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Leveraging cross-species transcription factor binding site patterns: From diabetes risk loci to disease mechanisms

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Genome-wide association studies have revealed numerous risk loci associated with diverse diseases. However, identification of disease-causing variants within association loci remains a major challenge. Divergence in gene expression due to cis-regulatory variants in noncoding regions is central to disease susceptibility. We show that integrative computational analysis of phylogenetic conservation with a complexity assessment of co-occurring transcription factor binding sites (TFBS) can identify cis-regulatory variants and elucidate their mechanistic role in disease. Analysis of established type 2 diabetes risk loci revealed a striking clustering of distinct homeobox TFBS. We identified the PRRX1 homeobox factor as a repressor of PPARG2 expression in adipose cells and demonstrate its adverse effect on lipid metabolism and systemic insulin sensitivity, dependent on the rs4684847 risk allele that triggers PRRX1 binding. Thus, cross-species conservation analysis at the level of co-occurring TFBS provides a valuable contribution to the translation of genetic association signals to disease-related molecular mechanisms.

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