

Protein Co-expression Signatures Associated with Imaging Markers of Cerebral Amyloid Angiopathy and White Matter Injury in Autosomal Dominant Alzheimer Disease

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Global white-matter injury markers capture shared, nonspecific molecular processes, whereas periventricular WMH and microhemorrhages reflect more specific CAA-related pathways.

Introduction

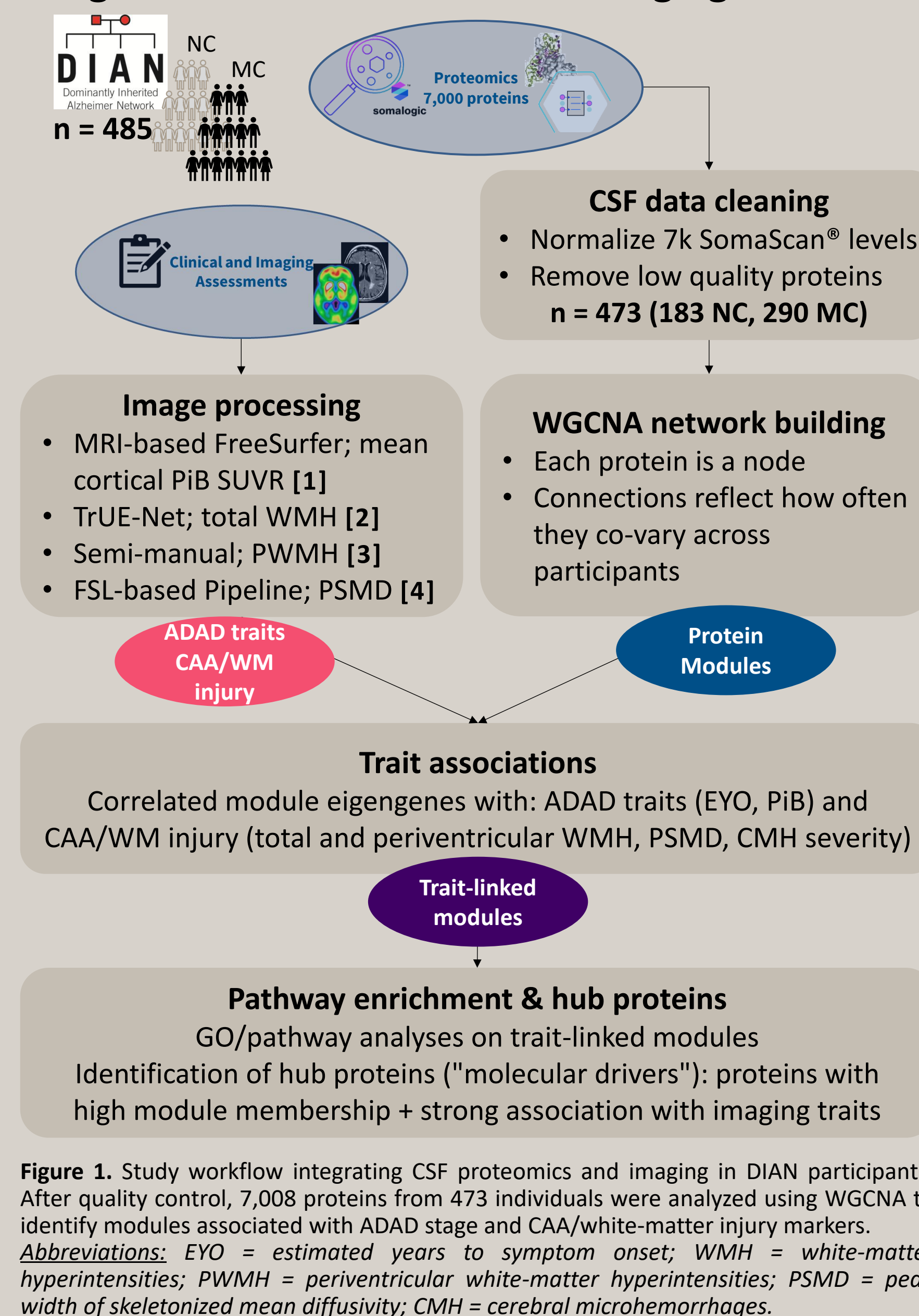
- Cerebral amyloid angiopathy (CAA) and white matter injury are associated with aging and Alzheimer disease (AD), including autosomal dominant AD (ADAD), despite its younger age of onset.
- Evaluating cerebrospinal fluid (CSF) proteomic signatures of ADAD and imaging markers of CAA and white matter injury may reveal distinct vs. shared pathways and yield new pathophysiological insights.

Objective of study

- Identify CSF protein networks associated with ADAD and CAA-related injury using data-driven methods.

Study Design, Cohort, and Methods

Integrated CSF Proteomics and Imaging in DIAN



Cohort Characteristics in CAA/WM Injury

Carriers exhibit greater imaging abnormalities

Table 1. Demographics and variables of interest by mutation status

Demographics	Non-carrier	Carrier	P-value
N (%)	183 (39)	290 (61)	–
Age, mean (SD), y	39.0 (11.5)	39.3 (10.6)	0.77
Female, n (%)	108 (59.0)	158 (54.0)	0.38
Education, mean (SD), y	10.9 (7.0)	10.6 (6.8)	0.70
APOE-ε4+ carriers, n (%)	59 (32.2)	84 (29.0)	0.51
EYO, mean (SD), y	–8.7 (11.7)	–6.0 (11.0)	0.09
CDR >0, n (%)	9 (5.0)	108 (37.2)	<0.0001
CDR-SB, mean (SD)	0.1 (0.3)	1.8 (3.4)	<0.0001
PiB-PET Positive, n (%)	3 (2.1)	133 (61.9)	<0.0001
Mean Cortical PiB SUVR, mean (SD)	1.1 (0.2)	2.1 (1.1)	<0.0001
Total WMH, mean (SD), mm ³	596.0 (967.0)	1707.1 (7553.7)	0.02
Periventricular WMH, mean (SD), mm ³	1703.0 (1644.0)	2868.4 (3036.4)	0.0005
PSMD, mean (SD), ×10 ^{–4} mm ² /s	2.6 (0.4)	3.0 (1)	0.0003
Microhemorrhages Present, n (%)	6 (3.3)	25 (8.8)	0.03
Hachinski Ischemia score, mean (SD)	0.15 (0.40)	0.35 (0.91)	0.001

Identified Modules and Relationship with Traits

Modules linked to ADAD were also associated with at least 1 CAA marker

- 19 modules total
- 7 linked to ADAD stage
- 3 positively and 4 negatively associated with disease stage

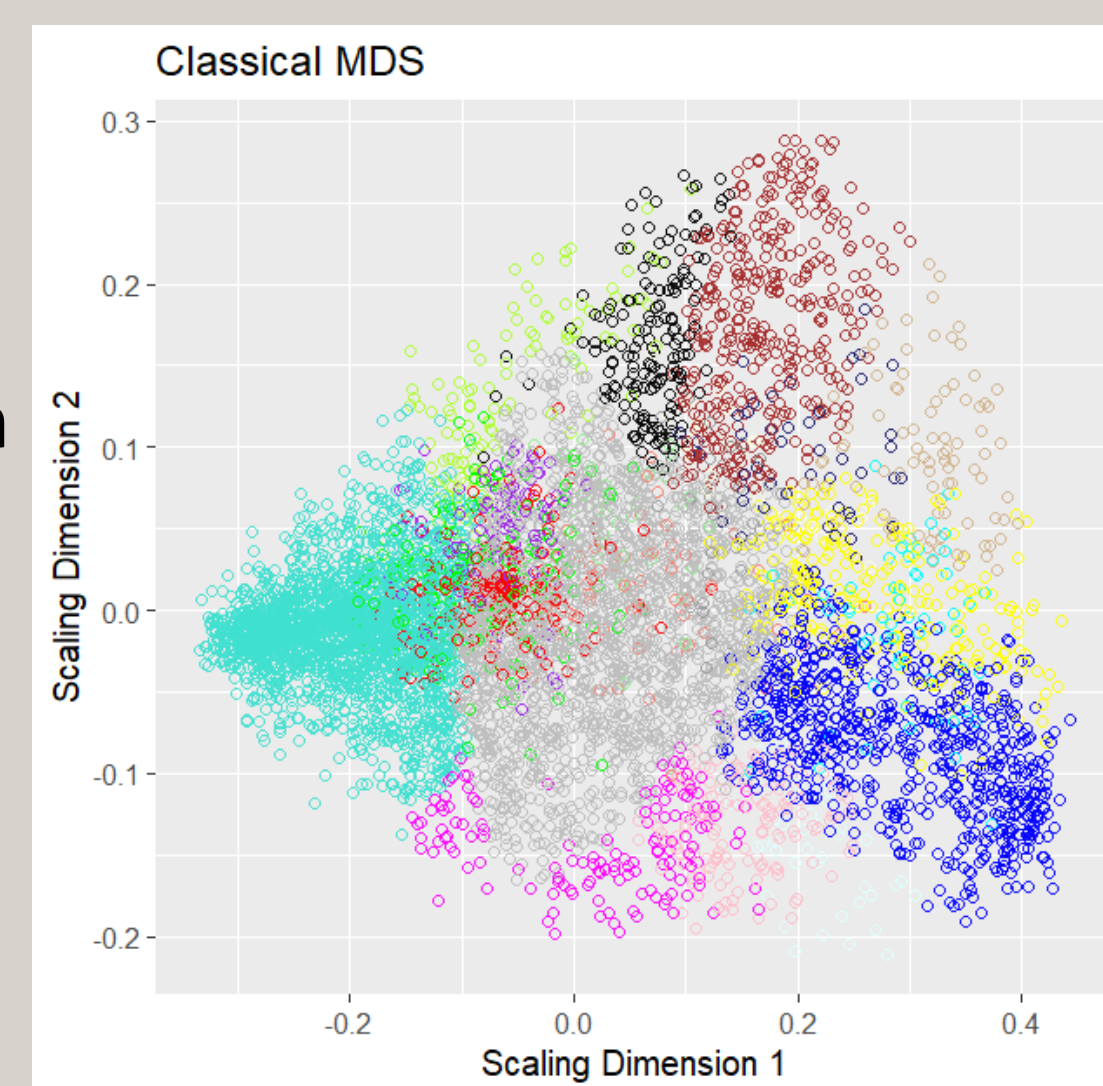
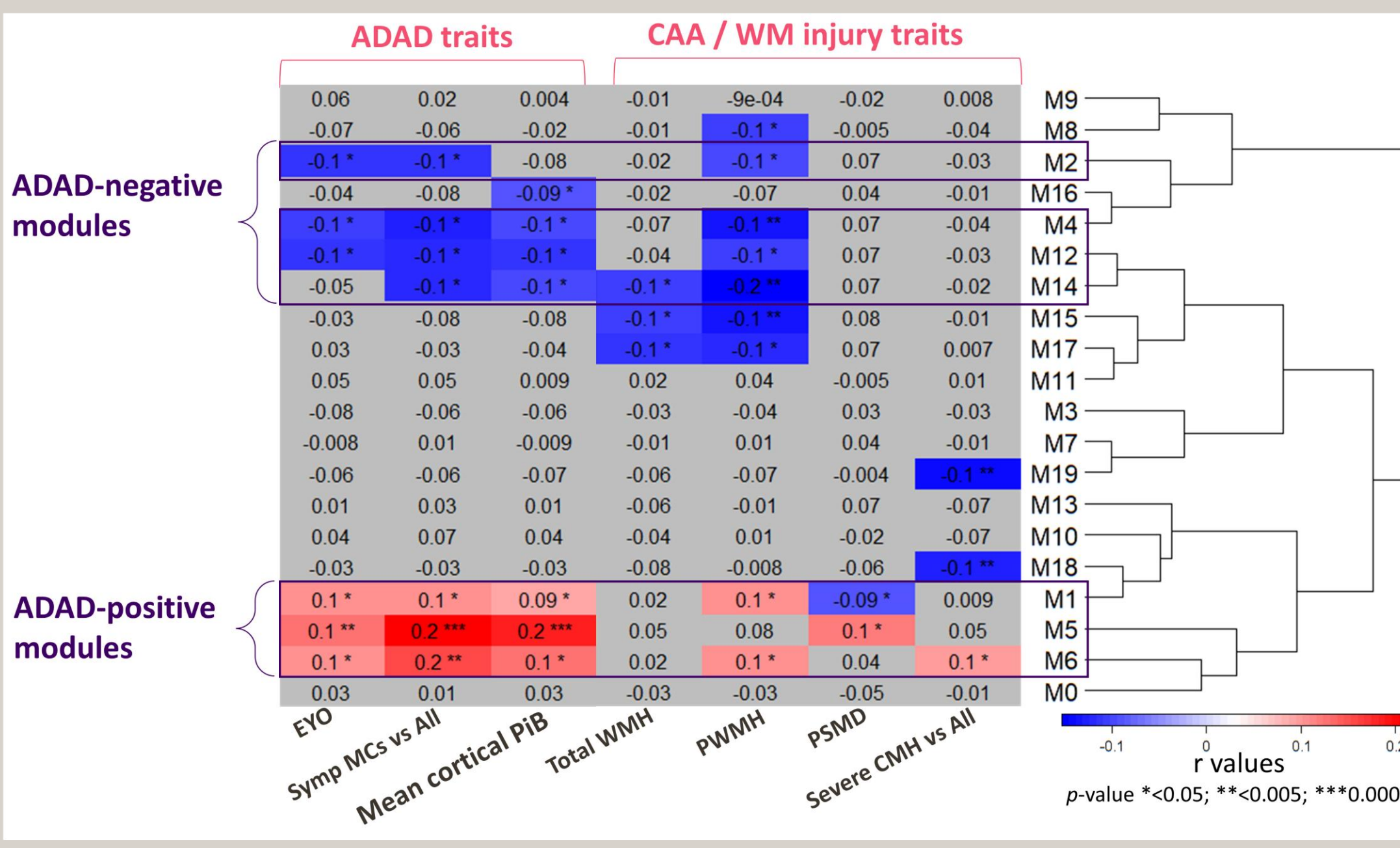


Figure 2. (Side) Network visualization of protein modules identified by WGCNA; the gray module (M0) contains unassigned proteins. (Bottom) Module–trait relationships showing associations between CSF protein networks and ADAD stage, total WMH, PSMD, periventricular WMH, and microhemorrhages. Distinct sets of modules are linked to disease stage and CAA-related imaging markers.



Enriched Pathways and Hub proteins

ADAD-positive modules

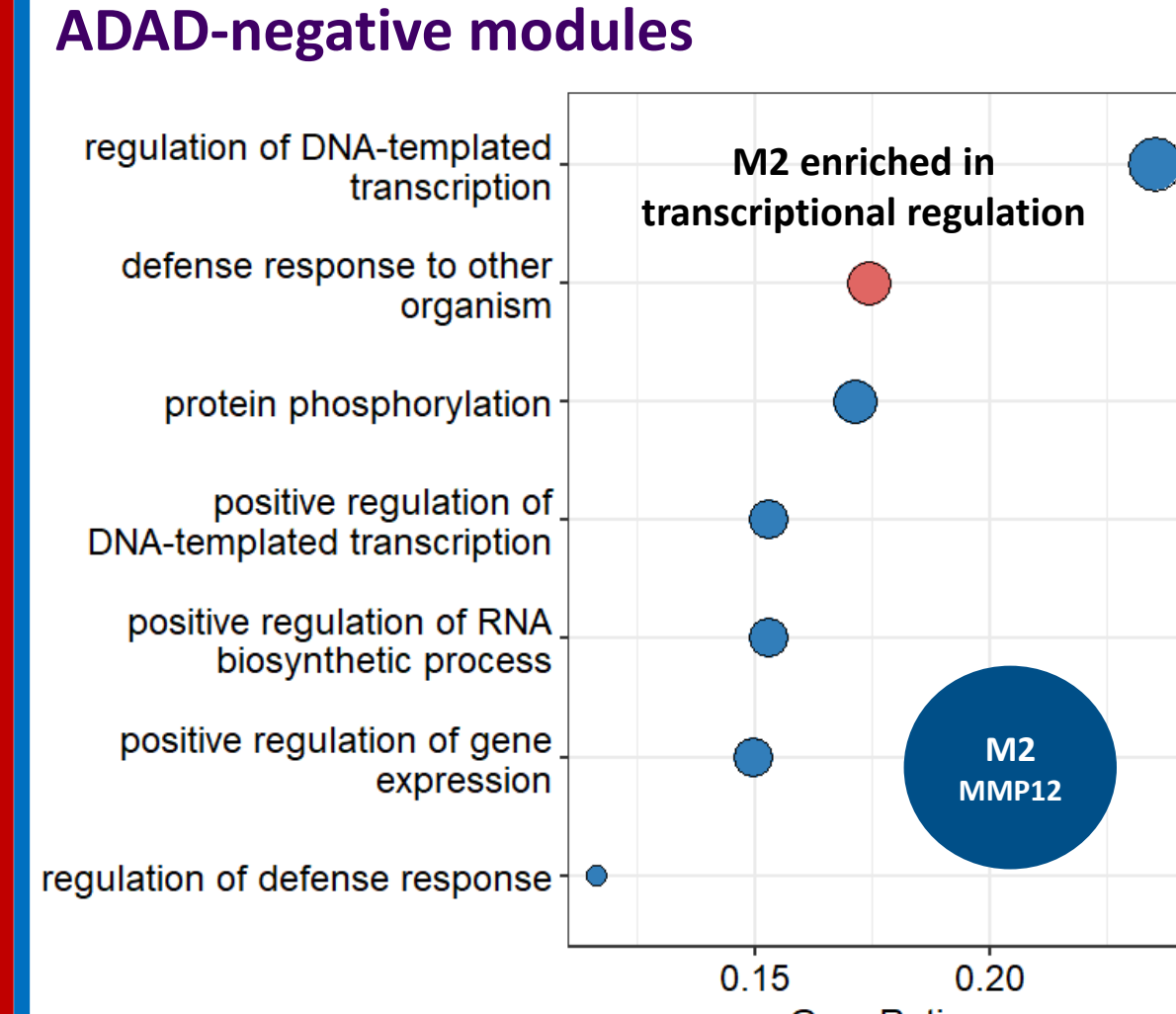
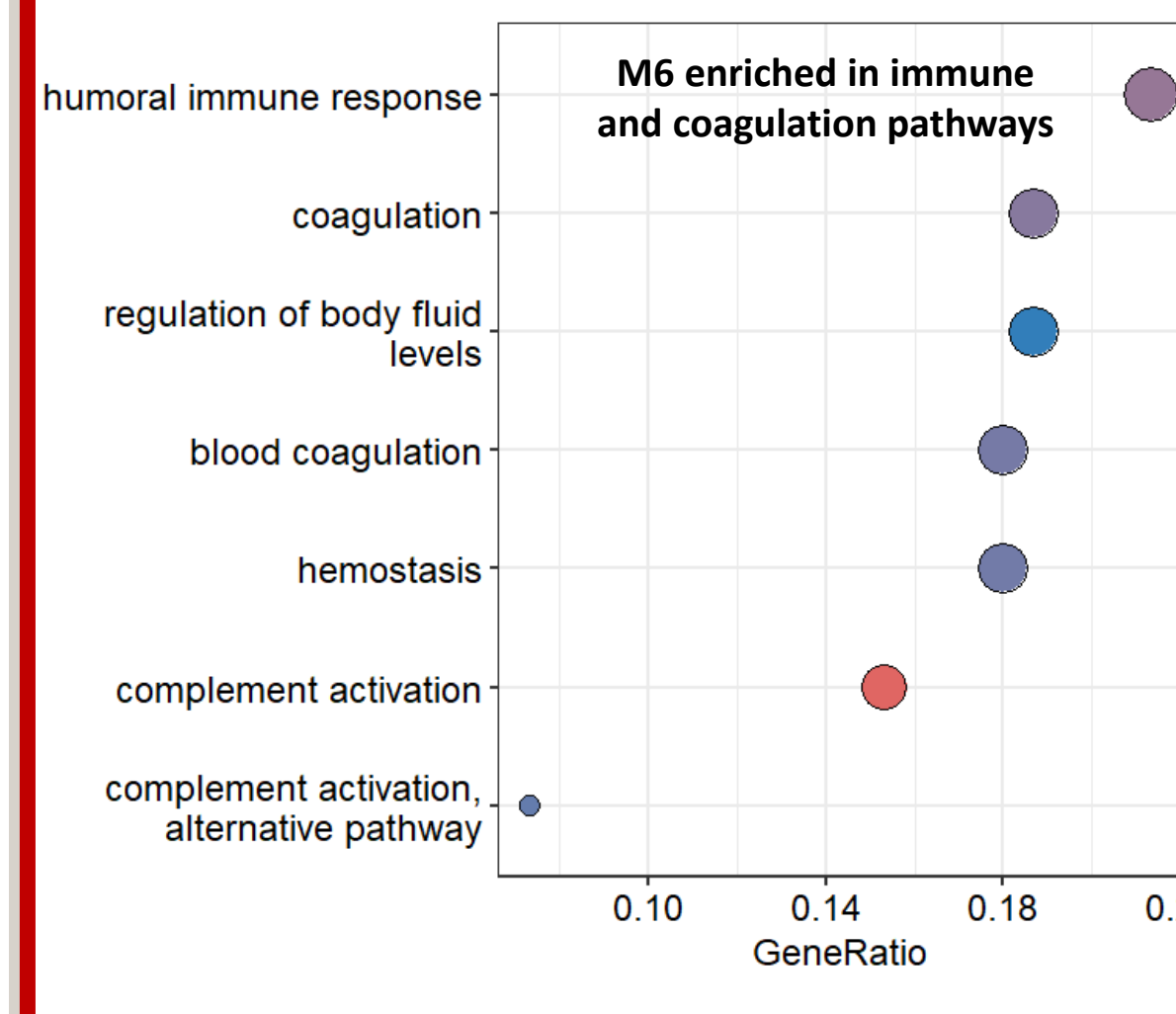
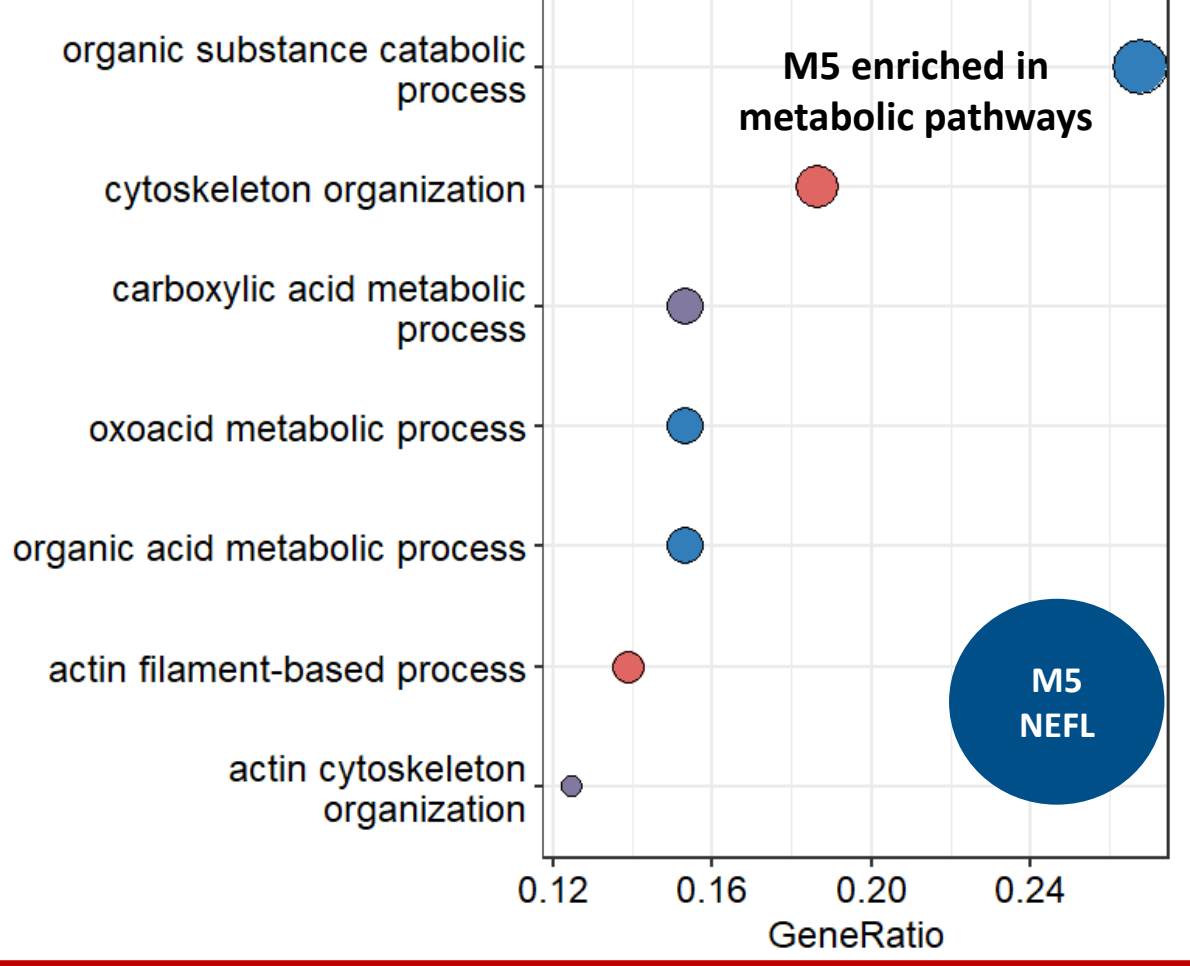
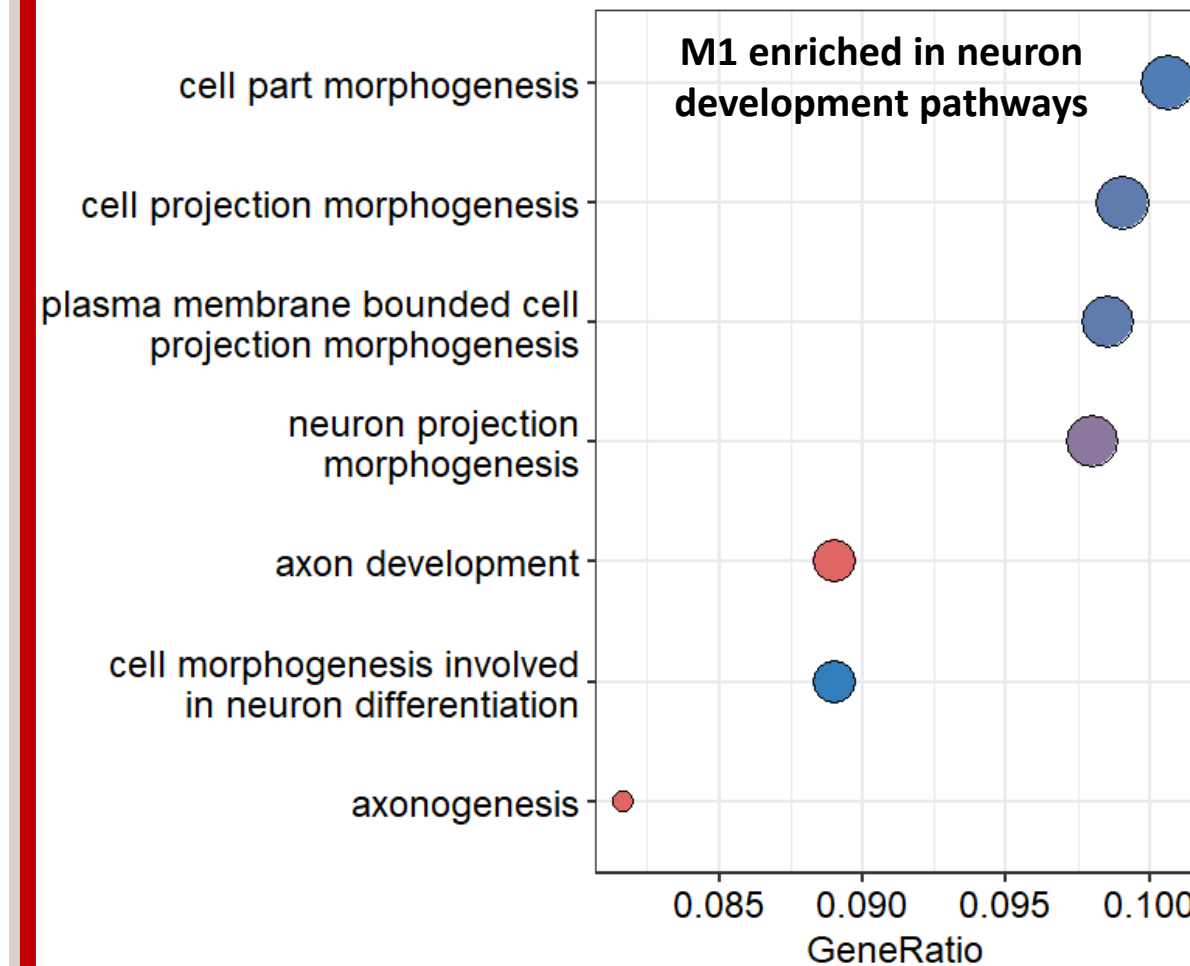
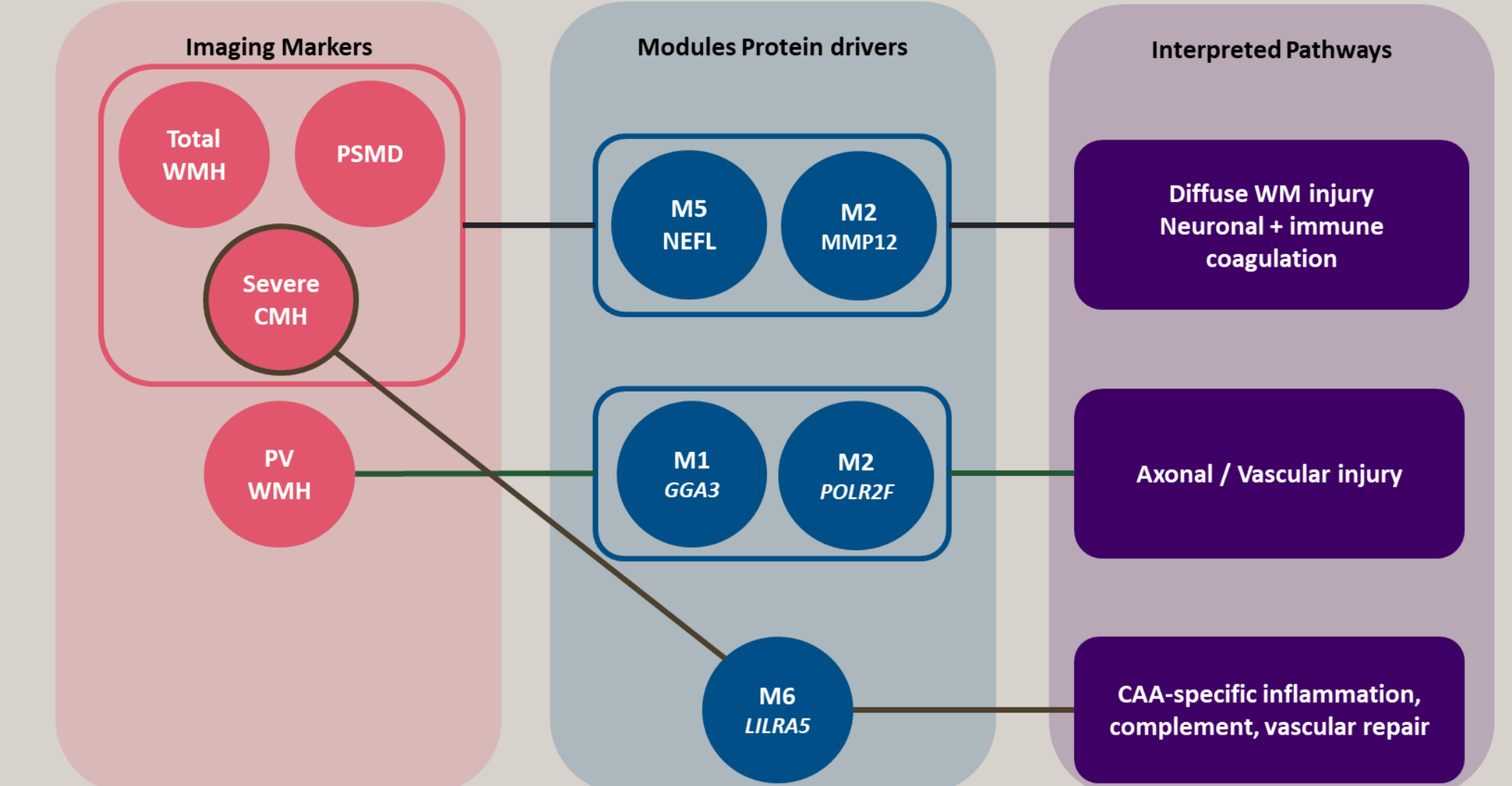


Figure 3. Functional enrichment of trait-associated modules highlights neuronal, metabolic, and immune/coagulation pathways. Representative hub proteins (e.g., NEFL, MMP12) illustrate key module–imaging associations.

Overview / Summary

- Shared proteomic signatures link total WMH and PSMD to global white-matter injury.
- Periventricular WMH is biologically distinct from other WM injury markers.
- Microhemorrhages are associated with a CAA-specific immune/coagulation signal.



Clinical implication: Distinct CSF proteomic signatures suggest that white-matter injury and microvascular damage arise from partially separable biological processes, supporting pathway-specific biomarkers.