We conducted a three-stage genome-wide association study (GWAS) of response to antidepressant drugs in an ethnically homogeneous sample of Korean patients in untreated episodes of nonpsychotic unipolar depression, mostly of mature onset. Strict quality control was maintained in case selection, diagnosis, verification of adherence and outcome assessments. Analyzed cases completed 6 weeks of treatment with adequate plasma drug concentrations. The overall successful completion rate was 85.5%. Four candidate single-nucleotide polymorphisms (SNPs) on three chromosomes were identified by genome-wide search in the discovery sample of 481 patients who received one of four allowed selective serotonin reuptake inhibitor (SSRI) antidepressant drugs (Stage 1). In a focused replication study of 230 SSRI-treated patients, two of these four SNP candidates, which were in perfect linkage disequilibrium. These two significant SNPs were confirmed also in a focused cross-replication study of 159 patients treated with the non-SSRI antidepressant drug mirtazapine (Stage 3). Analysis of the Stage 1, Stage 2 and Stage 3 samples combined (n = 870) also revealed GWAS significance for these two SNPs, which was sustained after controlling for gender, age, number of previous episodes, age at onset and baseline severity (P = 3.57 × 10−8). For each SNP, the response rate decreased (odds ratio = 0.31, 95% confidence interval: 0.20–0.47) as a function of the number of minor alleles (non-response alleles). The two SNPs significantly associated with antidepressant response are rs7785360 and rs12698828 of the AUTS2 gene, located on chromosome 7 in 7q11.22. This gene has multiple known linkages to human psychological functions and neurobehavioral disorders. Rigorous replication efforts in other ethnic populations are recommended.

TRANSLATIONAL PSYCHIATRY (2015) 5, e633; doi:10.1038/tp.2015.127; published online 8 September 2015

INTRODUCTION
Response rates in drug treatment of major depression are unsatisfactory.1 Initial antidepressant treatments fail in at least one-third of patients.2 In addition, there are no biomarkers of treatment response. On the basis of family studies of response to antidepressants,3,4 genetic markers hold promise for improving this record.5

Selecting candidate genes related to antidepressant response is difficult because of our limited knowledge of the underlying biology. In addition, most pharmacogenetic studies that have focused on a few candidate genes (for example, serotonin transporter gene, SLC6A4) have shown results that lack sufficient predictive power to be useful in clinical practice.6 Recently, several genome-wide pharmacogenetic studies of antidepressant treatment in major depressive disorder (MDD) were conducted to overcome these limitations.7–11 However, none of their full-sample results reached genome-wide levels of statistical significance, and the top results were also inconsistent.6 These failures underscore the heterogeneous phenotype and the complex nature of clinical depression. In addition, these large, multisite studies risk being confounded by heterogeneity of case material, ethnicity and recruitment practices.12,13

In this study, we conducted a genome-wide pharmacogenetic study in ethnically homogeneous patients, with careful quality control. The discovery phase was conducted in a single, experienced clinical research site. The resulting significant findings were then validated in an independent, ethnically identical sample (replication sample). Our hypothesis is that common DNA variations are associated with antidepressant response to selective serotonin reuptake inhibitors (SSRIs). As a secondary question, we investigated whether the same genomic associations held true for a non-SSRI antidepressant drug in the same homogeneous ethnic group (cross-replication sample).

MATERIALS AND METHODS
Definition of cohorts
We enrolled a total of 1039 patients overall. For the discovery and replication phases, we enrolled 859 SSRI-treated patients. Of these, 760 were seen at the Samsung Medical Center (SMC; Seoul, Korea), and 99

1Department of Psychiatry, Samsung Medical Center, Seoul, Korea; 2Sungkyunkwan University School of Medicine, Seoul, Korea; 3Center for Clinical Research, Samsung Biomedical Research Institute, Seoul, Korea; 4Biostatistics Team, Samsung Biomedical Research Institute, Seoul, Korea; 5Department of Psychiatry, College of Medicine, Korea University, Seoul, Korea; 6Soonchunhyang Medical Institute, College of Medicine, Soonchunhyang University, Asan, Korea; 7Department of Laboratory Medicine and Genetics, Samsung Medical Center, Seoul, Korea and 8Pacific Behavioral Research Foundation, Carmel, CA, USA. Correspondence: Dr J-W Kim, Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea or Dr DK Kim, Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea. E-mail: kimjw@skku.edu or paulkim@skku.edu
9These authors contributed equally to this work.
10These authors contributed equally to this work.

Received 26 March 2015; revised 20 June 2015; accepted 8 July 2015
were seen contemporaneously at a second site—Korea University Medical Center (Seoul, Korea). After dropouts as detailed in Figure 1, there were 500 completer patients in the SSRI discovery set in the first phase of this project and 230 completer patients in the SSRI replication set in the later phase of the project. Thus, the overall protocol completion rate was 85.0% (730/859) among the SSRI-treated patients. In addition, 19 completer cases were removed from analysis of the discovery set because identity-by-descent analysis revealed possible relatedness with a previously enrolled patient. The enrolled cross-replication set comprised 180 mirtazapine-treated patients, all of whom were seen at SMC (Figure 1). Of these, 159 completed the protocol with a protocol completion rate of 88.3% (dropsouts detailed in Figure 1). Thus, the overall successful protocol completion rate was 85.5% (889 of 1039 enrolled cases). The completer cohorts analyzed after removal of the identity-by-descent cases comprised 481 patients in the SSRI discovery set; 230 in the SSRI replication set; and 159 in the mirtazapine cross-replication set—a total of 870 cases (Figure 1 and Table 1). The SSRI drugs given in the 481-patient discovery set and in the 230-patient replication set are shown in Table 1.

Study patients from the SMC

We enrolled the patients from April 1999 through April 2012. A total of 940 patients with MDD, were recruited from the clinical trials program of the Samsung Medical Center Geropsychiatry and Affective Disorder Clinics. These included 101 of 136 subjects reported previously and recruited within the time window of the present report. All cases were clinically referred and all were of unrelated Korean ancestry. Consistent with current genome-wide association study (GWAS) strategy, the study was conducted in a naturalistic clinical setting rather than in a placebo-controlled clinical trial. Inclusion criteria were 18 years of age or older, the existence of a current unipolar major depressive episode as verified by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision (DSM-IV-TR) criteria for MDD, and being capable of providing informed consent. The diagnosis was based on an initial clinical interview, followed by a structured research assessment, the Samsung Psychiatric Evaluation Schedule, which includes the Structured Clinical Interview for DSM-IV. The final diagnosis was made by a board-certified psychiatrist after review of ongoing clinical observations, medical records, past histories and Structured Clinical Interview for DSM-IV interview. The baseline minimum 17-item Hamilton scale for depression (HAM-D) score required for enrollment was 15. Exclusion criteria were pregnancy, significant medical conditions, abnormal laboratory baseline values, unstable psychiatric features (for example, suicide attempt), histories of alcohol or drug dependence, seizure, neurological illness, including significant cognitive impairment, or concomitant DSM-IV Axis I psychiatric disorder. Patients with MDD who met DSM-IV criteria for the specifier ‘Severe With Psychotic Features’ were excluded because they would normally receive concurrent antipsychotic medication. No patient had received psychotropic medication within the current episode, an average duration of 3–5 months and a minimum duration of 4 weeks (Table 1).

Procedures

Patients received monotherapy for 6 weeks with an antidepressant drug. As shown in Figure 1 and Table 1, 481 completer patients in the discovery cohort and 230 completer patients in the replication cohort received one of four allowed SSRI drugs (total 711 SSRI-treated patients), whereas 159 patients in the completer cohort of the cross-replication sample received mirtazapine. The clinician’s antidepressant choice was naturalistic, taking account of anticipated adverse effects. Dose titration was completed within 2 weeks. Trough plasma samples were drawn at the end of week 6 for plasma drug concentrations. Lorazepam (0.5–1 mg) was allowed at bedtime for insomnia.

Patients were seen by a psychiatrist, who monitored their adverse events by the Udvalg for Kliniske Undersøgelser scale at weeks 0, 1, 2, 4 and 6. HAM-D was administered by a single trained rater every 2 weeks. During the 13 years of this study, five clinical psychologists performed the HAM-D ratings. All raters had received HAM-D training, supervised by two licensed clinical psychologists. They reviewed and rated demonstration tapes of HAM-D ratings. An intraclass correlation coefficient of 0.91 was obtained for the 17-item total HAM-D score.

The rater and genotyper were blinded to the hypotheses and to drug assignment. HAM-D and genotype data were not disclosed to the psychiatrist, and the rater was blinded to the genotype data. To maintain the blindness, a trained research coordinator managed the data and schedules. At 6 weeks, response was defined according to standard conventions as ≥50% decrease in the HAM-D score. Remission was defined as a HAM-D score of less than 8 at 6 weeks.

Figure 1 shows the flow of patients through the study. As this is a discovery project, outcome analyses included only subjects who completed 6 weeks of treatment with adequate drug plasma levels. Detailed description for the flow is provided in Supplementary Material and Methods (Supplementary Text S1).

The analyzed replication set included 85 completer patients of 99 enrolled patients recruited from the Pharmacogenomic Research Center for Psychotropic Drugs of the Department of Psychiatry, Korea University Medical Center. The procedures followed at this site were closely similar to those described for SMC patients. The significant exceptions were that these patients did not provide samples for antidepressant blood level determinations and there was no information on duration of current episode. The detailed protocols were described in previous reports from Korea University Medical Center. The protocol was approved by the ethics review board of SMC and by the ethics committee of the Korea University Medical Center. Signed informed consent was obtained from all participants.

Genotyping

We used the Affymetrix Genome-wide Human single-nucleotide polymorphism (SNP) array chip 6.0 for 905,431 SNPs for genotyping the discovery set. Four candidate SNPs \( p < 1.00 \times 10^{-5} \) were identified in the
Table 1. Clinical and demographic characteristics of analyzed complete cohorts

| Characteristic                              | Discovery set (N = 293) | Replication set (N = 159) | Cross-replication set (N = 159) |
|--------------------------------------------|-------------------------|---------------------------|---------------------------------|
| **Total**                                  | Responders | Nonresponders | Responders | Nonresponders | Responders | Nonresponders | Responders | Nonresponders |
| **Gender, female (%)**                     | 118 (41%)     | 118 (41%)     | 68 (42.8%) | 68 (42.8%)     | 68 (42.8%) | 68 (42.8%)     |
| **Age, year (years)**                      | 57 (45, 67)   | 58 (45, 67)   | 58 (45, 67) | 55 (43, 69)    | 59 (39, 69) | 50 (36, 69)    |
| **Number of episodes**                     | 3 (2, 4)      | 3 (2, 4)      | 2 (1, 4)   | 2 (1, 4)       | 2 (1, 4)   | 2 (1, 4)       |
| **Duration of current episode, months**    | 56 (48, 66)   | 56 (48, 66)   | 56 (48, 66) | 56 (48, 66)    | 56 (48, 66) | 56 (48, 66)    |
| **HAM-D baseline**                         | 19 (17, 23)   | 19 (17, 23)   | 19 (17, 23) | 19 (17, 23)    | 19 (17, 23) | 19 (17, 23)    |

**Abbreviations:** HAM-D, Hamilton depression rating score; SSRIs, selective serotonin reuptake inhibitors.

For non-normally distributed continuous variables, results are presented as the median and interquartile range, and nonparametric tests (the Wilcoxon rank-sum test and the Kruskal–Wallis test) were used to compare groups. Categorical variables are summarized as frequencies and proportions. Fisher’s exact test was used to compare groups on categorical variables. P-values were corrected by Bonferroni’s correction in case of multiple testing, and marked as ‘corrected P’.

RESULTS

**Subject characteristics**

Clinical and demographic characteristics are shown in Table 1. Subjects were mostly elderly, and experiencing their second or later episode of MDD. Approximately one-fifth of the patients had a positive family history of depression. The median pretreatment HAM-D score was 19, which indicates moderately severe depression. Observed response rates were above 50% in the discovery and replication sets, and a higher response rate was seen in the cross-replication set. The remission rate as a proportion of the response rate was 0.63 in the discovery set, 0.67 in the replication set, and 0.59 in the cross-replication set. These proportions are typical of antidepressant trials and they suggest that rating bias was not present. There were statistically significant but clinically minor differences among sets with respect to gender, age, age at first episode and number of past episodes. Number of episodes, duration of current episode and baseline HAM-D score in the discovery set, gender, duration of current episode and baseline HAM-D score in the replication set, and number of episodes in the cross-replication set were associated with response. Drug choice within the SSRi class differed between the discovery set and the replication set, but was not associated with response rate differences across the two sets (Table 1).

**Genetic-association analysis of SSRI treatment response in discovery set**

Four SNPs rs10924309, rs7785360, rs12698828 and rs8017553, all with $P < 1.0 \times 10^{-5}$, were identified in the discovery set. These were then tested as candidate SNPs for the replication phase. These candidate SNPs resided on chromosomes 1q44, 7q11 and 1q41. The graphical summary of genome-wide association results is shown in a Manhattan plot (Figure 2). The results of association analyses for these four SNPs are shown in Table 2, and the top 100 ranked SNPs are presented in Supplementary Table S1. The detailed results including quality control, quantile–quantile plot (Supplementary Figure S1), and multidimensional scaling analysis (MDS plot, Supplementary Figure S2) are provided in Supplementary Results (Supplementary Text S1).
Genetic-association analysis of SSRI treatment response in replication set
A focused replication study was performed for the four candidate SNPs from the three chromosomal loci shown in Table 2. Two intronic polymorphisms on 7q11.22 in perfect linkage disequilibrium (LD), rs7785360 and rs12698828, showed the most significant association with response in the replication set (nominal \( P = 1.48 \times 10^{-3} \), corrected \( P = 0.006 \) Table 2). These two SNPs are part of the AUTS2 gene in 7q11.22. The directions of association of these SNPs in the replication set were identical to those in the discovery set. None of the remaining two candidate SNPs was replicated (corrected \( P > 0.05 \)).

In a combined analysis of the discovery and replication sets, the two intronic SNPs (rs7785360 and rs12698828) of the AUTS2 gene in 7q11.22 showed genome-wide significance (nominal \( P = 1.48 \times 10^{-3} \), corrected \( P = 0.006 \) Table 2). These two SNPs are part of the AUTS2 gene in 7q11.22. The directions of association of these SNPs in the replication set were identical to those in the discovery set. None of the remaining two candidate SNPs was replicated (corrected \( P > 0.05 \)).

Genetic-association analysis of antidepressant response in cross-replication set
The two SNPs in the AUTS2 gene (rs7785360 and rs12698828) on chromosome 7 that showed genome-wide significance in the combined discovery and replication sets were also associated with antidepressant response to mirtazapine in a focused study of the cross-replication set (nominal \( P = 0.02 \), corrected \( P = 0.04 \), Table 2). The directions of this association were identical to those in the SSRI-treated combined discovery and replication sets. For each SNP, the minor allele frequencies of responders were lower than for non-responders (0.04 versus 0.12). In addition, these SNPs were not associated with any subject characteristics, drug choice or drop-out (\( P > 0.05 \)).

Genetic-association analysis of all-combined set
In a combined analysis for all analyzed completer patients (\( n = 870 \)), the two SNPs each showed genome-wide significance (\( P = 6.60 \times 10^{-16} \)) for association with antidepressant response (Table 2) in univariate analysis. Next, we tested potential confounding variables of this association. Responders had fewer previous episodes, shorter duration of current episode, older age at onset and lower baseline HAM-D scores than non-responders in the all-combined set (Supplementary Table 2). In addition, number of previous episodes was significantly associated with the two SNPs (\( P = 0.02 \)), but gender, age, family history, duration of current episode, age at onset, baseline HAM-D score and drug choice were not. Therefore, number of previous episodes was considered as a possible confounding variable and entered in the multiple
logistic regression model. The GWAS-level associations between each of these two SNPs and antidepressant response were preserved after controlling for gender, age, number of previous episodes, age at onset and baseline HAM-D scores \((P=3.57 \times 10^{-8}, \text{ Supplementary Table 3})\). For each SNP, the response rate decreased (odds ratio = 0.31, 95% confidence interval: 0.20–0.47) as a function of the number of minor alleles (non-response alleles). However, the explanatory power of this logistic regression model was relatively small (Cox and Snell’s \(R^2 = 0.09\)).

Genetic-association analysis of remission

The top 100 ranked SNPs in the discovery set for the association with remission are presented in Supplementary Table S4. The top results between response and remission were inconsistent. In addition, we tested the association between these SNPs and remission. The two SNPs in perfect LD did not show genome-wide significance \((P=1.94 \times 10^{-8})\) for association with the remission status in a combined analysis for all patients. This trend-level result was expected based on the smaller number of remitters compared with responders.

**DISCUSSION**

In this study we investigated the whole genomic associations of antidepressant response to SSRIs. We identified associations between response and two intronic SNPs \((rs7785360 \text{ and } rs12698828)\) in the \(AUTS2\) gene on 7q11.22, and we replicated these findings in an independent sample. In addition, we showed in a cross-replication set that these SNPs were also associated with antidepressant response to mirtazapine, a non-SSRI antidepressant, with identical directions to those in the SSRI-treated sets. In the combined discovery and replication samples of 711 patients who received SSRIs the identified SNPs achieved genome-wide significance \((P=1.60 \times 10^{-8})\). Likewise, genome-wide significance was determined for the combined three completer cohorts numbering 870 patients, with \(P=6.60 \times 10^{-10}\) (Table 2).

In addition, these significance levels were preserved after controlling for gender, age and number of previous episodes \((P=2.35 \times 10^{-8})\).

The \(AUTS2\) gene product is a nuclear protein that is expressed in the central nervous system in humans, especially in the cortical plate and ventricular zone, as well as the dentate gyrus, cornu ammonis (CA) 1 and CA3 areas of the hippocampus. The \(AUTS2\) gene has been repeatedly implicated in neurodevelopmental disorders including autism, intellectual disability and developmental delay. In studies of human evolution, the \(AUTS2\) gene was found to have significant changes between modern humans and Neanderthals, which has led to suggestions that \(AUTS2\) might be involved in cognitive traits specific to humans. In addition, \(AUTS2\) expression has significant associations with nicotine dependence, cannabis dependence, alcohol sensitivity and anti-social personality. The \(AUTS2\) locus is implicated in schizoaffective or bipolar affective disorder patients. A recent pedigree analysis reported an association of the \(AUTS2\) gene and suicide.

In the present study, we found two SNPs \((rs7785360 \text{ and } rs12698828)\) of the \(AUTS2\) gene associated with antidepressant response. This result was replicated and cross-replicated, as described in Results. A next-generation sequencing study may be linked with a final common action of different antidepressants. SSRIs increase the level of serotonin in the synaptic cleft. In addition, mirtazapine has
a dual action profile on both the noradrenergic and serotonergic neurotransmitter systems. There is a possibility that the serotonergic system could be linked to an unknown pathway with which these SNPs are related. A previous protein expression study found that the AUTS2 gene is expressed in frontocortical glutamatergic neurons. These excitatory neurotransmitter neurons are involved in mood circuitry. Depressed patients have abnormalities in glutamatergic neurotransmission. In addition, the glutamate system is modulated by antidepressants that affect serotonin. Therefore, the glutamatergic system could be a connecting link between the AUTS2 gene and antidepressant response. Another possible link is brain-derived neurotrophic factor. It has been shown that both SSRIs and mirtazapine induce brain-derived neurotrophic factor production in the brain. In addition, brain-derived neurotrophic factor and the AUTS2 gene have been linked to autism spectrum disorder. Further studies with the pathway of the AUTS2 gene are required to clarify these possible connections. The second possibility is that these SNPs are associated with nonspecific improvement (placebo effect) rather than with specific antidepressant response. Similar to previous GWAS studies for antidepressant response, our study was a naturalistic one; therefore, it did not have a placebo-treated group. Further studies with placebo-treated groups or groups treated with non-pharmacological interventions will be helpful to clarify this issue.

So far as we know, there have been no previous GWAS of antidepressant response among Asian patients except a Japanese pilot study with small sample size \(n = 92\). In addition, this is the first GWAS that found significant associations between SNPs and response to multiple antidepressants in any ethnic group. Most previous GWAS studies were not able to identify associations that reached genome-wide statistical significance. Garriock et al. reported a GWAS of response to citalopram in patients of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. They suggested trend-level associations of three SNPs near the Ubiquitin protein ligase E3C (UBE3C) gene (rs6966038), the bone morphogenic protein 7 (BMP7) gene (rs6127921) and a third intronic SNP in the RAR-related orphan receptor alpha (RORA) gene (rs809736). Another group, the Munich Antidepressant Response Signature study, suggested different markers, also at a trend level: rs6989467 in the Cadherin-17 gene (CDH17) and rs1502174 in the Ephrin type-B gene (EPHB1). However, none of those suggested loci achieved GWAS significance. Another GWAS conducted by Uher et al. reported two gene markers with only ‘suggestive’ significance: rs2500535 in the interleukin-11 gene (IL11) and they reported that rs2500535 in the Uronyl 2-sulphotransferase gene (UST) showed significant association only in a subgroup analysis of patients who received nortriptyline. In addition, Tansey et al. reported negative results in a GWAS of over 2000 European-ancestry individuals with MDD. None of these associations was replicated, and the top results were also inconsistent among those studies, as well as with our study. None of our significant SNPs were replicated in a meta-analysis of the open data sets of STAR*D, GENDEP and Munich.

Figure 3. Regional association plot. P-values (ordinate axis, upper panel) are from the Cochran–Armitage trend test in the discovery set (circles: genotyped single-nucleotide polymorphisms (SNPs) and squares: imputed SNPs) and combination set (diamonds: the discovery and replication sets, triangles: discovery, replication and cross-replication set) in upper panel. The blue lines indicate the recombination rates in cM per Mb estimated using HapMap samples (upper panel). A horizontal line indicates the location of the AUTS2 gene (middle panel). A linkage disequilibrium map based on \(r^2\) values was computed using the Hapmap JPT+CHB data (the International HapMap Project data, bottom panel).
Antidepressant response genome-wide association study
W Myung et al

Antidepressant Response Signature (http://www.broadinstitute.org/mpg/ricopill) that included only European-ancestry cases.\textsuperscript{51}

We can suggest several reasons for such discrepancies in these GWAS studies of antidepressant response. The first is ethnicity: as Porcelli et al.\textsuperscript{22} reported, a genetic marker could have different significance according to the ethnicity of subjects. In a systematic meta-review of 33 studies, they showed that the serotonin transporter gene promoter polymorphism (5-HTTLPR) could be a predictor of antidepressant response and remission in Caucasians, whereas in Asians it does not appear to have a major role. Similarly, the STAR\textsuperscript{D} group showed that the association they observed between a gene (HTR2A) and treatment outcome of depression was confined to Caucasians.\textsuperscript{23} In addition, a GWAS of antidepressant response conducted by the STAR\textsuperscript{D} group reported no correlation of the SNP rankings across ancestry groups.\textsuperscript{7} These studies suggest a possibility that ethnic groups differ in their specific genetic markers for antidepressant response. Our previous report\textsuperscript{24} that investigated serotonin transporter genotype and function showed that functional differences associated with ethnicity could be a reason for this discrepancy of significant genetic markers. A recent investigation for the consistency of genome-wide associations across ancestral groups lends weight to this interpretation. Ntzani et al.\textsuperscript{25} analyzed more than a hundred genome-wide associations with nearly a thousand data sets, and reported differing risk estimates and considerable heterogeneity across ancestry groups. In addition, there is a possibility that the potential environmental modifiers could result in such discrepancies.\textsuperscript{26} In the field of antidepressant pharmaco-genomics, further replication attempts, supported if possible by functional studies, in well-defined ethnic groups are needed.

Another possible factor for the lack of agreement between our results and previous reports is the age stratification of the depressed populations studied. Our patients were mostly of mature age (81.6\% aged \(>50\) years), and most of them (62.3\%) had the first onset of depression after the age of 50 years. Previous studies that compared antidepressant response and age of first onset showed no relationship,\textsuperscript{57,58} and some previous pharmacogenetic studies reported similar results with elderly and younger patients. However, several studies have suggested that age at onset can distinguish subtypes of depression, especially in terms of heritability.\textsuperscript{59,60} Therefore, there is a possibility that the relatively large proportion of elderly patients in our study might be associated with reduced genetic and also clinical heterogeneity.

In a recent meta-analytic review, Undurraga and Baldessarini\textsuperscript{61} suggested that increasing subject numbers and recruitment sites have led to falling effect sizes in antidepressant trials. They recommended better quality control of diagnostic and clinical assessments as an alternative to the strategy of recruiting very large samples. From this point of view, strengths of our study include a limited number (2) of well-designed programs, managed by experienced research teams, with strictly blinded quality control. Other strengths of our study are ethnic homogeneity, confirmation of compliance by drug plasma level, inclusion of only clinically referred cases, clinical diagnoses by experienced psychiatrists in advance of confirmatory research diagnostic interviews\textsuperscript{52} and outcome assessments by consistent raters in person rather than by telephone. Moreover, we did not enroll subjects who had been exposed to any psychotropic drugs, including especially antidepressants, in the current episode of depression. By these means, heterogeneity and confounding of the case material were moderated in comparison with previous GWAS reports.

Although our sample is comparable in size to some previous GWAS reports,\textsuperscript{8,9,11} there are others with larger sample sizes that reported negative results.\textsuperscript{7,10} However, we enrolled an ethnically homogeneous sample, as confirmed by the MDS plot (Supplementary Figure S2). In addition, the Korean population is genetically homogeneous.\textsuperscript{63} Therefore, we could avoid a population stratification step that might reduce statistical power in those previous studies, and we more precisely controlled the problem of ethnic heterogeneity than using rough classification by self-reported ancestry.

A potential limitation of our study is its naturalistic design. This design is the rule in GWAS of depression because it reflects the real world of depression management. With this design, clinical judgment enters into the choice of drug. Thus, there could be a selection bias for different drugs on the basis of prescriber preference and patient characteristics. However, any such selection bias would not affect the genetic associations with response in a drug class. A further limitation is that we found only a trend-level significance of association between the two SNPs and remission. This result was expected because the remission rate is always lower than the response rate in typical antidepressant trials,\textsuperscript{29} therefore, for adequate power a larger sample size would be required for analyses of remission. In addition, the low explanatory power of our result should be noted. It suggests that the prediction with the significant SNPs will not be sufficient for personalized treatment of depression at this stage. Another consideration is that because our patients were mostly elderly, the generalizability of our results to depressed patients in other age groups may be limited.

In conclusion, we conducted a GWAS of antidepressant drug response in Korean patients. We found a significant association between response to SSRIs and the two SNPs rs7785360 and rs12698828 in the AUTS2 gene on chromosome 7, and the association generalized to response to mirtazapine with identical direction. These results may elucidate the common biological mechanisms of antidepressant drug action and they may further the search for genomic-based selection of antidepressant treatments. Further studies in a variety of ethnic populations will be required.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENTS
This study was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2014R1A2A1A0052419, to DDK), the Korean Health Technology R&D Project through the Korea Health Industry Development Institute (HIHID) funded by the Ministry of Health & Welfare, Republic of Korea (HIH-IC2071, to DDG), Lundbeck (to DDG) and the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2014M3C7A1046049, to J-WK).

DISCLAIMER
The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS
DDK and J-WK had full access to all data in the study and final responsibility for the decision to submit for publication. Study concept and design: DDK, J-WK, WM, JK, S-WL, Sangha K and H-HW. Study supervision: DDK, J-WK and J-resolution of the manuscript for important intellectual content: DDK, J-WK and BJ-C. Statistical analysis: JK, Seonwook K and WM. Obtained funding: DDK and J-WK. Study supervision: DDK.

Translational Psychiatry (2015), 1 - 9
REFERENCES

1. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L et al. Efficacy of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163: 28–40.
2. Hennings JM, Ovsashi T, Binder EB, Horstmann S, Menke A, Kloiber S et al. Clinical characteristics and treatment outcome in a representative sample of depressed inpatients - findings from the Munich Antidepressant Response Signature (MARS) project. J Psychiatr Res 2009; 43: 215–220.
3. Franchini L, Serretti A, Gasparrini M, Smeraldi E. Familial concordance of fluvoxamine response as a tool for differentiating mood disorder pedigrees. J Psychiatr Res 1998; 32: 255–259.
4. O'Reilly RL, Bogue L, Singh SM. Pharmacogenetic response to antidepressants in a multicase family with affective disorder. Biol Psychiatry 1994; 36: 467–471.
5. Laje G, Perls R, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. Psychiatr Serv 2009; 60: 1446–1457.
6. Laje G, McMahon FJ. Genome-wide association studies of antidepressant outcome: a brief review. Prog Neuropsychopharmacol Biol Psychiatry 2011; 35: 1553–1557.
7. Garrick HO, Kraft JB, Shyn SJ, Peters EJ, Yokoyama JS, Jenkins GD et al. A genomewide association study of citalopram response in major depressive disorder. Biol Psychiatry 2010; 67: 133–138.
8. Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S et al. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. Arch Gen Psychiatry 2009; 66: 966–975.
9. Uher R, Perroud N, Ng MY, Hauser J, Henigsberg N, Maier W et al. Genome-wide pharmacogenetic antidepressant response in the GENDEP project. Am J Psychiatry 2010; 167: 355–364.
10. Tansey KE, Guignoni M, Perroud N, Bondolfi G, Domenici E, Evans D et al. Genetic predictors of response to serotonergic and noradrenergic antidepressants in major depressive disorder: a genomewide analysis of individual-level data and a meta-analysis. PLoS Med 2012; 9: e1001326.
11. Ji Y, Biemarca JM, Hebbirgin S, Chai Y, Jenkins GD, Batzler A et al. Pharmacogenomics of selective serotonin reuptake inhibitor treatment for major depressive disorder: genomewide associations and functional genomics. Pharmacogenomics 2013; 13: 456–463.
12. Demirtack MA, Faries D, Herrera JM, DeBrota D, Potter WZ. The problem of...
52 Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. Eur Neuropsychopharmacol 2012; 22: 239–258.

53 McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet 2006; 78: 804–814.

54 Myung W, Lim SW, Kim S, Kim H, Chung JW, Seo MY et al. Serotonin transporter genotype and function in relation to antidepressant response in Koreans. Psychopharmacology (Berl) 2013; 225: 283–290.

55 Ntzani EE, Liberopoulos G, Manolio TA, Ioannidis JP. Consistency of genome-wide associations across major ancestral groups. Hum Genet 2012; 131: 1057–1071.

56 Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, Montimurro J, Kay DM et al. Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson’s disease modifier gene via interaction with coffee. PloS Genet 2011; 7: e1002237.

57 Driscoll HC, Basinski J, Mulsant BH, Butters MA, Houck PR et al. Late-onset major depression: clinical and treatment-response variability. Int J Geriatr Psychiatry 2005; 20: 661–667.

58 Rush AJ, Wisniewski SR, Zisook S, Fava M, Sung SC, Haley CL et al. Is prior course of illness relevant to acute or longer-term outcomes in depressed out-patients? A STAR*D report. Psychol Med 2012; 42: 1131–1149.

59 Power RA, Keers R, Ng MY, Butler AW, Uher R, Cohen-Woods S et al. Dissecting the genetic heterogeneity of depression through age at onset. Am J Med Genet B Neuropsychiatr Genet 2012; 159B: 859–868.

60 Nierenberg AA, Trivedi MH, Fava M, Biggs MM, Shores-Wilson K, Wisniewski SR et al. Family history of mood disorder and characteristics of major depressive disorder: a STAR*D (sequenced treatment alternatives to relieve depression) study. J Psychiatr Res 2007; 41: 214–221.

61 Undurraga J, Baldessarini RJ. Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. Neuropsychopharmacology 2012; 37: 851–864.

62 Carroll BJ. Problems with diagnostic criteria for depression. J Clin Psychiatry 1984; 45: 14–18.

63 Kim YJ, Jin HJ. Dissecting the genetic structure of Korean population using genome-wide SNP arrays. Genes Genom 2013; 35: 355–363.