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Identifying pathogenic cell type of disease associated variants

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Disease associated SNPs are enriched in transcriptional enhancers and are hypothesized to contribute to disease through disruption of gene regulation. Here, we describe a novel approach to identify the 'pathogenic cell type', the cell type in which a given risk variant functionally contributes to disease pathology. For the study of traits with complex etiologies that involve multiple tissues and cell types, first delineating where risk variants act is an essential step for moving from disease association to new insights into disease pathology.

Our approach utilizes 3D chromatin structure to evaluate the multiple enhancers that physically interact to regulate a shared target gene. We identify "outside variants," SNPs in weak LD with GWAS risk SNPs that physically interact with the same target promoter and significantly modify clinical risk. We hypothesized that the chromatin state at outside variants could be used to identify the 'pathogenic cell type' of diease associated loci. As proof of principle, we applied this approach to multiple sclerosis. We generated cell type predictions for ~2/3 of MS risk loci including the anticipated enrichment of T-cell predictions. Excitingly, when we applied the approach to brain tissues, we identified 2 risk loci predicted to dysregulate genes involved in the same pathway in oligodendrocytes. We independently validated the association of this pathway with chemical genetics and MS patient tissue studies. Together, these results suggest that our approach could facilitate rapid delineation of the pathogenic effects of noncoding risk loci. We will present progress in the application of this approach to addiction.