Schizophrenia risk loci from xMHC region were associated with antipsychotic response in chronic schizophrenic patients with persistent positive symptom

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We examined whether common variants from the extended major histocompatibility complex (xMHC) region contribute to the response to antipsychotic drugs (APDs) in patients with schizophrenia with persistent psychosis. Subjects participated in a prospective longitudinal study of the effect of APDs on psychopathology were temporally split into discovery (n = 88) and replication (n = 42) cohorts. The primary endpoint was a change in Brief Psychiatric Rating Scale at 6-week or 6-month after treatment. rs204991 (β = 3.917, p = 3.72 × 10^-5), the strongest signal associated with response at 6-week was located near C4A/C4B after a linear regression adjusted for covariates. xMHC SNP imputation disclosed much stronger signals (rs9268469, β = 5.140, p = 1.57 × 10^-7) and other weaker signals (p < 1 × 10^-5) spanning the entire xMHC region. All the variants were previously identified schizophrenia risk loci. Conditional fine-mapping revealed three subgroups of SNPs which were the eQTLs (p < 1 × 10^-7) for C4A, HLA-C, and BTN3A2 in disease-relevant tissue. Epistasis between HLA-C and C4A was observed (p = 0.019). Minor allele (G) carriers of rs204991, eQTL for C4A, having decreased risk for schizophrenia and lower imputed expression of C4A, had a better response to APDs. Some imputed HLA alleles associated with a decreased risk for schizophrenia had a positive association with improvement in psychotic symptoms. An independent cohort validated the association of change in psychosis with C4A. We provide evidence that genetic risk factors for schizophrenia from the xMHC region are associated with response to APDs and those variants significantly altered the imputed expression of C4A, HLA-C, and BTN3A2. The minor alleles predicting higher C4A level are associated with diminished improvement in psychotic symptoms after APD treatment.

INTRODUCTION

Schizophrenia (SCZ) is a complex syndrome affecting 1% of the population worldwide. There are likely diverse abnormalities during and after development underlying the positive, negative, and cognitive symptoms that characterize the illness. However, immune dysfunction and chronic inflammation have been of major interest in this regard [1]. Post-mortem morphological evidence, including loss of white matter and cortical gray matter without observed cell death [2], excessive synaptic pruning of mature or new dendritic spines in cortical pyramidal neurons [3, 4], and activation of microglia during adolescence and early adulthood [5], has led to the suggestion that these abnormalities may be due, in part, to immune system dysfunction. This may be the result of major histocompatibility complex (MHC) molecules (HLA I & II) mediated antigen-presentation and the complement-mediated classical pathway, producing microglial engulfment and led to enhanced negative symptoms [6–10]. The hyperactivated microglia could be the major basis for excessive synaptic elimination [5, 11].

Functional implications of MHC genes in neuropsychiatric disorders, particularly schizophrenia, were strongly supported by genome-wide association studies (GWAS) which indicated that the extended MHC region (xMHC, a total of 7.6 Mb on the short arm of chromosome 6 with genetic coordinates between 25 M and 34 M) were the most significant and replicable genetic associations with SCZ [12–14]. A functional study showed that the level of C4A, a pivotal complement molecule, partially account for this association [7]. This landmark study integrated the genetic, autoimmune, and neurobiology (e.g., excessive synaptic pruning) theories of schizophrenia. It was proposed that overexpression of C4 in mouse prefrontal cortical neurons negatively affected dendritic spine development by the enhancement of microglia-induced synaptic engulfment and led to enhanced negative symptoms [15, 16]. Transcriptional imputation of SCZ GWAS summary statistics confirmed the increased expression of C4A, BTN3A2 from xMHC in several brain regions associated with schizophrenia, including dorsolateral prefrontal cortex (DLPFC) [7, 17].

There is some evidence that neuroinflammation has a significant impact on the course of schizophrenia. Significantly higher plasma levels of C3 and C4, as well as other acute-phase proteins have been reported in APD-treated compared to non-medicated SCZ patients [18]. A significant increase in cerebrospinal fluid C4 levels was observed in SCZ patients [19]. The HLA...
system has been linked to clinical response to the haloperidol [20] and chlorpromazine [21]. Although some single nucleotide polymorphisms (SNPs) at xMHC region predicted the treatment response to the atypical APDs, olanzapine, and risperidone [22], none of those markers have been linked to risk for SCZ or have a functional impact on alteration of gene expression at the xMHC region. C4A or C4B expression, imputed by copy number analysis of long and short forms of C4A and C4B, does not contribute to the risk and severity of tardive dyskinesia in SCZ patients [23]. There is a paucity of studies which have examined the role of C4 in treatment response to APDs in schizophrenia patients or other populations [24].

The purpose of this study was to identify common variants contributing to the treatment response to APDs in chronic schizophrenic patients in a candidate gene study of the xMHC region. The primary endpoint was the change in the subscales of the Brief Psychiatric Rating Scale (BPRS) at 6-week or 6-month after treatment with atypical APDs, including clozapine, olanzapine, risperidone, and lurasidone. A secondary fine-mapping approach was conducted to prioritize the potential causal genes associated with improvement in psychotic symptoms.

METHODS
Subjects and clinical evaluation of treatment response
A structured interview, the Schedule for Affective Disorders and Schizophrenia for DSM III or IV [26], provided the basis for diagnosis. This was integrated with all available data to make the final diagnosis by consensus according to the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) criteria. Prior to the Diagnostic interview, all patients met DSM-IV criteria for schizophrenia or schizoaffective disorder. Data from patients with either diagnosis were combined. Over 75% of patients were unmedicated or had a drug-free period of 3–10 days prior to baseline assessment.

All participants were temporally split into discovery (n = 88) and replication (n = 42) cohorts. Demographics and clinical information for the discovery and replication cohorts were provided in Table 1. For quantitative variables, Shapiro–Wilk test confirmed the approximately normally distributed data for these variables (p > 0.05) and Welch’s t-test was conducted to compare the difference between two cohorts with an assumption of equal variance or unequal variance determined by Levene’s test; for categorical variables, Fisher’s exact test was conducted to examine the significance of the association between two kinds of classification. The subjects selected for GWAS had participated in a prospective clinical trial of the effect of atypical APDs. Diagnosis and classification as treatment-resistant schizophrenia (TRS) or non-treatment-resistant schizophrenia (NTRS) were based on severity of positive symptoms and poor functional outcome after two or more trials of APDs of usually adequate duration [27]. The subjects selected for GWAS had participated in a clinical trial (NCT00539071, NCT00179062) or prospective longitudinal studies of the effect of clozapine (n = 60), olanzapine (n = 15), or risperidone (13). 62.5% patients in the discovery cohort were classified as TRS [29]. An additional 42 subjects were studied at Vanderbilt University and Northwestern University [30]. The subjects selected for GWAS had participated in a clinical trial (NCT01569659, NCT00179062) or prospective longitudinal studies of the effect of lurasidone (n = 14), risperidone (n = 16), clozapine (n = 1), or ziprasidone (n = 2).

Here we use the classical 18-item Brief Psychiatric Rating Scale (BPRS) with 0 to 6 scaling for each item. All ratings were conducted by trained neuropsychiatric technicians who were blind to the hypothesis of this
study. The BPRS positive symptom subscale, BPSY, includes assessment of suspiciousness, hallucinatory behavior, and unusual thought content. The BPRS negative subscale, WR, which stands for BPRS negative subscale, is comprised of three items: emotional withdrawal, motor retardation, and blunted affect. Quantitative treatment response was evaluated at 6-week and 6-month, using the change in ΔBPSY or ΔWR. Only patients with moderate to severe psychosis (baseline BPSY ≥ 6) were included in the analysis. Different cutoff values for BPSY had been implemented to avoid selection bias, and BPSY ≥ 6 gave the strongest signal compared to BPSY ≥ 0, ≥ 2, ≥ 4, and ≥ 8 (see the Supplementary Table 1 for effect size and power analysis), with ≥ 8 of previously reported 174 patients [29] included in the discovery cohort. Therefore, the same baseline cutoff values were applied to the replication cohort. 42 out of 71 patients were stratified as positive psychotic.

After a description of the study, written informed consent was obtained from every subject. All patients provided written informed consent to remain drug-free during the assessment. The drug-free period was terminated if patient well-being required it. Some were not receiving psychotropic drugs prior to admission because of non-compliance. This study was approved by institutional review boards from Case Western Reserve University, Vanderbilt University, and Northwestern University.

Quality control of genotyping data and association testing

Genome-wide SNP genotyping was performed using Illumina 610 K quad BeadChip” for discovery cohort [29] or Illumina PsychArray” for replication cohort [30].

DATA QC was conducted to exclude samples with minor allele frequency (MAF) ≤ 0.05, genotyping per SNP ≤ 0.95, and significant deviation from Hardy-Weinberg equilibrium (p < 10^-6) (Discovery) and 272.589 (Replication) SNPs available for further analysis. Total genotyping rate in the remaining individuals was >99.96%.

Regional SNP imputation for xMHC (Chr6: 25 M to 34 M) was conducted by IMPUTE2 using 1000 Genome Project (April 2014) as reference panel. Briefly, after prephasing by SHAPEIT2 using 37 macGT1 data as reference, we conducted a stepwise imputation in 5-Mb segment using Quest High Performance Computing Cluster. The imputed data was finally converted to PLINK format by GTOL. SNPs with imputation quality core >0.9 were used in the following association testing. All cases were considered as unrelated individuals (PIHAT = 0.20 as a cutoff) based on the pairwise identity-by-descent (IBD). All patients (discovery and replication) recruited in this study were self-described Caucasians which was verified by Principal Component Analysis (PCA) [29, 30]. The association testing was conducted by PLINK 1.9. The primary endpoint was change in psychotic (ΔBPSY) or negative (ΔWR) symptoms of BPRS at 6-week and 6-month after treatment with APDs. Linear regression in an additive model of minor alleles, adjusted for covariates, three first principal components (PC1-3), gender, and drug, was utilized. TRS status was tested as a covariate in the linear regression model but had no significant impact on the association for the top variants. Therefore, it was not included as a covariate in the summary statistics. False discovery rate (FDR) corrections for multiple testing were calculated using the Benjamin-Hochberg (BH) procedure for the regional association testing. Mapping cis-eQTL in disease-related tissues was conducted by three components mapping by a candidate region approach

Based on the LD pattern between rs9268469 and other weaker signals (rs9268469, rs6904596, rs7775397) which were in LD with two imputed SNPs, rs150353632 and rs59134830. The association of top SNPs with symptom improvement at 6-month was tested. Only SNPs (rs204991, β = 2.57, p = 0.006, Fig. 2B) near C4A/C4B, TRS status was tested as a covariate in the linear regression model but has no significant impact on the association for the top variants (for rs204991, β = 0.64; for rs6904596, p = 0.91). The medication was not the significant covariate in the genotype-phenotype association for the top hit, rs204991 (p = 0.488 and p = 0.193 in both discovery and replication cohorts). However, we retained it as a covariate in the full regression model.

The subsequent fine-mapping by a candidate region approach (Fig. 1) was conducted after regional SNP imputation in order to identify causal variants or genes from xMHC associated with treatment response to APDs. SNP imputation disclosed much stronger phenotype association for the top hit, rs204991 (pBH-FDR = 1.57 × 10^-7) for rs9268469 and other weaker signals (p < 1 × 10^-3) spanning the entire xMHC region.

The top signals associated with improvement in psychotic symptoms at 6-week were labeled in the regional association plot (Fig. 2A) and listed in Table 2 after LD-based clumping. We also listed the results from two genotyped SNPs, rs6904596 and rs7775397 which were in LD with two imputed SNPs, rs150353632 and rs59134830. The association of top SNPs with symptom improvement at 6-month was tested. Only SNPs (rs204991, β = 2.57, p = 0.006, Fig. 2B) near C4A, but not those closest to BTN3A2 (rs6904596, β = 0.9, p = 0.309, Fig. 2C) showed a significant association (p < 0.01) but with smaller effect size (β).

Conditional linear regression analysis to identify independent signals

Based on the LD pattern between rs9268469 and other weaker signals with pBH-FDR < 0.05 (Fig. 2A), we partitioned the regional association plot into 3 blocks, block 1 (r² < 0.2), block 2 (0.2 < r² < 0.4), and block 2 (r² > 0.4). In order to identify the independent effects, three representative SNPs which showed high LD (rs2240991, r² > 0.8), intermediate LD (rs3132541, 0.2 < r² < 0.4), and poor LD (rs6904596, r² < 0.2), with rs9268469, from the corresponding three subregions, were selected as the fixed effect and added to the original linear regression model (Supplementary Fig. 3). The strength of the association of rs9268469 with treatment response in BPSY was attenuated from β = 5.14 (p = 1.57 × 10^-7) to β = 3.99 (p = 0.001) after adjusting for rs3132541 (Supplementary Fig. 3A), suggesting the associations from rs3132541 and that from rs9268469 were not completely
The purpose of this study was to identify common variants contributing to treatment response to APDs in chronic schizophrenia. Our study focused on the xMHC region, which is comprised of three items: emotional withdrawal, motor retardation and blunted affect.

Fig. 1 Overview of the strategy for the fine-mapping causal variants/genes from xMHC region in association with treatment response to APDs. ∆BPSY, change in positive symptom subscale including suspiciousness, hallucinatory behavior, and unusual thought content; eQTL, expression quantitative trait loci; EUR, European ancestry; HWE, Hardy–Weinberg equilibrium; INFO, an information score, which takes a value between 0 and 1, reported by IMPUTE2, with a value near 1 indicating high certainty of imputed genotype; MAF, minor allele frequency; PCA, principal component analysis; QC, quality control; PheWAS, phenom-wide association studies; ∆WR, change in withdrawal symptom subscale which is comprised of three items: emotional withdrawal, motor retardation and blunted affect.

### Discussion

Several key findings emerged from our study. First, we identified several genetic variants located within the xMHC region that were associated with treatment response to APDs. These variants were found to be strongly linked to changes in positive symptom subscales, supporting the hypothesis that genetic factors play a significant role in treatment response.

Second, we observed significant interactions between these genetic variants and clinical response to APDs. This finding suggests that genetic predispositions may influence individual responses to antipsychotic medications, highlighting the importance of personalized treatment approaches.

Finally, our study underscores the potential for genetic markers to serve as biomarkers for predicting treatment response in chronic schizophrenia. This could have significant implications for improving treatment outcomes and guiding the development of novel therapeutic strategies.

In conclusion, our study provides valuable insights into the genetic basis of treatment response in schizophrenia, highlighting the importance of genetic factors in shaping clinical outcomes. Further research in this area is necessary to validate these findings and to explore the mechanisms underlying these genetic associations.
schizophrenic patients with persistent psychotic episodes using xMHC fine-mapping approach. Although no genome-wide significant locus was identified after linear regression adjusted for covariates (n = 88), rs204991 (p = 3.72 × 10^{-5}) located near C4A/C4B, was among the top-tier signals. Regional SNP imputation disclosed even stronger signals with the lowest p = 1.57 × 10^{-7} for rs9268469 and other weaker signals (p < 1E−5) spanning the entire xMHC region. All these variants show genome-wide significant risk for SCZ. The subsequent LD-based conditional fine-mapping revealed three subgroups of SNPs which were found to be eQTLs (p < 1 × 10^{-5}) for C4A, HLA-C, and BTN3A2 in disease-associated tissue such as DLPFC, basal ganglia, and whole blood. Genetic evidence of epistasis between HLA-C and C4A was observed (p = 0.019). Minor allele (G) carriers of rs204991, eQTL for C4A, who had decreased risk for SCZ and lower expression of C4A, had a better response to APDs at both 6-week and 6-month; Minor allele (A) carriers of rs6904596, eQTL for BTN3A2, who had decreased risk for SCZ have a better response to APDs only at 6-week. In line with these findings, HLA imputation showed the presence of some HLA alleles which decrease the risk for schizophrenia [12] have a positive association with improvement in psychotic symptoms. An independent cohort (n = 42) validated the genetic association between response to APDs and the C4A expression. These top SNPs associated with treatment response in schizophrenia were also related to several autoimmune-related diseases (e.g., coeliac disease, hyperthyroidism/thyrotoxicosis). Neuroinflammation could be a part of systemic dysfunction of immune system in SCZ. A recent meta-analysis confirmed an overall positive association between non-neurological autoimmune disorders and psychosis with a larger effect size (odds ratio) in pernicious anemia, pemphigoid, psoriasis, celiac disease, and Graves’s disease [34]. Prolonged inflammatory/immune response may contribute to treatment resistance in some schizophrenic patients [24, 35, 36]. Together, we provide evidence that some genetic risk factors for SCZ in the xMHC region are associated with treatment response/resistance to APDs and those variants significantly alter the gene expression of C4A, HLA molecules (HLA-C), and other immune-related genes (BTN3A2).

Linking the genetic risk for disease to treatment outcome or other intermediate phenotypes

The initial attempts to map SCZ risk loci to the MHC region were first reported in 1974 [20]. Since then, many reports provide additional evidence [37] but the definitive evidence for MHC involvement in SCZ was the result of three GWAS of SCZ patients with EUR descent published in 2009 [12–14]. One of the most significant association signals, rs13194053 with p = 9.54 × 10^{-5}, was located at the extended MHC region. Others including rs6932590 (p = 1.4 × 10^{-4})...
Table 2. Summary of the top genetic variants or genes at xMHC regions in association with symptom improvement.

| SNP_ID        | SNP information (LD clumped) | 1KG | Discovery (610 K QUAD) | Replication (PsychArray) | PGC GWAS | Discovery (610 K QUAD) |
|---------------|------------------------------|-----|------------------------|--------------------------|----------|------------------------|
|               |                              |     | 5BPSY_6wk              | ΔBPSY_6mon               | A1/A2    | ΔWR_6wk                |
|               |                              |     | β                           | P                          | OR       | P (n = 42)             |
| n4967772      | 26496578                     | 0.04-0.0-0.028                      | 0.19                       | 0.73     | 0.19                   | 0.73       |
| n147925578    | 26937830                     | 0.04-0.0-0.010                      | 0.18                       | 0.72     | 0.18                   | 0.72       |
| n144022448    | 27456052                     | 0.06-0.0-0.028                      | 0.19                       | 0.73     | 0.19                   | 0.73       |
| n6904596      | 27491299                     | 0.04-0.0-0.010                      | 0.18                       | 0.72     | 0.18                   | 0.72       |
| n59134830     | 27670111                     | 0.04-0.0-0.010                      | 0.19                       | 0.73     | 0.19                   | 0.73       |
| n75722488     | 28301099                     | 0.04-0.0-0.010                      | 0.19                       | 0.73     | 0.19                   | 0.73       |
| n131945040    | 28630691                     | 0.04-0.0-0.010                      | 0.19                       | 0.73     | 0.19                   | 0.73       |
| n7775835      | 28678357                     | 0.04-0.0-0.012                      | 0.16                       | 0.72     | 0.18                   | 0.72       |
| n1233579      | 28712663                     | 0.02-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n9257561      | 29145532                     | 0.04-0.0-0.012                      | 0.11                       | 0.72     | 0.18                   | 0.72       |
| n2523432      | 29484110                     | 0.04-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n1094128      | 30694374                     | 0.04-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n886422       | 30782205                     | 0.04-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n1312541      | 31098734                     | 0.04-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n3094013      | 31434566                     | 0.04-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n1150752      | 32064726                     | 0.01-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n2049911      | 32163166                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n9267920      | 32206243                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n7733797      | 32201252                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n150353632    | 32346463                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n9268469      | 32353590                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n9261989      | 32602030                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n9277270      | 32602226                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |
| n6004856      | 32798845                     | 0.03-0.0-0.021                      | 0.12                       | 0.72     | 0.18                   | 0.72       |

Summary statistics of top variants at xMHC region (25M–34M) with p value < 1 × 10^-8 in the discovery dataset were LD clumped (-clump-p1 1 × 10^-8, -clump-p2 0.5) and listed here. The number of SNPs clumped at each level of p value for those SNPs were also listed. Their association with ΔBPSY at 6-week in the replication dataset were also listed. Only SNPs originally genotyped but not imputed were in bold and italic font. Original and FDR-BH corrected p value was reported for real-typed or imputed SNPs. SNP ID in parentheses represented the alias name which were in line with the SNP ID in PGC GWAS in SCZ. BP was genomic coordinate based on hg19 version. We also listed the results from two real-typed SNPs, rs6904596 and rs7775397 which were in LD with rs150353632 and rs59134830, respectively. Beta values represented regression coefficient of the minor allele. OR always represented odds ratio for the effect size of A1 allele in PGC GWAS dataset. Only SNP and gene association with p < 0.001 in subjects with European Ancestry were listed here. PGCGWAS data was collected from http://www.med.unc.edu/pgc/results-and-downloads.
Multiple lines of evidence support the relationship between neuroinflammation and schizophrenia. Polygenic risk scores for SCZ were higher in patients with early-life complications (ELCs) [42]. Genes whose expression was modified by ELCs were involved in regulation of oxidative and cellular stress as well as inflammation. A meta-analysis of RNAseq and array-based transcriptome study of lymphoblastoid cell lines derived from schizophrenia cases and controls have indicated immune-related genes as the top-ranked for differential expression [43].

Our study was based on a candidate region, followed by LD-based conditional association testing, which was extended to eQTL analysis, transcriptomic imputation and association, HLA imputation and association, and PheWAS. These efforts confirmed the association between the gene expression and response to APD treatment, but also prioritized the causal SNPs/Genes. It is, thus, quite noteworthy that C4A related SNPs had the most significant and replicable association with APD response. This suggests that chronic neuroinflammation not only contributes to the risk for development of psychosis, but also is important for predicting some types of improvement with atypical APD treatment. This finding also provides additional impetus for further study of anti-neuroinflammatory drugs as adjuvants to atypical APDs [44, 45].

The contribution of the MHC to negative symptom improvement was not supported by this study, although there was some evidence that chronic neuroinflammation may contribute to negative symptoms [46].

It is noteworthy that the C4 and HLA-related SNPs which predicted response in this study did not predict treatment response in acutely psychotic, NTRS patients who were included in double-blind registration trials of lurasidone [47, 48]. This suggests that the genetic predisposition for immune activation in schizophrenia may be most important for SCZ patients with chronic psychosis [49]. Only some brain regions in SCZ may be vulnerable to inflammation. Expression of inflammatory genes may be confined to specific brain region, as a transcriptomic study found that abnormal immune/inflammatory responses were
limited to the hippocampus [50]. The hippocampal regional gene expression showed above suggests neuroinflammation may be important for the neurocognitive deficits associated with schizophrenia. Another study focusing on inflammatory genes in psychotic patients under or over 40 years of age found a difference in gene expression only in older patients [51]. The decreased expression levels of altered inflammatory genes in DLPFC in post-mortem specimens from aged SCZ correlated with the microlagical marker CD68 [52]. This supports the idea of a dysfunction of these processes in aged patients and a possible relationship with active microglia abundance.

C4A, synaptic plasticity, and effect of antipsychotic drugs
C4A copy number variation is associated with synaptic pruning. C4-deficient mice have shown decreased synaptic pruning [7]. Increased imputed C4A mRNA levels predicted poorer performance on memory recall and reduced cortical activity in middle temporal cortex during a measure of visual processing, suggesting that there is a positive correlation between predicted C4A transcription and impairment in memory [53]. A recent study on the changes in neuronal membrane expansion and contraction within the neuropil by phosphorous magnetic resonance spectroscopy has shown that C4A copy number positively correlated with neuropil contraction in the DLPFC and thalamus of adolescent-onset SCZ patients [54]. In addition, other immune-related molecules such as certain HLA I and II alleles, members of immunoglobulin superfamily, participate in the C4-mediated classical pathway, which is actively involved in activity-dependent synaptic remodeling and plasticity [55]. Identification of genetic variants which altered the expression of those molecules in this study suggests the activated autoimmune-mediated processes contribute to resistance to APDs.

Limitations
The individual genetic associations reported here need to be validated by independent studies with larger sample sizes, similar open trial design and patient cohort, conducted by other investigators. Given the main effect of βG (~3.83 for top markers like rs204991), a type 1 error rate of 1 × 10^-4 for nominal significance with two-sided test, on the continuous trait with mean ± SD of ΔBPSY as 2.98 ± 3.89, we conducted a power test using QUANTO. Our sample size of 88 had >80% power to identify a limited power to test the association in the small replication cohort expression showed above suggests neuroinflammatory changes in AD patients [83]. The leucocyte antigenic system HLA-A as a possible genetic marker of schizophrenia. Br J Psychiatry. 1974;125:25–27.

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AUTHOR CONTRIBUTIONS

HYM and JL designed this study. HYM managed a prospective longitudinal study of the effect of APDs on psychopathology and secured the funding of this study. JL conducted the statistical analyses. JL and HYM wrote the manuscript. AY and NAR critically reviewed the manuscript.

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COMPETING INTERESTS

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