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A single-cell atlas of transcribed cis-regulatory elements in the human genome

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Transcribed cis-regulatory elements (tCREs), including promoters and enhancers, are crucial for gene expression and cell identity. We created a tCRE atlas using single-cell 5'-RNA-seq from over 340,000 cells across 23 human tissues, capturing both gene and tCRE expression. This atlas, containing more than 175,000 tCREs, enhances functional cis-regulatory element annotations in the human genome and reveals patterns of gene regulation, including connections between broadly expressed promoters and cell type-specific distal tCREs. We demonstrate that tCREs are enriched for functional annotations compared to conventional accessibility methods. Using a novel tCRE module-based approach, we assessed trait heritability at single-cell resolution, uncovering nuanced trait-gene regulatory relationships across cell populations. This study bridges gene regulation and trait heritability, highlighting the potential of single-cell 5'-RNA-seq to elucidate the genetic foundations of complex traits and setting the stage for future research on genetic variations in diseases at the individual level.