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Original Research

Genome-Wide Association Study of Clinical Characterized Schizophrenic Patients Reveals Locus for Cognitive Phenotype Cataphasia

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Abstract

Introduction: Schizophrenic psychoses are highly heterogeneous in their clinical manifestation including their outcome and their dynamics. While psychoses show a high heritability, details of genetic contribution on the phenotype level are still unknown. We wanted to examine if differentiated phenotyping according to clinical homogenous subgroups enhances the search for new disease-associated loci.

Methods: We applied the classification of endogenous psychoses according to Karl Leonhard to take account of clinical details within schizophrenic spectrum. Patients diagnosed with schizophrenia were, depending on their clinical symptoms, assigned to one of nine phenotypes, which in turn represent three forms of progression. Patients (n = 1255) and controls (n = 1555) were genotyped as part of the PGC initiative. We conducted Genome wide association studies (GWAS) for each phenotype and each course of illness. We also calculated polygenic risk scores (PRS) for each form of progression based on the PGC samples of schizophrenia and bipolar disorder.

Results: GWAS revealed a genome wide significant ($p < 5x10-8$) locus on chromosome 11 within the CTSD gene for phenotype Cataphasia with distinctive cognitive manifestations. PRS for schizophrenia were highest in patients with a poorer outcome whereas PRS for bipolar disorder were highest in phasic remitting as compared to chronic progressive forms.

Conclusion: Our study shows possible advantages of a differentiated approach in the genetic research of schizophrenic psychoses and may contribute to phenotype-genotype correlations. Bipolar and schizophrenia PRS scores reflected outcome and treatment response thus strengthening the idea of different biological underpinnings for phasic and treatment resistant schizophrenic psychoses.

INTRODUCTION

No other psychiatric disorder embodies the missing heritability problem [1] as much as schizophrenia. Since the early 20th century, family studies strongly supported the clinical observation that schizophrenia is a hereditary disease. Subsequent studies including a meta-analyses of 12 twin studies [2] and, more recently, national population-based cohorts in Sweden [3] and Denmark [4] and Danish twin registers [5] consistently placed heritability estimates for schizophrenic psychoses between 64 and 81%. However, single genetic variations can explain only a fraction of the variance [6] While psychoses show a high heritability, details of the genetic contribution on the phenotype level are still unknown. While this suggests a complex genetic architecture, it may also be an indication of the heterogeneity of the concept of schizophrenic psychoses. The more heterogeneous a trait is, the less likely it is to get enough signal to find a specific causal variation [7]. With clinical presentation spanning from acute phases with complete remission to a chronic and disabling course, schizophrenia as defined by the DSM and ICD, is a very heterogeneous trait indeed.

To reduce the heterogeneity of the phenotype, a closer look at the psychopathological characteristics of individual patients might be helpful. This concept of detailed phenotyping underlies the classification of endogenous psychoses according to Karl Leonhard [8]. One of the advantages of this approach is that outcome of disease can be inferred from specific syndromes resulting in consistent schizophrenic phenotypes. Several studies confirmed prognostic value of the classification [9]; three forms of progression are analogue to rule of thirds in first-episode psychosis: Cycloid psychoses, which are phasic with complete remission after each phase of the disease, non-system schizophrenias, featuring a relapsing course with exacerbations and increasing development of residual symptoms, and lastly system schizophrenias that are chronically progressive. Non-

system schizophrenias show a familial accumulation and genetic effects play a significant role in these latter forms due to the frequent reoccurrence over several generations, sometimes with anticipation. In each form of progression, three distinct phenotypes are differentiated by the mainly impaired neuropsychological domain: Affect, thought or psychomotricity. This results in a total number of nine subphenotypes of schizophrenic psychoses defined by their specific clinical syndrome and course of disease. Phenotypes with good prognosis include psychotic bipolarity e.g., paranoia with fear of death in one pole and delusion of world rescue in the other. Based on clinical observations and theoretical considerations we formed the following two questions: Can differentiated phenotyping lead to more homogenous subgroups, which in turn could make the search for new disease-associated loci more effective? Does genetic liability for schizophrenia and bipolarity represented by polygenic risk scores (PRS) - based on the PGC samples of schizophrenia and bipolar disorder - correspond to psychopathological characteristics and prognosis?

METHODS

Sample collection

Patients (n_{preQC}= 1619; n_{postQC}=1255) and controls (n_{preQC}= 1659; n_{postQC}=1555) were genotyped as part of the Psychiatric Genomics Consortium initiative. None of these samples was part of a previously reported patient cohort. Recruitment was conducted between 1995 and 2017 in the Psychiatric Department of the University Clinic in Wuerzburg. Patients were identified through hospital records and during hospitalization or a routine visit to the policlinic and were initially contacted by their treating physician. All research subjects and, where applicable, their legal guardians provided a written informed consent to participate in the study. The ethical committee of Wuerzburg reviewed and approved the study. DNA samples of the participants were extracted from peripheral blood. Inclusion criteria were European ancestry and an ICD-10 diagnosis of schizophrenia (F20.x) or schizoaffective disorder (F25.x), whereby a consensus diagnosis was made by at least two independent, trained raters based on all available clinical information standardized by the AMDP-System (Manual for Assessment and Documentation of Psychopathology in Psychiatry) [10]. Exclusion criteria were mental disorders due to known physiological conditions or acute intoxication.

Controls were recruited as blood donors or by their participation in other studies of our clinic during which they gave consent to their genetic data being used as a control sample. Inclusion criteria were the absence of any psychiatric disorder, substance abuse as well as severe somatic illnesses.

Sample description

Of the 1255 patients that remained after quality control, 315 suffered from remittent (cycloid) psychoses, 709 had relapsing non-system schizophrenias and 231 had chronic system schizophrenias (**supplement table 1**). Cases were predominantly males, (64%) with an average age at onset of 27 years and an average age at recruitment of 41 years. The volunteer control subjects (48% males) had an average age at recruitment of 28 years. One-way omnibus analysis of variance (ANOVA) was used to test for overall significance in gender distribution, age at inclusion and age of onset. Post-hoc pairwise comparisons were conducted to identify significant differences between individual groups when the overall test was significant. The groups of cycloid psychoses and non-system schizophrenias did not differ significantly regarding gender distribution and age of onset. System schizophrenias however showed a significantly higher percentage of men and a significantly lower age of onset. The age at inclusion in the study differed significantly amongst all three groups.

Phenotyping

We applied the classification of endogenous psychoses according to Karl Leonhard [8] to determine the subphenotype of patients suffering from schizophrenic psychoses. Several studies confirmed prognostic value of the classification [9]. For each of the three forms of progression, three psychopathologic domains (affect, thinking and psychomotor) distinct the specific phenotype. This results in a total number of 9 subphenotypes of schizophrenic psychoses defined by their specific clinical syndrome and course of disease (**supplement table 2**). Patients were assigned by experienced clinical raters according to their clinical symptoms to one subform and thus also to its respective course of progression. Hospital records were used to verify outcome and treatment response. All patients met the criteria for schizophrenia (F20.x) or schizoaffective disorder (F25.x) according to ICD-10.

Genotyping and imputation

All cases and controls were genotyped on Illumina's PsychChip array (Illumina, San Diego, CA, USA). Our data set was processed through the same RICOPILI data processing and imputation pipeline that was also used for the entire 'PGC3' dataset. SNPs and insertion-deletions were imputed analogously to the method described in the paper of Trubetskoy et al (2022) [6].

Quality Control

The filtering process applied the following criteria (N of excluded cases/controls): a pre filter variant-level call rate of < 0.95 (0/0), a sample-level call rate < 0.98 (0/0), an FHET value <0.2 or >0.2 (1/0), sex-check violations (22/22), a variant-level call rate <0.98 (248 SNPs), a missing difference > 0.02 (184 SNPs), invariant SNPs (132374 SNPs) and a HWE p $<1e^{-6}$ in controls (35 SNPs) and HWE p $<1e^{-10}$ in cases (0 SNPs), populations outliers (64), related samples (358). In a second QC iteration with the same parameters one additional sample (case) was excluded due to a variant-level call rate < 0.98. In the third QC iteration all samples and variants passed all filters.

PCA was performed on the 'bgs' best guess data set of our sample. We performed a first round of quality control (starting number of SNPs: 3231849) removing SNPs with a call rate < 95%, individuals with a genotyping rate < 98%, related individuals (based on the inbreeding coefficient FHET >0.2 or <-0.2), individuals with sex check violations, SNPs with a call rate <

98%, SNPs with a call rate difference between cases and controls > 2%, invariant SNPs and SNPs with a HWE p <1e^{-6} in controls and HWE p <1e-^{10} in cases. Since the data set had already gone through an extensive QC pipeline only 15 SNPs were removed (final number of SNPs following all QC steps: 3231834). Prior to PCA we performed a stricter QC removing high-LD-regions and non-autosomal SNPs (144485), SNPs with a HWE p < 1e-3 (2985) and SNPs with a MAF < 0.05 (13055). We then produced a pruned subset of markers with window size 3000kb, step size 300 and r^2 threshold 0.1 resulting in 41641 SNPs for the principal-component analysis (PCA).

GWAS

14 individual GWAS were performed using logistic regression with imputation probabilities ('dosages') adjusted for the first 4 principal-component analysis (PCA) covariates. Genome wide association studies (GWAS) were performed for all cases with schizophrenia as umbrella phenotype, for each subphenotype and each course of illness as well as for phenotypes that develop residual symptoms. All groups were tested against healthy controls plus all subjects that do not share the respective phenotype in order to find associated loci. We decided to add patients without the phenotype in question to enhance power and to bring out the associations for the subphenotype rather than schizophrenic psychoses in general.

Polygenic risk score analyses

We also calculated polygenic risk scores (PRS) for each form of progression based on the PGC samples of schizophrenia and bipolar disorder as well as for major depressive disorder and the traits neuroticism, subjective wellbeing, hippocampal volume and educational attainment (list of publications for summary statistics see **supplement Table 3**). We chose this set of traits due to an LD score regression analysis of the PGC2 SCZ summary statistics as well as theoretical considerations about the clinical presentation of the subphenotypes.

Polygenic scores for our sample were generated for all disorders and traits with the respective sample as discovery sample and our imputed sample as target sample. Regarding the target sample, only SNPs with an INFO (imputation quality) score >0.6 and a MAF (minor allele frequency) >0.01 and <0.99 were used. In the discovery samples, we excluded strand ambiguous SNPs. For all overlapping SNPs of the discovery and target samples, we performed P-value-informed clumping with a cutoff of $r^2 = 0.1$ using a 500-kb window (index variant p-value threshold = 1, clumped variant p-value threshold = 1) with the European subsample of the 1000 Genomes Project phase [11] as a reference. We calculated scores per individual for 10 p-thresholds (0.00000005, 0.000001, 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1).

Regressions

The proportion of variance in case-control status explained, Nagelkerke's R^2, was computed by a full model (first 4 covariates plus PRS) score to a reduced model (first 4 covariates only). The form of progression in question was compared to healthy controls. Relaxing the threshold beyond p < 0.05 showed no gain of variance explained (Figure 3).

RESULTS

Genome wide significant locus associated with Cataphasia

A sign test was used to confirm that the common variant architecture in our sample corresponded to that in the independent PGC's schizophrenia sample. 101 of 135 independent genome-wide significant index SNPs showed the same pattern of allelic association, which is more than would be expected by chance ($P = 6.6 \times 10^{-9}$). While no genome-wide significant association could be found for the broad phenotype of schizophrenia, GWAS indentified the genome wide significant variant rs72850959 (chr11:1781808, $p = 1.557 \times 10^{-9}$) on chromosome 11 (Figure 1) within the intron 2 of the CTSD gene (Figure 2) for the Cataphasia subphenotype (n = 151).

Locus associated with chronic forms of schizophrenia

GWAS with non-system schizophrenias and system schizophrenias combined as a phenotype that reflects chronic forms of schizophrenia which develop residual symptoms, revealed a locus within the CRADD gene falling just short of genome-wide significance ($P = 4.887 \times 10^{-8}$, see **supplement Figures 1,2**).

PRS for schizophrenia and bipolar disorder reflect psychopathological observations of residual symptoms and bipolarity

Regarding schizophrenia PRS, Nagelkerke R^2 was highest among non-system schizophrenias with 0.118, 0.084 in system schizophrenias and 0.065 in cycloid psychoses (Figure 3), which provides molecular validation of this sample as a schizophrenia sample even for the bipolar subtypes. If non-system and system schizophrenias (i.e. the two forms with residual symptoms) were combined, R^2 was 0.123. In contrast, PRS for bipolar disorder were highest in bipolar, i.e. phasic remitting and relapsing progressive ($R^2 = 0.044$) as compared to chronic progressive forms ($R^2 = 0.014$). These results are not likely to be distorted by schizoaffective patients in the discovery sample as they made up only 5% of the sample size.

PRS for major depressive disorder, educational attainment, subjective well-being, hippocampal volume and neuroticism provide molecular profile in line with clinical characteristics

PRS for major depressive disorder (MDD) were highest in chronic forms of schizophrenia ($R^2_{system} = 0.003$, $R^2_{non\text{-}system} = 0.004$) as opposed to cycloid psychoses ($R^2_{cycloid} = 9.82 \times 10^{-6}$). Regarding educational attainment (EA), chronic progressive forms of schizophrenia had the lowest PRS ($R^2_{system} = 2.36 \times 10^{-5}$), while bipolar forms had higher scores ($R^2_{cycloid} = 0.001$, $R^2_{non\text{-}system} = 0.005$). Scores for subjective well-being (SWB) were about equal in all groups ($R^2_{cycloid} = 0.003$, $R^2_{non\text{-}system} = 0.001$, $R^2_{system} = 0.003$). PRS for hippocampal volume (HC) were lowest in non-system schizophrenias ($R^2_{non\text{-}system} = 3.26 \times 10\text{-}5$) and higher in

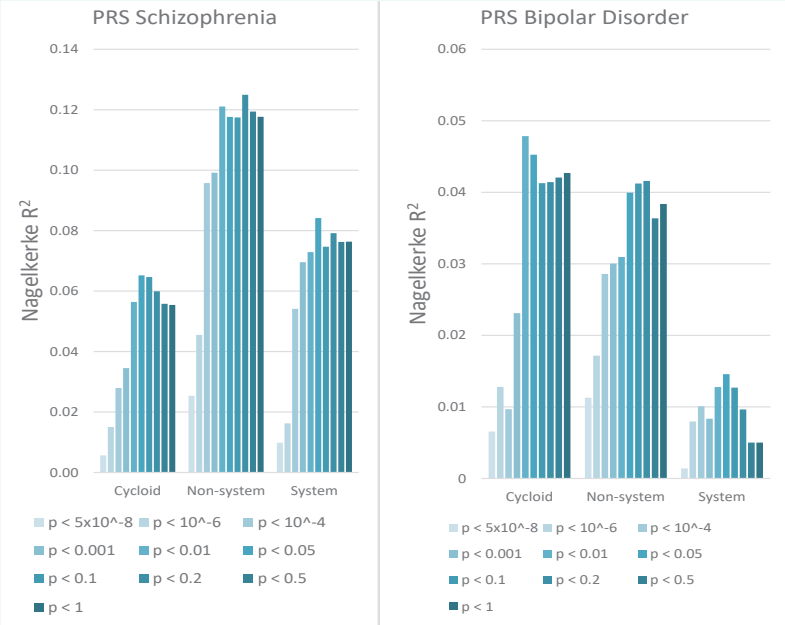
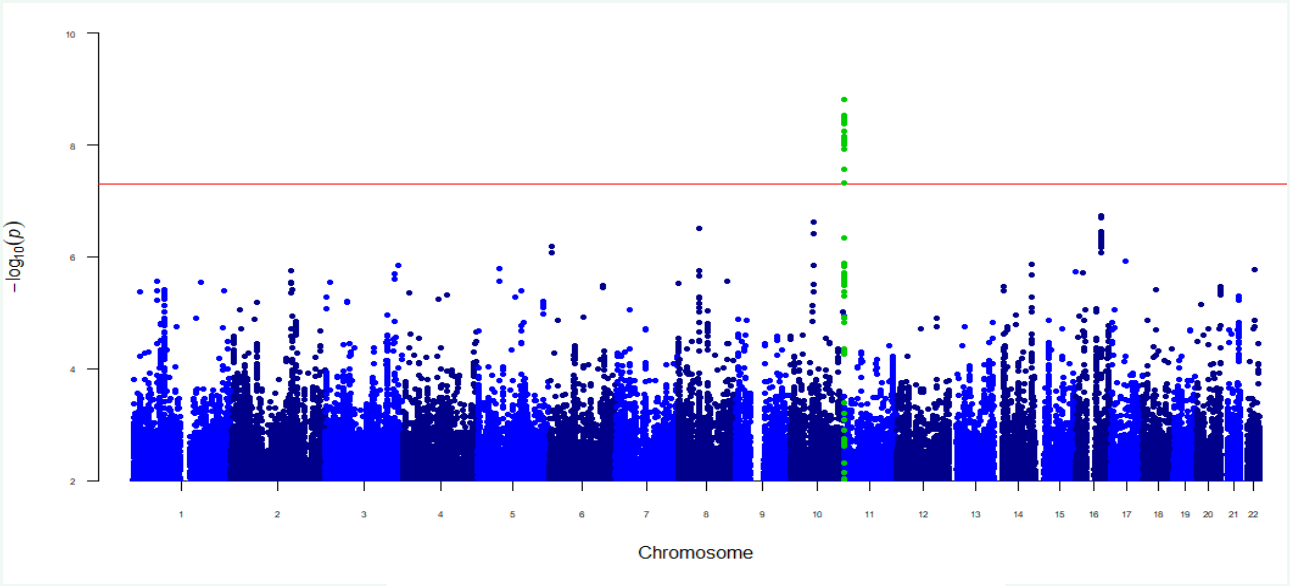


Figure 1 Polygenic risk scores for schizophrenia and bipolar disorder in all three forms of progression across several p-value thresholds.



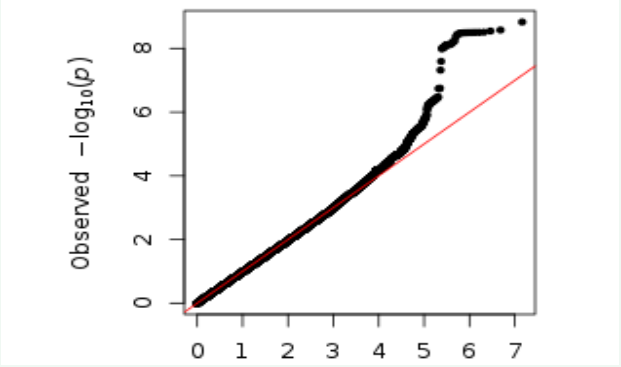


Figure 2 Manhattan plot and QQ plot for the Cataphasia phenotype. Manhattan plot: red line: genome wide significance (P = 5 x 10-8), SNPs highlighted in green: suggestive locus on chromosome 11. QQ-Plot: red line: observed p-value=expected p-value.

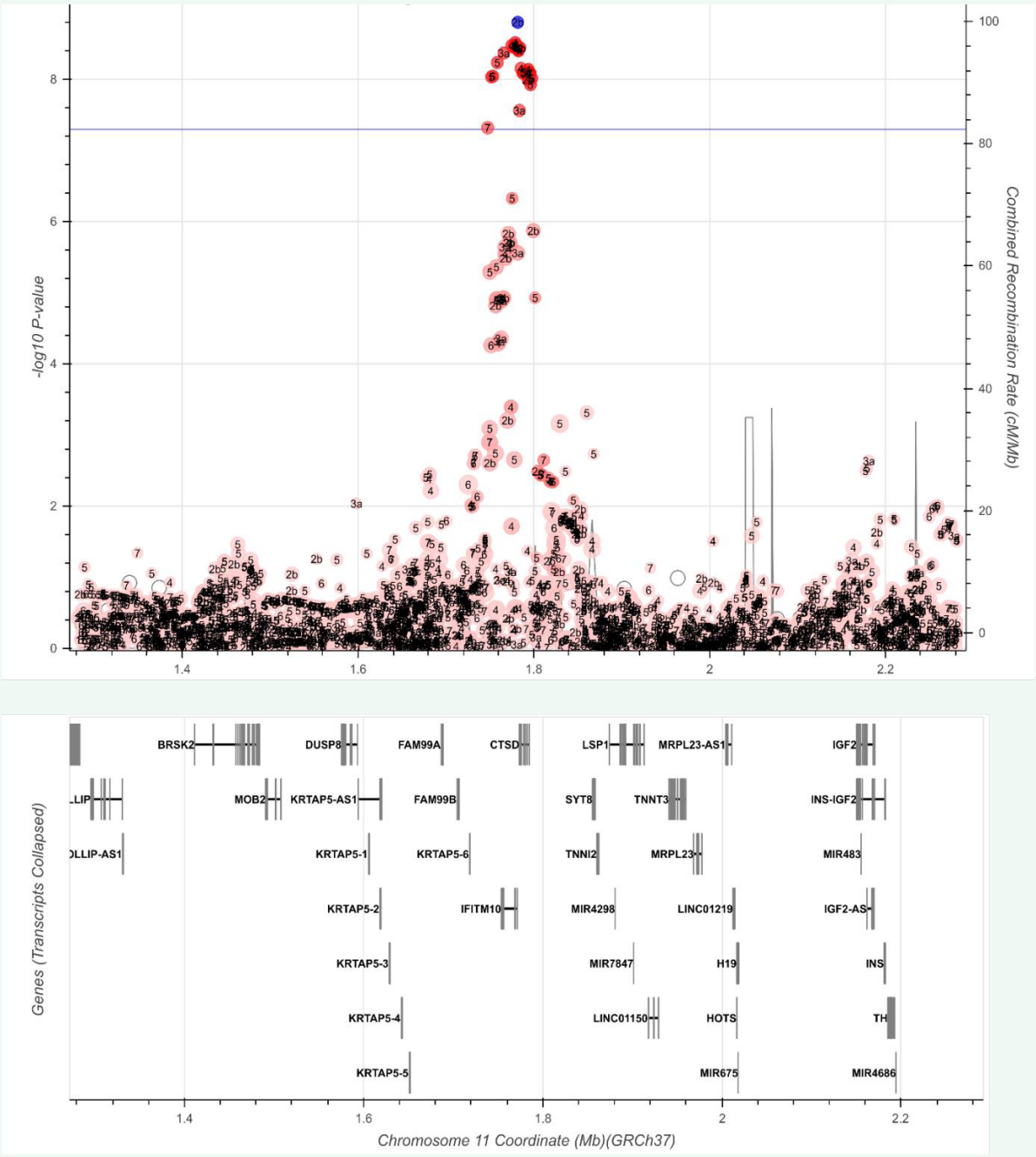


Figure 3 Region plot for the locus on chromosome 11 associated with Cataphasia within the CTSD gene.

both cycloid psychoses and system schizophrenias ($R^2_{cycloid}$ = 0.001, R^2_{system} = 0.001). Finally, PRS for neuroticism (NEUROT) were highest in non-system schizophrenias ($R^2_{non\text{-}system}$ = 0.002) and lower in both cycloid psychoses and system schizophrenias ($R^2_{cycloid}$ = 0.0001, R^2_{system} = 0.0001). For Nagelkerke R^2 across all thresholds and traits see **supplement table 4**).

DISCUSSION

We sought to determine whether subdividing patients with schizophrenia into clinically more homogenous subgroups could facilitate the search for new disease-associated loci. Despite the decrease in sample size that comes with subdivision, a nominal significant locus was found for the cognitive Cataphasia subphenotype [8] in the CTSD gene on chromosome 11. Specific syndrome includes incoherent and illogical thinking and language disorganization with syntactic and semantic errors. CTSD encodes Cathepsin D, which is a lysosomal protease. Homozygous or compound mutations in this gene with subsequent Cathepsin D deficiency play a causal role in neuronal ceroid lipofuscinosis (NCL)-10, an early-onset neurodegenerative lysosomal storage disorder [12]. NCLs are characterized by a buildup of lipopigments that results in death of neuron cells causing

progressive neurological impairment, motor and intellectual deterioration, seizures and often-visual failure. While most NCLs manifest within the first few years of life and very quickly lead to death, there are adult forms (known as Kufs disease) presenting with progressive myoclonus epilepsy or progressive cognitive decline and motor signs while vision is not impaired [13]. Patients with Cataphasia do not show any neurological symptoms such as seizures, ataxia or motor signs, but the age of onset in adulthood and the characteristic thought disorder match up well. Decreased cathepsin D activity due to loss of progranulin has also been associated with frontotemporal dementia, a group of neurodegenerative disorders characterized by cognitive and behavioral impairments [14] and a polymorphism in CTSD has been associated with Alzheimer's Disease [15], further linking CTSD variation to a decline of cognitive function. On a molecular level, Cathepsin D might be involved in recycling and biogenesis of synaptic vesicles [16]. Cathepsin D deficiency in knockout-mice is associated with synaptic dysfunction [17] and dysmyelination [18] in the murine brain providing altered neuronal function as a correlate of the neuropsychological phenotypes discussed earlier. In line with these findings, cathepsin-dysfunction was proposed to play a role in different psychiatric diseases such as major depressive disease, bipolar disorder, and schizophrenia [19].

In our GWAS for the two chronic forms of schizophrenia that develop residual symptoms, a locus within the CRADD gene was falling just short of genome-wide significance. The CRADD gene codes for an adapter protein that downstream activates CASP2 and triggers apoptosis. It has been associated with thin lissencephaly [20,21], a cortical development malformation defined by frontotemporal pachygyria, resulting in intellectual disability as well as delayed speech and language development. CRADD has not yet been associated with schizophrenia spectrum disorders, but some patients show a neuropsychiatric phenotype with need for antipsychotic medication [21].

The second question we addressed was if genetic liability as determined by polygenic risk corresponds to psychopathological characteristics such as outcome and psychotic bipolarity. Our results are in line with previous observations [22] by Ruderfer et al. of schizophrenia PRS being associated with more severe illness. However, in our sample schizophrenia PRS indicated a poorer outcome defined by the development of residual symptoms rather than via its association with psychotic symptoms as in the aforementioned study. These findings might help with disentangling of symptom severity in the acute phase from long-term prognosis. PSR for affective bipolar disorder reflected psychotic bipolarity in our sample, which is in accordance with findings of a positive correlation between PRS of BD and manic symptoms in SCZ [22]. Each form of progression has a specific profile of SCZ and BD PRS that suggest a different biological basis for their clinical presentation. Splitting schizophrenic psychoses into these three groups might facilitate genetic research of prognostic features.

PRS for major depressive disorder, educational attainment, subjective well-being, hippocampal volume and neuroticism mostly matched clinical observations. Chronic forms of schizophrenia had higher scores for MDD, which possibly represents an overlap of depressive and residual (negative) symptoms, which manifests in impaired social functioning further down the line. Scores for educational attainment were lowest in chronic progressive forms of SCZ, which fits with their earlier age of onset and poor prognosis that often hinder academic success. PRS for subjective well-being did not differ between all courses of disease supporting the notion that all forms of SCZ cause a loss in quality of life. Hippocampal volume deficits in schizophrenic patients have been associated with a longer duration of untreated psychosis [23] and were found to be higher in unmedicated patients [24]. The lower PRS scores for hippocampal volume - and thus higher volume deficits - in non-system schizophrenias suggest a long period without treatment, e.g. because of a long latency between onset and treatment. This is supported by the much higher age at assessment as compared to retrospective age of onset in this group (**supplement Table 1**).

About the limits of our study, the small sample size, which further decreases with the subdivision into subphenotypes, makes our investigations more prone to false associations. The proven classification we used is based on in depth clinical assessment rather than operationalized symptom dimensions [8]. However, our study shows advantages of a differentiated psychopathological approach in the genetic research of schizophrenic psychoses. Despite the small sample size, we found a possible variant, though replication might be helpful needed for final confirmation. It would be desirable if more samples could be analyzed according to Leonhard`s classification to validate our results. While our findings are not among the top associated loci in the latest PGC analysis representing the complete schizophrenic spectrum [6], our data could complement those results in view of specific phenotypes. To the best of our knowledge, our study is the first to associate CTSD with schizophrenic psychoses and with formal thought disorder as a specific symptom dimension in particular.

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