# A157 · Leveraging naturally occurring sex chromosome variation in humans to identify loci that shape transcriptomic sex differences

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Sex chromosome constitution is a fundamental axis of human genetic variation that influences phenotypes well beyond the reproductive tract, including height and susceptibility to neurological, developmental, and autoimmune disorders. Recent published analyses of gene expression across approximately 200 individuals, with constitutions ranging from 45,X and 47,XXY to 49,XXXXY and 49,XYYYY, found that roughly 20% of expressed autosomal genes respond to the dosage of the inactive X (Xi) or Y chromosome. Here, we present an updated computational framework for characterizing these responses and localizing their sex-linked regulators. Using STAR and salmon, we remap and quantify RNA-seq libraries against the telomere-to-telomere hs1 reference for patient-derived lymphoblastoid cell lines (LCLs) and fibroblasts spanning diverse sex chromosome constitutions. We model gene expression as a function of cell-type-specific Xi and Y dosage effects in a single dream mixed model with donor random effects, enabling joint analysis of paired cell types and repeated donors. The reanalysis recovers the broad autosomal response to Xi and Y dosage reported previously, while identifying additional dosage-responsive genes. We then extend the framework to incorporate cell lines carrying structurally variant sex chromosomes, such as X and Y isochromosomes or X-Y translocations, for fine-mapping sex chromosome dosage response. Each rearrangement partitions the sex chromosomes into discrete segments, generating correlated patterns of segmental dosage. Bayesian sparse regression can assign posterior inclusion probabilities to these segments and can construct credible sets of candidate loci for each chromosome-responsive gene or expression program. This framework connects chromosome-wide dosage effects to specific sex-linked regulatory intervals.

*Leveraging naturally occurring human sex chromosome variation to map the sex-linked loci that shape the autosomal transcriptome*

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