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Leveraging genetic effects in Grave's disease via cell type-specific network diffusion

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Graves' disease (GD) is the most common type of autoimmune thyroid disorder with a high contribution of genetic factors up to 80%. One of the characteristic clinical features of GD is the oscillating state of thyroid functions between hyper- and hypothyroidism. For decades, over a thousand genetic variants were reported as putative causal variants for GD, whereas their exact mechanisms in gene expression regulation or secondary effects in regulome-wide scale at each cell type in the human thyroid are still not fully revealed yet. 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 quantitative and directional 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 that were constructed for the eight cell types based on the normal thyroid tissues, re-prioritizing 189 genes. Our approach had replicated 27 gold-standard GD markers, exceeding the recently published network-based gene prioritization framework. We also validated our approach by utilizing publicly available dataset on 10X Visium platform, which is nearly single cell-level data on human thyroids. Total of 22 genes from 4 cell types showed concordant direction of gene expression changes with our network-based re-prioritization. We applied an identical framework to hyper- and hypothyroidism to identify shared or distinct regulome features with GD. By calculating the Spearman's correlation coefficients for each co-expression module, we found four and three shared and specific regulomes for GD, respectively. Here, we suggest an alternative approach for investigating genetically induced network-wise effects of the traits. Throughout this approach, we reprioritized 189 genes for GD and identified seven key regulomes that can explain the genetic basis of oscillating thyroid states in GD.