Molecular mechanisms of schizophrenia

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Background
Schizophrenia (SZ) is a severe psychiatric disorder, defined by psychotic symptoms, delusions, hallucinations, and altered cognitive functioning.

Despite the considerable research efforts that have been made in the field in the last two decades, we are still unable to fully understand the mechanisms implicated in SZ. Several genome-wide association studies on SZ have reported a few different susceptibility genetic variants for SZ. Although SZ heritability is estimated to be ~70%, it is likely that non-genetic factors also play a role in SZ aetiology.

We are currently interrogating genome-wide patterns of DNA methylation, gene expression and microRNA expression in post-mortem brain samples from SZ patients and controls, using tissue from multiple regions of the brain (prefrontal cortex, cerebellum, striatum and hippocampus).

Gene expression & miRNA expression
The transcription from DNA to RNA is influenced and regulated by different factors, including DNA methylation. We have recently suggested that epigenetic processes directly influencing transcription are likely to play a role in SZ.

Dysregulated expression of several genes has been associated with SZ, however the consequences of these abnormalities are still poorly understood.

METHOD: We will use RNA-sequencing to interrogate genome-wide gene expression abnormalities in SZ, using post-mortem brain samples from SZ patients and controls.

miRNAs are small non-coding RNA molecules that have transcriptional and post-transcriptional gene expression regulation functions. Several miRNAs have been reported to be dysregulated in SZ.

METHOD: We will use qPCR to quantify the expression of several biologically relevant miRNAs in post-mortem brain samples from SZ patients and control.

Samples
Post-mortem brain samples from SZ patients and controls collected from three different brain banks.

105 individuals:
- 49 schizophrenia
- 56 controls

Four brain regions:
- 49 prefrontal cortex
- 52 cerebellum
- 44 hippocampus
- 103 striatum

DNA methylation
DNA methylation is an epigenetic process that involves the addition of a methyl group to the 5th carbon of a cytosine nucleotide.

DNA methylation plays a role in several cellular processes, including regulation of gene expression.

Dysregulation of epigenetic processes is known to be associated with several diseases, such as cancer. DNA methylation dysregulation as been suggested to play a role in several psychiatric disorders, including SZ.

METHOD: We used microarray Illumina technology to interrogate genome-wide DNA methylation status in post-mortem brain samples. We have already identified several DNA methylation changes associated with SZ.

Preliminary results
DNA methylation

Conclusions
The results to date show DNA methylation differences associated with SZ

We hope that our integrative molecular analysis will provide a profile of epigenomic and transcriptomic features of SZ and consequently help to:

- Understand the interplay between the different molecular mechanisms implicated in SZ
- Understand the roles of the different brain regions in SZ aetiology
- Identify new therapeutic targets for SZ

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