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In silico analysis of mobile elements-derived sequences in schizophrenia-related genes

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Background

Regulation of Transposable Elements (TEs) expression has already been associated with complex human diseases, in particular cancer [1]. Also, complex diseases cannot be explained only by genetic factors and are likely to be the result of gene-environment interactions with the contribution of TEs. The detection of retroviral transcripts in the brains of schizophrenics suggests that activation or upregulation of distinct human endogenous retroviruses (HERVs) may play a role in the etiopatho-genesis of neuropsychiatric diseases [2], with increasing complications if we consider that TE insertions generate somatic mosaicism in neuronal cells [3]. In addition, mobile elements have been heavily involved in tissue-specific promoter activity [4] that makes them good candidates for brain specific activation of genes related to schizophrenia. Eventually, TEs are thought to be important in regulation of methylation and DNA accessibility to transcription factors [5]. They are also an important source of small RNAs, which usually act to silence TEs [6]; a particular family of small RNAs, miRNAs, has already been shown to alter neural receptors' function [7].

Main aims of the study

Our aim is to investigate the functional relationship between TE-related sequences and genes identified as "best" candidates from genome wide association studies (GWAS) in psychiatric disorders, reconstructing their regulatory network with computational methods, and eventually validating them with exon-expression array. The same will be done independently with TE-related transcriptional start sites.

All this - together with methylation pattern analyses and target sequencing (without repeat masking) that we are planning - could be the start of a novel way of looking at the molecular bases of schizophrenia.

We found preliminary evidence of alternative regulation of tissue-specific gene expression in schizophrenic patients vs controls from genes that we identified as associated to schizophrenia from our GWAS and we present results for both tissue specific expression and alternative TSS in pivotal disease-related genes.

Conclusion

This *in silico* work is meant to predict and better understand the relationship between TEs and complex disease, paving the way for future experiments that will hopefully confirm and expand current knowledge of what was previously considered just "junk" DNA. This will allow us and others to extract many more data from GWAS by considering also results in previously discarded areas, and we also hope to give a general contribution to the understanding of genome regulation.

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