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A Spectra-Based Framework Identifies Transcriptionally Defined Neuronal Subpopulations Enriched for Somatic Mutations in Neuropsychiatric Disorders

Somatic mutations accumulate in post-mitotic neurons and have been implicated in neuropsychiatric disorders, yet their functional consequences remain poorly understood. We developed a novel computational algorithm to classify single cells based on transcriptomic profiles characterized using Spectra-derived latent factors. This approach enables the identification of transcriptionally defined cell subpopulations enriched for somatic mutations across diagnostic groups.

Applying this framework to single-nucleus RNA-seq data from individuals with opioid use disorder (OUD), major depressive disorder (MDD), comorbid OUD and MDD (COM), and controls, we identified discrete neuronal clusters exhibiting increased somatic mutation burden. In OUD, mutation-enriched clusters were observed in L2/3 intratelencephalic (L2/3-IT) neurons from deep cortical layers and D1-matrix medium spiny neurons from the caudate nucleus of the striatum. Parallel analyses revealed additional mutation-enriched clusters in MDD and COM samples, suggesting both shared and disorder-specific vulnerability patterns.

Beyond detecting mutation-enriched populations, our algorithm provides mechanistic insight by linking somatic mutation burden to transcriptional programs. Mutation-enriched clusters showed upregulation of oxidative phosphorylation and calcium signaling pathways, consistent with established mechanisms of oxidative stress–related DNA damage. Furthermore, these clusters displayed altered neural activity signatures and elevated DNA damage–associated expression profiles, which may represent either drivers or consequences of increased somatic mutation rates. Together, this framework enables integrative characterization of mutation-enriched neuronal states and offers a systems-level approach to understanding the molecular mechanisms and potential functional impact of somatic mutations in OUD, MDD, and their comorbidity.

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