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# Genetic Variants Within Molecular Targets of Antipsychotic Treatment: Effects on Treatment Response, Schizophrenia Risk, and Psychopathological Features

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## Abstract

Schizophrenia (SCZ) is a common and severe mental disorder. Genetic factors likely play a role in its pathophysiology as well as in treatment response. In the present study, we investigated the effects of several single nucleotide polymorphisms (SNPs) within 9 genes involved with antipsychotic (AP) mechanisms of action. Two independent samples were recruited. The Korean sample included 176 subjects diagnosed with SCZ and 326 healthy controls, while the Italian sample included 83 subjects and 194 controls. AP response as measured by the positive and negative syndrome scale (PANSS) was the primary outcome, while the secondary outcome was the SCZ risk. Exploratory analyses were performed on (1) symptom clusters response (as measured by PANSS subscales); (2) age of onset; (3) family history; and (4) suicide history. Associations evidenced in the primary analyses did not survive to the FDR correction. Concerning SCZ risk, we partially confirmed the associations among COMT and MAPK1 genetic variants and SCZ. Finally, our exploratory analysis suggested that CHRNA7 and HTR2A genes may modulate both positive and negative symptoms responses, while PLA2G4A and SIGMAR1 may modulate respectively positive and negative symptoms responses. Moreover, GSK3B, HTR2A, PLA2G4A, and S100B variants may determine an anticipation of SCZ age of onset. Our results did not support a primary role for the genes investigated in AP response as a whole. However, our exploratory findings suggested that these genes may be involved in symptom clusters response.

**Keywords** Schizophrenia · Genetics · Antipsychotics · Deep phenotyping

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## Introduction

Schizophrenia (SCZ) is a chronic, complex mental disorder that is among the most disabling conditions in western countries (Beers et al. 2006). It runs in families (Sullivan et al. 2003) and genetic factors play a role in its development (Schizophrenia Working Group of the Psychiatric Genomics 2014). Similarly, antipsychotic (AP) treatment effectiveness is influenced by genetics (Crisafulli et al. 2012; Gressier et al. 2016; Porcelli et al. 2016; Pouget and Muller 2014), with large variability both in terms of efficacy and tolerability among patients. Therefore, genetic research in SCZ could contribute not only to identify the biological hallmarks of the disorder, but also to predict treatment response, leading to an optimization of treatment (Owen et al. 2016). A significant step forward in SCZ genetics and pharmacogenetics fields was reached with the development of genome-wide association studies (GWAS), which were able to investigate the entire human genome, although not with a complete coverage. As a matter of fact, the largest GWAS performed so far on SCZ identified 108 independent genetic loci associated with SCZ (Schizophrenia Working Group of the Psychiatric Genomics 2014), raising new hypotheses about SCZ genetic background (Sullivan et al. 2012). Nonetheless, further confirmatory studies are needed in different populations. Furthermore, the sample sizes required for GWAS (i.e., > 10,000 subjects) do not allow to perform a deep phenotyping of the subjects recruited, limiting the possibility to elucidate the possible modulatory effects of the genes identified in the complex psychiatric phenotype (O'Connell et al. 2011). Taking into account these considerations, in the present study, we investigated the effects of a set of genetic variants within 9 genes associated with SCZ in GWAS (Schizophrenia Working Group of the Psychiatric Genomics 2014) on AP response in two independent, well-phenotyped samples. These 9 genes were selected because they are involved in AP mechanisms of action (Kusumi et al. 2015). In particular, we focused on genes coding for the direct targets of several APs, as reported in detail in Table 1. The choice to use two samples with different ancestries may help to evaluate possible ethnicity effect. In the secondary analysis, we investigated the effects of the variants in exam on SCZ risk. Finally, we also performed some exploratory analyses to better elucidate the role of these variants in SCZ, investigating their effects on AP response of symptom clusters and other psychopathological features.

## Methods

### Samples

Two independent samples were investigated in the present study, one recruited in Korea and one in Italy (see Table 2).

The Italian sample comprised of 83 SCZ subjects recruited in a naturalistic setting at the Psychiatric Inpatient Unit, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy. Patients were enrolled into the study when admitted to the inpatients unit for psychotic relapse. Inclusion criteria were age from 18 to 75 and a SCZ diagnosis according to DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al. 1998). Patients were treated according to current clinical practice. Exclusion criteria were the presence of severe medical conditions or moderate to severe dementia. Clinical and demographic characteristics of patients were assessed at the recruitment. The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) was administered at the admission and every 3 days during the hospitalization until the discharge by trained medical staff. Scorers were trained with good inter-rater reliability ($k = 0.8$). One hundred ninety-four healthy subjects were also recruited as controls. The control sample was extracted from a bigger sample already reported. The features and the assessment employed for the control sample were described elsewhere (De Ronchi et al. 2005). Both study protocols were approved by the local ethical committee.

The Korean sample comprised of 176 SCZ patients recruited at the Department of Psychiatry of the Catholic University of Korea, College of Medicine. Three hundred twenty-six healthy controls, with Korean ethnicity, were also recruited by the same institution. Briefly, all patients were admitted to inpatient unit for psychotic relapse and they were discharged when clinical conditions allow continuing treatment as outpatients. PANSS was administrated at the admission and at the discharge by trained staff. Scorers were trained with good inter-rater reliability ($k = 0.8$). For detailed inclusion, exclusion parameters as well as other criteria please refer to (Porcelli et al. 2015). The study was approved by the local ethical committee.

### Genes' Selection

The genes investigated were selected because they are within or near the loci consistently associated with SCZ by GWAS studies or large meta-analyses (Ohi et al. 2016; Schizophrenia Working Group of the Psychiatric Genomics 2014). Further, we restricted the pool of genes selecting the ones whose products were direct targets of AP drugs, since our primary outcome was the AP response. Unfortunately, because of different laboratory protocols and the different ethnicity, the subset of investigated genes was partially different between the two samples and it was not possible from a technical point of view to subsequently input the SNPs not originally genotyped in the Italian sample. SNPs within each candidate gene were chosen on the basis of literature data and to guarantee an adequate coverage of genetic variation of the genes investigated

(tagging method). At the end of the selection process, 12 SNPs within 5 genes were investigated in the Italian sample and 49 SNPs within 9 genes were investigated in the Korean sample (for detail see Table 1).

**Table 1** Investigated genes and SNPs in the two samples

| Gene | Extended name | SNPs | |
|---|---|---|---|
| | | Italian sample | Korean sample |
| CHRNA7 (Bertelsen et al. 2015) | Cholinergic Receptor Nicotinic Alpha 7 Subunit | – | rs11071511;<br>rs1392808;<br>rs1514250;<br>rs2175886;<br>rs2337980**;<br>rs3826029*;<br>rs4779565;<br>rs4779978;<br>rs6494223**;<br>rs7179008+;<br>rs8030315;<br>rs868437 |
| COMT (Matsuzaka et al. 2017) | Catechol-O-methyltransferase | rs174696;<br>rs4680** | rs174696;<br>rs4680** |
| | | – | rs2239393+;<br>rs5993883+;<br>rs740603**;<br>rs933271 |
| CREB1 (Crisafulli et al. 2012) | CAMP responsive element binding protein 1 | – | rs2254137+;<br>rs6740584+ |
| GSK3B (Chen et al. 2015) | Glycogen synthase kinase 3 beta | rs1381841 | – |
| | | rs2037547 | rs2037547 |
| | | – | rs2873950;<br>rs1719895;<br>rs6782799+ |
| HTR2A (Yildiz et al. 2013) | 5-Hydroxytryptamine receptor 2A | – | rs1328685;<br>rs582385;<br>rs7997012+;<br>rs1923886+;<br>rs2224721+;<br>rs2296973;<br>rs6311** |
| | | rs17288723 | – |
| | | rs6313**;<br>rs643627+ | rs6313**;<br>rs643627+ |
| MAPK1 (Pereira et al. 2009) | Mitogen-activated protein kinase 1 | – | rs1063311;<br>rs8136867+;<br>rs9610417 |
| PLA2G4A (Smesny et al. 2010) | Phospholipase A2 group IVA | – | rs10798069;<br>rs6695515;<br>rs7414079 |
| | | rs10489407;<br>rs12144159 | rs10489407;<br>rs12144159 |
| | | rs10737276 | – |
| S100B (Milleit et al. 2016) | S100 calcium binding protein B | – | rs2186358+;<br>rs2839350+;<br>rs2839364;<br>rs2839365;<br>rs2839366;<br>rs3788266+;<br>rs9722** |
| SIGMAR1 (Ohi et al. 2011) | Sigma non-opioid intracellular receptor 1 | – | rs10814130 |
| | | rs4879809 | – |

** already investigated in literature and associated with SCZ; * already investigated in literature, but no association reported with SCZ; + associated with other psychiatric and/or neurodegenerative pathologies. Only one reference for gene was reported in table for practical reasons (for further detail, please refer to dedicated reviews, e.g., (Kotlar et al. 2015) and (Pouget and Muller 2014))

### Genotyping

Genomic DNA of Korean samples was purified from whole blood using the QIAamp DNA Blood Midi Kit (Qiagen, CA, USA). Genotyping was performed through a pyrosequencer (Biotage AB, Sweden). PCR primers (sequences available on request) (Bioneer, Daejeon, Korea) and sequencing primers (Bioneer) used for the pyrosequencing assay were designed by using the Pyrosequencing Assay Design Software v.1 (Biotage), with 1 biotinylated primer for each pair.

Genomic DNA of Italian samples was extracted from blood sample thorough an automated magnetic beads-based nucleic acids extractor (Maxwell, Promega, Madison, WI) (Berensmeier 2006). Standard protocols were used for the above procedure (Maxwell, Promega, Madison, WI). Presence of the investigated SNPs within each sample was checked by a multiplex Sequenom MassArray platform (Sequenom Inc., CA, USA). Sequenom's MassARRAY Designer software was used to designs PCR and extension primers (sequences available on request) for each investigated SNP.

At least two readings were performed for each sample. Samples showing ambiguous alleles were discarded if they showed the same features on repeated genotyping. The final call rate was more than 99.6% for each SNP. All analyses were executed by personnel blind to diagnostic and clinical status of the subjects.

### Statistical Analyses

Haploview 3.2 software for Windows (Barrett et al. 2005) was used to test Hardy-Weinberg Equilibrium (HWE) and to build a linkage disequilibrium (LD) map for haplotype analysis. The samples were tested for genotype and alleles. The false discovery rate (FDR) correction was applied to the primary and secondary analyses (Benjamini et al. 2001) (considering 11 and 49 SNPs for the Italian and the Korean samples, respectively). The software IBM SPSS package for windows (http://www.ibm.com/) was used for ANOVA, repeated measures ANOVA and $chi^2$ tests. The primary outcome was the AP response, as measured by the improvement at PANSS from hospital admission and discharge, analyzed with repeated measures ANOVA (i.e., PANSS scores at baseline and at discharge were used as repeated measures to evaluate AP response). The percentages of improvement at PANSS scale were calculated according to literature indications (Obermeier et al. 2011) and reported in Tables 2 and 3 only to show to the reader the effects of the SNPs investigated. Secondary outcome was the SCZ risk (case-control analysis). Exploratory outcomes included AP response of specific symptom clusters (as measured by improvement at PANSS subscales), age of onset, suicide history, and psychiatric family history. All *p*-values were 2-tailed. With these parameters ($p = 0.05$), we had a sufficient power (0.80) to detect a small-medium effect size ($w = 0.14$) in the Korean sample. "R" (http://cran.r-project.org/), and the related statistic package "haplo.stat" was used for haplotype analysis. One hundred thousand permutations were performed to estimate the global significance of the results. For the haplotype analysis of AP response, the percentage of improvement from baseline to the discharge was considered after appropriate normalization (Obermeier et al. 2011).

## Results

Clinical and socio-demographic features of the samples were shown in Table 2. Briefly, the two SCZ samples did not significantly differ for age, sex, PANSS scores, age of onset, and SCZ duration. Age in the Italian control sample was higher than the other groups.

The SNPs under investigation were tested for variance, Hardy-Weinberg equilibrium (HWE), and LD in both samples (detailed results were shown in supplementary tables 1 and 2 and supplementary figures 1 and 2). SNPs which were not in HWE were excluded from the analysis.

### Primary Outcomes

Genotypic analyses in the Italian group revealed no associations with AP response. Trends of association with AP response were evidenced in the Korean sample for rs11071511 and rs2337980 within CHRNA7 ($p = 0.021$ and $p = 0.045$, respectively). In the allelic analysis, a trend of association between rs12144159 within PLA2G4A and AP response was detected in the Italian sample ($p = 0.025$). In the Korean sample, rs11071511 and rs2337980 within CHRNA7 ($p = 0.02$ and $p = 0.014$, respectively), and rs6740584 within CREB1 ($p = 0.044$) were associated with AP response. Nonetheless, none of the above associations survived to the FDR correction (for details see Table 3). Finally, in the haplotype analysis, no associations were found in the two samples.

### Secondary Outcomes

Concerning SCZ risk, no associations were found in the Italian sample both in the genotypic and allelic analysis, as well as in the haplotype analysis. On the contrary, in the Korean sample rs1063311 within MAPK1 was nominally associated with SCZ ($p = 0.039$) in the genotypic analysis, although this association did not survive to the FDR correction. In the allelic analysis, rs174696 ($p = 0.025$) within COMT and rs1063311 ($p = 0.019$) within MAPK1 were nominally associated with SCZ risk, although also these associations did not survive to the FDR correction (for detail see Table 3). Finally, haplotype analysis found an association between SCZ risk and the haplotype rs2296973 T - rs582385 T - rs2224721 C within

**Table 2** Clinical and socio-demographic features of the two samples

| Variables | Italian sample | | | Korean sample | |
|---|---|---|---|---|---|
| | Controls | Schizophrenia | | Controls | Schizophrenia |
| | ($n = 194$) | ($n = 83$*) | | ($n = 326$) | ($n = 176$) |
| | | Schizophrenia baseline | Schizophrenia and response | | |
| Gender | | | | | |
| Males | 88 (45.4%) | 44 (60.3%) | 32 (62.7%) | 147 (45.1%) | 102 (57.9%) |
| Females | 106 (54.6%) | 29 (39.7%) | 19 (37.2%) | 179 (54.9%) | 74 (42.0%) |
| Age (years) | | | | | |
| | 83.4 ± 7.1 | 42.3 ± 13.96 | 40.9 ± 14.21 | 45.36 ± 13.09 | 37.19 ± 12.67 |
| Family history of psychiatric disorders | | | | | |
| Yes | / | 28 (38.3%) | 17 (33.3%) | / | 29 (16.5%) |
| No | | 25 (34.2%) | 21 (41.2%) | | 147 (83.5%) |
| No data | | 20 (27.4%) | 13 (25.5%) | | / |
| Suicide attempts | | | | | |
| Yes | / | 17 (23.3%) | 33 (64.7%) | / | 33 (18.7%) |
| No | | 38 (52.0%) | 9 (17.6%) | | 143 (81.2%) |
| No data | | 18 (24.6%) | 9 (17.6%) | | / |
| PANSS positive score | | | | | |
| Baseline | / | 21.12 ± 7.97 | 23.39 ± 7.10 | / | 24.74 ± 4.72 |
| Discharge | | | 16.83 ± 7.94 | | 19.74 ± 4.04 |
| PANSS negative score | | | | | |
| Baseline | / | 18.66 ± 7.82 | 19.37 ± 7.90 | / | 21.89 ± 5.32 |
| Discharge | | | 15.65 ± 6.66 | | 20.19 ± 4.20 |
| PANSS general score | | | | | |
| Baseline | / | 40.45 ± 13.08 | 42.92 ± 10.91 | / | 47.83 ± 8.24 |
| Discharge | | | 31.52 ± 8.47 | | 35.90 ± 6.02 |
| PANSS total score | | | | | |
| Baseline | / | 80.23 ± 23.93 | 85.69 ± 19.61 | / | 94.46 ± 14.26 |
| Discharge | | | 64.00 ± 20.01 | | 75.84 ± 8.85 |
| Substance abuse | | | | | |
| No | / | 34 (46.6%) | 24 (47.0%) | / | / |
| Alcohol | | 3 (4.1%) | 2 (3.9%) | | |
| Illicit drugs | | 17 (23.4%) | 15 (29.4%) | | |
| Missing | | 19 (26.0%) | 10 (19.6%) | | |
| Antipsychotic drug | | | | | |
| Aripiprazole | / | 5 (7.6%) | | / | / |
| Clozapine | | 9 (13.6%) | | | / |
| Haloperidol | | 24 (36.4%) | | | / |
| Olanzapine | | 2 (3.0%) | | | 108 (61.4%) |
| Quetiapine | | 2 (3.0%) | | | 45 (25.6%) |
| Risperidone | | 19 (28.8%) | | | 23 (13.1%) |
| Others | | 12 (18.2%) | | | / |
| Other parameters | | | | | |
| Education (years) | / | 12.41 ± 4.70 | 12.10 ± 4.86 | / | / |
| Age of onset (years) | | 24.36 ± 9.09 | 24.58 ± 9.50 | | 28.76 ± 11.47 |
| SCZ duration (years) | | 15.64 ± 12.80 | 13.89 ± 12.85 | | 9.41 ± 10.79 |
| Admission duration (days) | | / | 10 | | 37.5 ± 17.08 |

*some patients with incomplete data

HTR2A gene (Global $p$ value = 0.04) (for detail see supplementary Table 3).

## Exploratory Outcomes

In exploratory analysis, trends of association were found in both the Italian and the Korean samples. We initially focused on AP response of symptom clusters, as measured by PANSS subscales, to better understand the effects of the genetic variants investigated. Detailed results are shown in Table 4. Briefly, in the Italian sample, only PLA2G4A rs12144159 was associated with positive symptoms response. On the other hand, in the Korean sample, (1) CHRNA7 rs11071511, HTR2A rs1328685, and PLA2G4A rs10798069 were associated with positive symptoms response; (2) CREB1 rs2254137 and rs6740584 were associated with general symptoms response; and (3) CHRNA7 rs2337980 and rs6494223, HTR2A rs643627, and SIGMAR1 rs10814130 were associated with negative symptoms response. Detailed results are shown in Table 4.

**Table 3** Primary and secondary results

| Gene | SNP | Var. Dep. | Italian sample | | | | Korean sample | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *p* value | Corrected *p* value | Hypothesized effect | | *p* value | Corrected *p* value | Hypothesized effect | |
| Genotypic analysis | | | | | | | | | | |
| CHRNA7 | rs11071511 | AP response | – | – | – | | 0.021 | > 0.05 | TT ↑ outcome | CC = 24.2 ± 59.1%<br>TC = 21.6 ± 16.4%<br>TT = 36.4 ± 8.3% |
| CHRNA7 | rs2337980 | AP response | – | – | – | | 0.045 | > 0.05 | TT ↓ outcome | CC = 21.4 ± 68.4%<br>TC = 28.9 ± 14.0%<br>TT = 11.1 ± 27.8% |
| MAPK1 | rs1063311 | SCZ Risk | – | – | – | | 0.039 | > 0.05 | AA ↑ risk | AA Case/Contr. Ratio: 2.333 |
| Allelic analysis | | | | | | | | | | |
| CHRNA7 | rs11071511 | AP response | – | – | – | | 0.02 | > 0.05 | C ↓ outcome | C = 23.7 ± 52.9%<br>not C = 36.4 ± 8.3% |
| CHRNA7 | rs2337980 | AP response | – | – | – | | 0.014 | > 0.05 | C ↑ outcome | C = 24.4 ± 53.5%<br>not C = 11.1 ± 27.8% |
| CREB1 | rs6740584 | AP response | – | – | – | | 0.044 | > 0.05 | C ↓ outcome | C = 23.1 ± 56.5%<br>not C = 28.4 ± 15.0% |
| PLA2G4A | rs12144159 | AP response | 0.025 | >0.05 | T ↑ outcome | $T = 42.0 \pm 25.2\%$<br>not $T = 2.4 \pm 80.6\%$ | > 0.05 | > 0.05 | – | |
| MAPK1 | rs1063311 | SCZ Risk | – | – | – | | 0.019 | > 0.05 | G ↓ risk | G Case/Contr. Ratio: 0.522 |
| COMT | rs174696 | SCZ Risk | >0.05 | >0.05 | – | | 0.025 | > 0.05 | T ↓ risk | T Case/Contr. Ratio: 0.466 |

For AP response variable mean improvement was reported. It was calculated as % of improvement after appropriate normalization (Obermeier et al. 2011). For risk variable we reported the case/control ratio for the allele/genotype associated with the outcome in exam

**Table 4** Exploratory data—AP response of symptom clusters

| Gene | SNP | Type of analysis | Italian sample | | | Korean sample | | |
|---|---|---|---|---|---|---|---|---|
| | | | *p* value | Hypothesized effect | Mean improvement (%)* | *p* value | Hypothesized effect | Mean improvement (%)* |
| Positive symptoms | | | | | | | | |
| CHRNA7 | rs11071511 | Genotypic | – | – | | 0.005 | TC ↓ outcome | CC = 27.4 ± 31.3%<br>TC = 9.0 ± 37.7%<br>TT = 45.0 ± 7.1% |
| | | Allelic | – | – | | 0.003 | T ↓ outcome | *T* = 10.8 ± 37.6%<br>not *T* = 27.4 ± 31.3% |
| HTR2A | rs1328685 | Genotypic | – | – | | 0.045 | AA ↓ outcome | AA = 21.6 ± 35.1%<br>AG = 36.6 ± 15.4%<br>GG = / |
| | | Allelic | – | – | | 0.045 | G ↑ outcome | G = 36.6 ± 15.4%<br>not G = 21.6 ± 35.1% |
| PLA2G4A | rs10798069 | Genotypic | – | – | | 0.013 | TT ↑ outcome | GG = 27.3 ± 28.3%<br>TG = 18.9 ± 35.4%<br>TT = 38.4 ± 28.1% |
| | | Allelic | – | – | | 0.006 | G ↓ outcome | G = 22.0 ± 33.1%<br>not G = 38.4 ± 28.1% |
| | rs12144159 | Genotypic | > 0.05 | – | | > 0.05 | – | |
| | | Allelic | 0.012 | T ↑outcome | *T* = 39.5 ± 42.6%<br>not *T* = −15.1 ± 87.4% | > 0.05 | – | |
| General symptoms | | | | | | | | |
| CREB1 | rs2254137 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.040 | C ↑ outcome | C = 39.6 ± 19.2%<br>not C = 31.8 ± 23.2% |
| | rs6740584 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.021 | T ↑ outcome | *T* = 39.9 ± 19.1%<br>not *T* = 31.3 ± 23.0% |
| Negative symptoms | | | | | | | | |
| CHRNA7 | rs2337980 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.016 | C ↑outcome | C = 7.5 ± 32.5%<br>not C = −38.2 ± 79.7% |
| | rs6494223 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.021 | T ↑ outcome | *T* = 7.5 ± 37.4%<br>not *T* = −3.8 ± 32.7% |
| HTR2A | rs643627 | Genotypic | > 0.05 | – | | 0.021 | AA ↑ outcome | AA = 18.4 ± 25.4%<br>AG = −0.4 ± 37.7%<br>GG = 8.3 ± 39.5% |
| | | Allelic | > 0.05 | – | | 0.016 | G ↓ outcome | G = 2.4 ± 38.4%<br>not G = 18.4 ± 25.4% |
| SIGMAR1 | rs10814130 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.039 | C ↓ outcome | C = 5.7 ± 33.5%<br>not C = 15.3 ± 39.5% |

Antipsychotic response was calculated as % improvement at PANSS scale after appropriate normalization (Obermeier et al. 2011). * Given the very limited number of subjects presenting the mutated variant, this data should be carefully interpreted since there is a high chance of a false positive

Other clinical and psychological feature were also tested for association. Briefly, in the Italian sample, HTR2A rs17288723 and rs643627, and PLA2G4A rs10737276 were associated with the age of onset of AD. Although these associations were not replicated in the Korean sample, another PLA2G4A SNP, rs12144159, showed a nominal association with AD age of onset in this sample. Furthermore, in the Korean sample, also GSK3B rs1719895 and rs2037547, and S100B rs2186358 and rs2839364 were nominally associated with AD age of onset. Detailed results are shown in Table 5.

Moreover, psychiatric family history was associated with GSK3B rs2037547 in the Italian sample. Finally, CHRNA7,

rs1514250, and rs8030315 showed nominal associations with suicide risk in the Korean sample.

Other trends were also found, but the limited number of subjects with the mutated allele, likely affected the accuracy of this data, increasing the likelihood of false positives. Further details are shown in Table 5. Given the exploratory nature of these analyses, we did not apply any statistical correction to them. Thus, these results should be interpreted carefully and only as possible suggestions for further investigations.

## Discussion

In the present paper, we investigated the effects of a set of previously identified genetic risk variants on AP response in two independent samples. The genes investigated were selected because of they were among the ones detected by the largest GWAS study on SCZ (Schizophrenia Working Group of the Psychiatric Genomics 2014) and they were known to be involved in the mechanisms of action of APs (http://www.drugbank.ca/). Although these genes have been widely investigated in SCZ field, results are still controversial and mainly related to SCZ risk. On the contrary, pharmacogenetic studies on these genes are relatively scarce, despite their involvement in APs mechanisms of action (Escudero and Johnstone 2014; Pouget and Muller 2014). We performed the analysis on two samples of different ancestries (Caucasian and Korean, respectively) in order to evidence a possible shared genetic background not influenced by ethnic differences. From this perspective, the lack of overlapping associations between the two samples in our analysis may hint to a differential impact of the genetic variants investigated in these two populations on the risk of SCZ and its treatment. As a matter of fact, ethnic differences in various parameters that may modulate the pathophysiology of psychiatric disorders have been repeatedly reported (Anderson et al. 2014; Frackiewicz et al. 1997; Lawson 1986).

In our primary analysis, we found only nominal associations among AP response and the investigated SNPs. However, the trends of association observed might support further investigations. In particular, variants within CHRNA7 and CREB1 genes in the Korean sample and variant within PLA2G4A gene in the Italian sample were nominally associated with AP response (see Table 3). CHRNA7 encodes for the $\alpha$7-nicotinic receptor subunit and maps on chromosome 15q14, a locus which was associated with SCZ (Freedman et al. 2001; Zhou et al. 2016). This gene was also associated with a deficit in inhibitory neuronal function, a condition associated with SCZ itself (Freedman 2014; Freedman et al. 2000; Leonard et al. 2002), and it is involved in cognition and social cognition mechanics, which are known to be impaired in SCZ (Ettinger et al. 2014; Schaefer et al. 2013; Sinkus et al. 2015). Our exploratory findings suggested that CHRNA7 may modulate the response of positive and negative symptoms in particular, rather than global AP response, as previously reported in literature (Kucinski et al. 2011; Martin and Freedman 2007; Olincy and Freedman 2012; Weickert and Weickert 2016). It has been hypothesized that alteration in CHRNA7 functions may result in an inappropriate modulation of dopamine system (Melis et al. 2013) with different effects across the brain, possibly explaining its associations with both positive and negative symptoms responses, as well as a possible relationship with suicidal behaviors. Moreover, impaired auditory sensory gating has been linked to the alpha7 nicotinic receptor gene (Martin and Freedman 2007). Thus, we could hypothesize that alterations within this receptor (and its subunits) may be associated with auditory hallucinations, one of the most important positive symptoms in SCZ. Finally, on the basis of its biological function, this gene may be implicated in cognitive symptoms as well. Unfortunately, PANSS did not assess specifically cognition and thus, we cannot investigate the effects of CHRNA7 variants on cognitive symptoms and further studies are needed to test this hypothesis. According to our findings, CREB1 may have a weak effect on AP response, although literature data are still controversial concerning this gene and its role in SCZ (Crisafulli et al. 2012). This gene encodes a signal transduction factor thought to be involved with SCZ pathophysiology and APs mechanisms of action. However, it is modulated by several factors, making it difficult to analyze its function only from a genetic perspective. Thus, the lack of observed associations may be explained by these confounding factors. Consistently, also in our exploratory analysis, we found only a weak association between CREB1 variants and general symptoms response. Finally, PLA2G4A enzyme catalyzes the hydrolysis of membrane phospholipids to release arachidonic acid and it is implicated in the initiation of the inflammatory response. Furthermore, this enzyme interacts with serotonin 2A and 2C receptors, modulating their activities (Eggers 2012). Thus, its observed effects on AP response may be mediated by an impaired regulation of inflammation, which has been previously associated with SCZ symptoms severity (Muller et al. 2015; Trepanier et al. 2016; Weickert and Weickert 2016), as well as by a modulation of serotonin transmission (Eggers 2012). These effects may be more relevant for positive symptoms, as suggested also by our exploratory analysis. This last hypothesis clearly needs further investigations to be confirmed. Concerning AP response, our exploratory analysis suggested some other associations which may deserve further investigations. Particularly, genetic variants within HTR2A were associated with positive and negative symptoms response in the Korean sample. Similar to CHRNA7, also alteration in HTR2A functioning may

**Table 5** Exploratory data—clinical and psychological features

| Gene | SNP | Type of analysis | Italian sample | | | Korean sample | | |
|---|---|---|---|---|---|---|---|---|
| | | | *p* value | Hypothesized effect | | *p* value | Hypothesized effect | |
| Suicide risk | | | | | | | | |
| CHRNA7 | rs1392808 | Genotypic | – | – | | 0.032* | GG ↓ Risk | GG Case/Contr. Ratio: 0.218 |
| | | Allelic | – | – | | 0.032* | T ↑ Risk | T Case/Contr. Ratio: 2.000 |
| | rs1514250 | Genotypic | – | – | | 0.028 | CC ↓ Risk | CC Case/Contr. Ratio: 0.154 |
| | | Allelic | – | – | | 0.025 | G ↑ Risk | G Case/Contr. Ratio: 0.365 |
| | rs8030315 | Genotypic | – | – | | > 0.05 | – | |
| | | Allelic | – | – | | 0.048 | T ↑ Risk | T Case/Contr. Ratio: 0.538 |
| Family history | | | | | | | | |
| GSK3B | rs2037547 | Genotypic | > 0.05 | – | | > 0.05 | – | |
| | | Allelic | 0.031 | T ↑ Family History | T Case/Contr. Ratio: 2.500 | > 0.05 | – | |
| HTR2A | rs582385 | Genotypic | > 0.05 | – | | 0.024* | TC ↑ Family history | TC Case/Contr. Ratio: NA[#] |
| | | Allelic | > 0.05 | – | | 0.024* | C ↑ Family history | C Case/Contr. Ratio: NA[#] |
| PLA2G4A | rs7414079 | Genotypic | – | – | | 0.045* | AG ↑ Family history | AG Case/Contr. Ratio: 0.423 |
| | | Allelic | – | – | | 0.025* | A ↑ Family history | A Case/Contr. Ratio: 0.393 |
| Age of onset | | | | | | | | |
| GSK3B | rs1719895 | Genotypic | – | – | | 0.012 | TT ↑ Age of onset | CC = Mean Age: 28 \| C.I.(27–30)<br>TC = Mean Age: 30 \| C.I.(25–35)<br>TT = Mean Age: 62 \| C.I.(40–84) |
| | | Allelic | – | – | | 0.003 | C ↓ Age of onset | C = Mean Age: 29 \| C.I.(27–30)<br>not C = Mean Age: 62 \| C.I.(40–84) |
| | rs2037547 | Genotypic | > 0.05 | – | | 0.012 | TT ↑ Age of onset | CC = Mean Age: 28 \| C.I.(27–30)<br>TC = Mean Age: 30 \| C.I.(25–35)<br>TT = Mean Age: 62 \| C.I.(40–84) |
| | | Allelic | > 0.05 | – | | 0.003 | C ↓ Age of onset | C = Mean Age: 29 \| C.I.(27–30)<br>not C = Mean Age: 62 \| C.I.(40–84) |
| HTR2A | rs17288723 | Genotypic | 0.026 | CC ↑ Age of onset | CC = Mean Age: 38 \| C.I.(28–48)<br>CT = Mean Age: 26 \| C.I.(20–33)<br>TT = Mean Age: 23 \| C.I.(20–27) | > 0.05 | – | |
| | | Allelic | 0.011 | T ↓ Age of onset | T = Mean Age: 24 \| C.I.(21–27)<br>not T = Mean Age: 38 \| C.I.(28–48) | > 0.05 | – | |
| | rs643627 | Genotypic | >0.05 | – | | > 0.05 | – | |
| | | Allelic | 0.044 | A ↓ Age of Onset | A = Mean Age: 24 \| C.I.(21–27)<br>not A = Mean Age: 38 \| C.I.(25–51) | > 0.05 | – | |
| PLA2G4A | rs10737276 | Genotypic | 0.009 | CC ↓ Age of onset | CC = Mean Age: 24 \| C.I.(21–27)<br>GC = Mean Age: 42 \| C.I.(29–54) | > 0.05 | – | |
| | | Allelic | 0.009 | G ↑ Age of onset | G = Mean Age: 42 \| C.I.(29–54)<br>not G = Mean Age: 24 \| C.I.(21–27) | > 0.05 | – | |
| | rs12144159 | Genotypic | > 0.05 | – | | > 0.05 | – | |
| | | Allelic | > 0.05 | – | | 0.040 | C ↑ Age of onset | C = Mean Age: 31 \| C.I.(28–34)<br>not C = Mean Age: 27 \| C.I.(25–30) |
| S100B | rs2186358 | Genotypic | – | – | | 0.012 | AA ↓ Age of onset | AA = Mean Age: 27 \| C.I.(26–29)<br>AC = Mean Age: 34 \| C.I.(30–37)<br>CC = Mean Age: 37 \| C.I.(21–53) |
| | | Allelic | – | – | | 0.003 | C ↑ Age of onset | C = Mean Age: 34 \| C.I.(30–37)<br>not C = Mean Age: 27 \| C.I.(26–29) |

**Table 5** (continued)

| Gene | SNP | Type of analysis | Italian sample | | Korean sample | | |
|---|---|---|---|---|---|---|---|
| | | | *p* value | Hypothesized effect | *p* value | Hypothesized effect | |
| | rs2839364 | Genotypic | – | – | 0.001 | TT ↑ Age of onset | CC = Mean Age: 27 \| C.I.(25–29)<br>TC = Mean Age: 34 \| C.I.(30–38)<br>TT = Mean Age: 46 \| C.I.(30–61) |
| | | Allelic | – | – | 0.001 | T ↑ Age of onset | T = Mean Age: 34 \| C.I.(31–38)<br>not T = Mean Age: 27 \| C.I.(25–29) |

*Given the very limited number of subjects presenting the mutated variant, this data should be carefully interpreted since there is a high chance of a false positive

# Within our sample, only cases presented the genotype/allele investigated

result in an inappropriate and different modulation of dopamine system across the brain (Melis et al. 2013), possibly explaining the found associations with both positive and negative symptoms responses. Finally, SIGMAR1 variants may modulate negative symptoms response, accordingly with our exploratory finding. Taking into account that SIGMAR1 may influence neurotransmitter systems (van Waarde et al. 2011), such as the glutamatergic and the dopaminergic ones (Hayashi and Su 2004), theoretically its effects on negative symptoms response may be mediated by these systems. Clearly, this hypothesis need further investigations to be tested.

Concerning the secondary analysis on SCZ risk, we found only trends of associations with variants within MAPK1 and COMT genes in the Korean sample. MAP kinases are involved in several processes such as the genesis of neural progenitors, learning, and memory (Peng et al. 2010), and were demonstrated to be essential for the induction of long-term potentiation (Miyamoto 2006; Peng et al. 2010). All these processes are thought to be altered in SCZ and consistently, variants within these genes have been repeatedly associated with this disorder (Varbanov and Dityatev 2016), as partially confirmed by our results. COMT enzyme is implicated in catecholamine degradation, particularly within the prefrontal cortex (Matsumoto et al. 2003) where alterations of its function significantly influence neurotransmitter levels (mainly dopamine). Variants within this gene have been repeatedly associated with psychiatric disorders, SCZ included (Ira et al. 2013), as partially confirmed by our results. Finally, we found an association between the HTR2A rs2296973 T- rs582385 T- rs2224721 C haplotype and SCZ risk. Some variants within this gene have been previously associated with SCZ (Gu et al. 2013). Although the SNPs in this haplotype were located in an intronic region, their effects on the gene may be exerted either on mRNA maturation level or on control of transcription. Clearly, further investigations are needed to confirm these secondary results, particularly because our sample sizes are smaller than the ones required by current standard for case-control analysis.

Concerning the other clinical parameters, we found some associations among genetic variants and SCZ age of onset. In particular, variants within PLA2G4A, GSK3B, and S100B genes in the Korean sample and variants within PLA2G4A and HTR2A genes in the Italian sample were associated with this feature (see Table 4). Partially consistent with our findings, variants within PLA2G4A (Nadalin et al. 2008; Pae et al. 2004; Wang et al. 2011) and HTR2A (Abdolmaleky et al. 2011; Ni et al. 2013; Vyas et al. 2012) genes have been already associated with SCZ age of onset. On the contrary, data about S100B are more controversial (Yelmo-Cruz et al. 2013) and this association has never been reported for GSK3B. Therefore, it could be

hypothesized that these set of genes contribute to increase the genetic load through SCZ, anticipating the age of onset of the disorder, maybe through their effects on neurotransmission and, consequently, on neurodevelopment. Partially supporting this hypothesis, variants within HTR2A and PLA2G4A genes in the Korean sample and within GSK3B gene in the Italian sample were also associated with family history of SCZ.

## Limitations

Some limitations should be mentioned with respect to our results. Firstly, because of the relative small sample sizes for genetic analysis, the possibility of both false positive and negative findings should be considered. Secondly, considering the high number of analyses performed, secondary and exploratory analyses should be considered carefully, since they have been performed only to better dissect the gene effect and to suggest further investigations. However the strong a-priori selection should guarantee versus false positive findings. Further, the coverage of the genes may not be complete, although the SNPs selection was done through the use of tagging method for coverage and literature data for phenotypic effects.

Further, the sets of SNPs selected on the two samples were partially different for ethnicity and technical reasons, allowing only a partial comparison between the samples.

This study was a naturalistic study, thus by nature, it was not possible to control for possible confounding factors, such as different dosages, duration of admission, and so on. On the other hand, naturalistic design allows investigating a setting more similar to real clinical practice, providing complementary information to RCTs. Finally, ethnic differences between the two samples should be taken into consideration in explaining the results obtained, although the use of two independents and well-phenotyped samples investigating previously relevant gene variants represent a worth of the study.

## Conclusions

In conclusion, our results did not support a primary role for the genes investigated in AP response. However, our exploratory findings suggested that these genes may play a role in symptom clusters response (i.e., negative and positive symptoms), rather than on AP global response. Furthermore, some of them, particularly PLA2G4A, seem to be associated with an anticipation of SCZ age of onset, suggesting an increased genetic load due to variants within these genes. Finally, although our samples are small for current standard in case-control analysis, some confirmatory findings emerged from our analysis about COMT and MAPK1 genes. However, limitations of the study should be carefully considered in the interpretation of results.

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