Chromosome conformation elucidates regulatory relationships in developing human brain.

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Public Summary:
Three-dimensional physical interactions within chromosomes can turn genes on and off in a tissue-specific manner. However, the 3D organization of chromosomes during human brain development and its role in neurodevelopmental disorders, such as autism or schizophrenia, are unknown. We performed genome-wide association studies to find schizophrenia risk genes. we then used genome editing of these discovered risk genes in human neural stem cells. Through these studies we found a candidate gene that is now a schizophrenia risk gene. Targeting this gene with drugs or gene editing may help alleviate this disorder.

Scientific Abstract:
Three-dimensional physical interactions within chromosomes dynamically regulate gene expression in a tissue-specific manner. However, the 3D organization of chromosomes during human brain development and its role in regulating gene networks dysregulated in neurodevelopmental disorders, such as autism or schizophrenia, are unknown. Here we generate high-resolution 3D maps of chromatin contacts during human corticogenesis, permitting large-scale annotation of previously uncharacterized regulatory relationships relevant to the evolution of human cognition and disease. Our analyses identify hundreds of genes that physically interact with enhancers gained on the human lineage, many of which are under purifying selection and associated with human cognitive function. We integrate chromatin contacts with non-coding variants identified in schizophrenia genome-wide association studies (GWAS), highlighting multiple candidate schizophrenia risk genes and pathways, including transcription factors involved in neurogenesis, and cholinergic signalling molecules, several of which are supported by independent expression quantitative trait loci and gene expression analyses. Genome editing in human neural progenitors suggests that one of these distal schizophrenia GWAS loci regulates FOXG1 expression, supporting its potential role as a schizophrenia risk gene. This work provides a framework for understanding the effect of non-coding regulatory elements on human brain development and the evolution of cognition, and highlights novel mechanisms underlying neuropsychiatric disorders.