Journal of Human Genetics (2015) 60, 343–344

www.nature.com/jhg

CORRESPONDENCE

No support for replication of the genetic variants identified by a recent mega-analysis of the treatment response to antidepressants

Journal of Human Genetics (2015) **60,** 343–344; doi:10.1038/jhg.2015.21; published online 5 March 2015

Antidepressants are the most commonly used treatment for patients with major depressive disorder (MDD). The remission rate, however, is insufficient; approximately one-third of patients taking these medications are considered to be 'treatment resistant'.[1] In addition, poor response or delay in finding an appropriate drug has a negative impact on the therapeutic effect. Therefore, a useful predictor for the treatment response is warranted in the clinical setting, and one of the best approaches is the pharmacogenetics/pharmacogenomics (PGt/PGx).

Although a large number of classical PGt studies have targeted candidate genes, there are no consistent results till date. Recently, to survey genetic variants at the genome-wide level, three PGx studies (GENDEP,[2] MARS[3] and STAR*D[4]) have been conducted. All of these, as well as their mega-analysis,[5] again revealed no single-nucleotide polymorphisms (SNPs) with genome-wide significance ($P=5\times10^{-8}$).

From the results of the mega-analysis,[5] where the sample size was maximized, the effect size of the SNPs with modest association was not extremely large (odds ratio (OR), ~1.5), although PGt/PGx phenotypes were presumed to have a larger effect size compared with that of complex diseases. Therefore, as the replication analysis is essential to avoid type II errors, we were motivated to conduct this replication study using a Japanese population.

Two-hundred and seventeen patients with MDD who were of Japanese ancestry were examined (males = 114, females = 103, mean age ± s.d. = 47.1 ± 15.0 years) in this study. All the subjects were treated by selective serotonin transporter reuptake inhibitor (SSRI) monotherapy for 8 weeks (fluvoxamine = 104, sertraline = 54 and paroxetine = 59, whereas in the mega-analysis,[5] a total of 2256 subjects in the Caucasian population were treated by a different medication in each PGx[2–4]). The Hamilton Depression Rating Scale (HAM-D: 17 items) score was evaluated at baseline (mean ± s.d. = 21.0 ± 4.9) and at 8 weeks after treatment (mean ± s.d. = 10.1 ± 6.1). Two phenotypes, the 'response-rate' and 'remission,' were evaluated in accordance with a previous study:[5] the 'response-rate' was the quantitative outcome in HAM-D scores between baseline and at 8 weeks, and 'remission' was defined as HAM-D score of <7 at 8 weeks (83 'remitters'/134 'nonremitters'). We did not evaluate 'responder/nonresponder' because ~80% of the 'remitter' and 'responder' overlapped, and the 'remission' outcome was more stringent.

The SNPs were selected based on the following criteria: SNPs with (1) *P*-value of $<5.0\times10^{-5}$ in the mega-analysis for the phenotype of either the 'response-rate' or 'remission' (105 SNPs: 46 SNPs from the results of the 'response-rate' only, 55 SNPs from those of 'remission' only and 4 SNPs from the those of both the 'response-rate' and 'remission') and (2) the minor allele frequency (MAF) of the Japanese population (HapMap Phase 3) of >5% (21 SNPs excluded). In addition, to extract SNPs with linkage equilibrium, linkage disequilibrium pruning was performed in our samples ($r^2>0.8$: 2 SNPs dropped). Finally, we genotyped a total of 82 SNPs (Supplementary Table 1) for the association analysis. All the SNPs were genotyped using the Sequenom iPLEX Gold (Sequenom, San Diego, CA, USA) with visual inspection. At the stage of quality control, six SNPs were also excluded (the missing call-rate per SNP of <5% (2 SNPs dropped); a Hardy–Weinberg equilibrium *P*-value of >0.0001 (3 SNPs dropped); MAF >1% (1 SNP dropped)), with a total of 76 SNPs being analyzed (Supplementary Table 1). Written informed consent was obtained from each subject. The Ethics Committees of the Fujita Health University and the University of Occupational and Environmental Health approved this study.

The association analysis of the 'response-rate' and 'remission' was performed using linear regression and logistic regression models, respectively, with the covariates of age, sex and collection site to assess the main effect of the SNPs. A meta-analysis was then performed using a fixed-effect model (I^2 heterogeneity index <50) or a random effect model (I^2 heterogeneity index ⩾50). These statistical analyses were performed using PLINK version 1.07.[6]

In the replication analysis of the 'response-rate,' we observed a nominal significant association with five SNPs ($P<0.05$), whereas four SNPs ($P<0.05$) were associated with 'remission,' two of which (rs1517928 and rs7032771) showed overlapping between these phenotypes (Table 1 and Supplementary Table 2). However, none of the SNPs showed a significant association after correction for multiple testing ($0.05/76=6.6\times10^{-4}$). In addition, it is of note that the same directionality of the effect by the risk allele reported in the original mega-analysis[5] was observed only in two SNPs (rs1517928 and rs6575651) out of these seven SNPs.

In the following meta-analysis merging the 'current' results into the original mega-analysis,[5] it was revealed that only one SNP with *P*-value <0.05 in the 'current'

Table 1 Results of the association analysis of the 'response-rate' and 'remission' for antidepressants

SNP	*Chr*	*BP*	*Selection criteria (samples)*	*Response rate*				*Remission*			
				P-*value*	*Beta*	*Direction*	P_{meta} *value*	P-*value*	*OR*	*Direction*	P_{meta} *value*
rs1517928	3	65007135	Remission (entire)	0.015	−0.085	+	**0.00023**	0.037	0.59	+	**5.57E-06**
rs4234541	3	17182697	Response rate (SSRI)	0.12	−0.043	−	0.56	0.026	0.65	−	0.66
rs942659	6	23784993	Remission (SSRI)	0.025	−0.068	−	0.94	0.22	0.77	−	0.75
rs7032771	9	120202577	Remission (SSRI)	0.0034	0.17	−	0.71	0.017	2.79	−	0.73
rs6575651	14	98755042	Response rate (SSRI)	0.043	−0.10	+	0.089	0.46	0.77	+	0.077
rs17746463	16	8262543	Response rate (SSRI)	0.058	0.077	−	0.52	0.038	1.79	−	0.91
rs311786	19	11568522	Response rate (SSRI)	0.011	−0.11	−	0.73	0.19	0.65	−	0.89

Abbreviations: Chr, chromosome; BP, base position based on hg19; OR, odds ratio; SNP, single-nucleotide polymorphism; SSRI, serotonin transporter reuptake inhibitor.
Pmeta: P-value for the meta-analysis ("current" and previous results[5]); selection criteria: based on the previous mega-analysis5 ("entire": the SNPs were selected from the results of the "entire sample" in the mega-analysis[5], 'SSRI': the SNPs were selected from the results of the "SSRI sample" in the mega-analysis[5]); Direction: the directionality of the SNP effect compared to that of the previous mega-analysis[5]; *: P-values with asterisk were calculated using ORs and SEs based on the previous results[5] for the entire sample. This is because the ORs/SEs for the alternative phenotype (i.e. if the SNPs were selected based on "response-rate" for the SSRI-treated patients, the results of "remission" for these subjects were not described in some case) were not listed in the paper, but could be downloaded by PGC database. The bold numbers represent significant association in the meta-analysis ($P<0.05$).

results (rs1517928, 300-kb downstream of *ADAMTS9* (ADAM metallopeptidase with thrombospondin type 1 motif 9)) improved the significance level ($P=5.57\times10^{-6}$, 'remission' for the entire sample of antidepressants) but did not show genome-wide significance (Table 1 and Supplementary Table 2).

The results of the present study did not replicate the top-hit variants based on the mega-analysis[5] as a predictive factor for the antidepressant response. These results support the previous finding of the mega-analysis,[5] where the effect size of the SNPs related to antidepressant efficacy was modest. Therefore, it is likely that a PGx trait in MDD treatment may have a small effect size; an extremely larger sample size such as those of complex diseases will be required. Also there is possible relevance that different drugs analyzed introduce the inconsistent result, as most of our 'top' SNPs in the current study (all of the samples were treated by SSRI) were selected based on the results targeting 'SSRI' sample in the mega-analysis.[5]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work is the result of 'Integrated Research on Neuropsychiatric Disorders' carried out under the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan; Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network and Glia assembly) from the MEXT of Japan; Grant-in-Aids for Scientific Research (B) and for Young Scientists (A) from the MEXT of Japan; Health Labour Sciences Research Grant from the Ministry of Health Labour and Welfare; the Takeda Science Foundation; Schizophrenia Clinical and Basic Research; and the SENSHIN Medical Research Foundation, Japan.

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Supplementary Information accompanies the paper on Journal of Human Genetics website (http://www.nature.com/jhg)