An Investigation of Gene Expression Changes in Schizophrenia: RNA-Seq Analysis of Whole-Blood Samples Pre- And Post-Stress Test

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INTRODUCTION

- Schizophrenia (SZ) is a highly heritable disorder with complex genetic and environmental influences, yet its underlying biological mechanisms are not fully understood.[1]
- Previous genome-wide association studies (GWAS) have identified hundreds of genomic loci associated with SZ at genes involved in neuronal function.[2]
- Stress plays a critical role in SZ onset and exacerbation of symptoms.[3]

However,

- Individual loci have small effects and multi-omic approaches are needed to tease apart to underlying pathophysiology.
- Blood-based RNA-seq studies provide a non-invasive way to detect gene expression changes, making them valuable for identifying biomarkers and pathways associated with SZ and its response to stress.

AIMS & OBJECTIVES

☑**Identify differentially expressed genes (DEGs) in SZ patients compared to healthy controls and identify stress-induced DEGs.**

By,

- Performing differential expression analysis (DEA) between healthy controls and SZ patients.
- Performing DEA for changes pre- and post-stress exposure.
- Exploring interaction effects between SZ status and stress response.

MATERIALS & METHODS

Samples were recruited for the Immune Response & Social Cognition in Schizophrenia (iRELATE) study that investigated the role of the immune system in SZ biology

What is involved in the study?

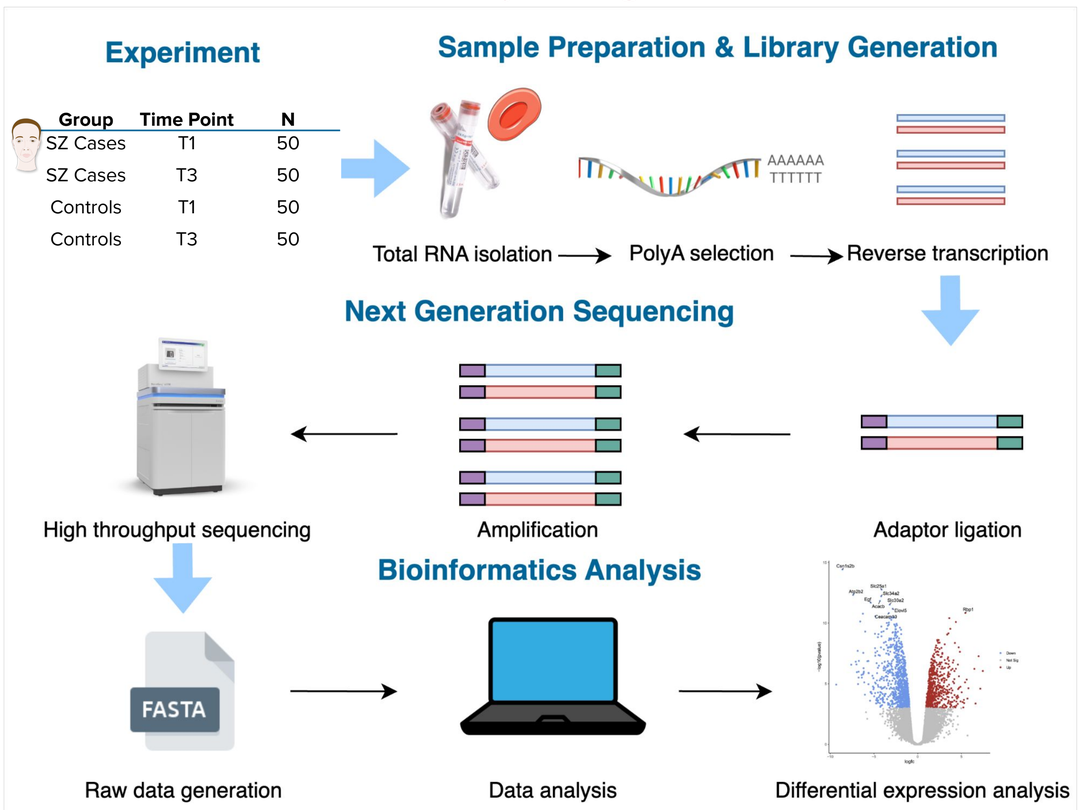
➔ Tasks to assess memory, concentration, emotion and early childhood experiences
➔ Trier stress test
➔ Blood samples to assess immune function and for genetic analysis
➔ Blood samples collected at two time points (T1 and T3) either side of stress test and used for RNA-Seq analysis

COVARIATES

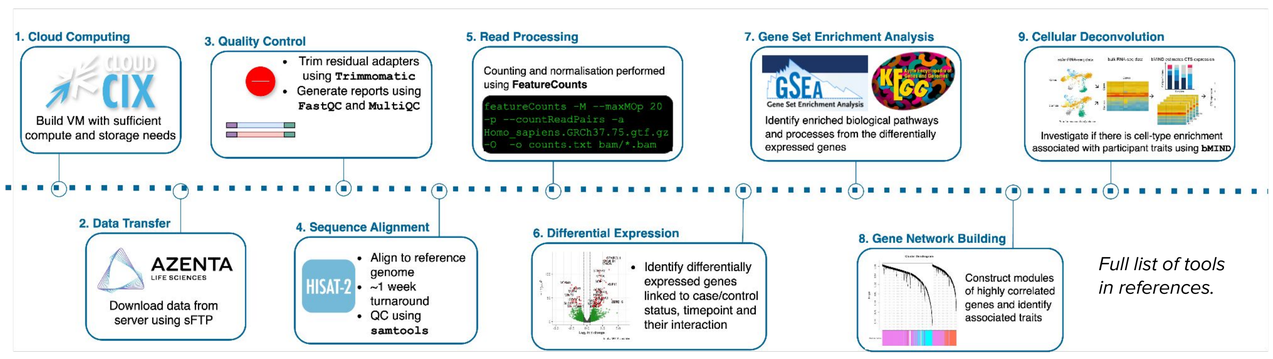
Age
Sex
BMI
Olanzapine
Tobacco usage
SZ status
Time-point

Covariates were adjusted for to account for potential confounding factors that can bias the results

Study Design



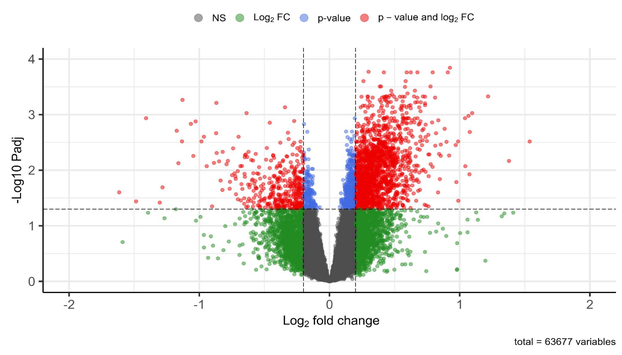
Bioinformatics Workflow



RNA-Seq analysis workflow included exploratory analysis such as differential expression, gene-set enrichment and cellular deconvolution.

RESULTS

1 DEGs linked to SZ status & stress test response



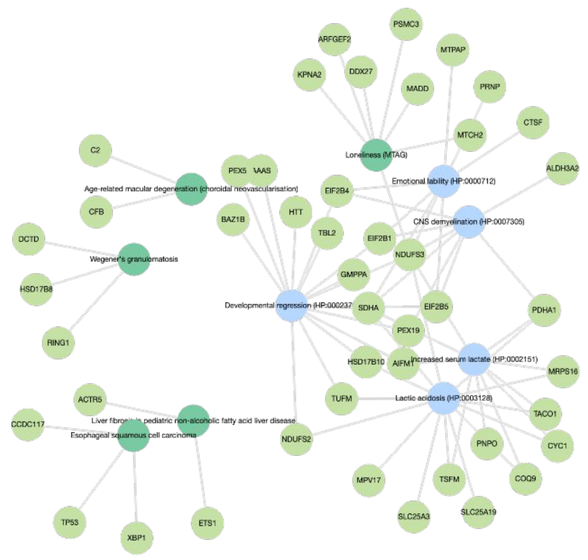
- **2545 DEGs (padj<0.05) detected for SZ status (Fig 1).**
- **770 DEGs (padj<0.05) detected in response to stress (top gene detailed in Table 1).**

Fig. 1: Volcano plots displaying DEGs linked to SZ status. Significant DEGs (Padj < 0.05) are highlighted in red and genes with Log_2 Fold Change (LFC) > 0.2 are highlighted in green. Blue indicates genes with Padj < 0.05 & LFC < 0.2.

Table 1: Top differentially expressed gene (DEG) associated with stress-related expression changes

GENE	BASE MEAN	log_2FC	lfcSE	Padj	DESCRIPTION
STIP1	283.2	-0.24	0.04	$4.47x10^{-5}$	Co-chaperone for heatshock proteins

2 Network construction



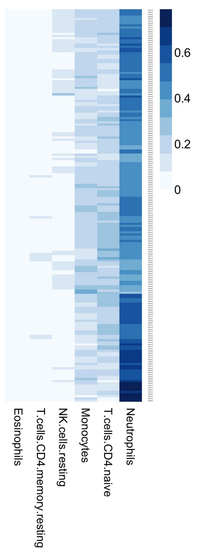
Top enriched pathways following gene-set enrichment analysis of 'floralwhite' gene network, constructed using WGCNA.

- **One constructed module has enriched expression linked to both SZ patients and stress response and is involved in CNS myelination.**

3 Pathway analysis

- **Enrichment for key pathways associated with neuronal and immune function.**

4 Cellular deconvolution



- **Used to impute gene expression profiles from single cell reference data.**
- **Significant proportional difference detected between cases and controls for T-cells CD4 naive.**

CONCLUSION & IMPLICATIONS

- Many DEGs identified for condition & time-point, no evidence for interaction.
- Top DEG for timepoint, *STIP1*, has functions related to stress.
- Pathway analysis revealed immune pathways associated with condition, timepoint and newly constructed gene modules.
- Cellular deconvolution showed significant enrichment in T-cells CD4 naive

The results highlight the value of blood-based RNA-Seq analysis for understand the underlying biological mechanism of brain-based disorders

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REFERENCES