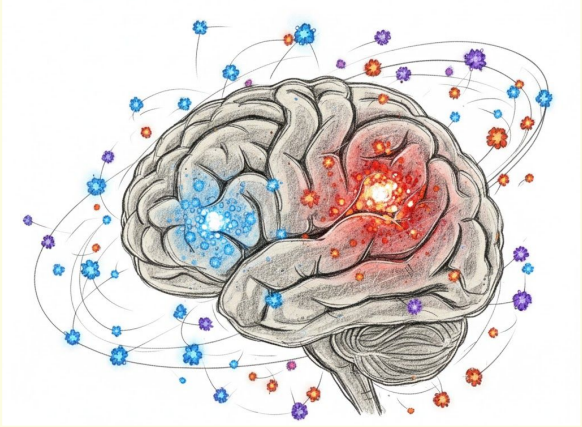
Autism Spectrum Sense

Staging the Future of Autism Care, Microglial Drivers

Vision: To move beyond subjective behavioral checklists and provide a precision-based genetic roadmap for neurodevelopment.



Problem

Current ASD (Autism Spectrum Disorder) diagnostics are based on external behavioral observations that fail to reflect the underlying molecular "severity" and transcriptional state of the brain.

Solution

Utilizing microglial "driver genes"—identifying early immune priming and late glial remodeling signatures—to objectively stage disease trajectory at the cellular level.

Goal

To enable early, severity-based medical intervention that prevents long-term impairments and maximizes patient autonomy.

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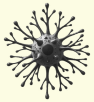
- *I'll include a "pulse" animation on the glowing nodes of the brain to represent active neural signaling*

The Evolution : Autism Spectrum Disorder

Historical Gap

1950s–1990s
Establishing Heritability



2000s–2010s:
The Immune Hypothesis

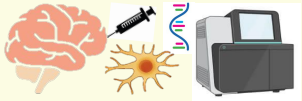
Wamsley et al. dataset

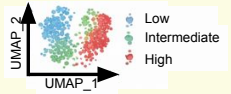
2024: The Single-Cell Breakthrough

History of the field is bit slow, necessary move from what we see to what cell is doing

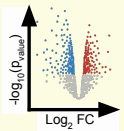
Present Technology: My Computational Workflow

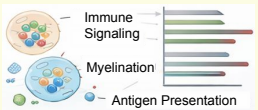
Brain scRNA Sequencing → Data Download & QC → Microglia PCA & UMAP





Gene Expression Analysis → Pathway Analysis → Driver Gene Classification





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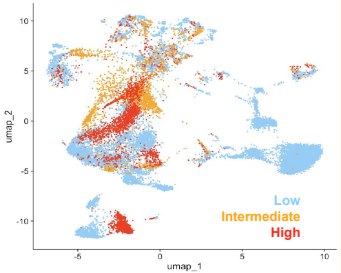
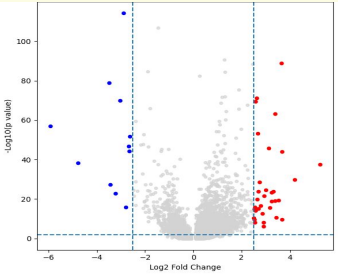
- *This page will have a smooth scrolling reveal for the computational workflow, so each step of the pipeline fades in as the user reads*

Result 1



Microglia Transcriptional Landscape Across ASD Severity : UMAP projection of microglia transcriptional profiles across ASD severity cohorts. Each dot represents a unique cell. Cells from each cohort occupy shared and distinct transcriptional clusters, suggesting a progressive alteration in global cell states.

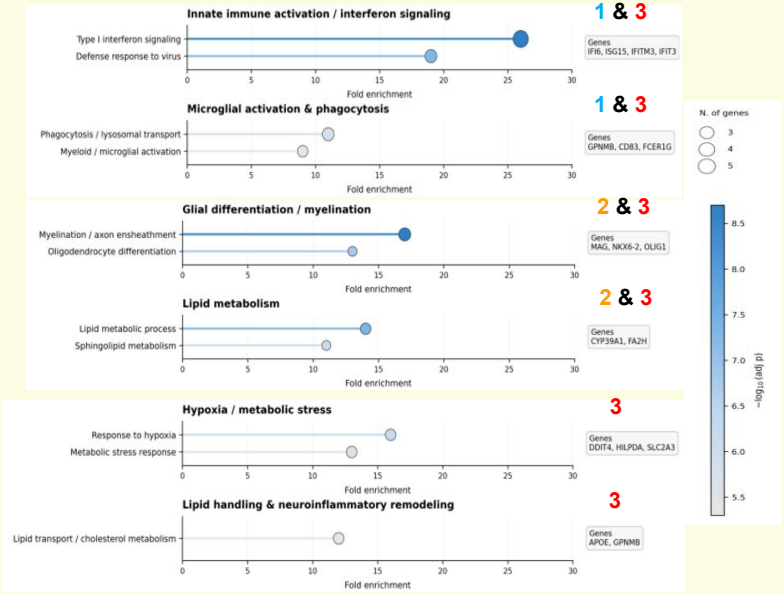
Result 2



Differential Microglial Gene Expression with ASD Severity: Volcano plot of significantly upregulated (red) or downregulated (blue) genes (individual dots) between intermediate and high severity ASD microglia. Table summarizes results across all three comparisons

Comparison	Significant Genes	Up-regulated	Down-regulated
1) Low vs Intermediate	53	45	8
2) Intermediate vs High	43	32	11
3) Low vs High	135	129	6

Result 3



Microglial Activation & Stress Responses Associate with ASD Severity GO Pathway enrichment analysis of differentially expressed genes across severity comparisons (1-3). Biological processes grouped by functional theme. Pathway gene fold enrichment plotted along with heat map of adjusted p value and number of involved genes (circle size)

In this space below, describe any special effects that might be applied to your webpage

- *Animated graph across all 3 results*

De-Identified Patient ID	Age	Gender	Cause of Death		Clinical Symptoms	Disease Severity
KMC3	48	Male	Natural	Cancer, Gastric carcinoma	Hyperkinesis, Pica	Low
2NA6	16	Male	Accident	Blunt force trauma	Bipolar	
493	26	Male	Accident	Drowning	Blind	
FXMW	29	Male	Natural	Cardiac Arrest	ADHD	
5023	16	Male	Accident	Blunt force trauma	Epilepsy, Diabetes	Intermediate
9714	60	Male	Natural	Cancer, Pancreatic	Epilepsy	
19511	8	Male	Natural	Cancer (Sarcoma)	Epilepsy	
5302	16	Male	Natural	Diabetic Ketoacidosis	Epilepsy	
6041	19	Male	Natural	Seizure	Epilepsy	
8792	29	Male	Natural	Acute pancreatitis-Renal Failure	Epilepsy	
12457	29	Female	Natural	Seizure	Epilepsy	
2YK7	17	Female	Natural	NA	Intellectual Disability, Epilepsy	High
3HUF	23	Male	Natural	Pneumonia	Intellectual Disability, Epilepsy	
VPSP	20	Male	Natural	NA	Intellectual Disability, Epilepsy, ADHD	
8XCF	27	Male	Natural	Acute pancreatitis-Renal Failure	Intellectual Disability, Epilepsy	
M9H3	59	Female	Natural	Seizure, Cardiac Arrest	Intellectual Disability, Epilepsy	
5842	19	Male	Natural	Cardiac Arrest	Intellectual Disability, Epilepsy	
13161	24	Male	Natural	NA	Intellectual Disability, Epilepsy, ADHD	

Inclusion Criteria: Diagnosis of ASD by DSM V

- Low Severity: No Epilepsy or Intellectual Disability Clinical Symptoms
- Intermediate Severity: Epilepsy (short term impairment) without Intellectual Disability (long term impairment)
- High Severity: Both Intellectual Disability and Epilepsy

Exclusion Criteria

- 15q Duplication Genetic Subtype n=5 (confounding molecular driver of disease)
- Unreported Clinical Symptoms n=10 (unclear severity)

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- *Animated color code across Disease Severity*

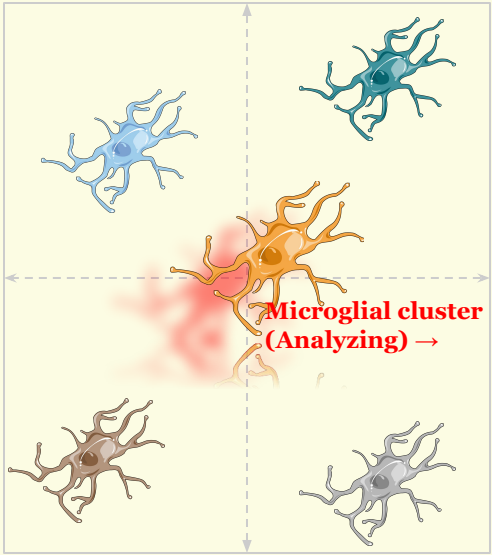
Autism Spectrum Sense

Precision Severity Dashboard

Input

De-identified Patient Id: **3HUF**
Input: **Microglial RNA Profile**

Biological Map



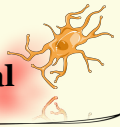
Driver Analysis

Early Drivers

- **ISG15 : Active**
- **IFIT3: Active**

Late Drivers

- **PLP1 : Critical**
- **ERBB3: Critical**



Recommendation

TIER 3 - Intensive Medical + Medical Support
IMMEDIATE ACTION REQUIRED

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- *I want the "Precision Severity Score" needle to physically rotate and settle on the gauge when the page loads to emphasize the diagnostic result*

Our project currently relies on post-mortem tissue. This clinical shift depends on two breakthroughs:

- **Non-Invasive Sensing:** We need to "read" microglial RNA without a biopsy. The goal is **liquid biopsies**—using simple blood samples to catch the specific RNA signatures that microglia leak into the bloodstream.
- **Predictive AI:** We need to validate **LSTM (Machine Learning) networks** that can process a patient's genomic profile. This tool would predict a child's developmental path with over 90% accuracy.

Planned Investigation: Proving the Drivers

To move from "finding" genes to "proving" they drive severity, I've designed a lab validation phase:

- **The Experiment:** will use **CRISPR-Cas9** to "knock down" (turn off) the early driver gene I identified, *ISG15*, in lab-grown microglial cells.
- **The Goal:** To see if silencing this "immune priming" gene stops the cellular shift into metabolic stress and inflammation. If turning off one gene prevents the "crash," we've found a legitimate target for future treatment.

Our Phase-by-Phase Approach

Phase 1

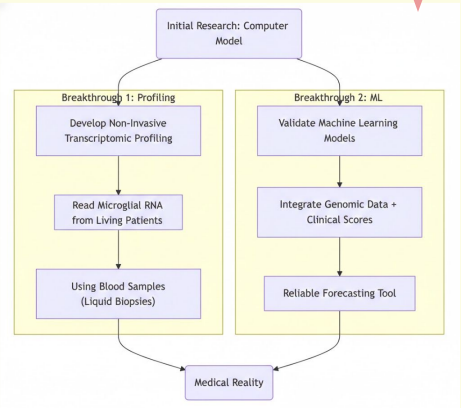
Clinical validation of driver genes across diverse pediatric cohorts.

Phase 2

Engineering the sensor technology for non-invasive RNA detection

Phrase 3

Integrating the **Precision** Severity **Dashboard** into hospital systems to automate staged treatment plans.



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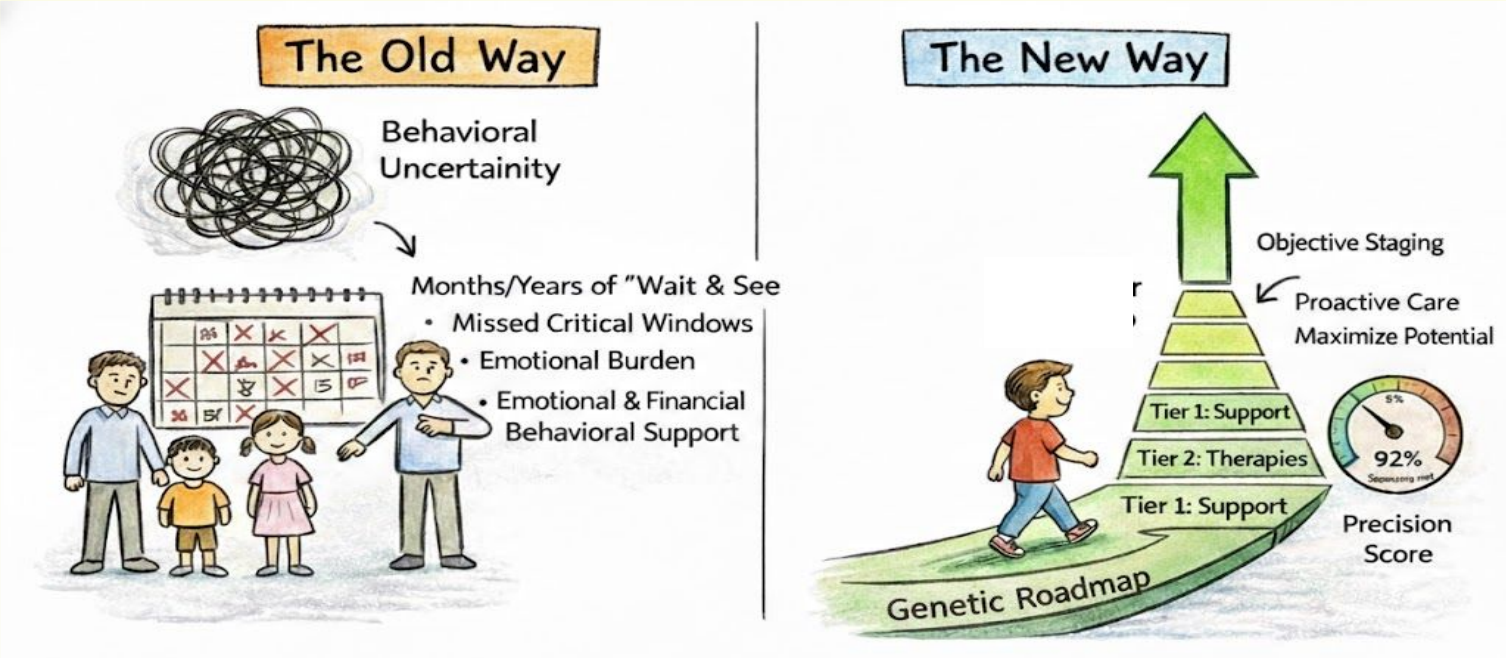
- *I'll add an interactive hover effect on the CRISPR-Cas9 diagram that highlights the specific gene being "knocked down".*



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- *This page will feature a "before-and-after" slider so users can swipe between the chaotic "Old Way" and the structured "New Way" of the molecular roadmap.*

Conclusions

- ASD severity-associated transcriptional changes in microglia follow a trajectory involving early immune priming, later glial/metabolic remodeling, and cumulative neuroinflammatory burden
- Lack of global drivers suggests distinct microglial molecular states associated with disease severity

Limitations

- Severity cohorts are based on broad clinical symptoms, which are likely different across patients
- Differential expression analyses is correlative and does not establish definitive causal relationships
- Conclusions are based on microglia data alone, key interactions with excitatory neurons and other brain cells to be explored

Future Directions

- Evaluate a machine learning model of disease severity and compare with current results
- Validate results in independent data sets
- Evaluate functional consequences of targeting driver genes in microglia in ASD disease models

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- *I plan to make the Team Sigma-A3 Genomics logo slightly interactive, where the DNA helix gently rotates when a user hovers over the contact information.*