Cognitive analysis of schizophrenia risk genes: focus on genes with epigenetic function

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Abstract

Epigenetic processes are disrupted in many psychiatric illnesses and may account for the cognitive deficits observed in these disorders, making genes involved in epigenetic processes interesting candidates to study in the context of schizophrenia. The effect of risk single nucleotide polymorphisms (SNPs) in 5 candidate genes on cognition was examined using an Irish dataset of psychosis cases (n = 905; schizophrenia, bipolar disorder, major depressive disorder and non-specific psychosis) and controls (n = 330) who had completed tests in 5 main areas of cognition. An association between risk alleles and cognitive functions such as attention and social cognition were found for 4 of the 5 candidate genes supporting our hypothesis that schizophrenia risk genes with epigenetic functions contribute to cognitive deficits in schizophrenia.

1. Introduction

Schizophrenia is a chronic psychiatric disorder affecting approximately 1% of the Irish population. Symptoms range from delusional thoughts and hallucinations to lack of motivation and social withdrawal. Affected individuals also display significant cognitive deficits in areas such as IQ, memory, attention and language. Disrupted epigenetic processes are observed in both complex and single gene brain disorders and epigenetic processes have been recently studied as potential targets of pharmaceutical intervention for the treatment of cognitive impairment. Therefore genes with epigenetic functions represent good candidate genes to study cognitive deficits in schizophrenia. Genome wide association studies (GWAS) have identified 108 chromosomal regions associated with risk of schizophrenia, implicating up to 350 genes [1].

2. Aim

The aim of this study was to identify risk genes for schizophrenia that functioned in epigenetic processes and test these genes for association with cognitive deficits in schizophrenia.

3. Methods

Cross referencing 535 genes with epigenetic functions with the 350 genes from the GWAS study identified 5 candidate genes for analysis: RERE (transcriptional co-repressor, binds chromatin) SATB2 (mediates chromatin remodelling), EPC2 (chromatin regulator), EP300 (histone acetyltransferase) and KDM3B (lysine (K)-specific demethylase). The effect of risk SNPs in these genes on cognition was examined using an Irish dataset of psychosis cases (n = 905; schizophrenia, bipolar disorder, major depressive disorder and non-specific psychosis) and controls (n = 330) who had completed tests in 5 main areas of cognition including IQ, working memory, episodic memory, attention and social cognition. Regression analysis was carried out in SPSS using a linear based model.

4. Results

For RERE, there was association between the schizophrenia risk allele and attention ($p = 0.03$). For SATB2, there was association with social cognition ($p = 0.003$). For EPC2, an association was found with 2 measures of IQ, full scale ($P = 0.004$) and performance ($p = 0.001$). An association was found between the schizophrenia risk allele for KDM3B and verbal IQ ($P = 0.038$).

5. Discussion

Overall this study revealed a sub group of schizophrenia risk genes that have epigenetic functions. This initial analysis of these 5 genes has highlighted some interesting results and may provide support for our hypothesis that risk genes that have epigenetic functions contribute to cognitive deficits in schizophrenia. The p values above are uncorrected and require replication in an independent sample.

6. References

[1] Schizophrenia Working Group of the Psychiatric Genomics, C., *Biological insights from 108 schizophrenia-associated genetic loci.* Nature, 2014. **511**(7510): p. 421-7.