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A Preliminary Study of Genetic Variation in the Dopaminergic and Serotonergic Systems and Genome-wide Additive Genetic Effects on Depression Severity and Treatment Response

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Introduction

Major Depressive Disorder (MDD) is a pervasive disorder (Kessler et al., 2012; Kessler & Bromet, 2013) with substantial economic costs (Kessler, 2012). Treatment of MDD with antidepressant medication is very common, with selective serotonin reuptake inhibitors (SSRIs) being the most prescribed class of medication (Olfson et al., 2002). Approximately 50% of depressed adults will respond to antidepressant treatment and only one third will achieve symptomatic remission (Trivedi et al., 2006). Thus, there is significant variability in response to antidepressant treatment among people diagnosed with MDD.

Genetic variation likely contributes to baseline depression severity and the change in severity observed during the course of treatment. There is familial aggregation of MDD (Klein, Lewinsohn, Seeley, & Rohde, 2001) and familial concordance to citalopram treatment response has also been observed (Franchini, Serretti, Gasperini, & Smeraldi, 1998; Serretti, Franchini, Gasperini, Rampoldi, & Smeraldi, 1998). Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that putatively contribute to depression symptoms (Wray et al., 2012) and antidepressant treatment response (Laje & McMahon, 2011). However, these identified SNPs, when considered in isolation, explain a very small proportion of the variance in these phenotypes (less than 1% of variance).

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Disclosures

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A recently developed bioinformatics technique, Genomic-Relatedness-Matrix Restricted Maximum Likelihood (GREML; implemented in genome-wide complex trait analysis (GCTA)), allows for the estimation of genetic effects accounted for by the aggregate of SNPs (Yang, Lee, Goddard, & Visscher, 2011). Univariate GREML uses genetic relatedness among individuals to estimate variance in a phenotype. Bivariate GREML estimates the genetic variance of each phenotype, as well as the genetic covariance among phenotypes that can be captured by all SNPs. Because it estimates the aggregated effects of the SNPs, GREML does not tell us which of the individual genotyped SNPs contribute to the phenotype. However, subsets of SNPs (e.g., candidate SNPs based on candidate gene lists, genomic regions, or chromosomes) can be examined to identify relative contributions.

To date, a number of studies have utilized GREML to study the genetic etiology of MDD. Variation in common genetic polymorphisms explained 32% of the variance in the presence versus absence of MDD (Lubke et al., 2012) and 51% of the variance in age at onset of MDD (Power et al., 2012). Understanding genetic contributions to depression from an etiological standpoint may also shed light on differences in treatment responsiveness. For example, other studies (Lee, DeCandia, et al., 2012; Tansey et al., 2013) have used GREML to attribute 42% of the variance in antidepressant treatment response (adjusted for initial severity) to common SNPs.

Given that genetic variability appears to contribute to depression pathology and antidepressant treatment response, an important question that remains unanswered is the extent to which genetic contributions to symptom change and initial depression severity overlap. Likewise, it is necessary to determine whether candidate systems, in particular, the dopaminergic and serotonergic systems (DA/5-HT), which are major components of the monoamine system (Fournier et al., 2010; Ruhe, Mason, & Schene, 2007), play a significant role in depression severity and treatment response.

Participants from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) present a unique opportunity to explore the sharing of genetic influences across depression severity and change in symptoms. The current study builds upon previously reported STAR*D analyses (Hunter et al., 2013; Tansey et al., 2013; Uher et al., 2013) by (1) examining the relative contribution of a subset of genes within the dopaminergic and serotonergic systems across established indices of depression severity (i.e., the Hamilton Rating Scale for depression [HRSD] (Hamilton, 1960) and the clinician-rated Quick Inventory for Depression Symptomatology [QIDS-C])(Rush et al., 2003), and (2) determining whether common genetic factors influence initial depression severity and change in depression following antidepressant treatment. Further, we examine if these effects are consistent across the HRSD and QIDS-C. We hypothesized that there would be some overlap in the genetic liability to initial depression and response to citalopram, which has been shown to modulate monoamine levels (Marsteller, Barbarich-Marsteller, Patel, & Dewey, 2007).

Materials and Methods

Participants

The current study utilized a large sample of unrelated participants selected from level 1 of the completed STAR*D study (Rush et al., 2004; Rush et al., 2006). Analyses were limited to a subset of the 1948 individuals (out of the original 4041 treatment seeking individuals) who provided DNA samples. Genetic data were obtained from the Center for Collaborative Genomic Studies on Mental Disorders (<http://www.nimhgenetics.org>). Genotyping for 500,453 markers on the 1948 subjects was conducted on two platforms. Nine hundred sixty-nine subjects were genotyped at Affymetrix on the Human Mapping 500K Array Set. The remaining 979 samples were genotyped using the Affymetrix Genome-wide Human SNP Array 5.0. Validation using twelve samples genotyped on both the 500K and 5.0 Arrays showed greater than 99% concordance in genotyped markers across the platforms (Garriock et al., 2010).

Genotyping Quality Control and Population Stratification Control

Quality control (QC) was done using SNP & Variation Suite v7.7.3 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com). Genotyping QC criteria for retaining markers were: minor allele frequency > 1%, Hardy Weinberg equilibrium p-value > 1E-4, and genotyping call rate > 98%.

Analyses focused on a subset of individuals of European ancestry identified via genomic principal component analyses (PCA). Participants who were more than two standard deviations away from the mean on the first ancestral principal component that distinguished subjects of European and African ancestry were excluded from the current analysis. PCA reduced the sample from a mixed population of 1948 individuals to a more homogeneous population of 1618 subjects of European ancestry. Application of the genotyping QC criteria to the 1618 subjects identified 357,589 markers (350,037 autosomal SNPs) from 1617 individuals (one individual was removed due to a low genotyping rate). The sex-check option in Plink (Purcell et al., 2007) was used to confirm gender based on heterozygosity rates using X chromosome data. Twenty-nine gender reports in the phenotype file did not match the gender identified by Plink. Information for these subjects was corrected based on the genetic observations.

To assess the additive genetic contribution of the DA/5-HT systems, we identified 83 genes that putatively influence serotonin and dopaminergic function to explain variance in the study phenotypes (see Supplemental Table S1 in the online Supplemental Material for a list of all 83 genes and references supporting the dopamine and serotonin pathways; see also (Rubino et al., 2015)). A total of 1573 autosomal SNPs (i.e., on chromosomes 1–22) were within 20Kb of 80 autosomal genes on the candidate gene list (i.e., not located on the X chromosome; variants in proximity to the three genes on the X chromosome were not included in our analyses). GREML analyses were conducted using all genotyped autosomal SNPs (350,037) simultaneously and subsets of SNPs (markers not in the dopaminergic and serotonergic systems gene set are referred to as “All Others”).

Depression Phenotypes

The primary study outcomes were: (i) depression *severity prior to treatment* (measured using the HRSD and QIDS-C), (ii) *change in severity* over the course of treatment (reflecting proportional improvement from enrollment until the last observation taken over the course of treatment [i.e., last observation carried forward]), and (iii) *remission/response* (i.e., a categorical variable based on clinical definitions of remission [post-treatment HRSD ≤ 7] and response [50% or greater change in QIDS-C]) (Trivedi et al., 2006).

Estimation of variance and covariance explained by genomewide SNPs

GREML was used to conduct univariate and bivariate analysis of the phenotypic variances and covariances, respectively. GREML uses chance genetic similarity across numerous SNPs to predict phenotypic similarity across individuals and produces a variance estimate that serves as a low-bound estimate of the genetic variance of a phenotype. The GREML approach consisted of two steps in which the genetic similarity between all pairs of individuals was obtained via a pairwise genetic relationship matrix (GRM; based on the genome-wide SNPs), followed by construction of a mixed effects model using genetic similarity as a random effect to predict the variance in each phenotype and the covariance among phenotypes. To limit the possibility of genetic effects that are confounded by common environmental factors, analyses were further restricted to 1361 unrelated individuals (i.e., one of each pair of persons who were no more related than second cousins were systematically removed to maximize sample size; GRM cut-off of 0.05). Analyses were executed in the full (N=1617) and unrelated (N=1361) set of subjects to assess any bias that could be attributed to cryptic relatedness.

Univariate models were fitted to each phenotype to derive the SNP heritability (h^2_{SNP}) using (1) all autosomal SNPs, (2) the set of SNPs in and around the dopamine/serotonin systems gene set (versus “All Other” SNPs), and (3) SNPs across individual chromosomes (with confidence intervals around R^2 for chromosomal effects computed using R2 (Steiger & Fouladi, 1997)). Results from the univariate models determined whether it was worth examining stratified effects (i.e., by gene set) in the bivariate models. The correlation of additive genetic effects between *initial severity*, *change in severity*, and *remission/response* was determined using bivariate GREML (Lee, Yang, Goddard, Visscher, & Wray, 2012). Six models were fitted to the full and unrelated samples to demonstrate the effects of the following covariates (i.e., Model I – with no covariates, Model II – controlling for number of weeks in treatment (log-transformed [$\log(\# \text{ weeks in treatment} + 1)$]), Model III – controlling for age, Model IV – controlling for gender, Model V – controlling for ancestral principal components (APCs) [to account for residual population stratification and/or batch effects], and Model VI – controlling for all covariates). Number of weeks in treatment was included as a log-transformed covariate to account for individual differences in treatment course. In general, longer participation in the STAR*D study resulted in a greater reduction in depression severity (e.g., $r_{\text{HRSD change in severity-weeks in treatment}} = 0.35$ [95% Confidence Interval: 0.30, 0.40]); a majority of the sample used in the analyses (89% [N=1438]) participated in the studies for 6 or more weeks, 5% (N=85) for 4–6 weeks, 4% (N=59) for 2–4 weeks, and 2% (N=33) for 0–2 weeks, with similar rates observed in the subset of unrelated individuals. None of the APCs were phenotypically related to the outcomes.

Results

Confirmation of the phenotypic correlations between *initial severity*, *change in severity*, and *remission/response* for both the HRSD and QIDS-C scales revealed that *initial severity* was modestly related to *remission* (e.g. $r_{\text{HRSD-initial severity}} = -0.21$ [95% CI: $-0.26, -0.15$]) and weakly related to *response* ($r_{\text{QIDS-initial severity}} = -0.08$ [95% CI: $-0.13, -0.03$]), but not *change in severity* (see Supplemental Table S2 in the online Supplemental Material). This suggested that participants who met criteria for remission had lower severity at enrollment. *Change in severity* and *remission/response* were highly correlated across both scales (e.g. $r_{\text{HRSD-change in severity:HRSD-remission}} = 0.80$ [95% CI: $0.78, 0.82$], $r_{\text{QIDS-change in severity:QIDS-remission}} = 0.85$ [(95% CI: $0.83, 0.86$)).

Table 1 presents the h^2_{SNP} estimates for all phenotypes. Notably, effects were largely consistent across the full and unrelated samples, suggesting limited confounding due to cryptic relatedness. SNP-heritability estimates using all autosomal genome-wide SNPs were consistent across assessment scales for the models that included no covariates and the models with covariates (see Supplemental Table S3 in the online Supplemental Material). Additive genetic effects on *initial severity* were greater for the HRSD scale than the QIDS-C scale; however, large standard errors preclude strong conclusions. Additive genetic effects on *change in severity* and *remission/response* indices were consistent across the HRSD and QIDS-C scales, though there was a tendency for higher point estimates on QIDS-C *response* measures.

Supplemental Table S4 (see online Supplemental Material) describes the observed additive genetic effect on all phenotypes stratified by chromosome (i.e., 1–22). Regression of the observed effects on chromosomal length indicated that longer chromosomes did not account for more variance in phenotypes from either scale (e.g., for HRSD *severity at enrollment*, $R^2 = 0.00$ [95% CI: $0.00, 0.18$]). While no one chromosome accounted for the majority of the observed effects on *initial severity*, chromosomes 4 and 18 accounted for roughly 10% of the variation in *change in severity* and *remission*.

Stratification of the univariate additive genetic effects into variance due to similarity across the markers proximal to the 83 DA/5-HT systems genes (versus the remainder of the genome) revealed that these DA/5-HT-related variants by themselves account for a relatively small proportion of the additive genetic variance in all phenotypes (i.e., 1%; see Table 1). This pattern of effect was generally consistent across the full and unrelated samples, as well as across depression scales, with the exception of genetic effects on *change in severity and remission* (as measured by the HRSD), which suggested that up to three percent of the variance could be explained by additive genetic factors. However, the interval for the effects in the full sample completely overlapped with those in the unrelated sample, suggesting that the change in the estimate could be due to sampling variance, as it is unlikely that shared environmental factors would impact only markers related to the dopaminergic and serotonergic systems.

Bivariate results were consistent across the full and unrelated samples (see Table 2). Based on the analyses conducted within unrelated subjects using all covariates, the estimated

genetic correlation between *HRSD severity at enrollment* and *HRSD change in severity* was limited ($r_{G-SNP} = -0.38 [-1.00, 0.24]$). Likewise, r_{G-SNP} using *HRSD-remission* was also non-significant ($r_{G-SNP} = -0.65 [-1.00, 0.18]$). Genetic correlations between *QIDS-C severity at pre-treatment* and *QIDS-C change in severity* and *response* followed a similar pattern. Overall, point estimates from the bivariate analyses suggest that genetic factors for depression severity at enrollment and treatment response measures may be modest at best. Supplemental Table S5 (see online Supplemental Material) provides a breakdown of r_{G-SNP} across models comprising different sets of covariates.

Discussion

GREML was used to examine genomewide genetic effects on initial depression severity and citalopram response using two measurement scales. Bivariate GREML also provided an indication of the genetic correlation between phenotypes, within each measurement scale. In addition to determining overall SNP-based heritability, we examined whether common variants in 80 autosomal genes that putatively influence serotonergic and dopaminergic function were associated with depression-related phenotypes. Much of the observed total genetic effects were largely attributable to genetic variation outside the set of DA/5-HT systems genes. Further, genetic variation that could be attributed to variation outside of the DA/5-HT systems does not appear to have common influences on *initial depression severity* and *change in severity* during treatment. However, it should be noted that only common genetic variation was measured. Our analyses do not include any genetic effects that may be attributable to fragment length polymorphisms, rare variants, copy number variants (CNV) or other non-common forms of genetic autosomal variation. There is growing evidence that rare variants have important biological and medical consequences (Tennessen et al., 2012) and should be measured in future studies.

To complement the above-mentioned findings, we also explored whether the variation along specific chromosomes might account for the majority of the genome-wide h^2_{SNP} . While most effects were modest, chromosome 18 had relatively large effects for *change in severity* and *remission/response* (across the HRSD and QIDS-C scale). Other noteworthy chromosomes of similar effect size were chromosomes 4 and 5. Interestingly, prior GWAS from this sample have identified genetic variants that predict treatment response and reside in a gene rich region of chromosome 18 (including histamine receptor H4 and pseudogene RAC1P1) (Adkins et al., 2010), although other GWAS studies have identified variants that reside elsewhere (Garriock et al., 2010). Additional work, perhaps using GREML methods, could further partition variation with these chromosomes to better narrow the regions of influence with the goal of understanding what is strongly contributing to the changes in depression severity during antidepressant-related treatment.

In an effort to identify sources of genetic variation that might substantially contribute to h^2_{SNP} , we utilized a gene set that included 80 autosomal genes (1,573 polymorphisms) that putatively influence serotonergic and dopaminergic function. We selected these genes based on the monoamine hypothesis: the idea that deficiencies in monoaminergic neurotransmission are a central cause of depression (Hirschfeld, 2000). Further, SSRIs have been shown to modulate dopamine and serotonin levels (Gessa et al., 2000; Witkin, Tzavara,

Davis, Li, & Nomikos, 2005). Despite long-standing interest in this idea, there was scant evidence (across both measures of depression) to suggest that genetic differences in serotonergic or dopaminergic neurotransmission (as best reflected by the variants identified in and around these genes) are strongly implicated in the pathophysiology of depression (Krishnan & Nestler, 2010) in this sample. Like many other genetic association studies that have examined components of the monoamine hypothesis in depression, we also found relatively little supportive evidence (Flint & Kendler, 2014). Thus, to identify genetic factors that substantially contribute to depression severity, research may need to move beyond the “usual suspects” involved in monoamine neurotransmission. It is also the case that our lack of findings could be explained by incomplete characterization of genetic variation in the 80 autosomal genes that is not well represented by SNPs on a GWAS array (e.g., rare variants). Consequently, it remains unclear what role common genetic variation in monoaminergic systems may have in depression.

Strengths and Limitations

The current study had a number of strengths and limitations that should be taken into consideration. Compared to other clinical trials, STAR*D's GWAS platform allows for the quantification of SNP effects across the entire genome. By capitalizing on the depth of genomic coverage and large sample size, we were able to use this whole genome approach to examine the liability to depression. A notable limitation for the current study is that STAR*D did not include a comparison group for the initial stage (i.e., Level 1) of the antidepressant trial. Due to the large sample size requirements of GCTA analyses, our analyses focused on these initial data, which limits our ability to attribute change in depression symptoms to antidepressant treatment per se. Notably, this limitation applies to all prior GWAS research with STAR*D. Future work would benefit from having a comparison condition (e.g., waitlist, placebo, or alternative treatment control) to identify the genetic contribution to symptom change specifically due to antidepressant treatment and a larger sample size to increase statistical power. It is also important to note that the current study was limited to autosomal markers, and as such markers in the dopamine and serotonin pathway gene list, such as MAOA and MAOB that are located on the X chromosome were not included in our analysis. Given the current challenges (Melis et al., 2004) in working with sex chromosome data from mixed sex samples, we elected to focus on autosomal SNPs. Given that roughly five percent of genes in the human genome reside on the X chromosome, it is likely that the effects presented here do not reflect all of the potential sources of genetic variation. Likewise, these analyses provide no indication of the magnitude of effect from rare variants (i.e., minor allele frequency < 1%) and non-additive genetic effects. Last, but not least, it should also be noted that these results are preliminary and require external validation to confirm whether the observed additive genetic effects and genetic correlations are specific to STAR*D or might also exist in other independent samples. Recent machine learning studies of depression (Chekroud et al., 2016; Kessler et al., 2016) underscore the need for validation because findings in a single study may be biased. Specifically, a mathematical model may fit data well in one population, but perform poorly in another. In the case of current analyses in STAR*D, the observed genetic effects may be biased and as such may not generalize to non-treatment populations or treatment populations that might not share clinical, etiological (e.g., alleles), or demographic similarities with STAR*D. In

short, additional studies are needed to replicate and validate these findings and provide insight into the role of rare variants and sex-determining chromosome variants.

Conclusion

Our findings provide much needed insight into whether pharmacologic interventions can be leveraged to help identify disease etiology. Although tentative and in need of replication, initial depression severity and change in severity during treatment appear to have limited overlapping genetic effects. Furthermore, observed genetic effects on depression severity and treatment response do not appear to be primarily attributable to selected genetic variation in the dopamine and serotonin systems. The additive effect of SNPs across the genome and the presence of relatively strong effects in certain chromosomes suggest that pathway and epistatic approaches that capture the combinatorial effects of the genome may help to shed further light on the etiology of both depression and response to depression treatment. Our findings using only a subset of common variants suggest that exploring the role of only dopamine and serotonin pathways in depression may have limited utility. As such, additional studies of alternative candidate pathways and rare variants in the entire monoamine system are needed. Nevertheless, results from the current study highlight the potential contribution of common genetic variation and simultaneously provide a novel way of utilizing clinical data to facilitate a comprehensive understanding of the etiology of depression and treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Additive genetic effects on HRSD and QIDS phenotypes.

Variable	Unrelated subsample			Full sample		
	Using all SNPs		Using Gene Sets	Using all SNPs		Using Gene Sets
	h^2 SNP	h^2 SNP-Monoamine	h^2 SNP-All Others	h^2 SNP	h^2 SNP-Monoamine	h^2 SNP-All Others
HRSD measures						
<i>No Covariates</i>						
Severity at enrollment (N=1359) ¹	0.49 [0.12, 0.87] ***	0.00 [-0.04, 0.04]	0.49 [0.11, 0.86] **	0.52 [0.24, 0.81] ***	0.01 [-0.02, 0.04]	0.52 [0.24, 0.81] ***
Change in severity (N=1174) ¹	0.47 [-0.02, 0.95] *	0.00 [-0.04, 0.04]	0.43 [-0.05, 0.91] ^a	0.58 [0.21, 0.94] ***	0.03 [-0.01, 0.07] ^a	0.58 [0.22, 0.95] ***
Remission (N=1359) ¹	0.33 [-0.16, 0.82]	0.01 [-0.03, 0.05]	0.28 [-0.20, 0.75]	0.40 [0.04, 0.75] **	0.04 [-0.01, 0.08] *	0.38 [0.03, 0.73] **
<i>Age, sex, weeks in treatment and 2APCs/3APCs as covariates</i>						
Severity at enrollment (N=1358) ²	0.35 [-0.07, 0.76] *	0.00 [-0.04, 0.04]	0.35 [-0.06, 0.75] *	0.48 [0.19, 0.77] ***	0.00 [-0.03, 0.03]	0.48 [0.19, 0.77] ***
Change in severity (N=1173) ²	0.37 [-0.12, 0.86] ^a	0.00 [-0.04, 0.04]	0.35 [-0.13, 0.83] ^a	0.30 [-0.09, 0.70]	0.00 [-0.04, 0.04]	0.31 [-0.09, 0.70]
Remission (N=1358) ²	0.29 [-0.20, 0.79]	0.00 [-0.04, 0.05]	0.26 [-0.22, 0.74]	0.23 [-0.15, 0.61]	0.02 [-0.02, 0.07]	0.22 [-0.16, 0.60]
QIDS-C measures						
<i>No Covariates</i>						
Severity at enrollment (N=1359) ¹	0.24 [-0.12, 0.60] ^a	0.00 [-0.04, 0.04]	0.23 [-0.11, 0.58] ^a	0.19 [-0.08, 0.46] *	0.02 [-0.02, 0.05]	0.19 [-0.08, 0.46] *
Change in severity (N=1174) ¹	0.52 [0.10, 0.95] *	0.00 [-0.03, 0.03]	0.52 [0.10, 0.94] *	0.59 [0.27, 0.91] ***	0.03 [-0.01, 0.06] *	0.58 [0.27, 0.90] ***
Remission (N=1359) ¹	0.56 [0.13, 0.98] **	0.00 [-0.03, 0.03]	0.55 [0.13, 0.98] **	0.57 [0.26, 0.88] ***	0.03 [-0.01, 0.06] *	0.57 [0.26, 0.88] ***
<i>Age, sex, weeks in treatment and 2APCs/3APCs as covariates</i>						
Severity at enrollment (N=1358) ²	0.12 [-0.29, 0.53]	0.00 [-0.04, 0.04]	0.11 [-0.28, 0.51]	0.21 [-0.10, 0.51]	0.00 [-0.03, 0.03]	0.21 [-0.10, 0.51]
Change in severity (N=1173) ²	0.48 [0.05, 0.90] *	0.00 [-0.03, 0.04]	0.48 [0.06, 0.91] *	0.41 [0.08, 0.75] *	0.01 [-0.02, 0.05]	0.41 [0.07, 0.74] *
Remission (N=1358) ²	0.64 [0.21, 1.06] **	0.00 [-0.04, 0.04]	0.64 [0.22, 1.07] **	0.49 [0.16, 0.82] **	0.01 [-0.02, 0.04]	0.49 [0.16, 0.81] **

Notations:

^a = p-value (p) < 0.10,

* = p < 0.05,

** = p < 0.01,

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= p < 0.001

¹ = actual sample size for analyses without covariates using the full sample was N=1615, except for “Change in severity,” which had an N of 1371.

² = actual sample size for analyses with covariates using the full sample was N=1610, except for the “change in severity” variable that had N=1366. Note that for the unrelated sample the first two ancestral principle components (APCs) are used to control for population stratification while the first three APCs are used in the analysis of full sample.

Table 2

Bivariate genetic correlations (rG-SNP [95% Confidence Interval]) of severity at enrollment of HRSD and QIDS-C depression measures with change in severity and remission measures using log-transformed treatment duration variable

Model	Unrelated Subsample		Full Sample	
	Change in severity	Remission/Response	Change in severity	Remission/Response
<i>No Covariates</i>				
HRSD Severity at enrollment	-0.38 [-1.00, 0.24]	-0.65 [-1.00, 0.18] ^a	-0.17 [-0.60, 0.26]	-0.41 [-0.93, 0.10] ^a
QIDS-C Severity at pre-treatment	-0.18 [-0.99, 0.63]	-0.39 [-1.00, 0.37]	0.37 [-0.21, 0.95]	0.06 [-0.57, 0.69]
<i>Age, sex, log transformation of weeks in treatment and 2APCs/3APCs as covariates</i>				
HRSD Severity at enrollment	-0.29 [-1.19, 0.60]	-0.50 [-1.49, 0.50]	0.09 [-0.56, 0.73]	-0.26 [-0.98, 0.46]
QIDS-C Severity at pre-treatment	-0.10 [-1.38, 1.17]	-0.49 [-1.74, 0.75]	0.51 [-0.35, 1.37]	0.08 [-0.65, 0.81]

Note: statistical tests are reported for the model likelihood ratio test,

^a = p<0.1;
* = p<0.05;
** = p<0.01;
*** = p<0.001; note that for the unrelated sample the first two ancestral principle components (APCs) are used to control for population stratification while the first three are used in the full sample.