S75
INTEGRATED ANALYSIS OF SNP, CNV AND DNA METHYLATION IN CHINESE SCHIZOPHRENIA TRIO FAMILIES

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Background: Schizophrenia (SZ) is a severe mental disorder affects approximately 1% of population worldwide. Strong evidences suggested SNP, CNV and DNA methylation contributed to schizophrenia pathophysiology, but most studies are based on case-control populations or conducted in European-ancestry populations. To reveal the combined role of SNP, CNV and DNA methylation in schizophrenia pathology, we performed an integrated analysis of them in Chinese schizophrenia trio families.
Methods: We performed exome sequencing, genome-wide analysis of copy number variation and DNA methylation in 100 Chinese family trios composed of a SZ affected offspring and the parents. Agilent 1×1M SurePrint G3 Human CGH Microarray and 1×244K Human Methylation Microarray were used. We performed TDT-like analysis on SNP, CNV and DNA methylation separately and machine learning method for an integrated analysis.
Results: We identified 26 exonic or splice-site single nucleotide polymorphisms (SNPs) on 18 genes with nominal significance ($P < 5 \times 10\text{-}4$) using a transmission disequilibrium test (TDT) in all the families. We identified several CNV loci with SZ susceptibility previously reported, and also identify eight novel loci conferring risk of SZ. We found DNA methylation loci with high risk might involve with functions of neuron. Integrated analysis revealed that prediction of disease status could be more effective by combined 3 factors than by 1 or 2 factors.
Discussion: We identified a list of putative candidate loci for SCZ using family-based approaches. We present a novel family-based model to combine SNP, CNV and DNA methylation to analyze their roles in the etiology of SZ. Our results give new insights into how the combination may be involved in the pathogenesis of SZ.

Disclosure: Nothing to disclose.

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GENETIC VARIATION OF THE ENDOCANNABINOIDS SYSTEM AND RISK OF FIRST EPISODE PSYCHOSIS

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Background: The endocannabinoid (eCB) system is a neuroregulatory lipid-signalling pathway involved in neurodevelopment and response to endogenous and exogenous danger signals. A consistent body of evidence suggests that disruptions in this system are implicated in the pathogenesis of Schizophrenia (SZ). Moreover, the most recent Psychiatric Genomic Consortium (PGC) GWAS on Bipolar Disorder (BD) revealed enrichment in the eCB pathway. Given that SZ and BD share part of their polygenic architecture, it is plausible to hypothesise that, to some extent risk variants within the eCB system may account for part of SZ and BD genetic overlap, increasing transdiagnostically the vulnerability of experiencing psychotic symptoms.

In this study, we sought to examine the eCB genetic variation in a First Episode Psychosis (FEP)-control sample, and the clinical predictive utility of an individual 'eCB Risk Score' (eCB-RS) based on combined SZ and BD external summary statistics. Regardless of diagnostic categories, we expected that the common variant liability to dysfunctions in the endocannabinoid signalling was associated with an increased risk of developing FEP.
Methods: FEP patients and population controls were recruited as part of the multinational EU-GEI study and genotyped using an Illumina HumanCoreExome-24 BeadChip array covering 570,038 genetic variants.

In plink, we generated the binary files containing the SNPs within the eCB gene-set, based on the Kyoto Encyclopaedia of Genes and Genomes database. In PRSice, we built the eCB-RS, by weighting individuals' eCB risk variants in our dataset by the log odds ratio from the most recent PGC combined GWAS on SZ and BD.

We estimated a logistic regression model to test the effect of eCB-RS on the case status, after covarying for sex, age, study site, and 20 principal components for population stratification. We chose the risk alleles P-value threshold that maximised the variance in FEP-control status, further controlling our findings for multiple testing by randomly resampling the case-control phenotype over 10,000 permutations and repeating the PRSice procedure to obtain an empirical distribution for the P-value.

Finally, we ran sensitivity analysis adding as a covariate in the logistic model the full SZ-BD Polygenic Risk Score, based on all the genes but excluding the eCB gene-set (no-eCB-RS).
Results: We examined data from 679 FEP patients and 1,041 population controls from six different countries, after excluding individuals of homogenous black ancestry.

One-thousand common variants within the eCB gene-set were retained for eCB-RS calculation after clumping.

Logistic regression showed a positive association between eCB-RS and the case status (P-value $= 9.7 \times 10\text{-}8$; empiric P-value $= 9.9 \times 10\text{-}5$) at the SNPs P-threshold of 0.006, which explained 2% of the phenotypic variance (Nagelkerke's R-squared $= 0.02$).

Sensitivity analysis confirmed that eCB-RS was strongly associated with the case status even adjusting the analysis for no-eCB-RS.
Discussion: We report substantial genetic variation of the eCB system between people suffering from psychosis and population controls. Our findings support the hypothesis

that this system is implicated in the pathogenesis of psychotic disorders.

Disclosure: Nothing to disclose.

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S77
SELF REPORTED PARENTAL AND GRANDPARENTAL RELATEDNESS IN A CASE CONTROL SAMPLE OF SCHIZOPHRENIA FROM PAKISTAN

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Background: Genetic studies of schizophrenia including genome wide association studies and sequencing studies are currently based on the populations with primarily European ancestry. Recently, the scientific community has become cognizant of the value of diversity of populations for genetic studies of schizophrenia. We have undertaken a project (GEN-SCRIP; Genetics of Schizophrenia in Pakistan) to ascertain, diagnose and collect DNA from 20,000 individuals with, and without, schizophrenia of South Asian ethnicity, in Pakistan. Pakistan, along with some other countries of the Middle East has a tradition of consanguineous marriages. This provides opportunity for study of repressively inherited variants, in addition to addition of a new ethnic group to the world-wide GWAS efforts.
Methods: Since beginning sample collection in August 2018, we have ascertained, diagnosed and collected blood/saliva for DNA from over 5,000 participants. We have now been consistently collecting over 100 cases of schizophrenia a week. To collect on this scale, we have established ~20 collection centers across the country and trained 35 interviewers. Typically, patients are referred to the study by their treating clinicians, after a clinical diagnosis. Our trained interviewers acquire consent and perform a phenotypic assessment, collecting demographic information and detailed clinical information using the Diagnostic Interview for Psychosis and Affective Disorders (Di-PAD). Differences between groups were tested using ANOVA and to compare different variables between cases and controls we performed logistic regression.
Results: As of June 24th, 2019, we have collected 2,024 cases of schizophrenia and 3,428 controls (~495 samples/month). Eighty-three percent of our participants are males. The mean age of cases is 33.42 (SD± 10.02) and mean age of controls is 26.05 (SD± 6.86) ($p = 1024 < 2e\text{-}16$). After controlling for this age difference, the mean age of the subject's parents is greater for cases than controls ($p < 0.001$).

Some self-reported physical health issues are higher in cases, compared with controls, when controlled for age and gender. However, there is no difference in body mass index between the cases and controls. Forty percent of the cases report symptoms of depression. Controls are screened to remove those with personal or family history of symptoms of depression, which removes approximately 10% of potential controls. When we examined the effect of self-reported consanguinity, we found it to be higher in cases (61.3%), as compared to controls (40.2%; $p = 7.54e\text{-}10$).
Discussion: We have established a large network of collaborating collection sites in Pakistan for the study of psychiatric genetics. In our first study (GEN-SCRIP), we are collecting almost 500 samples a month to contribute the global effort led by the PGC to discover genetic loci for schizophrenia. This initial analysis of the clinical data already suggests that consanguinity is an independent risk factor for the development of schizophrenia, in the Pakistani population. We will see if this observation remains significant, as we increase the size of the sample, and more importantly, if increased runs of homozygosity (ROH) are associated with case status and earlier age of onset. In the future, we hope to extend the GEN-SCRIP project to other psychiatric disorders, such as Bipolar Disorder, Schizoaffective Disorder, Major Depression, Autism and OCD.

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SCHIZOPHRENIA GWAS OF YORUBAS IN SOUTHWESTERN NIGERIA

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Background: In the past decade, genome wide association studies (GWAS) have yielded an upsurge in discovery of genetic variants associated with schizophrenia, which promises to revolutionise our understanding of the illness and our therapeutic arsenal. It has become increasingly recognised that while Africa is a rich source of genetic diversity, there has hitherto been a paucity of studies of genome wide association studies for schizophrenia. This study therefore aimed to make a preliminary assessment of common variants in a population of Yoruba ancestry.
Methods: The study was conducted at the Neuropsychiatric Hospital, Aro Abeokuta, Nigeria. 200 Patients with a diagnosis of schizophrenia were enlisted as well as 200 healthy control subjects. All participants filled a sociodemographic questionnaire while patients were also interviewed with the Positive and Negative Syndromes Scale (PANSS). Standard Oragene saliva kits were used to obtain samples for DNA extraction. Genotyping was done on Infinium™ Global Screen-