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A genetic locus in 7p12.2 associated with treatment resistant schizophrenia

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ABSTRACT

Approximately 30% of patients with schizophrenia are treatment resistant (TRS), i.e. have persistent psychotic symptoms despite adequate trials of at least two antipsychotic drugs (APDs). Most TRS patients are candidates for clozapine treatment which is underutilized because of its side effects and difficulty in identifying TRS. We conducted a genome-wide association study (GWAS) of 79 TRS and 95 non-treatment resistant (NTRS) Caucasian schizophrenia patients to identify possible biomarkers for TRS, which might also provide insight into the pathobiology of TRS. The single nucleotide polymorphism, rs2237457, located in 7p12.2, a region reported to have imprinted inheritance, was found to have the lowest p value in an allelic association test (unadjusted $p = 5.53 \times 10^{-6}$). Haploview disclosed a 30 kb block flanking this SNP within GRB10, 70 kb upstream of L-dopa decarboxylase (DDC), an enzyme which is rate-limiting in the synthesis of trace amines and neurotransmitters implicated in schizophrenia and the action of APDs. This SNP or haplotype was identified as an exclusive *cis*-acting eQTL for DDC in human dorsolateral prefrontal cortex by BrainCloud®. A replication sample genotyped for this SNP produced a weaker result, but in the same direction. After combining the two samples, rs2237457 remained significantly associated with TRS (unadjusted $p = 5.66 \times 10^{-7}$ in recessive mode; 9.42×10^{-5} in allelic association). If replicated in an independent sample, rs2237457 may provide a biomarker to identify a significant proportion of Caucasian TRS. The results implicate trace amines and their synthesis in the pathophysiology of TRS.
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1. Introduction

It is estimated that 1% of adults meet current criteria for schizophrenia. Treatment with typical or atypical antipsychotic drugs (APDs) produces significant reductions in delusions and hallucinations in about 70% of people with schizophrenia. The other 30% of schizophrenia patients are referred to as treatment resistant (TRS) or refractory schizophrenia (Kane et al., 1988a; Conley and Kelly, 2001; Tiihonen et al., 2006). TRS is operationally defined as persistence of moderate to severe positive symptoms despite two or more trials of 4–6 week duration with typical or atypical APDs other than clozapine, the only drug approved for TRS (Kane et al., 1988a; Kane et al., 1988b; Meltzer, 1997; Suzuki et al., 2012). Although most TRS patients have poor functional outcome, due in part to persistent negative symptoms and cognitive impairment, these features, which are shared by many non-TRS (NTRS) patients, are not the basis for TRS as defined here (Meltzer, 1997). It is highly likely that the neurobiology of persistent positive symptoms is only partially related, if at all, to that of cognitive impairment and negative symptoms (Meltzer, 1997).

Excluding inadequate APD trials, the differences in efficacy of APDs in TRS and NTRS patients may be based on pharmacokinetic or pharmacodynamic causes, or some combination of both. Pharmacokinetic differences in APD metabolism have rarely been shown to be causally related to poor response to APDs, but may be relevant for individual patients and drugs (Tugg et al., 1997; Meltzer, 2013). Indeed, TRS patients often receive higher doses of APDs and, despite that, have higher plasma levels. Since schizophrenia is a heterogeneous syndrome, differences in the causes of psychotic symptoms, e.g. excessive limbic dopaminergic activity, enhanced serotonin 2A receptor stimulation, or deficient GABAergic or glutamatergic activity, could be the basis for psychosis and, thus, difference in response to APDs, perhaps related to genetic and epigenetic differences.

During the past decade, there have been a number of GWAS or candidate gene studies in search for genetic marker(s) related to schizophrenia and to TRS (Supplemental Table 1). The reported effect sizes are generally small and require replication.

2. Methods and materials

2.1. Subjects

The discovery GWAS included 174 self-described Caucasian patients diagnosed with schizophrenia or schizoaffective disorder by DSM-IV

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Table 1
Demographic and clinical features for patients who are self-described Caucasians in GWAS dataset and additional dataset.

Characteristics	GWAS sample		Additional sample		p value
TR status	TR (N = 79)	NTR (N = 95)	TR (N = 70)	NTR (N = 125)	(GWAS/additional)
Male (%)	53 (67.09%)	63 (66.32%)	45 (64.29%)	79 (63.20%)	0.914/0.880[a]
Age of first onset (years)	20.37 ± 0.75	22.55 ± 0.83	19.71 ± 1.29	20.94 ± 0.76	0.058/0.380[b]
Subdiagnosis	69 (87.34%) — schizophrenia 10 (12.66%) — schizoaffective	64 (67.37%) — schizophrenia 31 (32.63%) — schizoaffective	38 (54.29%) — schizophrenia 32 (45.71%) — schizoaffective	46 (36.80%) — schizophrenia 79 (63.20%) — schizoaffective	0.002/0.018[a]
BPRS	32.96 ± 1.41	26.12 ± 1.11	31.37 ± 1.02	22.42 ± 1.17	<0.001/<0.001[b]
BPOS	11.75 ± 0.61	8.42 ± 0.46	11.04 ± 0.42	6.62 ± 0.48	<0.0001/<0.0001[b]
BMI	26.68 ± 0.68	28.77 ± 0.79	29.11 ± 0.90	30.68 ± 1.00	0.002/0.219[c]

Data was presented as Mean ± SE. BPRS represents Brief Psychiatric Rating Scale. BPOS is the sum of four positive symptoms (suspiciousness, hallucinatory behavior, unusual thought content, and conceptual disorganization) of 18 items in BPRS.
[a] Chi-square test.
[b] *t*-Test.
[c] ANCOVA test adjusted by Gender.

criteria. Those subjects had participated in prospective clinical trial or longitudinal study of the effect of clozapine (Meltzer, 1997). An additional 195 subjects with these diagnoses who had been prospectively classified as TRS or NTRS were identified from subsequent clinical trials or cross-sectional study in our laboratory.

2.2. Genotyping and data analysis

SNP genotyping was performed using 610K quad BeadChip® (Illumina) or Taqman® assay (Applied Biosystems). Quality control of genotyping data was described in Supplemental information. Association testing was conducted with PLINK 1.0.7 software (Purcell et al., 2009) and SPSS. QUANTO 1.2 was used for power test. BrainCloud (Colantuoni et al., 2011) was used to identify the potential *cis*-eQTL. ENCODE and UCSF Brain Methylation Database (Maunakea et al., 2010) were applied for functional prediction as *cis*-regulatory elements.

3. Results

Clinical characteristics and demographic feature for the GWAS sample: TRS (n = 79) and NTRS (n = 95) patients, and for the additional subjects who were genotyped (TRS: n = 70 and NTRS: n = 125) are reported in Table 1. There was no significant difference between the four groups in gender. Age at onset was nearly significantly earlier in the TRS patients, consistent with our previous report of a larger sample (Meltzer et al., 1998).

SNPs which differentiated TRS and NTRS by allelic association test (Fig. 1A) and Cochran–Armitage trend test (Supplemental Fig. 2A) are demonstrated in a Manhattan plot (Fig. 1A). No SNP met genome-wide significance for association with TRS. Six SNPs had unadjusted $p < 10^{-5}$ after relaxing the corrected p value for FDR-BH to 0.56 (Supplemental Table 2).

3.1. GRB10

rs2237457, a GRB10 SNP, one of the top hits associated with TRS, resides in a well-known imprinted genomic region, 7p12.2 (GRB10–DDC), in human (Blagitko et al., 2000; Yoshihashi et al., 2000) and mouse (Arnaud et al., 2003; Menheniott et al., 2008; Garfield et al., 2011). Due to unclear parental origin of risk allele, we re-analyze the GWAS dataset by excluding the 71 cases with heterozygous genotype for rs2237457, leaving 53 NTRS cases and 50 TRS cases. The association with TRS was significantly enhanced, from $p = 5.53 \times 10^{-6}$ with the heterozygotes to $p = 4.99 \times 10^{-12}$, by allelic association test. There were no other SNPs across the whole genome close to the same level of significance as rs2237457, or SNPs in LD with rs2237457, in a

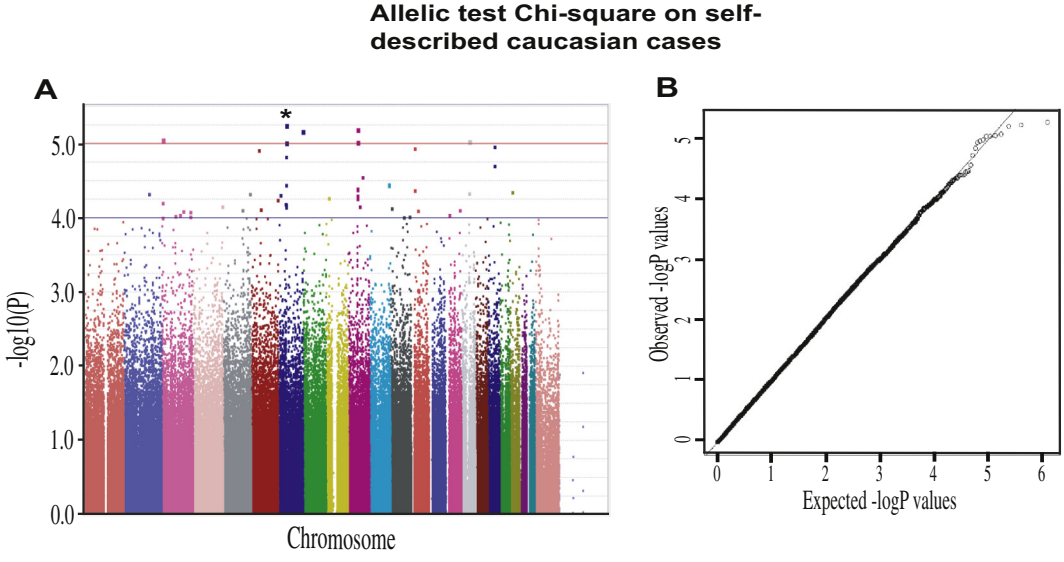

Fig. 1. Manhattan plot and Q–Q plot of genome-wide association with allelic Chi-square test. Panel A shows a Manhattan plot for all self-described Caucasian cases in the GWAS. "*" marks regions on chromosome 7 that reach highest genome-wide significance ($p < 10^{-5}$). Values for each chromosome are shown in different colors for visual effect. Panel B shows the Q–Q plots for the corresponding test of association. This plot shows no deviation from the null distribution, except in the upper tail of the distribution, which corresponds to the SNPs with the strongest evidence for association. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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