M42. USING POLYGENIC SCORES BASED ON SCHNEIDERIAN FIRST RANK SYMPTOMS TO CHARACTERIZE DISEASE TRAJECTORIES IN SEVERE MENTAL ILLNESSES

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Background Mental illnesses such as bipolar disorder (BD), schizoaffective disorder (SA) and schizophrenia (SZ) have a huge impact on people's lives and due to expensive treatments also on our health systems. Despite our advances in genetic and clinical research, it is still unknown what determines the highly variable courses of illness. Recent studies have focused on determining phenotypes more suitable for genetic analyses. Most analyses use diagnostic criteria based on DSM or ICD, however, the question arises whether it may be useful to classify subgroups of patients based on domains of psychopathology across diagnostic classification systems. To date, few studies exist that examine phenotypes based on such domains. We examined the presence/absence of Schneiderian first-rank symptoms (FRS) as a potential phenotype in a genome-wide association study (GWAS) analysis. The results of this analysis were used to calculate polygenic risk scores in an independent sample in which longitudinal clusters of psychopathology have been defined. We aim to explore the association of cluster membership with the individual load on first-rank polygenic risk scores (FR-PRS).

Methods Discovery sample: Individuals with SZ, SA and BD (n=1621) were selected from a large multi-site study (BoMA) in Germany and phenotyped using a comprehensive inventory for phenotype characterization (IPGS), including the SCID-I, the OPCRIT and the GAF. Presence/ absence of FRS served to identify diagnostically heterogeneous subgroups. GWAS was carried out with PLINK 1.07 using as covariates: age, age of onset, mode of onset, poor premorbid social adjustment, gender, course of illness and 4 population structure PCs.

Test sample: A subsample of individuals (n=198) with SZ, SA and BD from a longitudinal, multi-site cohort study (www.kfo241.de; www.PsyCourse.de) comprehensively phenotyped at 4 time points over 18 months. DNA samples were genotyped and imputed using the 1KG Phase3. 67 longitudinally measured variables

derived from clinical symptom scales entered the cluster analyses. FAMD was applied to compute abstract data dimensions, which were used to derive longitudinal trajectories. Based on these trajectories, k-mean clustering for longitudinal data yielded 2 distinct subgroups. Identified clusters served as predictors for FR-PRS at 11 thresholds.

Results Two clusters of longitudinal trajectories were identified: i) consistently low psychopathology scores and ii) consistently high psychopathology scores. Cluster membership was not significantly associated with the FR-PRS in either cluster.

Discussion Although the results are preliminary and thus need to be interpreted with caution, the approach of longitudinal clustering to identify cross-diagnostic homogeneous subgroups of individuals appears feasible. The fact that more severe psychopathological features were not associated with increased genetic risk burden should be explored further. One possible explanation is a lack of power, another is that maybe psychopathology may be more influenced to a larger degree by other factors than genetics that may be easier to modify for future treatment options.

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