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Pharmacogenetics Studies in STAR*D: Strengths, Limitations, and Results

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Abstract

Several lines of evidence support an important genetic contribution to the wide individual variation in therapeutic response to antidepressant medications. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study provided the largest cohort assembled to date of DNA from patients with nonpsychotic major depressive disorder, uniformly treated with citalopram and followed prospectively for up to 12 weeks. This pivotal study changed the face of pharmacogenetics research by increasing the sample size by an order of magnitude as well as by providing detailed prospective information about antidepressant response and tolerability. Several groups have identified markers in genes and tested the replication of previous findings of genes associated with outcome and side effects of antidepressant treatment. Variants in HTR2A, GRIK4, and KCNK2 were associated with citalopram treatment outcome. Replication was achieved in markers in the FKBP5 gene. Other findings in PDE11A and BDNF were not successfully replicated, and reports of potential confounders in previous associations with serotonin transporter variation (SLC6A4) were identified. Polymorphisms in pharmacokinetic genes involved in metabolism and transmembrane transport were also not associated with antidepressant response. Adverse events were also tested. Treatment-emergent suicidal ideation was associated with GRIK2, GRIA3, PAPLN, IL28RA, and CREB1. Sexual dysfunction was linked with variation in GRIN3A, GRIA1 GRIA3, and GRIK2. Reported and future findings of pharmacogenetics studies in STAR*D could help elucidate pathways involved in major depression and those pertinent to

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Disclosures

Dr. Laje, Dr. Rush, and Dr. McMahon are listed as coinventors on a patent application filed by NIH that is based in part on the diagnostic technology described in this article. The authors are not involved in the negotiation and execution of this license, but under federal law NIH is required to pay them a portion of any royalties NIH receives under the license. The authors do not endorse any commercial use of the patent. Dr. Rush has been an advisory board member, consultant, or speaker for Advanced Neuromodulation Systems, Astra-Zeneca, Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Gerson Lehman Group, GlaxoSmithKline, Jazz Pharmaceuticals, Magellan Health Services, Merck, Neuronetics, Novartis, Ono, Organon, Otsuka, Pam Labs, Pfizer, Trancept, and Wyeth. Dr. Perlis has received advisory or consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer, and Proteus LLC; he has received speaking fees or honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Pfizer; and he has equity holdings and patents with Concordant Rater Systems, LLC.

antidepressant outcome and side effects. Replication of these findings in independent samples could lead to the development of new treatments and to optimization of available treatments.

Major depression is a severe medical condition that is predicted to be the second leading cause of death and disability worldwide by the year 2020 (1). Few predictors of response to pharmaco- and psychotherapeutic treatments are known (2), and finding the most effective treatment for each patient is difficult. Response rates for any single medication are about 50%. For only a minority of patients do symptoms fully remit after about six months of treatment and sometimes with trials of two or more medications (3). Tolerability and adverse events are common factors contributing to nonadherence and treatment discontinuation, which result in persisting symptoms and disability. In addition, concerns about rare but severe side effects, such as treatment-emergent suicidal ideation, may reduce access to and acceptability of treatment (4).

These facts suggest that a better understanding of the pathophysiology of depression and identification of useful biological markers, including genetic markers, could improve treatment selection and help match treatment to desirable clinical outcomes, leading to new therapeutic strategies, drug targets, and conceptualizations of depression. For example, genetic markers may help predict antidepressant treatment response or adverse events; however, few clinical applications have resulted (5).

Technological advances in human genetics over the past decade, along with the availability of large treatment cohorts for study, such as in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (6), promise to transform pharmacogenetics into one of the foundations of evidence-based medicine. This article reviews the implications of STAR*D findings for pharmacogenetics research.

What did STAR*D contribute to pharmacogenetics research?

Two major developments in recent years that have begun to move the field of pharmacogenetics forward are the availability of large, well-characterized samples and the advent of genomic technologies of unprecedented power and efficiency. The role of STAR*D has been pivotal in the advancement of the pharmacogenetics of antidepressant response and adverse effects. STAR*D provided for the first time a sample of well-characterized, prospectively followed participants large enough to detect even modest genetic effects. The genetic studies conducted to date include investigations of single-nucleotide polymorphisms (SNPs) in multiple candidate genes. In the serotonin transporter gene (SLC6A4), the 43 base pair promoter-linked insertion-deletion region (LPR) and the variable-number tandem repeat (VNTR) polymorphism in the second intron have also been studied. In addition, a preliminary genomewide association study (GWAS) has been performed with selected participants, and a GWAS of the full set of participants who provided DNA is under way.

Sample characteristics

The STAR*D centers enrolled a clinically representative cohort of about 4,000 adults with nonpsychotic major depression. All were treated with citalopram at level 1 for up to 12 weeks and evaluated prospectively for treatment response and adverse events. About 2,000 individuals were asked to provide a DNA sample—most of whom agreed—but participants who dropped out early are underrepresented among the available DNA samples (see below).

Large samples are a key element of robust findings in genetic and pharmacogenetics studies (7), and STAR*D represents an order-of-magnitude increase over the size of all previously studied samples with major depression. An added advantage of large samples is that without

complete loss of statistical power, they allow for stratification and inclusion of covariates that might represent important confounders.

The intent of STAR*D investigators was to enroll a cohort of outpatients that resembled those seen at primary and specialty care clinics around the United States, including a typical mix of race, ethnicity, and socioeconomic status. Therefore, few exclusion criteria were used, and participants with medical conditions or anxiety disorders (except primary obsessive-compulsive disorder) were included in the trial. STAR*D had no placebo arm; thus all participants received active treatment. In the overall sample, over 70% of participants had experienced two or more prior episodes of depression or a sustained episode during the two years before study entry, and about 60% had one or more comorbid psychiatric disorders (3).

Treatment was organized into four levels. Each offered a number of treatment options for up to 12 weeks. All participants began with 10–60 mg per day of citalopram as tolerated (first step or level 1). Participants who did not respond sufficiently could choose random assignment to level 2, which included options for switching to any of three other antidepressants (sertraline, bupropion, or venlafaxine) or to cognitive therapy or for augmenting citalopram with either of two other medications (bupropion or buspirone) or with cognitive therapy. For level 2 participants who did not respond sufficiently, random assignment to level 3 included two medication switch options (mirtazapine or nortriptyline) and two medication augmentation options (lithium or thyroid hormone). Level 4 included one of two switch options (tranylcypromine or the combination of mirtazapine and venlafaxine).

Participants at any level who responded sufficiently to treatment were transitioned to follow-up status for up to 12 months. DNA samples were available from 1,914 level 1 participants, 883 level 2 participants, and 255 level 3 participants and from the 85 participants who continued to level 4.

The various pharmacological and nonpharmacological approaches used could potentially provide information on antidepressant outcomes and tolerability of the other therapeutic agents; however, the samples may not be large enough to screen for alleles of small effect.

Power

The large size (N=1,914) of the uniformly treated sample is crucial to obtain the necessary power to detect differences in treatment outcome or emergence of adverse events. Relatively low effect sizes can be detected even in the presence of rare phenotypes, such as treatment-emergent suicidal ideation (STAR*D prevalence 6.3%), and markers with low (<10%) minor allele frequencies, such as those described in GRIK2 (8) (see below).

Diversity

Few, large, well-characterized samples of patients treated with antidepressants are available for study along with their DNA. The availability of samples from racial-ethnic minority groups is significantly more problematic. STAR*D included all patients regardless of race and ethnicity. This provided both an opportunity to study racial-ethnic differences in treatment response and side effects and the option of analyzing these groups as separate cohorts. STAR*D had a subsample of 313 self-reported African-American participants; however, the sample may not be large enough to provide the statistical power to study genetic variants with small effects or low allelic frequency. This is also the case for the Hispanic subgroup of 274 participants (eight black and 247 white Hispanic participants [19 mixed race]). Other racial-ethnic groups were represented by only small numbers of participants, including 21 Asians, 16 Native Americans, eight Pacific Islanders, and a cohort

of 68 “multiracial” participants (all self-reported). The largest group included 1,279 white, non-Hispanic participants.

As noted, a group of individuals with a variety of racial-ethnic backgrounds should be analyzed carefully, with consideration of potential confounders, such as racial stratification. Current methods to address these issues include calculating posterior probabilities of racial-ethnic group membership derived from genotypes obtained from the sample by use of publicly available software such as STRUCTURE (9,10) or EIGENSTRAT (11). These values can be used as covariates in the association equation to “weight” racial-ethnic background in the overall result.

Prospective assessment of outcome and side effects

Participants in the STAR*D trial were assessed at baseline and about every two weeks thereafter for up to 12 weeks at each level. The instruments used to assess outcome were the 17-item Hamilton Depression Rating Scale (HAM-D) (12,13) and the clinician-rated and self-rated 16-item Quick Inventory of Depressive Symptomatology (QIDS-C and QIDS-SR) (14). The baseline visit also included the 30-item Inventory of Depressive Symptomatology (15). The HAM-D was used only at baseline and each level endpoint. Both the QIDS-C and QIDS-SR were completed at every visit. In addition, all postbase-line visits included a systematic assessment of adverse effects that used the Frequency, Intensity and Burden of Side Effects Rating and the Global Report of Side Effect Burden (16). Although a detailed discussion of the instruments used in STAR*D is beyond the scope of this article, these instruments have been widely cross-validated and had a good inter-rater reliability (17). Participants were followed closely, allowing for multiple datapoints in regard to ongoing symptoms and experience of side effects, which minimized recall bias.

Treatment

Another significant advantage of STAR*D is that all participants were treated with citalopram at level 1. This highly selective serotonin reuptake inhibitor (SSRI) was chosen because of its proven efficacy in major depressive disorder, good tolerability profile, and low potential for pharmacokinetic interactions with other medications, particularly those used by patients with general medical illnesses. Although treatment with a single drug limits potential generalizability of findings to other antidepressants, it has the advantage of having fewer pharmacokinetic and pharmacodynamic confounders for assessment of adverse effects and outcome. It is important to note that one of the general principles in STAR*D was to ensure that participants on all regimens had an adequate treatment trial of at least four to eight weeks of drug administration at recommended dose ranges.

As noted, citalopram nonresponders were offered options to switch or augment their ongoing treatment. At level 2, participants augmented their citalopram treatment with bupropion (N=184), buspirone (N=177), or cognitive therapy (N=63) or switched to other drugs, including bupropion (N=135), sertraline (N=139), and venlafaxine (N=154), or to cognitive therapy (N=31). At level 3 patients could be switched to mirtazapine (N= 74) or nortriptyline (N=80) or have their ongoing treatment augmented with lithium (N=30) or thyroxine (N=33). At level 4, the options were limited to tranycypromine (N=45) or a venlafaxine-mirtazapine combination (N=40).

In levels 2 through 4 pharmacogenetics studies of outcome and analyses of side effects are complicated by the fact that the samples are small; however, exposure to other antidepressants implies little or no response to the previous regimen, which suggests that there is a subgroup of patients who do not respond to a variety of pharmacological interventions.

What are the limitations of STAR*D as a pharmacogenetics study?

Perhaps the greatest advantage of STAR*D from a clinical perspective is also its greatest limitation for study of pharmacogenetics. Specifically, as an effectiveness study, STAR*D by design included patients with substantial medical and psychiatric comorbidity. Because participants were drawn from primary as well as specialty care settings, the general medical burden exceeds that of a typical clinical trial (18). Participants could also receive concomitant treatment with medications, such as beta blockers, that could have an impact on mood or treatment response. Similarly, individuals with ongoing substance misuse were eligible for participation as long as they did not require additional treatment targeting their co-occurring conditions (19, 20). Consistent with other clinical trials, STAR*D excluded patients with severe suicidality and limited the sample to nonpsychotic outpatients. Although the broad inclusion criteria greatly increase the generalizability of STAR*D findings to clinical practice, they also introduce heterogeneity that may make genetic effects more difficult to detect. On the other hand, if one goal of pharmacogenetic testing is to develop clinically useful diagnostic tools, clinically representative populations are precisely the ones that require study.

Several other features of STAR*D may increase sample heterogeneity and thereby diminish power to detect genetic associations. First, STAR*D did not include detailed assessments of medication adherence at level 1 (citalopram), such as pill counts or measurement of blood citalopram levels. Failing to consider nonadherence could lead to misclassification of outcomes (for example, when poorer outcome is a result of treatment non-adherence). This concern is likely to be more than theoretical, because adherence to treatment with antidepressants is known to be poor in general practice (21). Second, although most of the relevant sociodemographic characteristics were ascertained, such as gender, race-ethnicity, income and employment, and marital status, others, such as social support or religiosity, that have been previously linked to antidepressant outcome were not included in STAR*D (22). Personality disorders have been reported as potential confounders of antidepressant treatment outcome in some studies, including recent meta-analyses (23), but not all (24,25). STAR*D did not assess personality traits; however, it is important to note the well-known inaccuracy of assessment of trait characteristics, such as personality disorders, in the context of depressive states (26).

Another STAR*D limitation is the absence of a placebo arm at level 1. As a result, participants classified as treatment responders can be considered as two admixed populations: those whose improvement was attributable to citalopram and those whose improvement was attributable to placebo. (In fact, the placebo literature suggests that the latter group can be subdivided further—for example, by identifying those whose improvement is attributable to time or regression to the mean and those whose improvement is a result of the placebo effect.) A very simplistic response to this aspect of the design is to raise concern about the specificity of any associations: for example, might variation in genes associated with treatment response simply be linked to shorter episodes of depression regardless of intervention? It can also be argued that specificity is a second-order question—that is, “after” finding effects one could then proceed to determine specificity in other data sets. Indeed, this next step would be necessary even with a placebo arm, because there was also no active comparator at level 1.

It also bears emphasis that strategies exist to partially address the problem of placebo response. One approach applied in clinical investigations is to examine “patterns” of response that are characteristic of “true-drug” response and patterns characteristic of placebo response (27–29), although more recent data cast some doubt on the utility of these parameters (30). Alternatively, one might focus on response to next-step treatments (that is,

level 2 and subsequent levels), presuming that placebo response should be greatly diminished after an initial treatment failure (31).

One further limitation in the STAR*D genetic data set is the difference between individuals who participated in the genetics study and the STAR*D cohort as a whole, which is discussed in detail elsewhere (32). Because the genetics portion of the study was added after study initiation, participants in that portion would be skewed toward those who entered the study later (which should not introduce bias) and those who remained in the study longer (either because of good treatment response and participation in follow-up or because of poor treatment response leading to continued participation in subsequent levels (which could well introduce bias). Moreover, a substantial literature documents that ethnic and racial groups may differ in their willingness to participate in genetics studies (33). In general, although these distinctions should have little impact on the detection of associations in most cases, they could certainly have an impact on the generalizability of results.

Biomarkers of depression treatment outcome have been scarce. Thus there was no justification for collecting serum or whole blood in STAR*D. However, new and more sophisticated techniques may arise that could provide important information about these phenotypes. The lack of these biological materials for STAR*D participants may limit associations between genetic variations and their function.

Finally, STAR*D has some limitations for investigation of tolerability outcomes that bear consideration. In particular, the primary measure of adverse effects by bodily system—the Patient-Rated Inventory of Side Effects—was not administered at study entry. Therefore, subsequent reports of adverse effects cannot be distinguished from preexisting symptoms. This consideration was apparent in analyses of sexual symptoms, where it was impossible to determine whether these symptoms were truly treatment emergent (34). To circumvent this problem, one approach is to consider only adverse effects not present at the initial postbaseline visit. Alternatively, some potential adverse effects, such as insomnia, can be identified by using items on ratings scales that were completed at baseline (Laje G et al., unpublished data).

Results of pharmacogenetics studies in STAR*D

The STAR*D study aimed at helping clinicians make treatment decisions by elucidating which options provided better efficacy and tolerability. STAR*D is the largest pharmacogenetics study of major depression. It has provided, and continues to provide, a tremendous opportunity to elucidate genetic determinants of treatment outcome and tolerability.

Two common genetic analytic approaches have been used in the STAR*D sample: candidate gene and genomewide association studies. We discuss results of candidate gene studies and describe the genomewide studies that have been conducted in a subsample of participants. The genomewide results for the whole sample are not yet published. Two general phenotype groups have been studied: antidepressant treatment outcome and treatment-emergent adverse effects (Tables 1, 2, and 3).

Antidepressant outcome

The STAR*D sample offered an unparalleled opportunity to search for new genes linked to antidepressant outcome and to replicate previous findings. Novel associations with citalopram response were reported within HTR2A (the gene that encodes the serotonin 2A receptor) (32) and GRIK4 (encodes the KA1 subunit of the glutamate-kainate receptor) (35).

The KCNK2 gene (encodes a potassium channel of the K subfamily) was associated with treatment resistance (31).

The serotonin transporter (SLC6A4) is a gene for which new variants have been described and replication of previous findings have been attempted (36,37). Other genes of interest that were previously reported to be significant included FKBP5 (38), PDE11A (39,40), and BDNF (41). Finally, genes with pharmacokinetic function were also assessed in this group and included CYP2D6, CYP2C19, CYP3A4, CYP3A5, and ABCB1 (42).

Although these reports use an outcome phenotype, the phenotype definition varies across groups (see below). This is particularly problematic when analyzing genes such as the serotonin transporter (SLC6A4) because tolerability is a confounder of outcome and the results could vary depending on whether it is included. This is particularly the case when vigorous dosing is used; that is, the nonresponding patient receives ever-increasing doses until intolerance is encountered or the intolerant patient cannot tolerate a therapeutic dosage.

Response and remission phenotype definitions

Four groups across the United States have tested outcome phenotypes in the STAR*D sample. Although the outcomes were antidepressant treatment response and remission, all the phenotype definitions have subtle yet significant differences.

The Intramural Research Program at the National Institute of Mental Health (NIMH), led by one of the authors (FJM) in close collaboration with another author (AJR) and others, crafted a phenotype based on stringent criteria for time taking the drug (six-week minimum), a HAM-D score of >10 at baseline, treatment adherence (by report), tolerability, and at least 50% improvement in QIDS-C (clinician-rated) scores for “response” or a score of ≤5 on the QIDS-C at endpoint for “remission.” A third phenotype, QIDS-C change, was defined on the basis of the same exclusions described above. This phenotype used the relative change in QIDS-C score between baseline and endpoint to define a percentage of improvement or worsening. The goal for such stringent phenotype definition was to guarantee, to the extent possible, that nonresponders would have had a fair chance to respond to the drug, achieving at least six weeks of treatment at a therapeutic dosage (32).

A group at Massachusetts General Hospital headed by another author (RHP) used definitions similar to those of the NIMH group but also examined outcomes without considering tolerability.

A group at the University of California, San Francisco (UCSF), led by Steven P. Hamilton, defined six interrelated phenotypes. On the basis of exposure to the drug (at least six weeks), patients were considered responders if they had a reduction of 50% or greater in QIDS-SR (self-rated) scores and nonresponders if the score had decreased less than 50% at the level 1 endpoint. Remitters were defined by using the same time criterion and a QIDS-SR score of <6. The UCSF group also defined a “specific responder” phenotype, in which the level of improvement needed to qualify as a responder was sustained after all remaining visits. The intent was to weed out possible placebo response. Finally, a tolerance outcome was based on study exit data. All participants who continued with citalopram were considered tolerant, and patients who refused to continue level 1 treatment or who left the study because of side effects were considered intolerant (42).

A group at the Mayo Clinic, led by David A. Mrazek defined three outcomes—remission, response, and citalopram tolerability—but reported only the definition and the results for remission. Remission was defined as a score of <6 on the QIDS-C at the last clinic visit. In

addition, participants needed a baseline QIDS-C score of ≥10 or greater, at least six weeks of treatment, and citalopram adherence (37).

The HTR2A and GRIK4 genes

The first pharmacogenetics results from STAR*D were reported by McMahon and colleagues in 2006 (32), who sampled 768 SNPs in 68 candidate genes. To address the issue of multiple testing, a split-sample design was used. The criteria for an association to be considered significant were same marker, same allele, and same test in both test and replication subsamples. Three phenotypes were tested: response, remission, and QIDS-C change from baseline to endpoint as described above (NIMH phenotype definitions). Results of the primary analysis showed two associated markers: one located in the second intron of the HTR2A gene (rs7997012) and the other located in the GRIK4 gene (rs1954787) (32,35) (Tables 1 and 2). The homozygous carriers of both the HTR2A and GRIK4 response-associated alleles were 23% less likely to be citalopram nonresponders than participants with none of these marker alleles. The area under the curve expressing the probability of correctly identifying a responder from a random pair of participants was .58, suggesting that these two markers have very small predictive value (35). These findings have yet to be replicated in an independent sample. However, positron emission tomography studies using [^{11}C]DASB, a selective tracer for measuring in vivo serotonin transporter density, have found associations with rs7997012 (HTR2A) in thalamus and rs1954787 (GRIK4) in the pregenual cingulate cortex, suggesting that these two variants might have a subtle regulatory effect on the serotonin transporter and thus influence antidepressant treatment through this mechanism (Laje G, Cannon DM, Allen AS, et al., unpublished manuscripts, 2009).

The serotonin transporter

The serotonin transporter (SLC6A4) and a functional polymorphism in its promoter region (known as serotonin transporter linked polymorphic region: 5-HTTLPR) have received the most attention by mental health researchers. As the proximal target for SSRIs, the most widely prescribed antidepressants, this gene is the most obvious pharmaco-dynamic candidate for association studies. This variant, the insertion of a 43 base pair segment in the promoter region (L-allele) together with the A-allele of the SNP rs25531 in the same region seem to affect gene expression in important ways (43), and thus differential expression of the SSRIs' target became a good hypothesis to explain SSRI efficacy. A meta-analysis of 15 published studies that included 1,520 patients concluded that there was evidence in favor of a significant association of the long (L) allele with better response to SSRIs (44). This result may reflect publication bias because negative studies tend not to get published.

The serotonin transporter was widely studied in STAR*D. Three publications reported results of SLC6A4 variation and treatment outcome (36,37,45) (Tables 1 and 2). Kraft and colleagues (45) reported no association between citalopram treatment response and nine tagging SNPs and the LPR. This study used the UCSF phenotype definitions. Hu and colleagues (36), using the NIMH outcome definitions, found that LPR variation, specifically the L_A allele, was associated with tolerability and not with treatment outcome, and thus carriers for the short (S/deleted) or the less functional L_G alleles had an increase in side-effect burden that could lead to discontinuation and nonresponse. Finally, Mrazek and colleagues (37) conducted analogous experiments but also selected four subsamples (N=60 each) of self-described Caucasians, African Americans, Asians, and Mexican Americans (N=240) from the Coriell Cell Repository and sequenced the entire SLC6A4 gene, reporting some novel variants that were later tested in STAR*D. This study concluded that for white non-Hispanic participants there was an association between remission of depression treated with citalopram and both the VNTRs 12/12 genotype in intron 2 and the LPR variant. Although this study's phenotype definition was close to the NIMH remission phenotype, it

did not include tolerability. This study specifically excluded 61 participants with known treatment nonadherence, but they may not necessarily have had tolerability issues.

The FKBP5 gene

The FKBP5 gene encodes a chaperone protein important for fine tuning of the hypothalamic-pituitary-adrenal axis (HPA axis). An association between variants in this gene and antidepressant treatment and recurrence of major depressive disorder was first described by Binder and associates (46). This gene departed from the monoamine realm but remains a good candidate on the basis of its relevance in pathways such as the HPA axis. Lekman and colleagues (38) conducted a replication study in the STAR*D sample and found the modest effect previously described in rs1360780 and proposed rs4713916 as a putative functional region (Tables 1 and 2). A subsequently published study has replicated the rs1360780 association in a small cohort of German patients (47); however, this variant was negative in a Han Chinese population (48).

The phosphodiesterase genes

In 2006 Wong and colleagues (49) published a report linking variation in PDE1A and PDE11A to antidepressant treatment outcome in a Mexican-American population (N=284). The PDE1A and PDE11A are two genes from the large phosphodiesterase (PDE) family. These genes are reasonable candidates because they metabolize cyclic adenosine and guanosine monophosphate (cAMP and cGMP). Cyclic AMP also binds to a response-element binding protein (CREB) in the nucleus and regulates gene transcription of brain-derived neurotrophic factor (BDNF) among others (50).

Two replication attempts were conducted with STAR*D data, the first one by Teranishi and colleagues (40) and the second by Cabanero and colleagues (39). The first group evaluated two markers, rs1549870 (PDE1A) and rs1880916 (PDE11A), using a response phenotype based on at least six weeks of treatment and >50% improvement in QIDS-SR score for response and a QIDS-SR score <6 for remission with Hispanic, Caucasian, and African-American subsamples (see UCSF definitions) (Table 1). Cabanero and colleagues analyzed the Hispanic subsample (N=268) and the entire cohort (N=1,914) (Table 2). Among other markers, those previously reported on PDE11A (rs1880916), PDE1A (rs1549870), and PDE9A (rs729861) were analyzed for association with treatment outcome by using both a phenotype similar to that used by Wong and colleagues and the NIMH outcome definition. Neither report found evidence of association with markers in PDE11A, PDE9A, or PDE1A on individual or haplotype tests in the Hispanic, Caucasian, or African-American subsamples or the entire cohort. However, in the study by Cabanero and colleagues, one of the markers—(rs4893975) in PDE11A —was found to be in Hardy-Weinberg disequilibrium in cases of depression, suggesting that this gene might have a role in major depressive disorder but not in antidepressant response.

The BDNF gene

The BDNF gene is a member of the neurotrophin family and is involved in neuronal growth and plasticity. Variation in BDNF has been thought to play a role in the etiology of affective disorders and the mediation of antidepressant treatment response (51). Furthermore, expression of BDNF has been shown to be modified by antidepressant treatment (52). A functional nonsynonymous SNP causing an amino acid substitution of valine to methionine has been identified in codon 66 (val66met; rs6265) (53,54).

Multiple studies support a potential role of BDNF variation in the pathogenesis of major depressive disorder (55–57), but not all studies have done so (58,59), including a recent

meta-analysis (60). The BDNF val66met polymorphism has been at the center of antidepressant treatment response with some positive (61) and negative (62) results.

A study by Domschke and colleagues (41) found no evidence of an association between treatment outcome and BDNF variation, including the val66met, in a German sample (N=268) or the STAR*D sample (N=1,914) (Tables 1 and 2).

Genes involved in pharmacokinetics of antidepressants

Genes that regulate the bioavailability of antidepressant drugs could also have a significant impact on response and tolerability. The majority of antidepressant compounds are metabolized by the liver through the cytochrome P-450 pathway and its enzymatic subgroups. Genes such as CYP2D6, CYP1A2, CYP3A4, and CYP2C19 have been studied and well characterized, but their clinical use has proven to be limited. The ABCB1, another pharmacokinetic gene, also known as MDR1 (multidrug resistance) encodes the p-glycoprotein and is expressed in tissues that have elimination or protective roles, such as the intestines, liver, kidney, and blood-brain barrier. Peters and colleagues (42) published a study using a split-sample design to assess 15 polymorphisms from five pharmacokinetic genes, including CYP2D6, CYP2C19, CYP3A4, CYP3A5, and ABCB1. Using the UCSF phenotype definitions, they found no association with citalopram outcome in any of these genes (Table 1).

The KCNK2 (TREK1) gene

On the basis of rodent models of anti-depressant response, Perlis and colleagues (31) examined variants in four genes—KCNK2 (TREK1), SLC18A2 (VMAT2), S100A10, and HDAC5—for association with treatment resistance in STAR*D, which they defined as not achieving remission despite two adequately tolerated treatment trials (that is, levels 1 and 2). The remission phenotype was defined as a QIDS-C score <6. Although no association with any of the four genes was found at level 1 alone, in the primary analysis of treatment resistance, variants in KCNK2 were associated with treatment response among patients with unsatisfactory response to both citalopram and one additional treatment level (Table 2). These findings suggest that genetic variation in KCNK2 may have a role in treatment resistance, but they suggest more broadly that animal models might be used in pharmacogenetics studies of antidepressant response.

Other genes

The initial study by McMahon and colleagues (32) sampled 68 candidate genes with 768 markers. These genes represented major neurotransmitter systems involved in depression. Marker coverage was limited by financial resources, and gene priority was established by an expert panel. Briefly, the sampled genes were serotonin related (HTR1A, 1B, 1D, 1E, 1F, 2A, 2B, 2C, 3A, 3B, 3C, 3D, 3E, 4, 5A, 6, 7, SLC6A4, TPH1, and TPH2), norepinephrine related (DBH and SLC6A2), glutamate ionotropic receptor and transporter genes (GRIN1, 2A, 2B, 2C, 2D, 3A; GRIA1-4, GRIK1-5, and SLC1A1), dopamine and neutrophic factors (COMT, TH, MAOA, BCL2, BDNF, and NTRK2), and other genes known to be relevant in depression (see reference 32, Table 2, for a comprehensive list).

Because of the number and size of these genes, some were not exhaustively covered. Therefore, although all of them were included in the outcome phenotype analyses, variation not sampled may still prove to be important to this phenotype. The findings imply a preliminary negative association of these genes and antidepressant outcome, but given the limited coverage the study could not rule out the presence of markers that might have some relevance to these phenotypes.

Peters and colleagues (63) selected five serotonin-related genes and resequenced the exonic and putatively regulatory regions of HTR1A, HTR2A, TPH1, TPH2, and MAOA in a fluoxetine-treated sample. These investigators uncovered some novel variants that were not associated with response to citalopram in STAR*D when the UCSF phenotype definitions were used.

Adverse effects

The emergence of adverse reactions is common to all pharmacological treatments. The severity of these effects, however, determines whether a patient will be partially adherent, continue, or discontinue treatment. Finding genetic predictors has been a priority for many groups, especially predictors of adverse events that would interfere with treatment because of their severity or risk. Two phenotypes have been studied in STAR*D: treatment-emergent suicidal ideation and sexual dysfunction (Table 3).

Treatment-emergent suicidal ideation

Suicidal ideation is an uncommon symptom than can emerge during antidepressant treatment. The Food and Drug Administration determined after a meta-analysis that there was sufficient evidence to issue a “black-box warning” highlighting the risk of treatment-emergent suicidality among patients taking antidepressants who were under age 25 (64). To address treatment-emergent suicidal ideation, two candidate gene studies and one genomewide study were conducted with STAR*D data.

First, in a candidate gene study of the cyclic adenosine monophosphate response-element binding protein (CREB1), Perlis and colleagues (65) reported two SNPs and two of the five SNP haplotypes associated with treatment-emergent suicidal ideation among men. The phenotype was defined as a QIDS-C score ≥2 on item 12 at any postbaseline visit for participants whose baseline score was 0 or 1. Subsequently, Laje and colleagues (8) used a different phenotype definition based on item 12 of the QIDS-SR, in which participants whose baseline score was 0 had a score ≥1 on any postbaseline visit. These investigators reported results from the 68 candidate gene data set from the NIMH group. In this study, two markers—one in GRIA3 (rs4825476) and another in GRIK2 (rs2518224)—were associated with treatment-emergent suicidal ideation. Different alleles on GRIA3 and GRIK2 were also implicated with treatment-emergent suicidal ideation in an independent sample of German inpatients with major depressive disorder in which the phenotype was derived from item 3 of the HAM-D (66).

Finally, the NIMH group conducted a genomewide study in a case-control subsample (N=274) using Illumina’s Human-1 BeadChip. The phenotype definition for the cases of treatment-emergent suicidal ideation was the same as previously reported by this group. However, control group participants were selected on the basis of a minimum of three visits, a baseline QIDS-C total score ≥10, adherence to medication, recurrent depression, no history of suicide attempts, and no report of suicidal thoughts throughout citalopram treatment as measured by the QIDS-C and QIDS-SR. Two more markers were implicated in treatment-emergent suicidal ideation: one residing in the PAPLN gene (rs11628713), which encodes papilin, a protoglycan-like sulfated glycoprotein, and another that showed a strong trend after permutation correction located in the IL28RA gene (rs10903034) that encodes an interleukin receptor (67). Although these markers offer promising results with some meaningful effect sizes, the findings are still not sufficient to warrant use of these markers in a clinical setting (Table 3).

Sexual dysfunction

Sexual dysfunction is a common adverse event that is a major contributor to treatment nonadherence among patients treated with SSRIs. One study of STAR*D data derived phenotypes from self-reports of erectile dysfunction, decreased libido, or anorgasmia on the Patient-Rated Inventory of Side Effects. When a set-based test was used, SNPs in glutamatergic genes were associated with decreased libido (GRIA3 and GRIK2), with difficulty achieving orgasm (GRIA1), and with difficulty achieving erection (GRIN3A) (34) (Table 3). These results will require replication in an independent sample.

Conclusions and future directions

Although several pharmacogenetics studies have been conducted using STAR*D data, there is still much work to be done. The initial genomewide association studies were performed with now-obsolete platforms that provide genomewide coverage but that do not have the accuracy, marker density, and comprehensive coverage of the newer platforms available today. Until we fully understand the mechanisms that regulate gene function, we should maximize the results we obtain from available samples not only with genotyping with denser coverage but also with techniques such as sequencing and gene expression.

Every study conducted with STAR*D data has attempted correction for multiple testing to avoid false positives. However, replication of findings in independent samples is important in increasing our confidence in the reported results. Achieving replication of results with small effects or low allele frequencies might require a sample at least as large and as uniformly treated and longitudinally assessed as the STAR*D cohort. Moreover, outcome predictors based on multiple markers require still larger samples. These new samples may require not only further clinical characterization but also functional data such as neuroimaging or other biological markers.

A consensus is needed on phenotype definitions, particularly of anti-depressant outcome. Without such definitions, replication studies and meta-analyses are difficult to interpret. Although more complex and thorough definitions might impair statistical power in small studies, STAR*D has helped to identify important confounders, such as tolerability, in analyses of the SLC6A4 (serotonin transporter). Adequate phenotype definitions for pharmacogenetic studies of antidepressant outcome should emphasize sufficient severity of baseline symptoms (for example, a HAM-D score of ≥14), sufficient exposure to the drug (for example, four to six weeks or more of treatment with an antidepressant), and adherence and tolerability. Without these characteristics, phenotypes could be uninterpretable and outcome results difficult to replicate across cohorts.

STAR*D has yielded a number of leads for future pharmacogenetics studies. Although results have not yet translated into findings that are clinically useful, genetic association studies are providing significant insights into the pathophysiology of depression. In summary, the next several years should bring significant progress to the field of pharmacogenetics. Investigators will continue to identify markers and genes involved in antidepressant treatment outcome and adverse effects that will increase our understanding of the biology of mood disorders and may identify predictors of outcome that would result in more effective treatments, fewer adverse events, and a greatly reduced burden of mood disorders for patients and society.

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Table 1

Pharmacogenetic studies of antidepressant treatment response conducted in Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Study and gene	Marker	p	Sample N	Phenotype definition[a]	Observations
Teranishi et al. (40)			1,804	UCSF	
PDE1A	rs1549870	ns			
PDE11A	rs1880916	ns			
Kraft et al. (45)			1,308	UCSF	White subset reported
SLC6A4	rs1042173	ns			
	rs140701	ns			
	rs140700	.03			
	rs6354	ns			
	rs2066713	ns			
	rs16965628	ns			
	rs2020934	ns			
	rs2020933	ns			
	rs25533	ns			
	5-HTTLPR	ns			
	rs25531	ns			
Hu et al. (36)			1,655	NIMH	Association with adverse effect burden
SLC6A4	5-HTTLPR	ns			
Leckman et al. (38)			1,809	NIMH	
FKBP5	rs1360780	ns			
	rs4713916	.04			
	rs3800373	ns			
Paddock et al. (35)			1,816	NIMH	
GRIK4	rs1954787	<.001			
Peters et al. (63)			1,953	UCSF & NIMH	
HTR2A	rs1923884	.02			
Peters et al. (63) and			1,953 and	UCSF & NIMH	
McMahon et al. (32)			1,329		
HTR2A	rs7997012	<.001			

Study and gene	Marker	p	Sample N	Phenotype definition[a]	Observations
McMahon et al. (32)		<.001	1,372	UCSF & NIMH	
HTR2A	rs6313	ns			
	rs6311	ns			
Domschke et al. (41)			1,953	NIMH	rs6265 (val66met)
BDNF	rs1519479	ns			
	rs2203877	ns			
	rs1519480	ns			
	rs6265	ns			
	rs11030104	ns			
	rs12273363	ns			
	rs7931247	ns			
	rs1491850	ns			
	rs7119334	ns			
	rs10742184	ns			
Peters et al. (42)			1,877	UCSF	
ABCB1	rs1045642	ns			
CYP2D6		ns			
CYP2C19		ns			
CYP3A4		ns			
CYP3A5		ns			

[a]UCSF, University of California, San Francisco; NIMH, National Institute of Mental Health

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Table 2

Pharmacogenetic studies of symptomatic remission conducted in Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Study and gene	Marker	p	Sample N	Phenotype definition[a]	Observations
Cabanero et al. (39)			1,914	NIMH	
PDE1A	rs1549870	ns			
PDE9A	rs729861	ns			
PDE11A	rs4893975	ns			
	rs6433687	ns			
	rs3770016	ns			
	rs1880916	ns			
Hu et al. (36)			1,655	NIMH	Association with adverse effect burden
SLC6A4	5-HTTLPR	ns			
Mrazek et al. (37)			1,503	Mayo Clinic	Adverse effect burden was not included in the phenotype. VNTR findings were significant only in the non-Hispanic white subsample[b]
SLC6A4	5-HTTLPR	.04			
	Intron 2	ns			
	VNTR	.04			
	rs25531	ns			
Lekman et al. (38)			1,809	NIMH	
FKBP5	rs1360780	ns			
	rs4713916	.003			
	rs3800373	ns			
Paddock et al. (35)			1,816	NIMH	
GRIK4	rs1954787	<.001			
Peters et al. (63)			1,953	UCSF & NIMH	
HTR2A	rs1923884	.01			
Peters et al. (63) and McMahon et al. (32)			1,953 and 1,149	UCSF & NIMH	
HTR2A	rs7997012	<.001			
McMahon et al. (32)		<.001			
HTR2A	rs1928040	.045	1,148	UCSF & NIMH	
HTR2A	rs6313	ns	1,183	UCSF & NIMH	
Domschke et al. (41)		ns	1,953	NIMH	rs6265 (val66met)

Study and gene	Marker	p	Sample N	Phenotype definition[a]	Observations
BDNF	rs1519479	ns			
	rs2203877	ns			
	rs1519480	ns			
	rs6265	ns			
	rs11030104	ns			
	rs12273363	ns			
	rs7931247	ns			
	rs1491850	ns			
	rs7119334	ns			
	rs10742184	ns			
Perlis et al. (31)			1,554	MGH	Remission achieved at STAR*D level 2
KCNK2	rs12031300	ns			
	rs2841616	.003			
	rs7538655	ns			
	rs7549184	.03			
	rs10494996	.01			
	rs2841608	.003			
	rs17546779	ns			
	rs12136349	.003			
	rs10779646	.03			

[a] NIMH, National Institute of Mental Health; UCSF, University of California, San Francisco; MGH, Massachusetts General Hospital

[b] VNTR, variable-number tandem repeats

Table 3

Pharmacogenetic studies of adverse events conducted in Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Study, adverse event, and gene	Marker	p	Sample N	Observations
Perlis et al. (34)			1,473	
Decreased libido				
GRIA3	rs2285127	<.001		
	rs2269551	.004		
	rs550640	.047		
GRIK2	rs513216	.002		
	rs9404130	.012		
	rs2518302	.031		
	rs2518224	.038		
Difficulty achieving orgasm				
GRIA1	rs10515697	.004		
	rs1994862	.004		
	rs1864205	.018		
Difficulty achieving erection				
GRIN3A	rs2050641	.002		
	rs1323423	.003		
	rs1323427	.004		
	rs2050639	.012		
	rs1983812	.019		
	rs1004362	.026		
	rs2417290	.035		
Laje et al. (8)			1,915	Genotypic test
Treatment-emergent suicidal ideation				
GRIK2	rs2518225	<.001		
GRIA3	rs4825476	<.001		
Laje et al. (67)			274	Genomewide association study in subsample
Treatment-emergent suicidal ideation				
PAPLN	rs11628713	<.001		
IL28RA	rs10903034	<.001		
Perlis et al. (65)			1,447	Male subjects only. Haplotypes CAATC (p=.004) and CAGTT (p=.009) were also associated in males
Treatment-emergent suicidal ideation				
CREB1	rs2709376	ns		
	rs2253206	ns		
	rs7569963	.005		
	rs7594560	ns		
	rs4675690	.005		