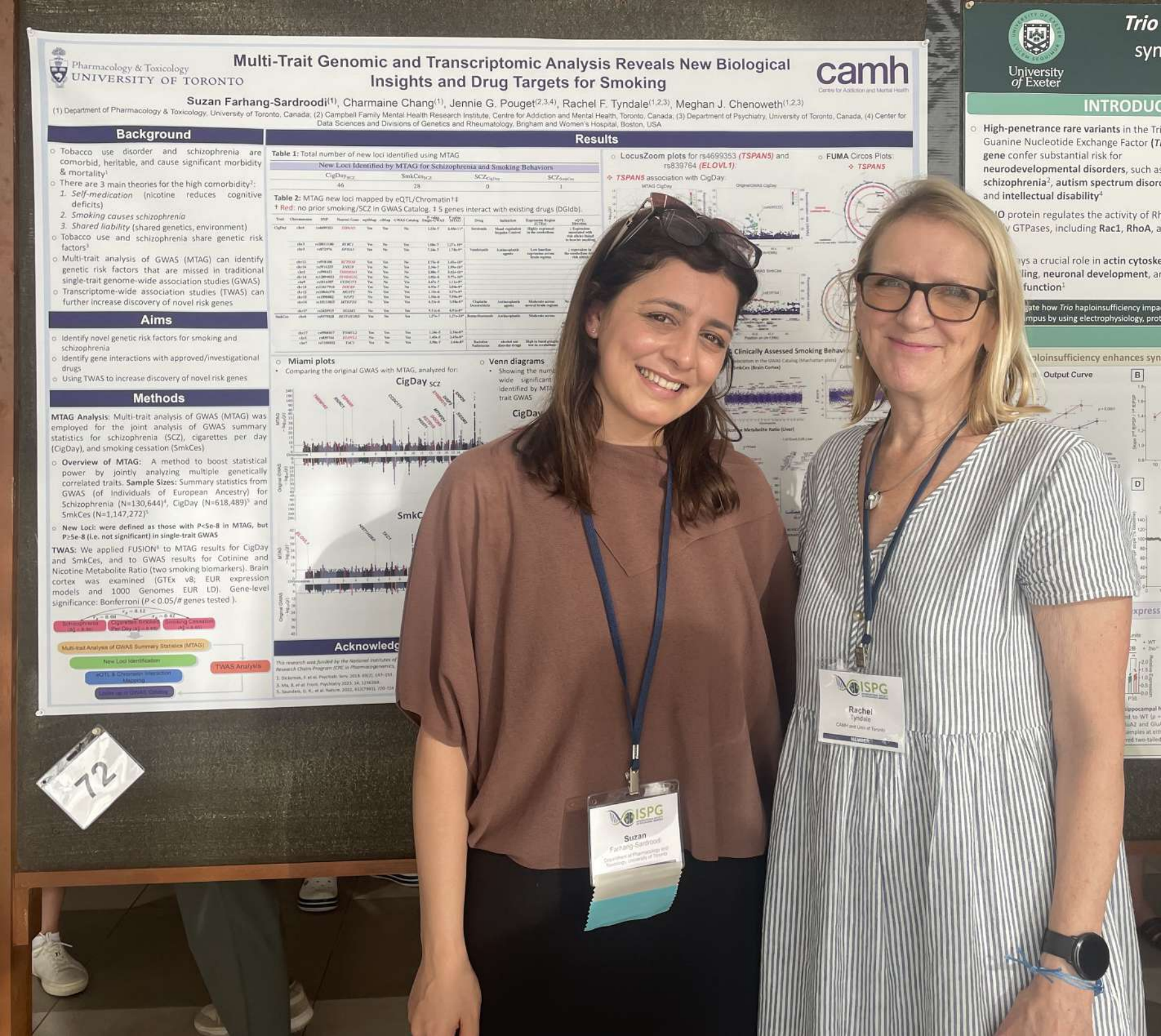
Pharmacology & Toxicology
UNIVERSITY OF TORONTO
Multi-Trait Genomic and Transcriptomic Analysis Reveals New Biological Insights and Drug Targets for Smoking
camh
Centre for Addiction and Mental Health
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Background
Tobacco use disorder and schizophrenia are comorbid, heritable, and cause significant morbidity & mortality[1]
There are 3 main theories for the high comorbidity[2]:
1. Self-medication (nicotine reduces cognitive deficits)
2. Smoking causes schizophrenia
3. Shared liability (shared genetics, environment)
Tobacco use and schizophrenia share genetic risk factors[3]
Multi-trait analysis of GWAS (MTAG) can identify genetic risk factors that are missed in traditional single-trait genome-wide association studies (GWAS)
Transcriptome-wide association studies (TWAS) can further increase discovery of novel risk genes
Aims
Identify novel genetic risk factors for smoking and schizophrenia
Identify gene interactions with approved/investigational drugs
Using TWAS to increase discovery of novel risk genes
Methods
MTAG Analysis: Multi-trait analysis of GWAS (MTAG) was employed for the joint analysis of GWAS summary statistics for schizophrenia (SCZ), cigarettes per day (CigDay), and smoking cessation (SmkCes)
Overview of MTAG: A method to boost statistical power by jointly analyzing multiple genetically correlated traits. Sample Sizes: Summary statistics from GWAS (of individuals of European Ancestry) for Schizophrenia (N=130,644)[4], CigDay (N=618,489)[5] and SmkCes (N=1,147,272)[5]
New Loci were defined as those with P<5e-8 in MTAG, but P≥5e-8 (i.e. not significant) in single-trait GWAS
TWAS: We applied FUSION[6] to MTAG results for CigDay and SmkCes, and to GWAS results for Cotinine and Nicotine Metabolite Ratio (two smoking biomarkers). Brain cortex was examined (GTEx v8; EUR expression models and 1000 Genomes EUR LD). Gene-level significance: Bonferroni (P < 0.05/# genes tested).
Multi-trait Analysis of GWAS Summary Statistics (MTAG)
New Loci Identification
eQTL & Chromatin Interaction Mapping
Look up in GWAS Catalog
TWAS Analysis
Results
Table 1: Total number of new loci identified using MTAG
New Loci Identified by MTAG for Schizophrenia and Smoking Behaviors
CigDay_SCZ 46
SmkCes_SCZ 28
SCZ_CigDay 0
SCZ_SmkCes 1
Table 2: MTAG new loci mapped by eQTL/Chromatin†‡
† Red: no prior smoking/SCZ in GWAS Catalog. ‡ 5 genes interact with existing drugs (DGIdb).
LocusZoom plots for rs4699353 (TSPAN5) and rs839764 (ELOVL1)
TSPAN5 association with CigDay
FUMA Circos Plots
TSPAN5
Clinically Assessed Smoking Behavi
Miami plots
Comparing the original GWAS with MTAG, analyzed for:
CigDay SCZ
SmkC
Venn diagrams
Showing the numb
wide significant
identified by MTA
trait GWAS
CigDa
Acknowledg
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INTRODUC
High-penetrance rare variants in the Tri
Guanine Nucleotide Exchange Factor (T
gene confer substantial risk for
neurodevelopmental disorders, such as
schizophrenia[2], autism spectrum disord
and intellectual disability[4]
O protein regulates the activity of Rh
GTPases, including Rac1, RhoA, a
ys a crucial role in actin cytoske
ling, neuronal development, a
function[1]
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