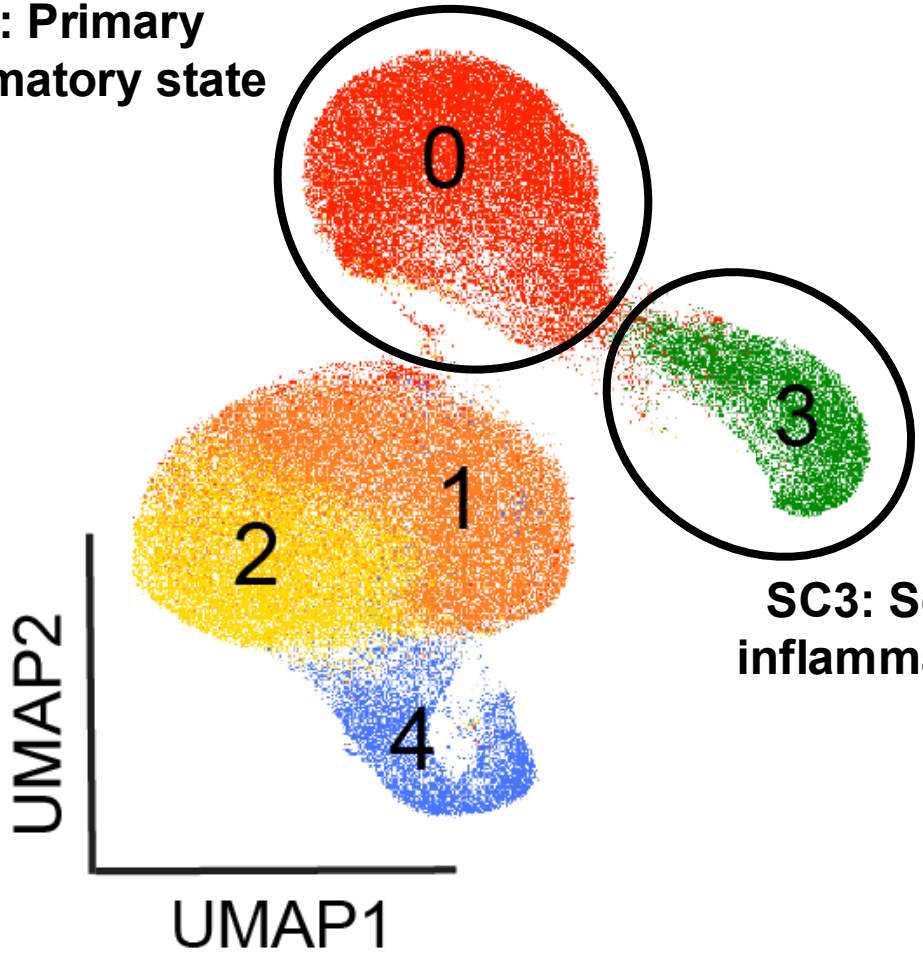




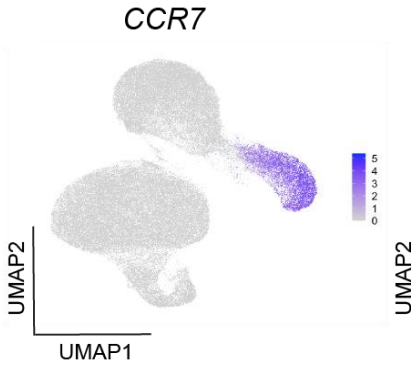
Model: Transitions of inflammatory-challenged microglial states are genetically-encoded, and failure to do so may increase risk for AD



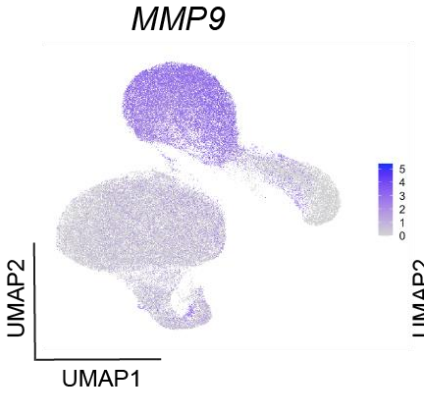
SC0: Primary inflammatory state



SC3: Secondary inflammatory state

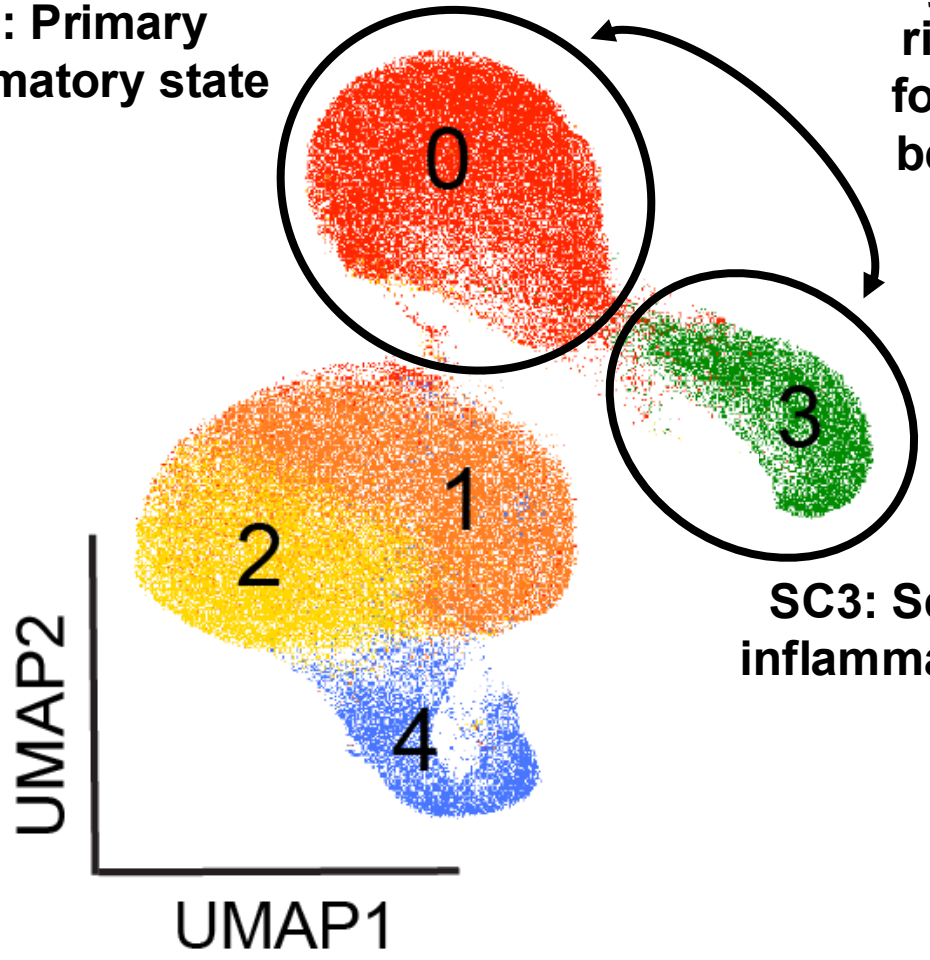


Model: Transitions of inflammatory-challenged microglial states are genetically-encoded, and failure to do so may increase risk for AD

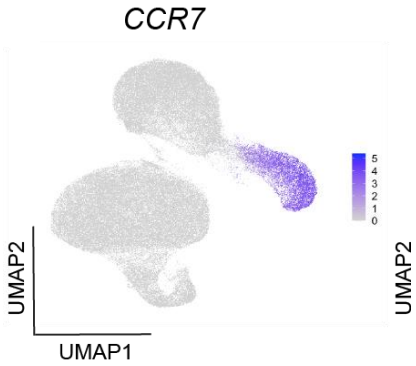


SC0: Primary inflammatory state

Hypothesis: polygenic risk factors important for AD control balance between SC0 and SC3



SC3: Secondary inflammatory state



Summary, Ongoing Questions & Future Work

- Studies of human populations have uncovered microglia and lipid-related biological domains as important contributors to AD risk- but why?
- Human iPSCs prove a valuable system to uncover the molecular and biological underpinnings of AD genetic risk factors
- Genetic editing of iPSCs allows for the specific manipulation and study of these genetic risk factors using a controlled, reproducible cellular environment
- We have discovered novel cellular and molecular events underlying ABCA7-related microglia dysfunction using these methodologies
- Capturing the diversity of the ROSMAP cohort in iPSCs allows for the elucidation of polygenic nature of AD risk, particularly as it relates to microglia immunological functions
- Current work continues to elucidate the genetic risk factors that are most likely to interact and drive aberrant cellular states, and how we can manipulate using personalized therapeutic approaches that can be tested in these cellular systems

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