Initial MEGENA Eigengene Work

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November 11th, 2025

Eigengene Analysis of JSD-Based MEGENA Networks

To investigate coordinated gene activity across retinal samples, we applied the Multiscale Embedded Gene Co-Expression Network Analysis (MEGENA) framework. Rather than relying on simple pairwise correlations, we quantified gene–gene similarity using the Jensen–Shannon Divergence (JSD), a symmetric measure of distributional difference. Low JSD values indicate genes that vary together across samples, suggesting shared regulation or functional relationships.

Within each MEGENA network, groups of highly co-expressed genes were identified as modules. To summarize the expression profile of each module, we computed its *eigengene*, defined as the first principal component (PC1) of all gene expression values within that module. The eigengene provides a single representative score that captures the dominant trend of the module's gene activity across all samples. High eigengene values reflect collective upregulation of the module, while low or negative values indicate reduced or baseline activity.

Combined Network (Control + Late AMD)

When MEGENA was applied to all samples jointly, the resulting network revealed several biologically coherent modules, including `c1_2` and `c1_3`, that clearly differentiated Control (MGS1) and Late AMD (MGS4) groups. Eigengene values in Control samples were centered around zero, representing normal baseline expression. In contrast, Late AMD samples exhibited significantly higher eigengene values, with several reaching magnitudes exceeding 10–15. This pattern indicates that genes within these modules are largely inactive in healthy tissue but become strongly co-activated in Late AMD, suggesting involvement in disease-associated biological pathways.

Control-Only Network

The network constructed from Control (MGS1) samples alone was relatively compact and stable. Modules such as `c1_2`, `c1_3`, and `c1_5` displayed eigengene values centered near zero with modest variability (standard deviations ≈ 2). This low variation implies consistent gene regulation among healthy samples, reflecting steady-state cellular processes characteristic of retinal homeostasis. Overall, the Control network represents a balanced, non-reactive transcriptional environment.

Late AMD Network

In contrast, the network derived from Late AMD (MGS4) samples exhibited substantially higher variability and complexity. Modules including `c1_2`, `c1_3`, and `c1_6` showed eigengene standard deviations of 3–4 and maximum values reaching approximately 19. This wide dynamic range indicates that the same gene clusters that were quiescent in Controls become variably and sometimes strongly activated in diseased samples. Such heterogeneity likely reflects different levels of disease progression or activation of stress-responsive, inflammatory, and remodeling pathways in Late AMD tissue.

Network	Eigengene Behavior	Interpretation
Combined (Control + Late)	Modules separate groups; higher eigengenes in Late AMD	Disease-related activation of specific gene programs.
Control-Only	Low variability; eigengenes near zero	Stable baseline gene regulation in healthy tissue.
Late-Only	High variability; strong positive outliers	Stress- and inflammation-associated activation in disease.

Table 1: Summary of eigengene behavior across JSD-based MEGENA networks.

Summary

In summary, eigengenes offer an intuitive way to represent the coordinated activity of large gene modules. Across all analyses, modules that remain quiet and stable in Control samples become variably and often strongly activated in Late AMD, highlighting their potential involvement in key processes driving disease progression.