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Leveraging genetic effects in thyroid dysfunctions via cell type-specific network propagation

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Advances in omics technology have enabled the identification of various risk loci and genes for hundreds of complex human diseases for the past decades. Still, it is difficult to investigate systems- and single cell-level mechanisms for complex diseases in hardly accessible tissues, tissues where biopsies are not easily obtained (i.e. thyroid). Hyper- and hypothyroidism are the chronic syndromes with 40 - 60% of heritability, and spontaneously oscillating functions in some rare cases. Therefore, understanding their systematic mechanisms in single cell-level need to be elucidated to solve complex problems in clinical application. In order to account for these issues, we propose an integrative approach combining eQTL-based transcriptome-wide association study (TWAS) and network propagation with a permutation-adjusted network smoothing method. We conducted TWAS to generate credible initial scores for each gene, which represent the genetically stimulated gene expression changes. Initial scores were then adjusted for cell type-specific expressions and subsequently propagated over the co-expression networks for 8 cell types constructed based on the normal thyroid tissues. Here, we suggest an alternative approach for investigating genetically induced network-wise effects of the traits with scarcely accessible biopsies. We also applied this approach to investigate cell type-specific regulome-level landscape of thyroid dysfunctions and suggested potential key distinctive and shared regulomes for hyper- and hypothyroidism.