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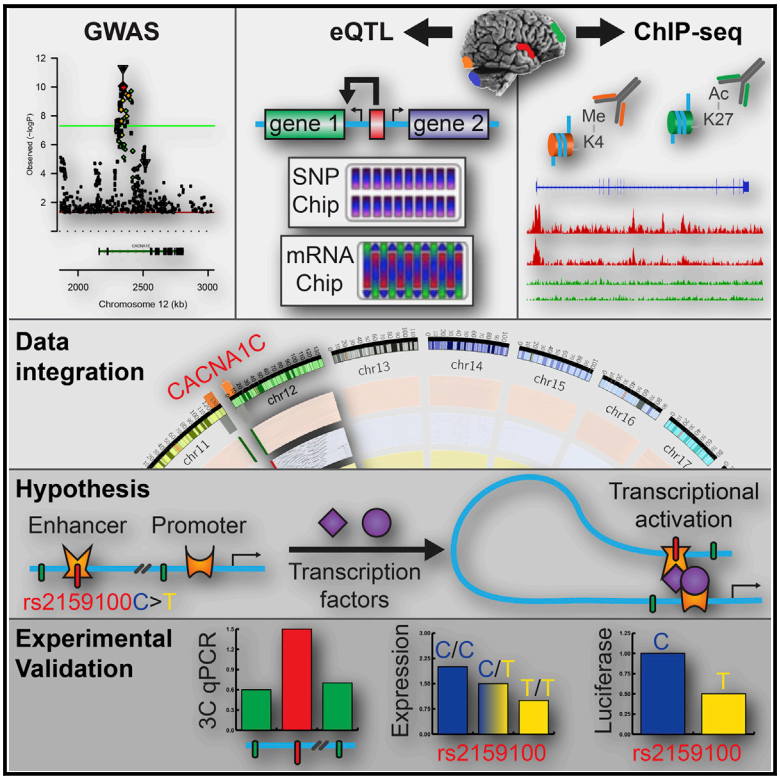
Cell Reports

A Role for Noncoding Variation in Schizophrenia

Graphical Abstract



Highlights

Schizophrenia SNPs are enriched for eQTLs and *cis*-regulatory elements

The enrichment is greater for enhancers in fetal and adult brain tissue

Schizophrenia risk SNPs participate in long-range promoter-enhancer interactions

CACNA1C variants are associated with transcriptional regulation in the brain

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In Brief

Roussos et al. find that schizophrenia risk variants are enriched for alleles that affect gene expression and lie within promoters or enhancers. For the L-type calcium channel (*CACNA1C*), the risk variant is associated with transcriptional regulation in the brain and is positioned within an enhancer sequence that physically interacts though chromosome loops with the promoter region of the gene.

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A Role for Noncoding Variation in Schizophrenia

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SUMMARY

A large portion of common variant loci associated with genetic risk for schizophrenia reside within noncoding sequence of unknown function. Here, we demonstrate promoter and enhancer enrichment in schizophrenia variants associated with expression quantitative trait loci (eQTL). The enrichment is greater when functional annotations derived from the human brain are used relative to peripheral tissues. Regulatory trait concordance analysis ranked genes within schizophrenia genome-wide significant loci for a potential functional role, based on colocalization of a risk SNP, eQTL, and regulatory element sequence. We identified potential physical interactions of noncontiguous proximal and distal regulatory elements. This was verified in prefrontal cortex and -induced pluripotent stem cell–derived neurons for the L-type calcium channel (*CACNA1C*) risk locus. Our findings point to a functional link between schizophrenia-associated noncoding SNPs and 3D genome architecture associated with chromosomal loopings and transcriptional regulation in the brain.

INTRODUCTION

A recent multistage genome-wide association study (GWAS) in schizophrenia (SCZ) identified 22 linkage disequilibrium (LD)-independent loci that reached genome-wide significance (Ripke et al., 2013). The majority of identified SNPs reside within noncoding regions of genes or in intergenic regions. Furthermore, the regions were frequently large and often contained multiple implicated SNPs due to local LD patterns. In order to be able to understand these associations mechanistically, it is important to develop strategies for honing in on regions and SNPs more likely to have functional effects. Thus, the elucidation of the function of noncoding disease-associated loci is an important next step toward the development of testable hypotheses regarding biological processes involved in the pathogenesis of SCZ.