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Genetic and Clinical Predictors of Sexual Dysfunction in Citalopram-Treated Depressed Patients

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Abstract

Sexual dysfunction is a major contributor to treatment discontinuation and nonadherence among patients treated with selective serotonin reuptake inhibitors (SSRIs). The mechanisms by which depressive symptoms in general, as well as SSRI exposure in particular, may worsen sexual function are not known. We examined genetic polymorphisms, including those of the serotonin and glutamate systems, for association with erectile dysfunction, anorgasmia, and decreased libido during citalopram treatment. Clinical data were drawn from a nested case–control cohort derived from the STAR*D study, a multicenter, prospective, effectiveness trial in outpatients with nonpsychotic major depressive disorder (MDD). Self-reports of erectile dysfunction, decreased libido, or difficulty achieving orgasm based on the Patient-Rated Inventory of Side Effects were examined among Caucasian subjects (n = 1473) for whom DNA and adverse effect measures were available, and who were treated openly with citalopram for up to 14 weeks. Of 1473 participants, 799 (54%) reported decreased libido; 525 (36%) reported difficulty achieving orgasm. Of 574 men, 211 (37%) reported erectile dysfunction. Using a set-based test for association, single nucleotide polymorphisms in glutamatergic genes were associated with decreased libido (*GRIA3*; *GRIK2*), difficulty achieving orgasm (*GRIA1*), and difficulty achieving erection (*GRIN3A*) (experiment-wide permuted p<0.05 for each). Evidence of association persisted after adjustment for baseline clinical and sociodemographic differences. Likewise, evidence of association was similar when the cohort was limited to those who did not report a given adverse event at the first post-baseline visit (ie, those whose adverse events were known to be treatment emergent). These hypothesis-generating analyses suggest the potential for glutamatergic treatment targets for sexual dysfunction during major depressive episodes.

Keywords

antidepressant; pharmacogenetic; serotonin; glutamate; adverse effect

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INTRODUCTION

Sexual dysfunction is common among individuals with major depressive episodes and may be triggered or exacerbated by treatment with the selective serotonin reuptake inhibitors (SSRIs), with a prevalence of up to 50–70% in some studies when sexual functioning is specifically assessed (Angst *et al*, 2002; Fava and Rankin, 2002; Montejo *et al*, 2001). Common symptoms include decreased libido, difficulty in arousal, and delayed or absent orgasm (Angst *et al*, 2002). Beyond their impact on quality of life, these effects frequently lead to medication intolerance and discontinuation (Bull *et al*, 2002; Montejo *et al*, 2001). Indeed, sexual dysfunction may be the most clinically significant SSRI-related adverse event among individuals age 18–40 (Bishop *et al*, 2006; Clayton, 2001).

The mechanism by which depression itself, or treatments such as SSRIs, may induce sexual dysfunction is poorly understood. Because the proximal site of action of SSRIs is believed to be the serotonin transporter, some sexual effects have been presumed to relate to serotonergic neurotrans-mission (Murray, 1998). However, the neuroanatomy of sexual functioning in general offers some additional direction about which neurotransmitter systems might be most likely to mediate these symptoms. Specifically, other monoamines, as well as glutamate, appear to have a function in male and female sexual behavior (Clayton, 2003).

Because of their potential importance in antidepressant efficacy, common variations in serotonergic, glutamatergic, dopaminergic, and other pathways implicated in antidepressant mechanism of action have been examined recently in a genetic association study in the STAR*D cohort (McMahon *et al*, 2006; Paddock *et al*, 2007). To attempt to clarify the mechanism by which depression and its treatments may contribute to sexual dysfunction, we performed a hypothesis-generating secondary analysis in which we examined these genes for association with sexual dysfunction.

METHODS

Clinical Methods

In the STAR*D trial, all patients were initially treated with the SSRI citalopram. Those who were intolerant of citalopram, or who did not achieve remission, could then be randomized to a next-step treatment option. The methods of the STAR*D study are described in detail elsewhere (Fava *et al*, 2003; Rush *et al*, 2004; Trivedi *et al*, 2006b) and are summarized below.

Study Organization

The STAR*D study, overseen by 14 regional centers (RCs), provided treatment at 41 clinical sites (18 primary care and 23 psychiatric care settings) across the United States.

Research outcomes were collected by telephone interviews conducted by a small team of trained research outcome assessors (ROAs) masked to treatment. ROAs received extensive

training in the administration of efficacy measures, with interrater reliability assessed periodically.

Study Population

The STAR*D clinical cohort consisted of 4041 subjects, of whom 1953 provided blood samples for extraction of DNA and 1910 were genotyped, including 1499 (78.5%) Caucasians. This report presents data from the 1473 Caucasians from this pool who returned for at least one follow-up visit (ie, a modified intent-to-treat cohort). As the study was designed to represent real-world clinical practice, only individuals who sought treatment at the clinical sites were recruited, and advertising was not permitted. Participants were informed of all risks, benefits, and adverse events associated with each study treatment and they provided written informed consent before study entry at each level, as well as for the genetic study. Participants could decline participation in the genetic protocol, which was initiated about 12 months after the clinical study initiation. The study protocol was approved by institutional review boards at all participating RCs, the National Coordinating Center, and the Data Coordinating Center. The study was overseen by an NIMH DSMB.

Participants met broadly inclusive and minimal exclusive criteria to enroll a representative sample. Male and female outpatients, age 18–75, with a DSM-IV diagnosis of nonpsychotic major depressive disorder (MDD), a baseline score ⩾14 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) by the clinical research coordinator (CRC), and for whom the treating clinician had determined that outpatient antidepressant treatment was safe and appropriate were enrolled. Exclusion criteria included a well-documented history of nonresponse or intolerability in the current major depressive episode to adequate doses (Fava, 2003) of one or more medications used in the first two treatment steps; lifetime diagnosis of MDD with psychotic features, schizophrenia, schizoaffective disorder, or bipolar disorder; a current primary diagnosis of eating disorder or obsessive-compulsive disorder; presence of severe, unstable concurrent psychiatric conditions likely to require hospitalization within 6 months (eg severe alcohol dependence with recent detoxification admissions); presence of concurrent medical or psychiatric conditions or concomitant medications that contraindicate a protocol treatment; and pregnancy or intent to conceive within the 9 months subsequent to study entry.

Research Outcome Assessments

The CRC at each study site completed the $HRSD_{17}$ at baseline to determine eligibility, reviewed other inclusion/exclusion criteria, and completed the 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}C_{16}$) (Rush *et al*, 2000, 2006a, 2003; Trivedi *et al*, 2004) at each treatment visitFa clinician-rated scale that assesses nine diagnostic symptoms/domains of MDD. The $QIDS\text{-}C_{16}$ was used to guide treatment implementation and dose adjustment (Rush *et al*, 2006b; Trivedi *et al*, 2006a), and was selected as the primary outcome measure for STAR*D genetics reports. The CRC also completed the 14-item Cumulative Illness Rating Scale (Linn *et al*, 1968; Miller *et al*, 1992) that quantifies the severity/morbidity of general medical conditions relevant to different organ systems. Each of the 14 illness categories was scored 0 (no problem) to 4 (extremely severe/immediate

treatment required/end organ failure/severe impairment in function). The present analysis examined total severity summed over all categories except psychiatry.

The ROA conducted a telephone interview with study participants within 72 h of the baseline and subsequent visits to complete the baseline blinded $HRSD_{17}$ and the 30-item Inventory of Depressive Symptomatology, Clinician-Rated ($IDS\text{-}C_{30}$) (Rush *et al*, 1996).

Individual adverse events were identified at each post-baseline clinical visit using the Patient-Rated Inventory of Side Effects (PRISE) (Rush *et al*, 2004), a nine-item patient-rated assessment of presence or absence of side effects in domains including gastrointestinal, cardiac, skin, nervous system, sensory organs, genital/urinary, sleep, sexual functioning, and other. In each domain, multiple symptoms may be endorsed. No standardized assessment of patient adherence to treatment was collected.

Intervention

Details of the STAR*D measurement-based care approach have been described elsewhere (Trivedi *et al*, 2006b). Following citalopram treatment at doses up to 60 mg per day for up to 14 weeks, participants who did not achieve remission ($QIDS\text{-}C_{16} \leqslant 5$) and/or who could not tolerate citalopram were encouraged to proceed to next-step treatments. Participants could discontinue citalopram and proceed to next-step treatment at any point in the event of intolerable side effects requiring change in medication, inability to increase to an optimal dose because of side effects or patient preference, or presence of significant depressive symptoms (defined as $QIDS\text{-}C_{16}$ score $\geqslant 9$) after 9 weeks at maximum tolerated dose.

Concomitant treatments for current general medical conditions, for associated symptoms of depression including insomnia, anxiety, and agitation, and for antidepressant-associated side effects were permitted based on clinical judgment. However, stimulants, anticonvulsants, anti-psychotics, alprazolam, nonprotocol antidepressants other than trazodone $\leqslant$200 mg at bedtime for insomnia, and psychotherapies targeted at depressive symptoms were not permitted (Trivedi *et al*, 2006b).

Genotyping methods

The process for selecting candidate genes based on evidence of involvement in antidepressant mechanism of action, and selection of single nucleotide polymorphisms (SNPs) to capture common variation, has been described elsewhere (McMahon *et al*, 2006). In brief, based on expert consensus, genes were selected in serotonergic ($n = 20$), glutamatergic ($n = 16$), dopaminergic ($n = 3$), adrenergic ($n = 4$), and neurotrophic ($n = 4$) systems, as well as other genes implicated in antidepressant mechanism of action ($n = 21$). The full list of genes is available in Table 2 of McMahon *et al* (2006). Genotyping was performed using the Illumina BeadArray platform and genotypic data were cleaned using methods previously described.

Analytic methods

Decreased libido, difficulty achieving orgasm, and difficulty with erections are three correlated but nonidentical phenomena assessed by the PRISE. Therefore, three sets of

primary analyses were performed examining each of these individually. Each symptom of sexual dysfunction was defined as report of that category of adverse event on the PRISE on at least one post-baseline visit. For follow-up analyses, we also defined 'emergent' symptoms (putative adverse events) as those that were absent at the initial post-baseline (ie the week 2) visit, but present on at least one subsequent visit.

Primary analysis pooled men and women, which would maximize power to detect associations provided effects were similar within these two groups. For SNPs with nominal $p<0.05$ in any genes identified in the primary test of association described below, follow-up analysis examined heterogeneity between odds ratios within strata (men and women) using the Breslow–Day test. This approach was guided by the recommendations of a recent structured review of methodological constraints in detecting sex-specific effects (Patsopoulos *et al*, 2007).

Clinical analyses

Degree of overlap between the three categories of sexual symptoms was examined using cross-tabulation and Spearman's ρ. Individuals with and without each sexual symptom were compared on baseline sociodemographic and clinical features using χ^2-test or unpaired *t*-test. Multiple logistic regression was then used to determine which of these to include in the multivariate models described below; any feature with $p<0.05$ in the multivariate regression model was included as a covariate in the association analyses. Symptom groups were also compared in terms of maximal citalopram dose, amount of decrease in QIDS-C_{16} from baseline to end point, achieving remission (QIDS-$C_{16}\leqslant 5$) at end point, number of study visits, medication tolerability (using an algorithm previously described), and presence or absence of sedative/hypnotic co-treatment.

Gene-based analyses

As suggested by Neale and Sham (2004) for analysis of association studies, we considered the unit of analysis in this study to be the single gene rather than SNP; that is, we were screening for association of a gene (understood as a SNP or set of SNPs) with the phenotype of interest using a set-based test (here, the 'set' in question includes the SNPs in a given gene). The set-based test provides a simple means of accounting for linkage disequilibrium between SNPs within a gene, and also will generally have greater power to detect associations if multiple SNPs within a gene are associated with the phenotype of interest. In brief, this test, analogous to that proposed by Ott and Hoh (2003), computes the test statistic (χ^2 for dichotomous outcomes) for each individual SNP within a gene, then calculates the average test statistic for the best single SNP per region, for the best two SNPs per region, and for the best three SNPs per region. The significance of these set statistics is then estimat by permuting (swapping) individual identifiers to generate a 'new' data set. This method allows an estimate of how often, if no 'true' association exists, a set statistic this large or larger would be observed by chance. It allows a determination of gene-wise significance, allowing for correlation between SNPs and tests, while controlling type 1 error at the single-gene level.

Primary analysis screened for association using the set-based test as implemented in PLINK (Purcell *et al*, 2007) for each gene. Significance of SNP combinations including between one and three SNPs was estimated, using 20 000 permutations. To further control type 1 error, the same approach to permutation was also used to account for all tests in all genes (experiment-wise *p*-values)Fhere, how often would test statistics this extreme, or more extreme, be observed in the 'permuted' data sets. Where experiment-wise $p<0.05$ for a gene was observed, all single SNP associations in that gene were then examined. For the set-based tests, where pairs of SNPs were in linkage disequilibrium with $r^2>0.8$, only one of the two, selected arbitrarily, was included in analysis, but all SNPs in a gene were included when follow-up analyses were conducted. Epistatic effects were not examined due to limited power to detect such associations.

To address the potential for confounding by associations with baseline clinical features or longitudinal outcomes, we also performed a series of planned follow-up analyses for any SNPs in genes with nominal evidence of association. First, we repeated single SNP association analyses with adjustment for individual baseline clinical and sociodemo-graphic features, or longitudinal outcomes that were associated with a given sexual symptom. Efficacy and tolerability can be strongly correlated in clinical trials and can therefore confound observed associations. For example, individuals who derive less benefit from an intervention might receive greater dosing or longer trials, leading to greater emergence of dose-dependent symptoms or adverse events. A particular concern was confounding by symptomatic worsening, which led us to examine in a *post hoc* analysis SNPs with nominal evidence of association. In Cox regression, with emergence of a sexual symptom as the event of interest, we examined models including both genotype and visit-to-visit symptom change, the latter as a time-dependent covariate.

We further addressed the possibility of population admixture as previously reported, generating probabilities of ethnic group membership using the program STRUCTURE (McMahon *et al*, 2006; Pritchard *et al*, 2000) to cluster individuals based on ancestry-informative markers. Single SNP analyses were repeated with adjustment for factor loadings assuming a three-population ($k = 3$) solution, previously found to represent the optimal number of populations in this cohort (McMahon *et al*, 2006).

RESULTS

Comparisons of the genetic cohort to the total clinical cohort in terms of baseline sociodemographic features have been presented elsewhere (McMahon *et al*, 2006). Of 1910 genotyped subjects, we excluded 36 subjects who failed to return for at least one post-baseline visit and therefore did not provide adverse event data, yielding a 'modified intent-to-treat' sample; a further 401 non-Caucasian subjects were excluded from primary analyses because allele frequencies for many of the genes in question differ across populations, resulting in 1473 evaluable Caucasian subjects.

Sexual Symptoms and Clinical Associations

Of 1473 participants, 799 (54%) reported decrease in libido, and 525 (36%) reported difficulty achieving orgasm; correlation between them was modest (Spearman's $\rho = 0.33$).

In all, 400 of 1473 (27%) reported both symptoms, and 524 of 1473 (36%) reported one symptom. Of 574 men, 211 (37%) reported erectile dysfunction (ED); Spearman's $\rho = 0.32$ between ED and libido and 0.44 between ED and orgasm. Of 574, 133 (23%) reported two of three sexual symptoms, and 118 (21%) reported. Table 1 compares those who did or did not report each of the three sexual symptoms in terms of baseline clinical and sociodemo-graphic features. For ED, greater age, duration of illness, severity of depression at study entry, severity of general medical comorbidity, and presence of an anxiety disorder were associated with greater risk. For decreased libido, earlier onset of illness, greater severity of depression, being married, and being male were associated with greater risk. For difficulty with orgasm, younger age and earlier age at onset, greater severity of general medical comorbidity, as well as being married, male, and treated in a specialty rather than primary care setting, were associated with greater risk (features of longitudinal course, including number of follow-up visits, symptomatic improvement or remission, medication tolerability, and use of concomitant sedative/hypnotic medication are similarly compared in Supplementary Table 1).

Genetic Associations

Erectile dysfunction in men.—Supplementary Table 2 shows results from the set-based test for association between the included genes and presence of ED. *GRIN3A* was associated with difficulty achieving erection (experiment-wise permuted $p<0.05$ for rs1323427, rs1323423, and rs2050641) and met the threshold for further examination. Among serotonergic genes, greatest evidence of association was observed in *HTR2A* (rs6314, rs2770296, rs594242; gene-wise $p = 0.05$, experiment-wise $p = 0.95$). Table 2 includes all single SNP allelic results with nominal $p<0.05$ for association. Odds ratios for ED ranged from 1.51 to 1.56 for the three SNPs with greatest evidence of association, indicating overall risk ~50–60% greater among individuals carrying these individual risk alleles. To address the possibility that the association was confounded by sociodemographic or clinical features, we repeated the single SNP analyses with adjustment for any variables significant in univariate analyses, yielding no evidence of confounding in terms of change in odds ratios (Table 2). Likewise, to examine the possibility of confounding by efficacy (eg patients with poorer response receiving greater citalopram doses), we repeated single SNP analyses with adjustment for maximum citalopram dose, again with little change in strength of association (Supplementary Table 5). In particular, incorporating a term for symptom change *vs* prior visit did not change any observed hazard ratios by greater than 10%, suggesting these associations are not confounded by symptom change (results not shown). Most, but not all, associations remained significant ($p<0.05$) following adjustment for population substructure (Table 4). Finally, when the cohort was limited to those individuals without ED at the first post-baseline visit ($N = 446$), 87 (20%) reported new onset of ED (Table 2). Effect sizes, in terms of odds ratios, were similar to those observed in the full cohort.

Changes in libido.—We examined changes in libido in a similar manner. Two genes, *GRIA3* (rs2285127, rs2269551, rs550640) and *GRIK2* (rs9404130, rs2518302, rs513216) showed experiment-wise evidence of association (permuted $p<0.05$; Supplementary Table 3). Single SNP tests are shown in Table 3. For the three top SNPs in *GRIK2*, risk of

decreased libido was 30–40% greater among those with the risk allele, and for *GRIA3*, risk was 20–30% greater. No serotonergic genes were significantly associated with libido; the gene showing greatest evidence of association was *SLC6A4* (rs7224199, rs2054847, rs2020942; gene-wise $p = 0.02$, experiment-wise $p = 0.69$). Once again, there was little change in odds ratios for association with decreased libido when analyses were adjusted for sociodemographic and clinical differences (Table 3), or features of longitudinal outcome (Supplementary Table 6). As above, in no case did adjustment for symptom change yield a change in hazard ratio of greater than 10% (results not shown). After adjustment for population substructure, most but not all SNPs remained significantly associated (Table 4). When the phenotype was restricted to those without the adverse event at the first post-baseline visit ($N = 937$) who subsequently developed decrease in libido (272 of 937; 29%), effect sizes were similar to those observed in the cohort as a whole.

Difficulty with orgasm.—One gene, *GRIA1* (rs1994862, rs10515697, rs1864205), showed evidence of association with difficulty with orgasm (Supplementary Table 4). Among serotonergic genes, strongest association was again observed in the same SNPs in *SLC6A4* (rs2054847, rs7224199, rs2020942; gene-wise $p = 0.003$, experiment-wise $p = 0.162$). Results from individual SNPs in this gene with nominal $p<0.05$ are given in Table 4. Overall, odds of difficulty with orgasm were ~40–50% greater among those with the risk allele. Adjusting these association analyses for potential baseline (Table 4) or longitudinal (Supplementary Table 7) confounders yielded little change in odds ratios. Again, adjustment for symptom change did not change observed hazard ratios for single SNPs by 10% or greater (results not shown). The two top SNPs remained significantly associated with difficulty with orgasm after adjust ment for ancestry-informative markers. Limiting the analysis to the subset without decreased orgasm at baseline ($N = 1153$) also yielded similar results (Table 4).

DISCUSSION

This secondary analysis of data from a large-scale candidate gene study of antidepressant response found multiple genes of the glutamatergic system, but none from the serotonergic system, to be significantly associated with sexual dysfunction of three correlated but nonidentical types. Follow-up clinical analyses suggest that these associations are not confounded by clinical features that are independently associated with such symptoms, including general medical comorbidity, or by overall symptomatic worsening. This latter finding is notable in light of a prior STAR*D report that also identified association between glutamate genes and treatment-associated suicidality (Laje *et al*, 2007).

Although glutamate has not been studied as a mechanism of depression, or antidepressant-associated sexual dysfunction, rodent studies highlight its importance in sexual function. In males, the medial preoptic area (MPOA), which integrates and coordinates sexual behavior (Hull and Dominguez, 2006), receives glutamatergic input from the medial amygdala and bed nucleus of the stria terminalis, and in turn (acting through nitric oxide (NO)) increases dopamine release in the MPOA. Injecting dopamine antagonists will interfere with copulation among male rats, whereas agonists have the opposite (facilitating) effect

(Dominguez and Hull, 2005). Treatment with glutamate agonists and antagonists has analogous effects (Dominguez *et al*, 2006, 2004).

The MPOA projects widely, including the paraventricular nucleus of the hypothalamus (PVN), which appears to mediate directly erection through oxytocinogenic neurons. Glutamate agonists induce erections when injected into the PVN; erections are blocked by injecting glutamate antagonists (Melis *et al*, 2000; Powell *et al*, 2003). Glutamate has also been implicated in animal models of female sexual behavior. For example, glutamate antagonists infused into the ventromedial hypothalamus increase lordosis among female rats (Georgescu and Pfaus, 2006), whereas glutamate agonists have the opposite effect.

Far less is known about the neurobiology underlying libido *per se*, which may be difficult to distinguish from sexual activity in animal models. Notably, however, at least one case report associates lamotrigine, which decreases glutamatergic neurotransmission, with spontaneous hyper-sexuality or improvement in sexual function or interest among epilepsy patients (Gil-Nagel *et al*, 2006; Grabowska-Grzyb *et al*, 2006).

In humans, a recent report using magnetic resonance spectroscopy demonstrated that citalopram administration increases a composite measure of glutamate and glutamine *in vivo* (Taylor *et al*, 2008). Indirect evidence in animal models or *in vitro* systems suggests that SSRIs may influence glutamatergic neurotransmission, though the mechanism is not known (Langman *et al*, 2006; Matrisciano *et al*, 2008; Shioda *et al*, 2004; Svenningsson *et al*, 2007). For example, an *in vitro* model of neurogenesis suggests synergy between SSRIs and glutamate receptor (mGluR2 and 3) agonists (Matrisciano *et al*, 2008).

To our knowledge, only one prior pharmacogenetic study examined SSRI-associated sexual dysfunction (Bishop *et al*, 2006); in that study of 89 outpatients, a noncoding polymorphism in the *HTR2A* gene (−1438GA; rs6311) was associated with sexual dysfunction in general, as well as difficulty with arousal. Although we did not directly genotype this polymorphism, for purposes of comparison we did examine rs1928040 in *HTR2A* which is reported to be in strong linkage disequilibrium with it (r^2>0.8 in the International Haplotype Map Phase II data), and a two-SNP combination which is reported to be in perfect linkage disequilibrium with it (rs1928040, rs985933), but found no evidence of association either in the cohort as a whole, or among male or female cohorts (results not shown; nominal p>0.05 for all three sexual adverse effects). We likewise found no significant evidence of association on a gene-based test for association of *HTR2A* with any of these phenotypes (Supplementary Tables 1–3); although ED was nominally associated with some SNPs in *HTR2A*, these modest effects did not survive correction for multiple comparisons. We note that our phenotype differs from that previously examined because of the lack of baseline symptom assessment or sensitive measures of sexual function, so cannot exclude the possibility that a larger cohort or more detailed phenotyping might have detected a significant association. Alternatively, although modulation of postsynaptic 5HT2A may be clinically relevant to SSRI-mediated sexual dysfunction (Clayton and Montejo, 2006), there may simply not be a genetic basis for the observable pharmacodynamic variation.

A limitation of the present report is that no detailed and validated assessment of sexual function, such as the Changes in Sexual Functioning Questionnaire (Clayton *et al*, 1997), was used. Therefore, our sensitivity to sexual symptoms and ability to dissect individual components affected is limited. On the other hand, this would tend to bias our results toward the null, so it does not diminish confidence in the positive findings. In addition, details of medical comorbidity or their treatment are not available to us, although adjustment for summary measures of such comorbidity yields no evidence of confounding. Another caveat is that, because there is no PRISE completed at baseline, our findings do not necessarily indicate that these symptoms are treatment emergent. Rather, they may indicate risk for sexual dysfunction regardless of treatment. We nonetheless relied on this assessment as our primary phenotype because it allowed us to examine the largest possible cohort, we expected that most such reported symptoms would actually be treatment emergent, and we reasoned that any association detected, regardless of specificity, would be of interest. However, a secondary analysis examining only those symptoms clearly absent at initial post-baseline visit, and thus more likely to be truly treatment emergent, yielded similar results.

A further limitation is our inability to exclude fully the potential confounding effects of population stratification despite adjustment using ancestry-informative markers, and inability to exclude type I error in the absence of a replication cohort (Sullivan, 2007). Conversely, it is possible that pooling men and women obscured true sex-specific associations, resulting in type II error. We did not detect sex-specific effects for the genes showing main effects and therefore did not pursue within-sex analyses except for the SNP in *HTR2A* previously associated with sexual symptoms.

Finally, in the absence of a placebo or active comparator, we cannot address the specificity of the observed associations. The observed associations might indicate proneness to report sexual symptoms, regardless of treatment, or might be limited to SSRIs such as citalopram.

In sum, in this large-scale candidate gene-based study, we find preliminary evidence for association of glutamatergic but not serotonergic genes with sexual dysfunction among individuals with MDD treated with the SSRI citalopram. In all cases, the SNPs identified do not lie in known coding or regulatory regions. Still, these results suggest that glutamatergic strategies may merit further consideration for the management of SSRI-associated sexual dysfunction. By considering variation in glutamatergic genes, as well as clinical features associated with differential risk, it may be possible to identify individuals at greater risk for experiencing sexual dysfunction during depressive episodes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline sociodemographic and clinical features of the STAR*D genetics/sexual dysfunction Caucasian cohort (n = 1473)

	Normal			Impaired			Total				*p*
	n	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***t***	
(a) Erectile function											
Age (years)	363	42.5	13.5	211	47.8	12.3	574	44.4	13.3	−4.71	**<0.001**
Onset age (years)	363	26.8	14.6	209	27.3	16.0	572	27.0	15.1	−0.40	0.686
Illness duration (years)	363	15.7	13.2	209	20.4	15.0	572	17.5	14.1	−3.88	**<0.001**
Episode duration (months)	358	23.3	54.4	210	32.1	65.4	568	26.6	58.8	−1.71	0.088
QIDS-C (base)	363	15.8	3.1	210	16.4	3.4	573	16.0	3.2	−2.25	**0.025**
CIRS-total severity (base)	363	4.2	3.7	211	6.3	4.5	574	4.9	4.1	−6.16	**<0.001**
		n	**%**	**n**	**%**		**n**	**%**		χ^2	**p**
Gender (male)	363	100.0		211	100.0		574	100.0		NA	NA
Married (yes)	165	45.5		107	50.7		272	47.4		1.48	0.224
Recurrent (yes)	258	75.0		151	78.2		409	76.2		0.71	0.398
Anxious (yes)	131	38.3		106	53.5		237	43.9		11.81	**0.001**
Setting (specialty)	243	66.9		128	60.7		371	64.6		2.30	0.129
	Normal			**Decreased**			**Total**				***p***
(b) Libido	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***t***	
Age (years)	674	43.0	14.3	799	42.4	12.9	1473	42.7	13.5	0.83	0.408
Onset age (years)	671	26.7	15.2	793	25.1	14.4	1464	25.8	14.8	1.96	**0.050**
Illness duration (years)	671	16.4	14.2	793	17.2	13.9	1464	16.9	14.0	−1.14	0.253
episode duration (months)	671	24.4	55.4	793	23.1	51.8	1464	23.7	53.5	0.44	0.661
QIDS-C (base)	673	15.8	3.3	797	16.4	3.3	1470	16.1	3.3	−3.49	**<0.001**
CIRS-total severity (base)	674	4.5	3.9	799	4.8	3.9	1473	4.7	3.9	−1.36	0.175
	n	**%**		**n**	**%**		**n**	**%**		χ^2	**p**
Gender (male)	244	36.2		330	41.3		574	39.0		4.00	**0.046**
Married (yes)	228	33.8		440	55.1		668	45.3		66.56	**<0.001**
Recurrent (yes)	479	75.2		583	78.8		1062	77.1		2.50	0.114
Anxious (yes)	268	41.3		346	45.4		614	43.5		2.34	0.126
Setting (specialty)	371	55.0		470	58.5		841	57.1		2.13	0.144

	Normal			Impaired			Total				*p*
(c) Orgasm	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	***t***	
Age (years)	948	44.2	13.5	525	39.9	13.2	1473	42.7	13.5	5.92	**<0.001**
Onset age (years)	941	27.0	15.3	523	23.8	13.5	1464	25.8	14.8	3.90	**<0.001**
Illness duration (years)	941	17.3	14.4	523	16.1	13.3	1464	16.9	14.0	1.63	0.103
Episode duration (months)	942	25.5	58.1	522	20.4	43.8	1464	23.7	53.5	1.77	0.076
QIDS-C (base)	946	16.0	3.3	524	16.4	3.4	1470	16.1	3.3	−1.77	0.078
CIRS-total severity (base)	948	4.9	4.0	525	4.3	3.5	1473	4.7	3.9	3.03	**0.003**
	n	**%**		**n**	**%**		**n**	**%**		χ^2	**p**
Male	302	31.9		272	51.8		574	39.0		56.56	**<0.001**
Married (yes)	398	42.0		270	51.4		668	45.3		12.16	**<0.001**
Recurrent (yes)	668	75.8		394	79.4		1062	77.1		2.35	0.125
Anxious (yes)	396	43.2		218	44.0		614	43.5		0.07	0.794
Setting (specialty)	513	54.1		328	62.5		841	57.1		9.65	**0.002**

The table shows the baseline sociodemographic and clinical features of genotyped citalopram-treated subjects and association with erectile dysfunction (a), decreased libido (b), and difficulty achieving orgasm (c) following treatment. Bold values indicates $p \leqslant 0.05$.

Table 2

Single SNP associations with ED (p<0.05) among 574 men treated with citalopram for up to 14 weeks

SNP	Minor	Major	Freq (affected)	Freq (unaffected)	Unadjusted				Adjusted (baseline)		Adjusted (ancestry)		Emergent symptoms	
					χ^2	*p*	OR	95% CI	*p*	OR	*p*	OR	*p*	OR
rs2050641	G	A	0.21	0.29	9.313	0.0023	0.64	0.48, 0.85	0.0069	0.67	0.0031	0.66	0.1642	0.76
rs1323423	G	A	0.27	0.20	8.923	0.0028	1.53	1.16, 2.03	0.0170	1.44	0.0028	1.54	0.0099	1.64
rs1323427	A	G	0.19	0.26	8.279	0.0040	0.65	0.48, 0.87	0.0060	0.65	0.0055	0.67	0.0902	0.70
rs2050639	C	G	0.26	0.33	6.352	0.0117	0.71	0.54, 0.93	0.0272	0.73	0.0140	0.72	0.0373	0.67
rs1983812	G	A	0.52	0.44	5.504	0.0190	1.33	1.05, 1.70	0.0346	1.32	0.0232	1.32	0.0832	1.34
rs1004362	A	G	0.17	0.13	4.947	0.0261	1.46	1.05, 2.04	0.1105	1.33	0.0299	1.45	0.0680	1.51
rs2417290	C	A	0.24	0.19	4.441	0.0351	1.36	1.02, 1.82	0.0998	1.31	0.0334	1.38	0.2645	1.26

Column headings refer to unadjusted association, association adjusted for baseline clinical features, association adjusted for ancestry-informative markers, and association with only confirmed emergent symptoms (ie those not present at initial follow-up visit).

Table 3

Single SNP associations with decreased libido (p<0.05) among 1473 individuals with MDD treated with citalopram for up to 14 weeks

SNP	Minor	Major	Freq (affected)	Freq (unaffected)	Unadjusted				Adjusted (baseline)		Adjusted (ancestry)		Emergent symptoms		
					χ^2	*p*	OR	95% CI	*p*	OR	*p*	OR	p (sex heterogeneity)	*p*	OR
GRIK2															
rs513216	A	G	0.31	0.26	10.04	0.0015	1.30	1.105, 1.526	0.0006	1.34	0.0017	1.30	0.9874	0.0027	1.39
rs9404130	C	G	0.10	0.08	6.37	0.0116	1.39	1.076, 1.801	0.0162	1.39	0.0122	1.40	0.7096	0.0006	1.75
rs2518302	A	C	0.19	0.22	4.65	0.0311	0.82	0.6843, 0.9823	0.0363	0.82	0.0322	0.82	0.2422	0.2643	0.87
rs2518224	C	A	0.10	0.13	4.30	0.0382	0.79	0.6278, 0.9875	0.0254	0.76	0.0407	0.79	0.4732	0.1128	0.77
GRIA3															
rs2285127	G	A	0.36	0.42	11.29	0.0008	0.75	0.6372, 0.8883	0.0009	0.75	0.0009	0.75	0.8167	0.0068	0.73
rs2269551	G	A	0.35	0.41	8.19	0.0042	0.78	0.664, 0.9264	0.0090	0.79	0.0041	0.78	0.2030	0.0135	0.75
rs550640	A	G	0.33	0.37	3.95	0.0469	0.84	0.7106, 0.9977	0.0697	0.85	0.0431	0.84	0.9318	0.0096	0.73

Column headings refer to unadjusted association, association adjusted for baseline clinical features, association adjusted for ancestry-informative markers, test for heterogeneity between men and women, and association with only confirmed emergent symptoms (ie those not present at initial follow-up visit).

Table 4

Single SNP associations with decreased orgasm ($p<0.05$) among 1473 individuals with MDD treated with citalopram for up to 14 weeks

SNP	Minor	Major	Freq (affected)	Freq (unaffected)	Unadjusted				Adjusted (baseline)		Adjusted (ancestry)		Emergent symptoms		
					χ^2	*p*	OR	95% CI	*p*	OR	*p*	OR	*p* (sex heterogeneity)	*p*	OR
rs10515697	T	A	0.31	0.26	8.189	0.0042	1.28	1.08, 1.51	0.0123	1.26	0.0139	1.25	0.4813	0.0005	1.49
rs1994862	C	G	0.31	0.26	8.104	0.0044	1.27	1.08, 1.51	0.0132	1.25	0.0146	1.24	0.4968	0.0006	1.48
rs1864205	G	A	0.36	0.32	5.636	0.0176	1.21	1.03, 1.42	0.0836	1.16	0.0628	1.16	0.9275	0.0391	1.26

Column headings refer to unadjusted association, association adjusted for baseline clinical features, association adjusted for ancestry-informative markers, test for heterogeneity between men and women, and association with only confirmed emergent symptoms (ie those not present at initial follow-up visit).