Robert Stowe MD, FRCPC, UCNS1,2, Guillame Poirier-Morency, BSc2,3, Sanja Rogic, PhD1,4, Adrienne Elbert, MD, PhD5; Kennedy Borle, MS5,6, CGC7; Ashley DeGraaf, MS6, CGC, CGC5, Predam Lahghei, BSc6, Jessica Jun, BSc6; Michelle Lisenek, BSc1; Natasha Verzosa; Olga Leonova, MD; Clara Westwell-Roper, MD, PhD; Clare Beasley, PhD1;9, Mahesh Menon, PhD1, Ivan Torres, PhD1; Jennifer Li, MD, PhD1; Harish Neelekanth, MD1; Veereel Willems, MD, MPH, FRCP5; Randall White, MD, FRCP5; Eric Wong, PhD; Joerg Gosner, PhD5,7, Andrew J. Mungall, PhD9; Monica Hrynchak, MD, FRCP5, FCCM5, Agata Minor, PhD, DABMMG5; Christine Tyson, PhD, FCCM5; Patrick Sullivan, MD1,12, Paul Pavlidis, PhD1,3,4.

1Department of Psychiatry, University of British Columbia (UBC); 2Department of Neurology, UBC; 3Centre for Brain Health, UBC. 4Michael Smith Labs, UBC. 5Residency Training Program, Department of Medical Genetics, UBC. 6MD Undergraduate Program, UBC. 7Department of Biochemistry and Molecular Biology, UBC. 8Canada’s Michael Smith Genome Sciences Centre, BC Cancer. 9Molecular Cytogenetics Laboratory, Royal Columbia Hospital. 10Department of Pathology and Laboratory Medicine, UBC 11Center for Psychiatric Genomics and Department of Genetics, Psychiatry, and Epidemiology, University of North Carolina. 12Karolinska Institutet, Stockholm.

**Metabolic and Genetic Explorations in Refractory Schizophrenia Project:** Findings from whole genome and RNA sequencing in the first 10 participants

**Background**
- The UBC MAGERS (Metabolic Explorations in Refractory Schizophrenia) Study is an intensive, multi-institutional project that integrates research and clinical care conducted with participants highly treatment-resistant schizophrenia (SCZ) or schizoaffective disorder (SAD). Hospitalized in the tertiary provincial BC Psychosis Program Unit at UBC Hospital.

**Objective:** The project aimed to identify genomic risk factors for schizophrenia by employing comprehensive genomic and proteomic profiling.

**Methods:**
- **Genomic Profiling:** Whole genome DNA and RNA sequencing (RNA-Seq) were performed on 4 samples per case.
- **Proteomic Profiling:** Additional prediction of house tools, including LIST-S2 and IDRBind.
- **Bioinformatics:** Variants were called using DGV, DGV Gold and gnomAD population frequencies, as well as GLA. Variants were visually curated as pathogenic or likely pathogenic.
- **Phenotyping:** The cohort was enriched for individuals with "extreme phenotypes" of psychosis, likely to be susceptible to ultra-rare and potent genomic risk factors in SCZ.

**Results:**
- In these 10 participants, we identified 195 moderate-high impact DNA sequence variants (mean 19.5, range 12-42). 3 cases harbored LoF (predicted loss-of-function) mutations (1 each) relevant to their neuropsychiatric phenotypes. There were 5 (2.6%) in-frame insertions/deletions. 177 (90.8%) were called as Novel.
- **Clinical Overview and Notable Variants:**
  - **PI:** P11 FOXP1
  - **PI:** P11 CNOT1
  - **PI:** P4 M, Sex, Diagnoses

**Conclusions:**
- Our preliminary results provide encouraging support for the hypothesis that patients with severe psychosis (mean admission and discharge PANSS scores of 90.3 and 69.2, respectively) are a good place to look for ultra-rare genomic risk factors in SCZ.
- Consistent with the literature, we found SDC2-associated ultra-rare variants (URVs) impacting pleiotropic ("broad-spectrum") NDD risk genes such as SETD1A, and conferring substantial risk for metabolic and cognitive phenotypes.

**References:**

**Acknowledgement and Declaration Statement:**

**Methods:**
- **RNA-Seq:** RNA-Seq was performed on 4 samples per case.
- **Gene Expression:** Gene expression, RNA and DNA analysis was performed in UBC's Michael Smith Labs (MSL). In the Pathlab's db (GPM, SR, PF), linked, bar-coded GDNAs were aligned to the reference hg19 using 10Genomics' Long Ranger pipeline. Single nucleotide variants (SNVs) and indels were called with GATK, GATK-Friend, and annovar with the Ensemble database.

**Table 1. Clinical overview and notable variants**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Genome</th>
<th>RNA-Seq</th>
<th>Clinical Features</th>
<th>Notable Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>51</td>
<td>5</td>
<td>Male with SCZ</td>
<td>P11 FOXP1</td>
</tr>
<tr>
<td>P2</td>
<td>51</td>
<td>5</td>
<td>Male with SCZ</td>
<td>P11 CNOT1</td>
</tr>
<tr>
<td>P3</td>
<td>51</td>
<td>5</td>
<td>Male with SCZ</td>
<td>P4 M, Sex, Diagnoses</td>
</tr>
</tbody>
</table>

**Table 2. Summary of mutations highlighted in next panel**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Mutation</th>
<th>Gene</th>
<th>Protein</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>P11 FOXP1</td>
<td>FOXP1</td>
<td>Unknown</td>
<td>Inferred</td>
</tr>
<tr>
<td>P2</td>
<td>P11 CNOT1</td>
<td>CNOT1</td>
<td>Unknown</td>
<td>Inferred</td>
</tr>
<tr>
<td>P3</td>
<td>P4 M</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Inferred</td>
</tr>
</tbody>
</table>

**Case examples:**
- **MOSCA1 Participant P1** had aggression and conduct disorder in childhood; and onset of psychosis by 17 years of age, later characterized by re-emergence of psychosis and high levels of agitation and acyclicity. His clinical presentations included hyper-refractory delusions, hallucinations, and autonomic dysregulation. His psychotic symptoms were refractory to numerous antipsychotics, including clozapine with augmentation by aripiprazole, olanzapine, sulpiride, ECT, SSRIs, and lamotrigine. He has a rare VS in 22q11.2 that is predicted to be pathogenic. This is consistent with the observation that this cohort is enriched for "extreme phenotypes" of psychosis, likely to be susceptible to ultra-rare and potent genomic risk factors in SCZ. In the SCA20 exome meta-analysis, with an odds ratio for IoF variants of 20.5 (6.88-108).
- **SETD1A Participant P6** with childhood-onset schizophrenia has a pathogenic mutation in SETD1A, the first gene in which LoF (loss-of-function) mutations were enriched in SCZ cohorts at a genome-wide significance level. SETD1A remains the most significant (p<2.00 x 10^-7) risk gene in the SCHEMA S2 exon meta-analysis, with an odds ratio for IoF variants of 20.5 (6.88-108).
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