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Enhancer-Promoter interactions in rat prefrontal cortex identified by Hi-C sequencing facilitate functional interpretation of genetic association studies on substance abuse traits

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The Hi-C assay is a chromatin conformation capture technique that reveals 3D genome architecture by measuring chromatin contact frequencies, thus uncovering the spatial organization of chromatin. These 3D structures are closely linked to the regulation of gene expression. Loop structures, in particular, can either facilitate or restrict interactions between regulatory elements, such as promoters or enhancers and their target genes - significantly affecting transcription. The Hybrid Rat Diversity Panel (HRDP) is a valuable tool designed for studies of complex traits and diseases, including substance abuse-related phenotypes. We conducted Hi-C sequencing on 10 selected strains from the HRDP and annotated a total of 58,992 loops. Additionally, we identified 5,767,921 CTCF motifs in the mRatBN7.2 reference genome, using FIMO (Find Individual Motif Occurrences). CTCF domains are believed to facilitate the formation of loops and promoter-enhancer interactions. We pinpointed 34,767 loops that had more than 18 CTCF motifs at each end. Utilizing these CTCF-bound loops, we located 122,615 non-coding SNPs within enhancer regions. Our data suggest that these non-coding SNPs potentially affect the function of distant genes by altering the binding of enhancers and consequently affect enhancer-promoter interactions, and the activity of RNA polymerase. The identification of associations between intergenic SNPs and genes in chromatin loops may improve the functional interpretation of SUD GWAS in rats.