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Functional Protein Kinase Atlas of Disorders of Cognition

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Background: Protein kinase activity is crucial in cellular signaling pathways, influencing various physiological processes as well as cognition. However, protein kinase-mediated signaling events are complex and involve multiple protein kinases, phosphatases, and signal integration molecules that form networks that coordinate cellular functions and pathological fates of cells.

Objectives: This study aimed to explore the nature of global signaling networks in the brain and their relationship to cognitive disorders. Specifically, we aimed to identify kinase network activity patterns associated with Alzheimer's Dementia (AD), Schizophrenia, and mild cognitive impairment (MCI).

Methods: We conducted a series of experiments using a high-throughput kinase activity assay across various substrates, including postmortem brain samples from disease-free controls, people with MCI, AD, and Schizophrenia. We also assayed patient-derived induced pluripotent stem cells (iPSCs). We analyzed the resulting datasets using established methodologies to generate a putative "map" of disease-related kinase network activity.

Results: Our analysis revealed top kinase nodes common to AD and Schizophrenia and active kinome signatures unique to each disease. These findings provide novel insights into the pathophysiology of these disorders.

Conclusion: Assessing active kinome networks provides a new approach to understanding cognitive disorders. Our study shows that probing the active kinome with multi-omics generates unbiased datasets and reveals novel pathophysiological insights for validation and causal studies. These findings inform drug target selection and guide future research.

Keywords: Alzheimer's Disease,Schizophrenia,Kinome,Active Kinome

