Significance and Benefit to Society Essay

Microglial Single Cell Transcriptomics Reveal Drivers of Autism Severity

Autism spectrum disorder (ASD) matters to me personally because my younger brother was diagnosed with autism spectrum disorder, and my family lives the reality behind the word "spectrum." One of the hardest parts is receiving a diagnosis and then trying to understand what "severity" means, what will actually help, and how to avoid years of expensive trial-and-error decisions. That experience is why I believe society needs a more molecular, objective way to study ASD heterogeneity—especially the biology that may relate to differences in impairment and support needs.

The significance of my work is that it provides a severity-aware framework for analyzing transcriptomic heterogeneity in ASD, focused on microglia. Many transcriptomic studies compare ASD versus control groups, which can obscure meaningful differences among individuals with ASD. In this project, I stratified ASD donors into severity groups using clinically defined comorbidities and analyzed microglial gene expression using a donor-level pseudobulk approach to reduce bias from uneven cell counts. I then developed a driver classification framework that organizes significant genes into early, late, or cumulative drivers based on when they emerge across severity transitions.

This approach has societal value because it prioritizes signals instead of producing a single long list of genes. By distinguishing early versus late signals, the framework can guide functional studies toward the most informative targets and help researchers test stage-linked

mechanisms. Because the pipeline uses public datasets and standard tools, it is scalable: it can be applied to additional ASD datasets, other brain regions, and other cell types (such as neurons and astrocytes) to evaluate whether severity-linked patterns are shared or cell-type specific. With replication and functional validation, severity-aware molecular staging could support better stratification in research studies, reduce wasted effort on trial-and-error targets, and accelerate progress toward biologically informed interventions.

This work qualifies as significant because it is an important advancement that can be replicated and built upon: it introduces a reusable, severity-aware analytic framework—not just a single result—using public datasets and standard tools. It is also interdisciplinary, combining neurobiology, immunology, and computational transcriptomics to generate testable, stage-linked hypotheses that can guide future functional studies and translational research.

I believe this work is significant because the core contribution is not only a set of results, but a framework that can be reused, tested, and improved. Next steps include validating the driver categories in independent cohorts with richer clinical severity measures and testing causality in experimental models such as iPSC-derived microglia, microglia–neuron co-culture systems, or organoids. I have experienced firsthand the need this research aims to address, and I hope this framework helps move ASD research toward clearer, more actionable biological understanding.