FINDINGS FROM WHOLE GENOME AND RNA SEQUENCING IN THE FIRST 10 PARTICIPANTS

Research Objectives: To identify candidate genetic drivers of highly treatment-resistant psychosis using whole genome and RNA sequencing and intensive genotype-phenotype correlation.

Methods: Genomic DNA (gDNA) and whole blood RNA from 32 deeply phenotyped participants with treatment-resistant psychosis was sequenced at BC's Genome Sciences Centre. Variants were filtered and prioritized using a custom pipeline developed at the Michael Smith Laboratories (UBC). After QC, variants were prioritized by pathogenicity prediction, allele frequency and conservation, then reviewed in the IGV in association with RNA-seq data, and manually curated using databases (e.g. SCHEMA, Varsome, SZGR2, OMIM, UniProt) and literature review. CNVs and small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically small deletions were called from linked-read WGS sequencing data. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances.

Results: Extensive variant annotation and review has been completed for the first 10 participants. Participants harbored between 12 and 42 prioritized sequence variants (mean ~19.5). 15 loss-of-function (LoF) mutations impacted genes including SETDIA (the schizophrenia risk gene most significantly enriched in LoF variants to date), the neurodevelopmental risk gene FOXP1, and ATP7B (heterozygous; biallelic ATP7B mutations cause Wilson's disease). Protein-altering variants were found in many mutation-intolerant genes relevant to the neurobiology of schizophrenia, including MDGA1, GGA1, GRK2, and NCDN.

Conclusion: While individually rare, as a class, potent single gene mutations may not be uncommon in treatment-resistant psychosis, and can potentially identify precision medicine treatment targets for further study.