

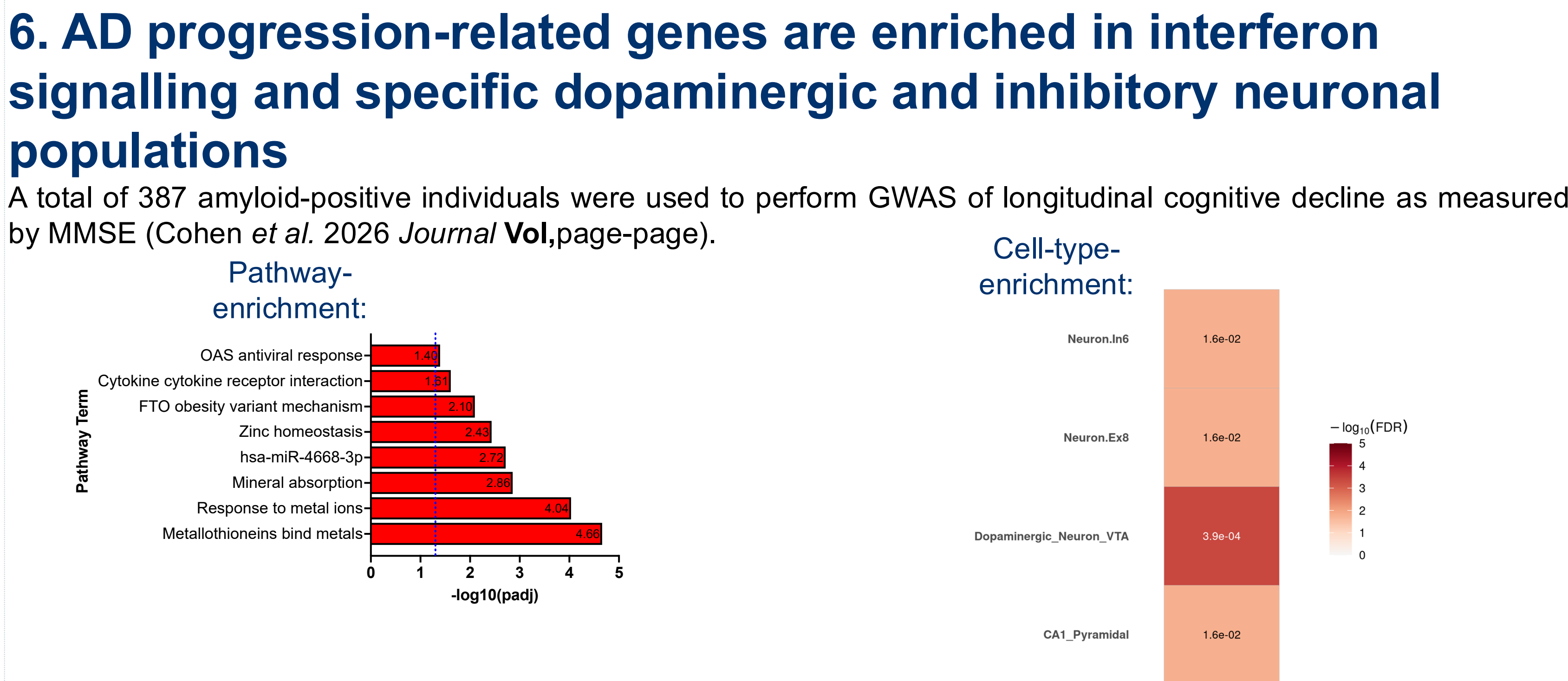
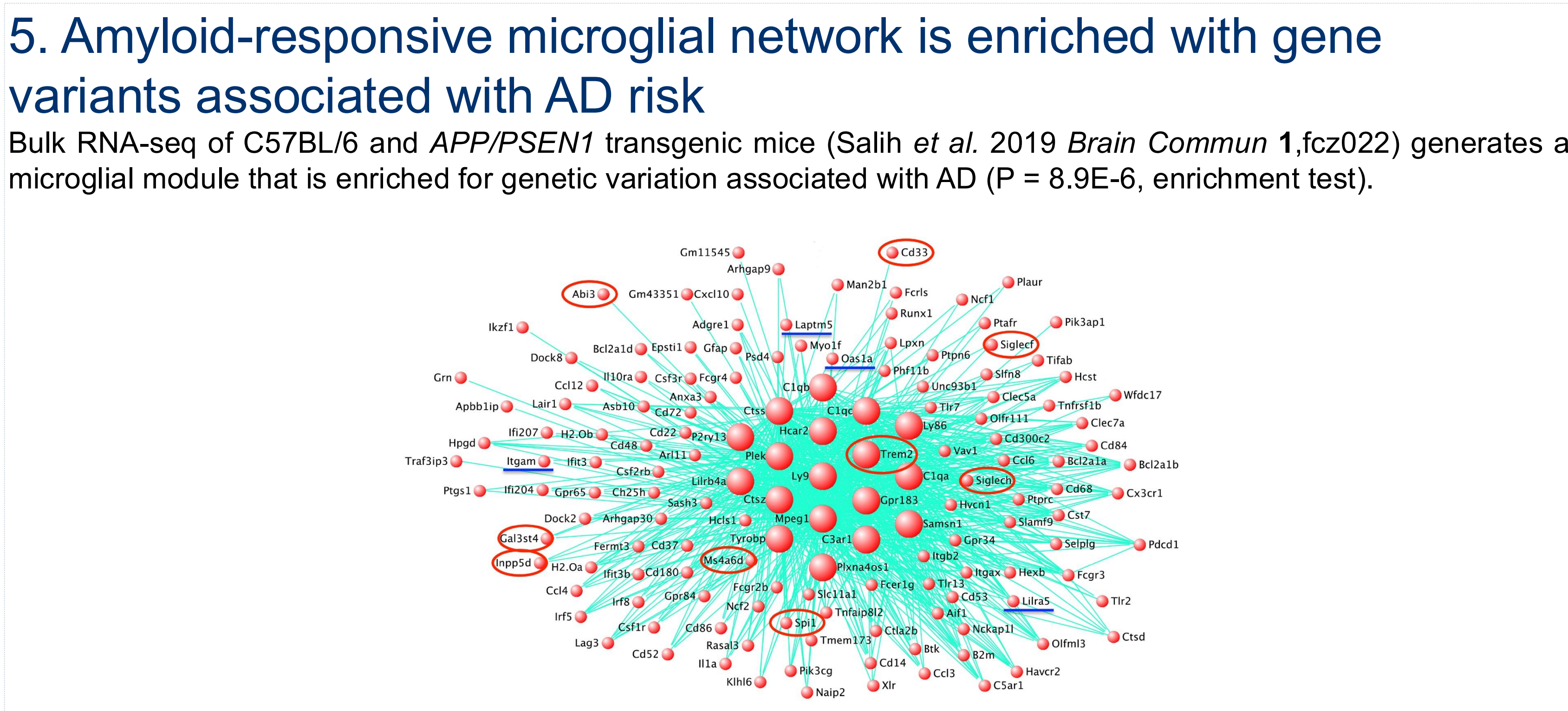
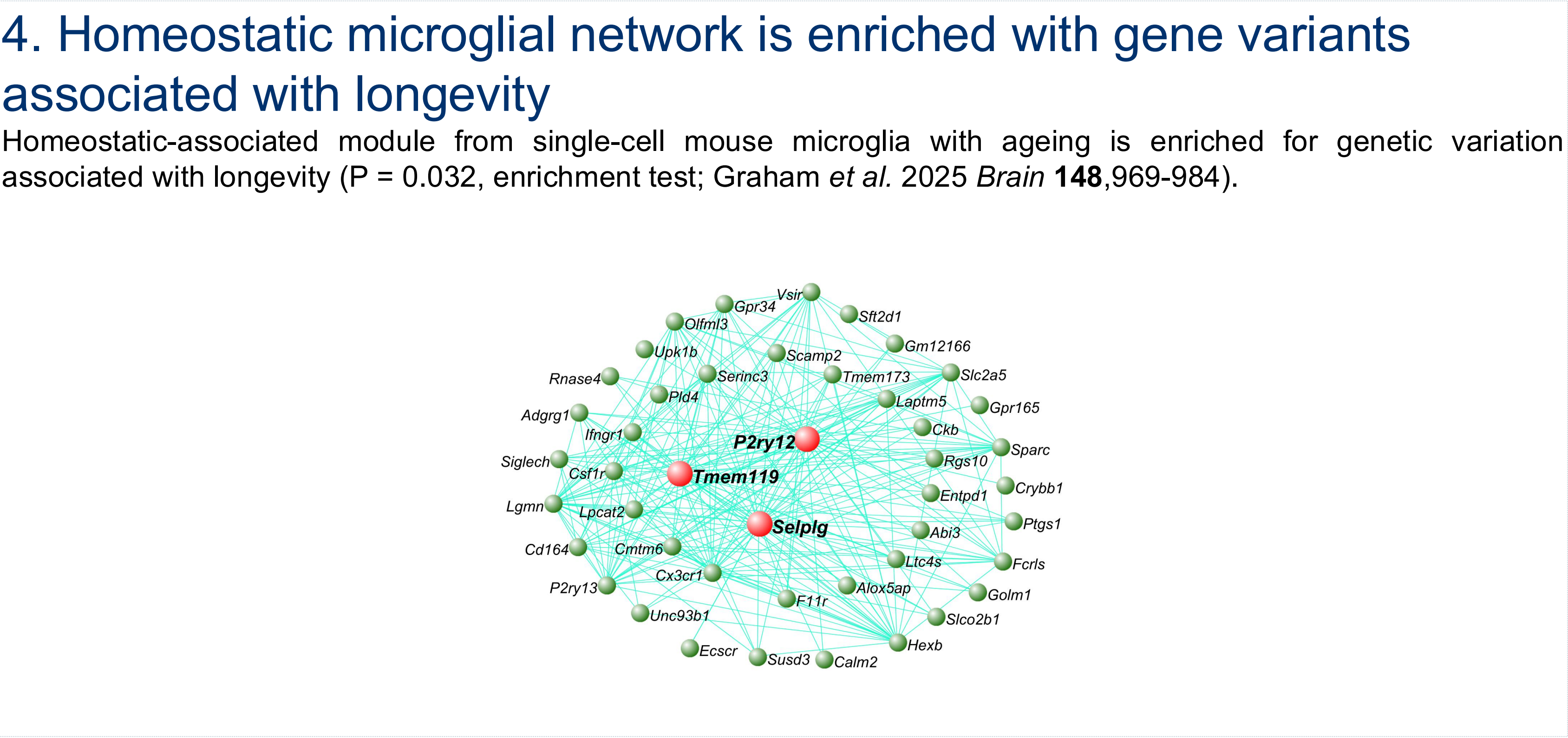
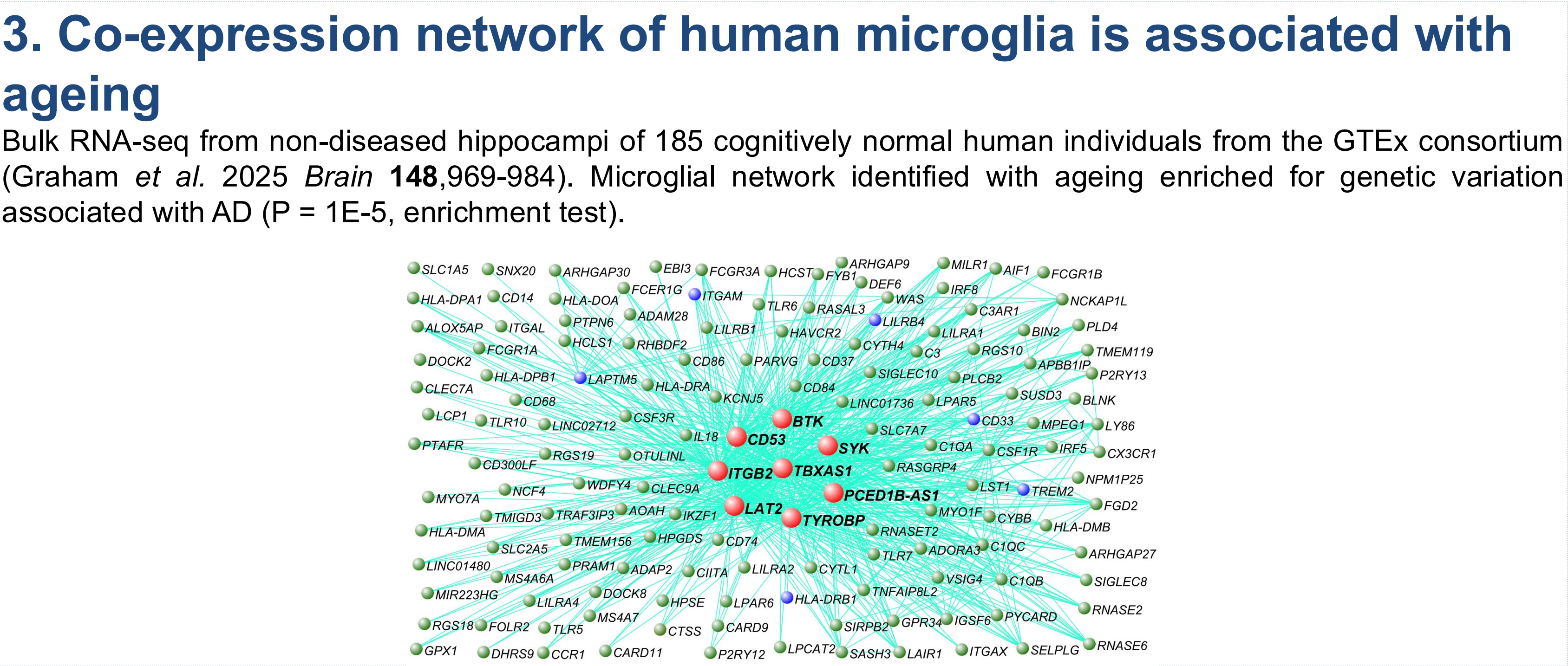
Ageing primes the expression of Alzheimer’s disease (AD) risk genes expressed by microglia. Amyloid induces a protective “Disease-Associated” state in microglia. Exhaustion of this protective microglial state permits the development of Tau pathology, in an APOE-dependent manner. AD progression is associated with interferon signalling pathways and distinct neuronal subpopulations related to Tau spread and neuronal death.

1. Introduction

Human genetics and transcriptomics have revealed the importance of microglia in Alzheimer’s disease (AD) through the discovery of risk genes such as *TREM2*, *PLCG2* and *SPI1*. Recent work has shown that the microglial response to amyloid pathology dictates the transition to Tau pathology, or not. Human genetics for AD has currently identified 75+ risk genes, which are largely expressed by microglia, and more remain to be identified. However, how these risk genes combine in pathways to coordinate microglial function and how these processes contribute to Tau pathology are not well understood.

2. Objective

To gain insights into the cellular and molecular mechanisms by which microglia respond to ageing (or resilience to AD), amyloid pathology, and Tau pathology. We are using an unbiased approach by integrating common human genetic variation associated with human lifespan, AD risk and AD progression from Genome-Wide Association Studies (GWAS), with co-expression transcriptome networks altered in the mouse and human central nervous system.



7. Importance

- 1) Ageing primes AD risk genes expressed by microglia.
- 2) AD risk genetic variants were enriched in amyloid-responsive microglia, not Tau-responsive.
- 3) AD progression-related genetic variants are enriched in interferon signalling and specific neuronal populations.