Genetic Studies of Drug Response and Side Effects in the STAR*D Study, Part 2

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In the previous part of this review, we reviewed the evidence for association between selective serotonin reuptake inhibitor (SSRI) response phenotypes and genetic variation in the serotonin transporter locus. It was notable that 4 studies from 3 groups using the same clinical data reached largely concordant findings for citalopram response, with differences in results highlighting the effect of minor changes in sample size and phenotype definition. The second part of this review will focus on candidate genes other than *SLC6A4*, alternative phenotypes such as adverse events, and how the STAR*D sample might further offer insights into the role of genetic variation in treatment response.

Other Candidate Genes and Remission

Several groups studied other candidate genes as well. These studies were typically carried out to replicate findings previously identified in the field or test specific hypotheses. We will briefly review these findings.

The most impressive finding so far from candidate gene investigations involves a comprehensive study of common variation in 68 genes chosen by an expert panel for their potential relationship to the mechanism of therapeutic action of antidepressants.[1] The authors of this study examined 768 single nucleotide polymorphisms (SNPs) in these genes and analyzed the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data using a 2-stage approach that provides an internal validation sample for observed associations. The authors detected association between response and a SNP (rs7997012) in the final intron of the serotonin receptor 2A gene (*HTR2A*),[1] a finding validated by another group[2] also using the STAR*D dataset, but with minor differences in phenotypic definition and analytic methods. Interestingly, subsequent research in the smaller Genome-based Therapeutic Drugs for Depression project found no association for this SNP in 429 UK cases of MDD treated with escitalopram, although they did report association to a different SNP approximately 21,000 base pairs distant.[3]

A reanalysis of the 68-gene data after adding genotypes for an additional 520 subjects led to a trivial diminution of the original *HTR2A* remission signal, as well as a new association with remission to a SNP (rs1954787) in the ionotropic KA1 glutamate receptor subunit gene (*GRIK4*).[4] The effect seemed most prominent in females and those who could tolerate citalopram during the trial. In a similar reanalysis of their data, the same authors focused on 2 previously genotyped SNPs and 1 newly genotyped SNP in FK506 binding protein 5 (FKBP5), which is a cochaperone of the glucocorticoid receptor.[5] This study sought to examine a previous association observed between a SNP in this gene (rs1360780) and antidepressant response.[6] While Lekman et al[5] did not find an association between this SNP and remission, they did find an association to depression itself. They also found association between a SNP (rs7413916) and remission in the STAR*D sample, a signal that was driven by the non-Hispanic Caucasian subsample. The finding suggests a modest increase in the likelihood of remission for those carrying the A allele of this SNP. The authors conclude that FKBP5 remains an interesting target for the understanding of both antidepressant response and depression itself.

Three SNPs in a gene encoding a potassium channel (*KCNK2* [TREK1]) have been reported to be associated with individuals who achieve remission at level 2 treatment stage of the STAR*D trial, which involves either augmentation of citalopram or switching to bupropion, sertraline, venlafaxine, or cognitive therapy.[7] This gene was studied on the basis of experiments showing SSRI inhibition of TREK1 activity, as well as the observation of a phenotype described as "depression-resistant" in mice deficient for the *TREK1* gene.[8] Interestingly, no association was seen at the citalopram-only level 1 treatment, perhaps suggesting an effect specific to a more treatment-resistant form of depression.

STAR*D Genetic Studies Showing No Association to Drug Response Phenotypes

A number of additional genetic findings in STAR*D have been reported that have shown no association between measures of therapeutic response and specific genes. They are mentioned here because they do represent the largest sample tested for this phenotype for many of these genes. Two groups[9,10] studied phosphodiesterase genes in STAR*D and found no association between remission and genetic variants in *PDE1A* or *PDE11A* in Hispanic subgroups that were larger than those found in the original study of North American Hispanic samples.[11] Two groups[7,12] examining the vesicular monoamine transporter 2 gene (VMAT2; *SLC18A2*) for association with remission failed to find association. The genotypic data gathered from McMahon et al[1] were reanalyzed for brain-derived neurotrophic factor, and no association was again noted to response phenotypes in STAR*D.[13] A number of pharmacokinetic genes (*CYP2D6, ABCB1, CYP2C19, CYP3A4,* and *CYP3A5*) showed no association to treatment phenotypes,[14] a finding that was not surprising given the redundant pathways for citalopram metabolism, coupled with the general lack of association between citalopram drug levels and therapeutic success. Uncommon SNPs identified through targeted DNA resequencing of several serotonin-related genes (*HTR1A, HTR2A, TPH1, TPH2,* and *MAOA*) found no association to treatment response.[2]

STAR*D Genetic Studies of Adverse Events Including Suicide and Other Phenotypes

Side effects were measured in several ways in STAR*D, each being amenable to genetic analysis. First, "tolerance" was defined by STAR*D investigators based on study exit data; all patients who continued with citalopram at the end of STAR*D level 1 treatment were considered tolerant, while patients who left the study for any reason in the first 4 weeks, or at any time due to side effects, were considered intolerant. Second, subjects were scored on the Patient Rated Inventory of Side Effects (PRISE), a self-report instrument used to qualify side effects by identifying and evaluating the tolerability of each symptom in 7 domains (eg, sexual functioning, sleep). Third, subjects filled out an instrument (Frequency, Intensity, and Burden of Side Effects Rating[15]) in order to quantify the overall side effect burden using a 7-point Likert-type scale for ratings of the frequency, intensity, and overall burden of all side effects experienced over the prior week. Genetic investigations have focused on several specific adverse events.

Tolerance and Side Effect Burden

Using the tolerance phenotype as described above, Hu et al[16] found no association to the composite serotonin transporter 5-HTTLPR/rs25531 genotype. When assessing side effect burden, the authors found an association between genotype and

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burden in the whole sample with the composite genotype or with 5-HTTLPR alone. Given the wide variation in allele frequency between ethnic groups, the authors also tested non-Hispanic Caucasians, the largest single group in STAR*D. In non-Hispanic Caucasians, the association between the composite genotype and side effect burden (as measured by a score of ≥4 on the Global Rating of Side Effect Burden) was less strongly supported, although the association was still statistically significant (corrected $P < .03$ for allele). On the basis of the hypothesis that gastrointestinal side effects contribute greatly to SSRI side effect burden, the authors carried out a multivariate analysis incorporating 5-HTTLPR/rs25531 composite genotype, citalopram dose, and treatment-emergent diarrhea present at the final visit and found a strong association to side effect burden.[16]

Suicidal Ideation

Laje et al[17] studied association of suicidal ideation and 68 genes and detected association with genes encoding ionotropic glutamate receptors (*GRIA3* and *GRIK2*). Suicidal ideation was measured by assessing a single item from the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) probing thoughts of death or suicide. Subjects with no such thoughts prior to treatment with citalopram who then endorsed any suicidal thoughts during the trial were considered to have treatment-emergent suicidal ideation. This could also include endorsing the item, "I feel that life is empty or wonder if it's worth living," as well as the 2 items specifically mentioning suicide. The authors found 1 SNP in each gene (rs4825476 in *GRIA3,* genotypic $P = .01$; rs2518224 in *GRIK2,* allelic $P = .003$) that conveyed susceptibility to development of suicidal ideation in response to citalopram treatment, with impressive odds ratios (*GRIK2*, 8.23; *GRIA3*, 1.94). The authors conclude that their findings represent the potential for identifying individual patients carrying high risk for the development of suicidal ideation while on citalopram treatment.

On the basis of their previous observation of association between SNPs in CAMP responsive element binding protein 1 (CREB1) and anger expression in a small MDD sample,[18] Perlis et al[19] analyzed the STAR*D sample for association between CREB1 variation and suicidal ideation and failed to find an overall association; however, they did find an association specific to men with suicidal ideation within 30 days of citalopram treatment and 2 of the 5 SNPs they investigated (rs7569963 and rs4675690; each, $P = .005$). Suicidality was defined as a score of zero for baseline suicidal thought, assessed by the QIDS-SR item, that then progresses to a score of 2 or 3 during treatment, both of which mention suicide. Using a similar approach, this same group analyzed the gene encoding the α-1C subunit of the L type voltage dependent calcium channel (*CACNA1C*). This gene was chosen based on observations in recent genome-wide association study (GWAS) data connecting *CACNA1C*, the target of medications like verapamil and nimodipine, to bipolar disorder.[20] The non-Hispanic Caucasian subsample of STAR*D was genotyped for 2 intronic SNPs and tested for association to a number of baseline clinical characteristics related to bipolar disorder, as well as worsening of selected symptoms with treatment. Both SNPs showed nominal association (ie, uncorrected for multiple hypothesis testing) with treatment-emergent suicidality (rs10848635, $P = .05$, odds ratio=1.28; rs1006737, $P = .03$, odds ratio=1.31), defined as a 1-point increase from baseline for the QIDS-SR item mentioned above.[21] These 2 SNPs also showed evidence of association with baseline agitation (rs10848635, $P = .03$) and depression severity (rs1006737, $P = .04$), but not with remission.

Sexual Dysfunction

Sexual side effects are commonly reported in response to citalopram treatment and are a common reason for discontinuation of treatment. Perlis et al[22] investigated the association of DNA variants in 68 genes (using 768 SNPs) with sexual side effects (decreased libido, difficulty achieving orgasm, and difficulty with erections) as assessed with the PRISE and found association for erectile dysfunction and the *GRIN3A* gene, decreased libido and *GRIA3* and *GRIK2*, and anorgasmia and *GRIA1* (permutation P value $< .05$).

Conclusions and Outlook

STAR*D provides a large sample to address hypotheses of association of genetic variants and antidepressant response. Given the literature to date, 3 of 4 studies, using the same data, found no evidence for association of the serotonin transporter gene and antidepressant response, strongly suggesting that this gene is not likely to play a role in one's ability to achieve remission from MDD in response to citalopram treatment. Several candidate gene studies show provisional evidence that some genes are or are not associated with citalopram response. Given the field's poor experience with replication of findings from single studies, all of the work cited here must be viewed as tentative. While some observed pharmacogenetic findings display dramatic effects, such as those seen for Stevens-Johnson syndrome and anticonvulsants in Asian populations,[23] it is not likely that similar strong effect sizes will be seen for antidepressant response. The implication of this is that even while the STAR*D sample is currently the largest available, it is still likely to be underpowered to reliably detect any true risk variant contributing a measurable, but small, effect on response. Future directions for study include higher-density investigations of hypothesis-driven candidate genes, assessment of structural variation (ie, the presence of rare large deletion or duplication events within the genome) at a genome-wide level, and perhaps, ultimately, collection of whole genome DNA sequence data for every subject. This last possibility is rapidly becoming feasible with new DNA sequencing technologies. Bioinformatic analysis of all of these approaches can be used to identify pathways relating to treatment response and uncover interaction by 2 or more genetic loci. It will be critical for any future findings coming out of STAR*D to be verified by replication in large independent samples, which are currently few in number. One example of such an approach would involve meta-analysis of GWAS data from multiple datasets, a method that has successfully identified risk genes for bipolar disorder that were not detectable from individual studies.[20] While it is debatable whether discovery of the many risk variants that increase the likelihood of drug response or drug side effects will be useful for predictive tests that can be used to guide prescribing practices, these findings will more likely illuminate previously unheralded biologic pathways involved in critical aspects of antidepressant effects on human brain.

Since the STAR*D trial was not designed with a pharmacogenetics study, there are a number of inherent limitations that pit the practical goals of the STAR*D trial against the experimental constraints that are often required in a human genetics study. While the genetics subset of STAR*D generally reflects the diversity of the whole study, there are a number of clinical and demographic characteristics that differ significantly between those who gave blood and those who did not. For example, a genetics subset subject was significantly more likely to come from a primary care clinic; be Caucasian and Hispanic; be married, older, and more educated; have recurrent depression; have a longer illness; and have more depressive episodes.[24] Given the "real world" design of the study, STAR*D may not be generalizable to other trials, but may actually be more generalizable to the general depressed population.[25] Pharmacogenetic findings from this study may thus have more applicability to the type of patients most clinicians treat, rather than to the subjects of highly controlled clinical trials. This inevitably leads to limitations in interpreting the effects of genetics findings, which may be confounded by the concomitant

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drug usage, the high level of comorbidity with psychiatric disorders and general medication conditions, the lack of a placebo arm, and the absence of a reliable measure of drug adherence. Even with these limitations, it is unlikely that another single study will be available in the foreseeable future that will allow testing of hypotheses relating to the genetic influence on drug treatment of depression.

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doi:10.4088/JCP.09ac05522
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