PgmNr 56: Single-cell RNA-sequencing reveals cell-type-specific levels of aneuploidy in mammalian nervous system.

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There are conflicting reports on the prevalence of aneuploidy in the mammalian nervous system, with estimates ranging from <1% to 33% of neurons exhibiting aneuploidy. Recent work suggests that subsets of human neurons harbor large-scale genome alterations, including copy-number variations and chromosomal changes.

To investigate the extent and functional relevance of neuronal aneuploidy, we leveraged three recent large-scale single-cell RNA-sequencing (scRNA-seq) datasets (Tabula Muris, Allen Brain Atlas, and mousebrain.org) to search for evidence of chromosome-level genomic alterations in mouse, macaque, and human cells. Specifically, we developed an integrated computational pipeline to de-noise sparse scRNA-seq data, ascertained aneuploidy status based on the statistical distributions of gene expression levels for each chromosome, and quality-controlled aneuploidy results by random permutation of de-noised matrices. This resulted in a comprehensive survey of more than 212K neurons and glial cells in total (194K mouse, 1K macaque, and 17K human).

We found that across the three species, there are significant variations in the prevalence of aneuploidy across different brain regions (0 - 14%), consistent with the widely varying results from previous studies. Importantly, cell type plays a key role, with vast majority of chromosome changes appearing in glutamatergic neurons. We observed diverse karyotype changes, but identified human chr22 and mouse chr18 to be hotspots for chromosomal gains. Additionally, aging is positively correlated with aneuploidy rate in humans, and genetic markers of aneuploidy are enriched in aging and neurodegenerative diseases, synaptic transmission, mitosis, cytoskeleton, and metabolic processes. Finally, in the mouse PNS, we found that myenteric plexus of the small intestine has the highest levels of aneuploidy (11%).

Overall, we have established a novel computational pipeline that can systematically identify aneuploidy using large-scale scRNA-seq datasets. Our results suggest that chromosomal changes are differentially regulated in different cell types and different regions of the mammalian nervous system which, given the recent evidence of ongoing adult neurogenesis in the human brain, can have profound implications in further elucidating the molecular mechanisms and disease relevance of neuronal aneuploidy.