Analyzing spatial transcriptomics and neuroimaging data in neurodegenerative diseases

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Summary

Neurodegenerative diseases are hallmarked by protein inclusions and cell loss in disease-related brain regions. Many studies have tried to understand the molecular mechanisms that lead to the pathological and symptomatic hallmarks of neurodegeneration. Although studies highlighted important genes and biological pathways, the exact disease mechanisms are still not fully understood.

In this thesis, we make use of bioinformatics approaches to analyze spatial molecular data from the human brain. Using different computational methods, we mainly focused our research on Parkinson's disease (PD) that is characterized by the loss of dopaminergic neurons in the substantia nigra and the progressive deposition of protein inclusions, called Lewy bodies, across the brain. These pathological findings are associated with symptoms including slowing of movements, tremor, and cognitive impairment, but the exact cause for PD remains unknown. To better understand the molecular mechanisms within brain regions associated with PD, and more general neurodegenerative diseases, we exploited a high-resolution spatial gene expression atlas of the healthy human brain generated by the Allen Institute of Brain Science. Spatial transcriptomics allows examining the molecular and functional organization of the human brain and can be combined with neuroimaging data to identify brain regions and anatomical structures that are vulnerable to cell loss in neurodegenerative diseases. By combining both data modalities, we examined healthy molecular functions in brain regions associated with disease vulnerability based on neuroimaging features, namely gray matter loss within brain networks in individuals with Parkinson's disease, Huntington's disease, and individuals at risk of schizophrenia. Here, the analyses were based on gene expression differences between regions associated with a disease in neuroimaging studies and a region that is considered unaffected (non-susceptible). While the consecutive analyses of both data modalities revealed interesting associations, integrated analysis of both data modalities revealed possible new relationships between gene expression levels and disease-related changes measured with neuroimaging. Since our main focus is on Parkinson's disease, we were also interested in gene expression patterns across Braak stage-related regions and our analyses revealed genes that may play a role in the progression and the pathological spreading of Lewy bodies in PD.

With this thesis, we have shown that by applying data-driven computational methods we can explore the whole genome and find gene expression patterns informative of regional brain vulnerability in neurodegenerative diseases. Our methods can similarly be applied to unravel the molecular mechanisms in other neurodegenerative diseases, and potentially even reveal shared mechanisms between neurological disorders.