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GEM-Finder: dissecting GWAS variants via long-range interacting cis-regulatory elements with differentiation-specific genes

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Interpreting the functional significance of non-coding GWAS variants remains challenging. While co-localizing variants with cell-type specific cis-regulatory elements (CREs) has improved our understanding, many variants remain unassociated due to the limited understanding of gene regulatory mechanisms. In this study, we propose GEM-Finder (Genomic Element Mapping for Fine Discovery of Promoter-Linked Variants), a novel analytical framework that integrates transcriptomic, epigenomic (H3K27ac ChIP-seq), and 3D chromatin interaction data to determine cell-type specific regulatory regions. GEM-Finder utilizes long-range chromatin interactions to identify CREs that are spatially adjacent to genes that are differentially expressed in specific cell types and stages. When we apply GEM-Finder to endothelial differentiation stages, unlike other conventional methods primarily focused on cell-type specific CREs, GEM-Finder identifies 7.6 times more disease/trait associations. Our enrichment analyses reveal both shared and unique links across 53 human diseases/traits, uncovering novel associations between endothelial differentiation and various human diseases/traits. These findings underscore the importance of incorporating long-range chromatin interactions for a more precise identification of disease-associated CREs and functional characterization of non-coding GWAS variants.