M50. POLYGENIC BURDEN ANALYSIS OF LONGITUDINAL CLUSTERS OF PSYCHOPATHOLOGICAL FEATURES IN A CROSS-DIAGNOSTIC GROUP OF INDIVIDUALS WITH SEVERE MENTAL ILLNESS

Eva Schulte1, Ivan Kondofersky2, Monika Budde3, Kristina Adorjan4, Fanny Aldinger5, Heike Anderson-Schmidt5, Till F. M. Andlauer5, Katrin Gade5, Urs Heilbronner3, Janos Kalman3, Sergi Papiol3, Fabian J. Theis2, Peter Falkai8, Nikola Müller9, Thomas G. Schultze10

1Psychiatrische Klinik des Klinikums der Ludwig-Maximilians Universität München, Munich, Germany, 2Institute of Computational Biology, Helmholtz Zentrum Munich, Germany, 3Institute of Psychiatric Phenomics and Genomics, Medical Center of the University of Munich, 4Department of Psychiatry and Psychotherapy, 5University Medical Centre Goettingen, 6Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry Munich, 7LMU Munich, Dep. of Psychiatry, 8Molecular and Behavioral Neurobiology, Department of Psychiatry, Ludwig Maximillians University, Munich, Germany, 9Regulatory Networks, Institute of Computational Biology, Helmholtz Zentrum München, 10Institute of Psychiatric Phenomics and Genomics, Ludwig-Maximilians-University Munich, Germany; Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany

Background Bipolar disorder (BD), schizophrenia (SZ) and schizoaffective disorder (SZA) can be disabling disorders associated with severe psychiatric symptomatology. Individual psychopathological features often overlap between these diagnostic groups and their severity can vary widely. More severe psychopathological features are generally associated with a less favorable outcome. Further, all three diseases are common complex genetic disorders with a polygenic genetic architecture in the majority of cases. The inherent heterogeneity with regard to disease severity has posed a significant challenge to both the study of the underlying disease mechanism and the clinical management. Therefore, stratification of cases into more homogeneous subgroups across diagnoses using both longitudinal clusters derived from psychometric data and genetic information could provide a means to identify individuals with higher risk for severe illness, mandating earlier and intensified clinical intervention.

Methods Individuals included herein partake in an ongoing multisite cohort study across Germany and Austria (www.kfo241.de; www.PsyCourse.de). Participants were characterized at 4 time points over an 18-months period using a comprehensive phenotyping battery. The subsample used here totals 198 participants (46.9±12.4 yrs; 46% female) with DSM-IV diagnoses of SZ, SZA or BD. Blood DNA samples were genotyped using Illumina’s Infinium PsychArray and imputed using the 1000 genomes. SZ-PRS were calculated using PLINK 1.07. Effect sizes and p-values were determined with the PGC2 SZ summary results as discovery sample. A set of 67 longitudinally measured variables derived from the Positive and Negative Syndrome Scale (PANSS), the Inventory of Depressive Symptoms (IDS) and the Young Mania Rating Scale (YMRS) entered the cluster analyses. Factor analysis for mixed data (FAMD) was applied to compute abstract data dimensions, subsequently used to derive the longitudinal trajectories which then served as inputs for a k-mean clustering for longitudinal data. Identified clusters were employed in a linear regression model as predictive variables for SZ-PRS at 11 thresholds.

Results Computed by FAMD, the strongest loadings were observed for PANSS and IDS on the first dimension and for IDS on the second dimension. Two clusters of
longitudinal trajectories were identified in these dimensions: (A) individuals with continuously low scores on both PANSS and IDS (70.7%) and (B) individuals with consistently high scores on both PANSS and IDS (29.3%). Clusters differed significantly with regard to Global Assessment of Functioning (GAF; higher in (A); FDR-adjusted p-value=2.23x10^{-10}), while there were no significant differences regarding sex, age, diagnoses, center, age at onset, family history or duration of illness. Cluster membership was not significantly associated with the SZ-PRS in either cluster.

**Discussion** Although the results are preliminary and have to be interpreted with caution, the approach of longitudinal clustering to identify cross-diagnostic homogeneous subgroups of individuals appears to be feasible. The fact that more severe psychopathological features were not associated with increased genetic risk burden will also be interesting to explore further.

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