

Contribution of Common Genetic Variants to Antidepressant Response

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Background: Pharmacogenetic studies aiming to personalize the treatment of depression are based on the assumption that response to antidepressants is a heritable trait, but there is no compelling evidence to support this.

Methods: We estimate the contribution of common genetic variation to antidepressant response with Genome-Wide Complex Trait Analysis in a combined sample of 2799 antidepressant-treated subjects with major depressive disorder and genome-wide genotype data.

Results: We find that common genetic variants explain 42% ($SE = .180$, $p = .009$) of individual differences in antidepressant response.

Conclusions: These results suggest that response to antidepressants is a complex trait with substantial contribution from a large number of common genetic variants of small effect.

Key Words: Antidepressant, GCTA, genetics, GWAS, heritability, pharmacogenomics

Antidepressants are among the most commonly prescribed drugs worldwide. Although, on average, antidepressant drugs are significantly more effective in treating depression than placebo, the therapeutic response is highly individually variable. The question of whether genetic markers can help predict response has major implications for personalizing treatment for depression. Given the importance of this question and the reliance of the field of antidepressant pharmacogenetics on the assumption that common genetic variants contribute to antidepressant response, it is surprising that there is no estimate of how heritable antidepressant response is. Although small family studies suggest that response to antidepressants is familial (1–3), there are no twin or adoption studies that would help separate the environmental and genetic components contributing to within-family similarity. Assembling sufficient number of twin pairs or adopted individuals who were exposed to the same antidepressant drug might be impractical, but recently developed methods of estimating heritability from genome-wide genotyping data provide an alternative (4). Here we use a novel method to estimate the contribution of common genetic variation to individual differences in response to antidepressants.

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Methods and Materials

Further information about samples, genotype, quality control, and the definition of the antidepressant phenotype included can be found in Supplement 1.

Samples

Two large samples of adults with major depressive disorder, with prospectively recorded outcome of antidepressant treatment and genome-wide genotyping were used in this analysis, the Novel Methods Leading to New Medications in Depression and Schizophrenia (NEWMEDS; <http://www.newmeds-europe.com>) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D; <http://www.nimh.nih.gov/trials/practical/stard/index.shtml>), to estimate the heritability of antidepressant response.

NEWMEDS includes 2146 individuals with available blood DNA, treated with serotonin-reuptake inhibiting (SSRI) (escitalopram, citalopram, paroxetine, sertraline, fluoxetine) or norepinephrine reuptake inhibiting (NRI) (nortriptyline, reboxetine) antidepressants for 6 to 12 weeks as part of several academic and industry-led clinical trials. Each study included in NEWMEDS was approved by institutional review boards, and all participants signed informed consent.

The STAR*D included 4041 treatment-seeking individuals with major depressive disorder, treated for up to 14 weeks with the SSRI citalopram, of which 1948 provided blood samples for genotyping. All participants provided a written consent after the procedures and associated risks were explained.

Genotyping and Quality Control

Quality control was implemented in PLINK (5).

The NEWMEDS samples were genotyped with the Illumina Human610-Quad or 660W-Quad (Illumina, San Diego, California) platforms. Markers were included if they had a minor allele frequency over .01 and Hardy-Weinberg equilibrium test $p > .001$ and at least 97% complete genotyping were retained. Genetic markers that differed significantly ($p < 1 \times 10^{-3}$) by genotyping center were excluded. Individuals were excluded for ambiguous sex, abnormal heterozygosity, cryptic relatedness up to third-degree relatives by identity by descent, genotyping completeness $< 97\%$, non-European ethnicity admixture detected as outliers in an iterative EIGENSTRAT analyses of a linkage

disequilibrium-pruned dataset, and invalid phenotypic information. Unrelated individuals ($n = 1790$) who passed stringent genotype quality control were included in our analyses.

The STAR*D samples were genotyped on the Human Mapping 500K Array Set and Affymetrix Genome-Wide Single Nucleotide Polymorphisms (SNPs) Array 5.0 (Affymetrix, South San Francisco, California) (6). Markers were included if they had a minor allele frequency over .01, Hardy-Weinberg equilibrium test $p > .001$, and at least 95% complete genotyping increasing to 99% if the minor allele frequency was below .05 following the criteria set by the Wellcome Trust Case Control Consortium when they used data from the same platform (7). To avoid batch artefacts, markers that differed significantly ($p < 1 \times 10^{-3}$) by genotyping center were excluded. Individuals were excluded for ambiguous sex, abnormal heterozygosity, cryptic relatedness up to third-degree relatives by identity by descent, genotyping completeness $< 97\%$, non-European ethnicity admixture detected as outliers in an iterative EIGENSTRAT analyses of an linkage disequilibrium-pruned dataset, and invalid phenotypic information. Unrelated Caucasian individuals ($n = 1107$) who passed stringent quality control were included in our analyses.

For the Genome-wide Complex Trait Analysis (GCTA) estimate, only autosomal SNPs common across the two genotyping platforms were used ($n = 71,297$). These were evenly spread out across the genome, capturing all autosomes.

Antidepressant Response Phenotype

To capture the degree of improvement with antidepressant treatment and avoid arbitrary cutoffs, antidepressant response was defined as a continuous variable reflecting proportional improvement in depression severity on the primary depression rating scale (Montgomery-Åsberg Depression Rating Scale, Hamilton Rating Scale for Depression, Beck Depression Inventory, or the clinician-rated Quick Inventory for Depression Symptomatology) from baseline to the end of treatment, adjusted for age, sex, and recruiting center/study (8).

Although primary outcome measures were different between studies, previous research has shown no differences between antidepressant responses as measured on different scales (9). Furthermore, the following steps were undertaken to minimize the effects of scale difference: 1) outcome measures within each study were converted to a single continuous metric of a standardized change score, adjusted for sex, age, and recruitment center within each contributing study; and 2) this adjusted change score was then Z-transformed within each study to remove any correlation between data origin and outcome before the analysis and to remove effects that are specific to individual contributing studies.

Heritability Estimation

Genome-wide Complex Trait Analysis was used to estimate the proportion of phenotypic variance in antidepressant response explained by common SNPs across the genome (4). The GCTA first determines the degree of genetic relatedness between all individuals and then estimates the proportion of phenotypic variance explained by the genetic relatedness matrix with a mixed-effect model (4). To provide a conservative estimate and avoid the possibility of confounding results through imputation, we restricted the analyses to 71,297 autosomal SNPs that were common across the two genotyping platforms. These SNPs were evenly spread out across the genome and covered all autosomes. To ensure an unbiased estimate of the proportion of phenotypic variation explained by the genetic markers, we

applied a stringent cutoff for relatedness (proportion of shared genetic material $< 2.5\%$) and removed one individual from each genetically related pair (4,10). Removal of closely related individuals helps to ensure that the estimate would not be confounded by common environmental factors or phenotypic correlation between family members (4). The GCTA was fitted with restricted maximum likelihood on the basis of a linear model of antidepressant response. To correct for the population substructure of the data, we included 20 principal components as covariates.

Results

To estimate the contribution of common genetic variants to response to any antidepressant, GCTA was first applied to the combined sample of 2799 unrelated individuals from NEWMEDS and STAR*D. The GCTA estimated that common SNPs explained .420 (SE = .180) of variance in antidepressant response. This estimate differed significantly from zero ($p = .009$). To assess the distribution of the genetic signal contributing to antidepressant response, we investigated the proportion of variance explained by each chromosome. There was a linear relationship between proportion of variance explained and chromosome length, with more variance explained by longer chromosomes (Figure 1).

Because genetic contribution to antidepressant response might be partly specific to a given antidepressant class (11), we also estimated heritability of response to the most commonly used class of antidepressants, the SSRIs. The analysis of 2273 unrelated individuals treated with SSRI antidepressants estimated that common SNPs explained .428 (SE = .230) of variance in

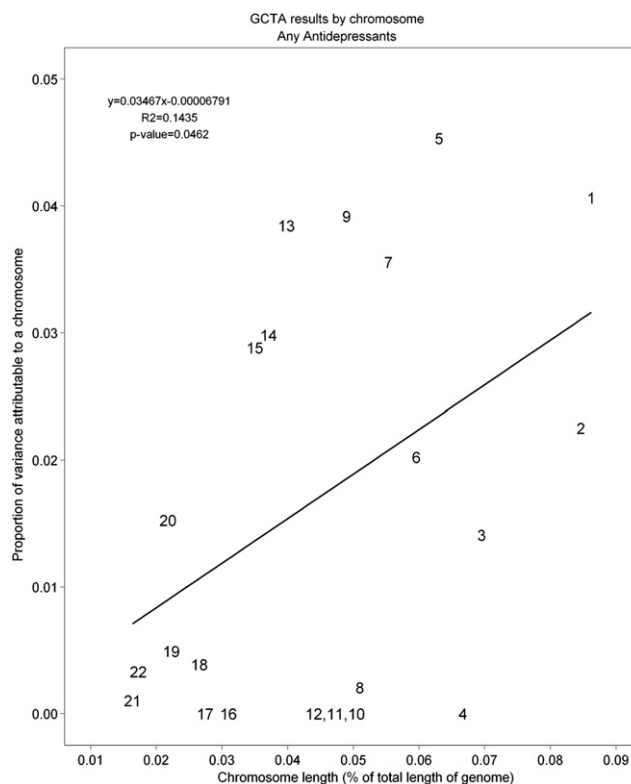


Figure 1. Proportion of common genetic variance explained by chromosome length for any antidepressant. The numbers represent the chromosome number. GCTA, Genome-Wide Complex Trait Analysis.

response to serotonergic antidepressants. This estimate differed significantly from zero ($p = .031$). Longer chromosomes contributed more to the variation of response to SSRI antidepressants.

Discussion

The work presented here demonstrates for the first time that there is a substantial genetic contribution to antidepressant response. We estimate that additive effects of common genetic polymorphisms across the human genome explain approximately 42.0% of individual variation in response to antidepressants. Similar estimates for any antidepressants and for SSRI antidepressants indicate that most of the genetic contribution is common between SSRI and NRI antidepressants. This estimate of variance of antidepressant response explained by common genetic variation together with the lack of any positive genome-wide association studies suggests that antidepressant response is a polygenic trait with a contribution from multiple common genetic variants across the genome, similar to other complex traits, such as schizophrenia (12,13) and height (10).

Several considerations should inform the interpretation of these results. First, the GCTA estimates are not equivalent to heritability estimates from twin studies. The GCTA is restricted to the role of common genetic variants and does not adequately capture information from uncommon polymorphisms and from genomic regions that are not adequately tagged by genotyping. This is particularly relevant to our analysis where we took a conservative stance and included only well-genotyped SNPs common across the two samples. By contrast, it is also possible that the GCTA overestimates the phenotypic variance explained by common genetic variation if the monotonicity assumption that a substantial part of the genome contributes to the trait is violated. However, for traits where both are available, GCTA estimates are invariably lower than those from twin studies (4,10,13,14).

The accuracy of estimates is limited by sample size. Although we have used the two largest pharmacogenetic samples in existence to date, the estimates have substantial SEs. We were unable to obtain an estimate for NRI antidepressants, because the sample was too small ($n = 568$) and underpowered for the analysis. The GCTA estimation might also be influenced by population stratification. To minimize any such influence, we applied stringent criteria for population homogeneity, on the basis of an iterative principal component analyses with HapMap reference populations. In the ethnically heterogeneous STAR*D sample, this resulted in a large portion of the sample being removed ($n = 681$). After combining the two samples, all 20 derived principal components were used as covariates in the analysis correcting for any remaining population sub-structure. After these procedures, the results presented here are unlikely to be biased by population stratification.

In conclusion, we have estimated for the first time the proportion of variance in antidepressant response explained by common genetic variation and find that it is significant and substantial (42.0%). The phenotype of antidepressant response is likely to be polygenic and involve a large number of SNPs with small effect sizes.

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Supplementary material cited in this article is available online.

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