A135 · Beyond Sex Chromosomes: Sex Differences in Transcriptional Signatures of Aged Brain and Alzheimer's Disease

Presenter: Danielle Firer — MIT

Authors: Danielle Firer, David Page, Ernest Fraenkel

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Most documented sex-biased genes reside on sex chromosomes, yet whether sex differences in transcriptional signatures emerge in autosomal gene expression remains a critical gap. Understanding these autosomal sex differences is particularly important in the context of Alzheimer's Disease (AD), which affects about twice as many females as males. However, it remains unclear whether this sex disparity reflects biological differences in disease pathogenesis. To further our understanding, it is important to identify underlying biological differences between male and female brains during aging. We leveraged ROSMAP single-nucleus RNA-sequencing (snRNA-seq) data from the prefrontal cortex of 427 donors (age >65) to characterize sex differences in transcriptional signatures of the aged brain. We trained binary classification models on 2.3 million cells to test whether donor sex can be predicted from autosomal gene expression in donors diagnosed with no cognitive impairment (NCI) and Alzheimer's Disease (AD). Models for each major cell type were trained on the cohort stratified by diagnosis. This design allows us to (1) establish baseline sex differences in healthy aging, and (2) distinguish aging-related from disease-related transcriptional changes. To benchmark the statistical power of autosomal versus sex-chromosomal features, we performed a sample complexity analysis characterizing classifier performance as a function of cell count. By establishing these benchmarks, we understand how technical limitations like zero-inflation and sparse sampling affect biological interpretation in single-cell studies. Using statistical methods, we determined which features are the most robust predictors of sex differences. We hypothesize that these sex-predictive genes will reveal mechanisms driving differential vulnerability to AD.

Beyond Sex Chromosomes: Sex Differences in Transcriptional Signatures of Aged Brain and Alzheimer's Disease

Danielle Firer*[1,2,4,5], David Page[2,3,4], Ernest Fraenkel[5]

1. Computational and Systems Biology PhD Program, Massachusetts Institute of Technology, Cambridge, MA, USA
2. Whitehead Institute, Cambridge, MA, USA
3. Howard Hughes Medical Institute, Chevy Chase, MD, USA
4. Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA
5. Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Most documented sex-biased genes reside on sex chromosomes, yet whether sex differences in transcriptional signatures emerge in autosomal gene expression remains a critical gap. Understanding these autosomal sex differences is particularly important in the context of Alzheimer's Disease (AD), which affects about twice as many females as males. However, it remains unclear whether this sex disparity reflects biological differences in disease pathogenesis. To further our understanding, it is important to identify underlying biological differences between male and female brains during aging. We leveraged ROSMAP single-nucleus RNA-sequencing (snRNA-seq) data from the prefrontal cortex of 427 donors (age >65) to characterize sex differences in transcriptional signatures of the aged brain. We trained binary classification models on 2.3 million cells to test whether donor sex can be predicted from autosomal gene expression in donors diagnosed with no cognitive impairment (NCI) and Alzheimer's Disease (AD). Models for each major cell type were trained on the cohort stratified by diagnosis. This design allows us to (1) establish baseline sex differences in healthy aging, and (2) distinguish aging-related from disease-related transcriptional changes. To benchmark the statistical power of autosomal versus sex-chromosomal features, we performed a sample complexity analysis characterizing classifier performance as a function of cell count. By establishing these benchmarks, we understand how technical limitations like zero-inflation and sparse sampling affect biological interpretation in single-cell studies. Using statistical methods, we determined which features are the most robust predictors of sex differences. We hypothesize that these sex-predictive genes will reveal mechanisms driving differential vulnerability to AD.