

GeneSTRATA: An Outcome-Aware Multimodal Hierarchical Bayesian Framework for Biologically Structured Autism Subtype Discovery and Prognostic Stratification

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Autism Spectrum Disorder (ASD) exhibits substantial heterogeneity in long-term developmental outcomes. Children with similar early symptoms often follow divergent cognitive and adaptive-function trajectories. Current diagnostic frameworks treat autism as a single spectrum, limiting clinicians' ability to predict trajectories or personalize interventions. This study presents GeneSTRATA, the first outcome-aware supervised latent subtype discovery framework, integrating graph-structured biological priors for clinically relevant ASD subtyping and prognostic stratification. Data from 27,606 individuals with autism were analyzed to characterize heterogeneity in relationships among polygenic burden, de novo damaging variants, developmental milestones, and the cognitive-adaptive gap. A novel hierarchical Bayesian mixture-of-regressions algorithm was developed that jointly learns latent subtypes and their outcome-specific predictive structure. Unlike conventional approaches, the framework employs a supervised latent variable formulation that prioritizes features based on their contribution to cognitive-adaptive outcomes and incorporates graph-based priors that encode biological relationships among genetic features and regularize parameter estimation. GeneSTRATA identified four reproducible ASD subgroups with distinct biological signatures: Synaptic, Transcription, Chromatin remodeling, and minimal-genetic-effect subtypes. The model explained 71.5% of variance in the cognitive-adaptive gap, outperforming pooled regression baselines of 6.2%. The findings were validated in an independent cohort of 4,044 children. A prototype stratification tool was developed to assign individuals to subtype-specific profiles, establishing a foundation for precision intervention planning in ASD.

Awards Won:

Third Award of \$1,200

Arizona State University: Arizona State University ISEF Scholarship (valued at up to \$32,000 each)